The role of contrast enhanced ultrasonography in post-operative surveillance of endovascular aortic aneurysm stent graft repair

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THE ROLE OF CONTRAST ENHANCED ULTRASONOGRAPHY IN POST-OPERATIVE SURVEILLANCE OF ENDOVASCULAR AORTIC ANEURYSM STENT GRAFT REPAIR

A thesis submitted to the University of London, for the degree of Doctorate of Medicine (Research) in the Institute of Cell and Molecular Science of Barts and The London, Queen Mary's School of Medicine and Dentistry; 2013

by

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"It has often been said
there's so much to be read,
you never can cram
all those words in your head.

So the writer who breeds
more words than he needs
is making a chore
for the reader who reads.

That's why my belief is
the briefer the brief is,
the greater the sigh
of the reader's relief is.

And that's why your books
have such power and strength.
You publish with shorth!
(Shorth is better than length.)"

Dr Theophrastue Seuss (Theodor Seuss Geisel: 02/03/1904 – 24/09/1991)

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ABSTRACT

Abdominal aortic aneurysms are common and responsible for many deaths. They are treated increasingly by EndoVascular Aneurysm Repair (EVAR) rather than conventional surgery. Approximately 25% of EVAR patients require re-intervention to prevent aneurysm enlargement which can rupture despite previous repair.

All EVAR patients undergo life-long surveillance for complications such as stent-graft migration or endoleak. Computed Tomography (CT) has been the 'gold-standard' for surveillance accounting for 65% of EVAR costs, and exposes patients to cumulative radiation and nephrotoxic contrast.

Duplex Ultrasound Scanning (DUS) has been proposed as an alternative for surveillance with lesser cost and patient risk. However, clinical studies have reported varying results. The addition of microbubble contrast significantly improves endoleak detection rates, making it comparable with CT.

The physical properties that affect endoleak detection with DUS have not been determined. It is also unknown specifically which endoleaks' detection are improved by Contrast Enhanced Aortic Duplex UltraSound Scanning (CEADUSS).

To investigate the physical properties of endoleaks, I constructed an EVAR phantom model with a simulated endoleak of variable velocity (fast/slow), position (near/far) and plane (anterior/lateral/posterior). Preliminary studies investigated the behavior of microbubble contrast in the phantom system, and then laboratory experiments tested subjects over 36 variable endoleaks using DUS and CEADUSS.

These laboratory experiments were translated clinically with a pilot study of CEADUSS in 10 patients with endoleaks on CT not detected by DUS, undefined endoleak type or origin, or a sac enlargement with no endoleak present.

My experiments reveal an insight into factors influencing ultrasound endoleak detection. With this knowledge, the use of these modalities for surveillance protocols can be increased,

reducing current CT burden, radiation and nephrotoxic contrast exposure, and overall EVAR cost. Clinical assessment of an endoleak, specifically noting physical characteristics (plane, position and velocity) will improve detection and surveillance.

DECLARATION AND COPYRIGHT

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning.

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Mr Shiva Dindyal

ACKNOWLEDGEMENTS

I would like to thank:

1) Dr. Mark P. Brewin, the other research fellow in the department of Clinical Physics who helped to design and modify the EVAR phantom. He also took part as the gold standard subject and provided much help with all aspects of my project.

2) Dr Abigail Thrush, Clinical Scientist, Clinical Physics Department, Barts and The London NHS Trust, The Royal London Hospital for helping with the design and ultrasound imaging of both the laboratory phantom and clinical experiments and participating as a subject.

3) Miss Kate Adams, Vascular Ultrasonographer, Barts and The London NHS Trust, The Royal London Hospital for performing all of the clinical patient's scans and taking part in the EVAR phantom laboratory project as a subject.

4) Dr Mustapha, Miss Helen Dawson, and Miss Kelly-Marie Barett, Vascular Ultrasonographers, Barts and The London NHS Trust, The Royal London Hospital for taking part in the EVAR phantom laboratory part of my project as subjects and performing the surveillance unenhanced scans.

5) Dr Nicos Fotadis, Dr Ian Renfrew and Dr Mathew Matson, Department of Radiology, Barts and The London NHS Trust, The Royal London Hospital for helping with the clinical part of the project by reporting scans and providing clinical images of patients.

6) Miss Louise-Marie Beck, Bracco UK Limited for providing me with samples of SonoVue ultrasound contrast and for also providing me with the contact details and visits to a number of contrast radiology experts.

7) Dr Dirk-André Clevert, Associate Professor of Radiology, University of Munich, Germany for allowing me to attend his unit to learn the technique of contrast ultrasound imaging as well as participating in his contrast enhanced ultrasound and endovascular aortic repair course.

8) Dr Paul Sidhu, Consultant Radiologist, Kings College Hospital, London for help with starting off my clinical project, scanning our first patient, teaching myself and Kate Adams the contrast ultrasound imaging technique.

9) Mr Joe Shalhoub and Mr Veeru Kasivisvanathan, Vascular Research Fellows, Charing Cross Hospital, Imperial College London for their invaluable help with my thesis analysis and statistics.

10) Professor Steve Bustin, Institute of Cell and Molecular Science, Barts and the London Queen Mary's School of Medicine and Dentistry for being an independent supervisor for my thesis and providing help with my thesis, university paperwork and assessments.
11) Dr Malcolm Birch, Clinical Scientist, Clinical Physics Department, Barts and The London NHS Trust for being a project supervisor and all of the help with all aspects of my project, his critical advice and time with my studies for all of its duration.
12) Mr. Constantinos Kyriakides, Consultant Vascular and Endovascular Surgeon, Barts and The London NHS Trust and Honory Senior Lecturer Barts and The London School of Medicine and Dentistry, for being my project chief supervisor who provided expert guidance and numerous opportunities for me during my time completing this project.

PREFACE

This thesis describes work, which I undertook, on the role of contrast ultrasonography in post-operative surveillance of endovascular aortic aneurysm stent graft repair while holding a Research Fellowship in the Circulatory Science Academic Unit, Department of Vascular and Endovascular Surgery, Barts and The London NHS Trust, The Royal London Hospital and Barts and The London School of Medicine and Dentistry, from August 2008 to August 2012.

My part of these investigations included: 1) searching and analyzing the literature, 2) planning the investigation and designing the experiments, 3) supervision of the study participants, 4) performing the laboratory and clinical experiments, 5) analyzing the images and data, 6) writing the papers that have been submitted for publication and presentation reporting this work, 7) preparing the thesis and papers on a personal computer.

It is a pleasure to thank the following people whose contributions made this work possible:

- Mr. Constantinos Kyriakides, Circulatory Science Academic Unit, Department of Vascular and Endovascular Surgery, Barts and The London NHS Trust, The Royal London Hospital and Barts and The London School of Medicine and Dentistry, for arranging my research post and for supervising the completion of this thesis.
- Professor Steve Bustin, Institute of Cell and Molecular Science, Barts and the London Queen Mary's School of Medicine and Dentistry for providing critical advice on the presentation of content of this thesis.
- Dr Malcolm Birch, Clinical Physics, Barts and The London NHS Trust, in whose laboratory the work was done, for helpful discussions during the course of the work and for critical analysis of the publications that resulted from it.

Finally, I would like to dedicate this thesis to my mother, father, late grandfather Sonny Dindyal, living grandmothers and my wife Dr Catherine Dindyal, for their tremendous support and encouragement through the many ups and downs of scientific research.

In loving memory of the late Sonny Dindyal (12th November 1927 – 16th July 2011)

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SECTION 1

INTRODUCTION

ABDOMINAL AORTIC ANEURYSMS

The term aneurysm is derived from the Greek *aneurynein* to widen, and *aeirein*, to heave. Today the term is used to describe a permanent, 50% or greater, focal or partial dilatation of a blood vessel compared with the normal proximal diameter. With respects to the abdominal aorta, the definition of aneurysm is given to dilatation 3cm or greater, irrespective of pathophysiology (Johnston 1991, Horejs 1988). The aneurysmal process may affect any vessel but more commonly occurs in medium and large arteries. The infra-renal aorta and common iliac arteries are most commonly affected, followed by the supra-renal aorta, popliteal, femoral and carotid vessels. Morphologically an aneurysm may be fusiform or saccular, the former being commonest.

Abdominal aortic aneurysms (AAA) are of particular clinical relevance. In the majority of patients the disease is asymptomatic however carries an inherent risk of rupture and death. The natural history of AAA is progressive enlargement until the aortic wall is weakened and ruptures causing internal hemorrhage. Sadly for a considerable number this may be the first presenting symptom of the disease. Symptoms progress from vague abdominal pain to a life threatening collapse in minutes to hours (Mell 2012a, Bergqvist 2010, Ernst 1993). Hence there is great interest in AAA.

In England, AAA are responsible for over 11000 hospital admissions per year (Office of Population Census and Surveys, Mortality Statistics, England and Wales London 1989). AAA rupture causes 9000 deaths in the United States (Wilt 2006, Thompson 1996, Gillum 1995, Bickerstaff 1984) and 6000-8000 deaths in England and Wales (Earnshaw 2011a, Hartshorne 2006, Thompson 2003). The mortality for AAA rupture may be up to 78-94% (Wang 2012, Brewster 2003). Unlike other atherosclerotic disorders, the prevalence of AAA has been increasing rapidly in Europe, North America and Australia, despite a recent worldwide decrease in other cardiovascular disorders (Anjum 2012, Darwood 2012a, Earnshaw 2012, Hultgren 2012, Mell 2012b, Mohan 2012, Mani 2011, Modfidi 2008, McPhee 2007, Acosta 2006, Filipovic 2005, Cao 1999, Bengtsson 1992a, Parodi 1991, Fowkes 1989, Melton 1984). Aneurysmal rupture is now the thirteenth commonest cause of death in the developed world (Wilt 2006, Jordan 2002, Bengtsson 1993, Fowkes 1989, Johansson 1986), and the tenth among men (Wilt 2006, Huber 2001, Gallagher 1999,

Lawrence 1999). Aneurysm rupture is the third most common cause of sudden death in the UK, after coronary heart disease and stroke (Jaunoo 2008), and represents 1.5% of the total mortality in men over the age of 55 (Hartshorne 2006, Thompson 2003). AAA usually affect men (Hultgren 2012, Modfidi 2008, McPhee 2007, Semmens 2000, Katz 1997) over 65 years old, with a prevalence of 4.2-8.8% and 0.6-1.4% for women (Fleming 2005). The presence of the condition in women is more sinister as evidence shows that AAA may grow faster and are three times more likely to rupture than in men (Mehta 2012, Sweeing 2012, Modfidi 2007, Powell 2007, Hartshorne 2006, Solberg 2005, Brown 2003, Vardulaki 2000, Brown 1999, Alcorn 1996).

The etiology and pathogenesis of AAA are poorly understood but the current theory is that the majority are caused by atherosclerotic deposits weakening the aortic wall, this results in a loss of medial elastin and smooth muscle cells. Hultgren et al, from Sweden, have recently published their analysis of 35418 AAA patients, demonstrating a correlation of disease distribution mirroring the exact geographical variations of coronary heart disease (Hultgren 2012).

Until the 1800's the majority of aneurysms were traumatic in origin (Bergqvist 2010, Bergqvist 2008). Today other causes include congenitally acquired elastin and collagen genetic defects (McAteer 2012, Bengtsson 1992b), family history (Linné 2012), geographical location, smoking (Sweeting 2012, Lloyd 2004, Lederle 2003a), hemodynamic stress such as hypertension, pathological degenerative proteolysis, infectious processes such as Chlamydia, adventitial vasa vasorum hypoxia and inflammatory reactive components (Walker 1972) which alter the aortic wall strength (Nordon 2011, Arrivé 1995, Cullenward 1986, Pennell 1985). These abnormalities reduce the tensile strength of the vessel and cause disruption of the extracellular matrix through widespread arterial wall inflammation, thus increasing wall weakness and constant vascular expansion.

In the community, the death rate from ruptured AAA is almost 90% (Bosch 2002, Noel 2001, Johansen 1991, Mealy 1988). Before reaching hospital 80% will die and approximately 50% (ranging from 32-70%) die during emergency care and surgical repair (Jaunoo 2008, Lindholt 2008, Wilt 2006, Eliason 2005, Noel 2001, Heller 2000, Kniemeyer 2000, Lindholt 1998, Ernst 1997, Katz 1994, Johansen 1991). Those lucky enough to reach hospital have

generalized abdominal tenderness and commonly profoundly shocked. In these patients the rupture tends to occur posteriorly and is contained by the retroperitoneum. Approximately a third of AAA will eventually rupture if left untreated (Fleming 2005, Nevitt 1989, Darling 1977).

The majority of AAA remains asymptomatic for years, but the likelihood of rupture increases proportionately with the diameter (Geroulakos 1992, Glimaker 1991, Guirguis 1991, Nevitt 1989). The strongest known predictor of rupture is based upon two high quality randomized controlled trials: The UK Small Aneurysm Trial and The Aneurysm Detection and Management Veterans Affairs Cooperative Study (Lederle 2002a, The UK Small Aneurysm Trial Participants 1998a, The UK Small Aneurysm Trial Participants 1998b). Small aneurysms (< 4cm) are generally benign and grow slowly (1-2mm/year), however there is a minority which expand rapidly (Sweeting 2012, Powell 2011a, Thompson 2010, Brady 2004, Brown 2003, Lederle 2002b) and don't conform to the simple mechanics of Laplace's law that states wall tension is a product of pressure and radius (Vardulaki 1998), therefore requiring surveillance. The annual rate of rupture for AAA <5.5cm is ≤1%. Rupture occurs in approximately 5% per year once the aneurysm reaches 6cm in anterior-posterior diameter. If managed non-operatively, the 1 year risk of rupture may be >10% for diameters >6cm and may exceed 25% at 6 months for diameters >8cm (Wyffels 2000). In the US, 30000-40000 cases of elective surgical repair of asymptomatic AAA occur, with a perioperative mortality ranging from 2-8% (Harris 2012, de Martino 2010, Hirsch 2006, Lucas 2006, Wilt 2006, Soisalon-Soininen 1999, Cambria 1994). It is good practice to repair aneurysms ≥5.5cm to prevent rupture. Those with diameters <5.5cm should be considered for repair in certain circumstances i.e. women, patients with saccular morphology, and those with rapid expansions (Eliason 2009).

In a study of 73451 predominantly male US veterans aged 50-79, with no history of AAA, 7.1% had ultrasonic infra-renal aortic diameters ≥3cm. The majority (>90%) of these AAA were small (<5.5cm), a minority being ≥6cm (0.4%) (Lederle 1997). Most of these were incidentally noted at autopsy and didn't require intervention during the patient's lifetime.

The UK Small Aneurysm Trial (UKSAT) (The UK Small Aneurysm Trial Participants 1998a & 1998b) and the Aneurysm Detection and Management study (ADAM) (Lederle 2001), are

two high quality randomized controlled trials (n=2226) assessing patients with AAA <5.5cm. They both concluded that active surveillance with delayed open surgical repair did not have a higher all-cause mortality compared with early open surgical repair. After a mean follow-up of 5 years, the overall relative risk was 1.21 (95% CI 0.95-1.54); and a 0.94 (95% CI 0.75-1.17, p=0.56) hazard ratio for all-cause mortality for UKSAT and ADAM combined (Wilt 2006). At 8 year follow-up for the UKSAT study, there was no significant mean survival difference between groups (6.5 years for surveillance vs 6.7 for early surgery, p=0.29) (United Kingdom Small Aneurysm Trial Participants 2002). In the ADAM study, AAA related mortality was not reduced by early open surgical repair (3.3%) vs surveillance and delayed repair (3.4%). Differences in quality of life measurements were small for both studies and the overall results confirmed by a Cochrane meta-analysis (Ballard 2008).

A recent systematic review of small AAA (3.0-5.5cm) rupture in 54 studies published prior to 2010 revealed that rupture detection, patient follow-up and cause of death were poorly reported and that diagnostic criteria for rupture were never reported (Powell 2011b). Rupture rates were available for only 14 of these studies which included 9779 patients (89% male) over the time period 1976-2006, but only 7 of these studies provided rupture rates specifically for small AAA (3.0-5.5cm). The authors concluded that the rupture rates of small AAA appeared to be extraordinarily low (between 0-1.61 per 1000 person-years). A major global limitation was that these studies were heterogeneous and poorly reported with no clear diagnostic criteria for defining rupture. A further publication by Powell et al, highlighted considerable variations throughout the literature for reporting growth rates of small aneurysms (Powell 2011a).

The English NHS is implementing an AAA Screening Programme (NAAASP) targeting men >65 with abdominal duplex color ultrasound (DUS) of the anteroposterior and transverse measurements of the infrarenal aorta maximum diameter to detect AAA (NHS AAA Screening Programme 2009, UK National Screening Committee 2008). The national screening program began in pilot form in March 2009 in England. The results are pending before phased implementation up to March 2013, to a population of 800000 men. Similar programmes are starting in Scotland (NHS National Services Scotland 2008), Wales, Northern Ireland (McCollum 2011) and others are advocating targeted screening of high risk patients, for example smokers with known atherosclerosis (Ferket 2012, Spronk 2011,

Lederle 2008, DeRubertis 2007, Wanhainen 2005, US Prevention Services Task Force 2005, Earnshaw 2004, Cornuz 2004, Brady 2004, Beard 2003, Lederle 2003b).

AAA screening fulfills the majority of the World Health Organization screening criteria (Bergqvist 2008, Lindholt 2008). It is a common, asymptomatic condition which is potentially life-threatening. It has a safe and accepted method of treatment in the early stage, which has a positive impact on morbidity and mortality. The use of DUS is a valid, suitable and acceptable non-invasive method of screening that has been proven to be accurate and reliable (Dabare 2012, Foo 2011, Manning 2009a, Wilmink 2002, Heather 2000). The intention is to detect asymptomatic AAA when they are at a size optimal for operative repair, treat electively prior to rupture and hence reduce subsequent morbidity and mortality. This has been reiterated by a recent meta-analysis (Dabare 2012, Lindholt 2011)

If an AAA is detected then the patient will be invited for regular surveillance programme and/or treatment if appropriate. Non-aneurysmal aortas (<3cm), will be classified as normal with respects to the screening programme and will not receive any further imaging or follow-up. Elective surgery will be recommended for patients with AAA ≥5.5cm and for AAA ≥4.5cm that have increased by ≥0.5cm in the last 6 months. Patients found to have AAA of ≤4.5cm will be followed-up by DUS every 6 months; AAA of 4.5-5.5cm every 3 to 6 months (Desai 2010).

The predicted figures for NAAASP are derived from the Multicentre Aneurysm Screening Study (MASS) data (Ashton 2002), funded by the Medical Research Council, which recruited and randomized 67770 men aged 65-74 from four UK centers for one-off DUS or placebo, between 1997-1999. It is thought that 240 men need to be invited (192 scanned) to save one AAA death over 10 years and for each 2080 men invited for screening (1660 scanned) results in one extra post-elective surgery death. These calculations use the MASS 10-year data and assume an 80% attendance for screening with 5% post-elective repair mortality. Consequently over 10 years, for every 10000 men scanned under the NAAASP, 65 AAA ruptures will be prevented, saving 52 lives (Dabare 2012, National Screening Committee 2009).

Large randomized trials of AAA screening have already been performed as have meta-analyses of their final results (Dabare 2012, Darwood 2012b, Flemming 2009, Cosford 2007,

Kim 2007a, Ashton 2007, Lindholt 2005, Norman 2004, Ashton 2002, Heather 2000, Scott 1995, Bengtsson 1991). AAA related mortality can be reduced by the introduction of population DUS screening; this survival advantage is maintained at 10 years (Thompson 2009, Kim 2007a) and 15 years (Ashton 2007). Several countries have already introduced screening and have demonstrated its cost-effectiveness, such as in the UK (Dabare 2012, Darwood 2012a, Darwood 2012b, Earnshaw 2012, Søgaard 2012, Spronk 2011, Buxton 2009, Scott 2008, Hartshorne 2006, Shaw 2002, Scott 1995), Canada (Montreuil 2008), Denmark (Dabare 2012, Lindholt 2010, Lindholt 2007, Lindholt 2006, Lindholt 2002, Multicentre Aneurysm Screening Study Group 2002) and Sweden (Mani 2010, Swedenborg 2008, Swedish council on technology assessment in healthcare 2008, Wanhainen 2006). However, some still disagree with the financial implications, and economic modeling has shown it to be expensive. This is difficult to interpret due to different costing tariffs, disparities between elective and emergency procedures and overall international healthcare outlay variances, especially using short term data (Kim 2010, Buxton 2009, Ehlers 2009, Mani 2008, Campbell 2007, Kim 2007b, Sculpher 2006, Henriksson 2005). Screening for AAA in women is not cost-effective due to its lesser incidence and so women have not been included in any surveillance programs, despite their 3-4 fold higher rupture rate and a poorer outcome when compared with men (Brown 2003, Brown 1999).

The proposed screening programme for AAA will have important service and financial consequences. Apart from the screening program costs, increasing resources for vascular services will be needed with higher AAA identification and repair rates (Hartshorne 2012, McCollum 2011), potentially shifting the balance from emergency rupture management to elective repair. This has been demonstrated by a meta-analysis of four randomized controlled trials (Ashton 2007, Kim 2007b, Norman 2004, Lindholt 2010). Following screening implementation in 125576 men both mid-term (3.5-5yrs) and long-term (7-15yrs) emergency repairs were significantly reduced and elective repair rate increased (Lindholt 2008).

The recently released first year results of the NAAASP show that approximately ten percent of the target population will be screened annually (Earnshaw 2011a), but some programmes are reporting initial low attendance rates (Badger 2011, McCollum 2011). In the first year 23000 have been screened and 404 AAA identified, which is a number lower than that expected (NHS Abdominal Aortic Aneurysm Screening Programme 2011). Sandiford et al,

have also found a smaller number of AAA than expected in their national screening program in New Zealand (Sandiford 2011). Both of these data suggest that the prevalence of AAA may be declining in these countries, mirroring the decreasing incidence of cardiovascular disease (Capewell 2009). It is ironic that this should occur just as screening programmes are being implemented (Earnshaw 2011a).

Screening programmes will produce further dilemmas. Those with AAA >5.5cm or symptomatic aneurysms will be offered repair. There will be a higher number of healthy individuals with asymptomatic AAA <5.5cm, who will be labeled with a potentially life threatening disease. These patients will have to undergo regular surveillance in a follow-up program until intervention is indicated. It is postulated that approximately 85-90% of those screened will fall into this category (Powell 2011b, Lindholt 2008, Cosford 2007, and Lederle 2003b). Those under surveillance will be encouraged to receive "best medical therapy" i.e. stringent blood pressure and diabetes control, smoking cessation, use of statins and inflammatory cytokines, for which the precise mechanism of lowering AAA progression is still unknown (Raux 2012, de Rango 2011a). The psychological impact of participating in a surveillance program and engaging with "best medical therapy" on quality of life because of their new disease 'label' cannot be underestimated. (Lindholt 2000a).

Should these men be offered the less invasive techniques of AAA repair at an early stage? The current available data regarding interventions for small AAA is based on conventional open surgical techniques; the newer alternative endovascular techniques carry a significantly reduced morbidity and mortality (Lederle 2007, EVAR Trial Participants 2005, Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group 2005, EVAR Trial Participants 2004). Though initially more expensive (McCollum 2011), their cost is continually falling and there is evidence that both types of repair have equivalent long-term expenditure (Mani 2008). Lastly an important consideration regarding cost is that endovascular repair could be offered to more patients deemed unfit for conventional surgery. Therefore the proportion of detected AAA being repaired will increase costs and these high risk "unfit" patients could skew the mortality and morbidity benefit of screening (Karthikesalingham 2011a, Mani 2010).

Another potential issue of screening has been highlighted by an analysis of the data from one of the earliest AAA screening programmes of 22961 men in Chichester (Scott 1991, Scott 1986). This has shown that 2.8% who had an initial "normal" aortic measurement at screening, who were discharged from their program, developed AAA over a median period of 5 years and 65% of these men had initial ectatic diameters between 2.5-2.9cm (Hafez 2008). The authors concluded that surveillance for this "normal" sub-group may reduce the incidence of developing AAA. Other groups have also reached similar conclusions (McCarthy 2003, Lindholt 2000b). The screening of these men should be considered in the future when NAAASP is established and initial data is analyzed.

The advantages of screening outweigh the disadvantages and only by following these patients will we learn the natural course of this common life-threatening disease. The cohort of surveillance patients with small aneurysms will be invaluable in subject provision for various randomized controlled trials (de Haro 2012) of medical therapies with the potential to reduce AAA growth rate e.g. statins (de Céniga 2012a, de Céniga 2012b, Piechota-Polanczyk 2012, Takagi 2012, Abisi 2008, Schouten 2006, Sukhija 2006), angiotensin-converting enzyme inhibitors (Hackam 2006), calcium channel blockers (Bailey 2012, Yamanouchi 2012), angiotensin II (Favreau 2012), macrolides, cyclo-oxygenase inhibitors, indomethacin, tetracyclines, vancomycin, doxycycline, roxithromycin and azithromycin. This potentially could avoid the need for intervention completely, which would be a financial incentive. By surgical repair of AAA, we are contributing to the maintenance of an increasing elderly population. This may in turn develop other vascular disorders, increasing the financial burden and causing ethical dilemmas over treatment cut-off age restrictions.

ANEURYSM REPAIR

Conventional open surgical repair

Historically several attempts have been made to treat AAA, but reconstructive treatments have only been possible since 1951. Until 1900, the treatment of aneurysms was essentially ligation of both proximal and distal aspects of the affected vessel. In 1818 Sir Astley Cooper used this technique in a long, spectacular procedure. The patient survived for a few days (Bergqvist 2010). Matas from New Orleans then proposed the reconstructive approach of aneurysmorrhaphy which is similar to 21st century repair. In 1888 he described the obliteration of the aneurysmal sac in a traumatic brachial aneurysm, leaving a patent channel in the middle (Matas 1888).

Knowing that aneurysm size and wall expansion rate were predictors of rupture, it was proposed that their stabilization would halt disease progression. Synthetic (plastic films and cellulose) and biological (fascia) materials were used with varying success. One of the most famous procedures was the wrapping of Einstein's AAA in 1948 by Nissen, which postponed Einstein's eventual death from rupture until 1955!

In the 1950's Leriche suggested that aortic reconstruction was possible in occlusive disease. This was first attempted with homographs by Oudot in 1951 (Oudot 1951), and repeated a few months later by Freeman in San Francisco (Freeman 1951). He used an inlay technique with a vein graft to re-establish circulation. One month afterwards, in Paris, Dubost (Dubost 1952, Dubost 1951), resected an AAA and reconstructed it with a homograft. This technique was reproduced in 1954, using pliable plastic tube synthetic material (Shumaker 1954) and also for a successful AAA rupture repair (Bahnson 1953).

Thus open surgical repair became the mainstay of treatment for AAA (Creech 1966). Open repair was the only available option for a number of years despite the technique involving extensive exposure of the aorta via a large midline incision (from sternum to pubic bone or across the waist). The aorta and both iliac arteries were cross-clamped to incorporate an artificial straight or bifurcated prosthetic graft, usually made of Dacron (Vardoulis 2011). This requires a lengthy hospital admission (mean 6 days) carrying high costs, mortality and morbidity (Al-Zuhir 2012, Freyrie 2012, Grant 2012a, Grant 2012b, Mann 2012, Mohan

2012, Salata 2012, Schneider 2012, Martin 2010a, Lees 2009, Tallgren 2007, Hartshorne 2006, Wald 2006, Greenhalgh 2004, Hertzer 2002, Hallin 2001, Wyffels 2000, Geroulakos 1997, Akkersdijk 1994a, Hollier 1986). Despite numerous advances in critical care medicine the mortality and morbidity of conventional open surgical repair has remained high (Gibbons 2008, Aylin 2007, Brown 2002, Bayly 2001), and is still performed in nearly half of UK AAA patients and the majority of European patients (Grant 2012a, Grant 2012b, Lees 2009, Gibbons 2008).

Laparoscopic repair

Laparoscopic aortic surgery is an evolving technique, combining conventional repair with minimally invasive approaches. Gastrointestinal surgery has been revolutionized by laparoscopy (Turnipseed 2002) which is now commonplace in the majority of units in the UK. In 1993 Dion et al, described the first laparoscopic techniques with respects to the aorta (Dion 1993, Luk 2010). They conducted a laparoscopically-assisted aorto-bi-femoral bypass and subsequently the technique has been refined and applied to perform bypass in occlusive disease and AAA repair.

In the UK in 2007, the National Institute for Health and Clinical Excellence (NICE) issued guidance regarding the use of laparoscopic AAA repair, highlighting the technical demand of the technique, and its steep learning curve. It recommended that only surgeons with advanced laparoscopic skills in specialized units should undertake the procedure, particularly for AAA repair, and report their outcomes in the National Vascular Database (Luk 2010, Founeau 2008). Long-term graft durability is still being assessed.

Surgery can be totally laparoscopic, where both dissection and anastamosis are performed. Alternatively non-dominant hand assistance can be employed to aid dissection and provide tactile feedback, thus reducing technical demands (Cochennec 2012, Veroux 2010, Ferrari 2006, The HALS Study Group 2000, O'Reilly 1996). Some surgeons use a combination of laparoscopic dissection with a mini-laparotomy to perform the anastamosis (Turnipseed 2002, Alimi 2001, Castronuovo 2000, Edoga 1998, Kline 1998, Dion 1997). A minority have instigated the use of a robotic system (Kolvenbach 2004). The approach to the aorta can be transperitoneal or retroperitoneal.

Laparoscopic techniques compare favorably to conventional open surgery with shorter hospital stays, reduced blood loss and less ischemic complications. However they do take longer to perform and are associated with longer aortic-clamping times (Luk 2010, Veroux 2010, Ferrari 2009, Cau 2008, Ferrari 2006, and Coggia 2005). Another advantage to laparoscopic AAA repair is that it can be applied to a number of patients deemed anatomically unsuitable for EVAR repair due to vessel morphology (Turnipseed 2002, Kolvenbach 2001). Strangely in contrast to EVAR, only a minority has adopted laparoscopic aortic surgery and numbers treated are small.

Endovascular aortic aneurysm stent graft repair

Another minimally invasive advance in AAA repair was by a Ukrainian, Volodos in 1986 (Bergqvist 2010), addressing the majority of open surgery disadvantages. He used a self-fixing synthetic remote endoprosthesis for aortic reconstruction, repeating the technique in 1988 to treat a thoracic aortic aneurysm.

In 1929, Forssmann passed a tube via an arm vein into his own heart, describing the first cardiac catheterization. Twenty four years later, Seldinger documented his technique, which is still used today for standard angiography and forms the basis of modern vascular interventions (Seldinger 1953). The first femoral angioplasty was performed in 1964 by Dotter in Oregon and continued with arterial embolisation by Djidjian and Rosch in 1967-70. Arterial balloon dilation of renal and coronary arteries was performed by Gruntzing in the mid-seventies. The concept of inserting a graft embedded within a metallic stent had been considered as far back as 1979 when the first patent for this idea was registered. Palmaz performed the first arterial stenting in 1985 (Lazarus 1988, Kornberg 1986a, Kornberg 1986b, Chaudhury 1979).

Volodos published his first two findings in Russian only, so his work is largely unknown outside of the Soviet Union. In 1991 he had his first English publication in Vasa (Volodos 1991). The more famous Argentinean, Parodi (Parodi 1991) described a similar technique in both animal and clinical trials using five human subjects. He implanted an intraluminal graft transfemorally with huge implications for endovascular aortic surgery.

The stent-graft system that Parodi reported was developed by Lazarus in 1987 (Lazarus 1988) He designed a device specific for endovascular AAA repair (EVAR) at the same time as Parodi. In Parodi's report, the device had one short Palmaz stent attached to a Dacron tube graft allowing adequate proximal anchorage only. In most cases reflux distally occurred and reintervention was needed. Nonetheless a comparative improvement in aneurysm size was found in all patients post-operatively, suggesting that EVAR was technically feasible.

Initially this technique was used to treat selected high-risk patients with home-made devices (Chadi 2012, Moore 1996, Marin 1995). The first tube graft that was created by Endovascular Technologies (later to be taken over by Guidant, Menlo Park, CA, USA) and first implanted in 1993 after a number of trials (Chuter 1994, Hagen 1993, Lazarus 1992). The first commercially available endografts were approved for use in 1999 in the US and currently there are five sanctioned by the Food and Drug Administration (FDA) (Rutherford 2012, Jim 2010, Sanchez 2009, Greenberg 2008, Wang 2008, Peterson 2007, and D'Ayala 2004, Zarins 2003a, Ohki 2001). The avoidance of a large intra-peritoneal operation was attractive and its uptake was very quick and widespread, before proper evaluation, which was met with great criticism by some (Grace 2002).

EVAR is now the most common method of AAA repair in the US (Chang 2012, Mohan 2012, Nichols 2011, Schanzer 2011, Kent 2010, Schwarze 2009, Dimick 2008, Anderson 2004). Its use is increasing rapidly in many parts of Europe, Scandinavia, Canada, China and Australia (Chadi 2012, Wang 2012, Mani 2011, Szmidt 2007). Many advocate EVAR as first-line therapy in anatomically suitable patients, except for the less common scenario of the young and fit, in who open repair should be strongly considered (Becquemin 2012, Chadi 2012, de Rango 2012, Eliason 2009).

Following the introduction of EVAR, elective repairs have increased, ruptured AAAs have decreased as has procedure-related mortality for both intact and ruptured AAA (Anjum 2012, Giles 2009a). This has led to a decrease in overall AAA-related death despite an unchanged mortality rate of elective open AAA repair.

EVAR technique

The newer EVAR technique uses a metallic stent (steel or alloy such as nitinol (Gotman 1997), an alloy of nickel and titanium developed from naval submarine technology in 1962) introduced via the femoral artery to completely exclude the aneurysm sac from within the circulation. In essence these devices allow the insertion of a percutaneous Y-graft within the aneurysm with the graft material on the inside or outside of the stent system. However, unlike open conventional grafts, the attachment sites are not sutured and the aortic side branches not ligated (Magennis 2002, Dubost 1951).

The lack of hand sutured attachment sites mean that the endovascular stent-grafts rely upon the radial force from self-expanding stents (passive fixation) or self-expansion in concert with hooks or barbs (active fixation), preventing endograft migration and providing haemostatic seal (Bown 2012, Gonçalves 2012, Saratzis 2012, Lawrence-Brown 1999, Parodi 1991, Volodos 1991). Suprarenal fixation requires an initial caudal migration of a few millimeters, usually exceeding the length of the barb (5mm) to allow them to embed into the aortic wall (Zhou 2007). With appropriate positioning and adequate fixation these devices prevent aortic pulsatile flow and shear stress from being transmitted to the aneurysmal sac (Martin 2011, Eliason 2009).

This option of two small groin incisions (vertical or oblique) to allow surgical exposure of the common femoral arteries for endograft delivery avoids a major abdominal procedure and avoids aortic cross clamping, enabling a faster recovery and reduced metabolic response to trauma. However, a purely percutaneous approach can be utilized with excellent results in selected patients (Georgiadis 2011, Lee 2008, Lee 2007a, Starnes 2006), which is discussed later.

The mainstay of intra-operative imaging remains conventional angiography. EVAR is performed in the operating room or angiographic suite under fluoroscopic guidance.

Percutaneous EVAR

Conventional EVAR requires bilateral femoral artery exposure via open dissection or "cut-down" to allow the delivery of a specific device for stent insertion. Advances over the last twenty years have reduced the diameter of delivery devices considerably and EVAR can now

be performed percutaneously. This technique minimizes invasiveness and reduces complications related to groin dissections such as infections and seroma formation (Al-Khatib 2012, Mathisen 2012, Metcalfe 2012, Sarmiento 2012, de Vries 2011a, Georgiadis 2011, Haulon 2011, Montán 2011, Phade 2011, Heyer 2009, Najjar 2007, Slappy 2003, Morasch 2004, Torsello 2003). It is based upon the work of Diethrich in 1997 (the first to describe closure of the cribriform fascia where it covers the common femoral artery access (Diehtrich 1997)). This technique is simple, easy to teach and reproduce (Harrison 2011a).

Harrison et al have recently published a series of 69 common femoral artery fascial closures after EVAR with an 87% success rate (Harrison 2011a). They had 9 primary failures, including 8 hemorrhages and 1 thrombosis, all of which underwent immediate, uncomplicated open revision. At 1 month four pseudoaneurysms were detected on surveillance duplex ultrasound imaging (DUS) and all resolved at 1 year follow-up with conservative management. Evidently this fascial closure technique is not without its complications. Larzon et al analyzed 131 sutured fascial cases during EVAR and had a similar complication rate of 13.7% (89% <24 hours post-EVAR), the majority being due to hemorrhage, early thrombosis or dissection (Larzon 2006).

An evolution of the fascial closure technique has allowed a wholly percutaneous EVAR procedure with subsequent closure of the femoral artery through a range of suture-mediated closure devices, such as the Perclose technique (initially described in 1999 by Hass et al (Haas 1999)). Several authors have reported on device malfunction and faulty punctures causing complications and failure during their early experience, suggesting an extended learning period for this method (Klocker 2011, Eisenack 2009, Jean-Baptiste 2008, and Watelet 2006).

Metcalfe et al, have demonstrated in a series of 186 femoral arteries that operator experience was a significant predictor of technical success ($p=0.01$) after adjustment for all confounding variables (Metcalfe 2012). Early attempts at this technique proved disappointing (Howell 2001, Traul 2000), however recent advances in stent-graft technology and reduction in delivery profile has led to a resurgence of interest. Technical success rates have been up to 94% with long-term complication rates of 1% in more recent series (Bensley 2012, Mathisen 2012, Metcalfe 2012, Sarmiento 2012, Bent 2009, Lee 2008, Starnes 2006). The reported rate

of pseudoaneurysm with this method has been reported as low as 1-2% (Starnes 2006) and the majority of them resolve without the need for secondary intervention (Mathisen 2012,).

A recent systematic review of 22 papers (Malkawi 2010) and a separate large prospective study of >2000 groins (Eisenack 2009) with wholly percutaneous EVAR have a primary success rate of 92% (90.1-93.9, 95% CI) and a low access-related complication rate of 4.4% (3.5-5.3, 95% CI). This technique was also associated with a lesser operating time. Success of percutaneous EVAR depends on a number of factors such as operator experience, the presence of groin scar tissue from previous procedures, vessel calcification and diameter, high femoral artery bifurcation and obesity (Bensley 2012, Mathisen 2012, Smith 2009, Goodney 2008). A major consideration for this technique is the additional cost of percutaneous closure devices. Hopefully shorter hospital stays may compensate for this (Al-Zuhir 2012).

Endografts

The basic design of all endografts is somewhat similar, the aortic aneurysm is "crossed" by a tubular graft that has a wide diameter and is anchored in position by self-expanding or balloon-expandable stents, supporting all or part of the graft. There are three broad categories of endovascular grafts (Veith 1999):

1. **Tubular unibody grafts** – Aorto-aortic tube grafts have been largely consigned to history because they require suitable distal necks just above the aortic bifurcation and have a high incidence of proximal migration and distal type I endoleaks, through loss of seal in the distal aorta (Wyss 2012, Hinchliffe 2002, Magennis 2002).
2. **Aorto unilateral grafts** with a contralateral iliac occluder which is followed by an open surgical femoro-femoral bypass. These aorto-uni-iliac grafts are a widely used design because they can deal with more difficult iliac anatomy. Femoro-femoral bypass graft patency rates are favorable if compared to their use in patients with occlusive disease and infection rates are low (Rehring 2000). However if the distal landing zone is narrow (< 12mm) then the patients may suffer from lower limb claudication.
3. **Bifurcated grafts –** These are the most popularly used grafts because they appear to be more "physiological" and do not require any surgical bypass.
4. **Modular multicomponent grafts**

Early endograft failures have led to a number of device improvements we see today. Important lessons learned include:

- Early occlusion of unsupported iliac limbs – solved by employing fully supported and conformable components (Nordon 2012, Carpenter 2001a).
- Aneurysmal expansion at attachment sites (D'Ayala 2004).
- Thin-walled grafts with stent row separation and weak modular component fixation have been discarded (Beebe 2000).
- A high incidence of migration has been noted in grafts of low columnar strength (Sternbergh 2004, Zarins 2003b, Albertini 2000, Harris 2000). These grafts were prone to kinking due to migration – current grafts are fully supported to increase columnar strength thus reducing kinking and migration (Nordon 2012, Arko 2011, Umscheid 1999, Boyle 1998).
- The majority of bifurcated devices remain modular and this allows "tromboning" of one graft component inside the other to accommodate any length discrepancy.
- It is important to cover the proximal aortic neck with graft right up to the lowest renal artery. Similarly it is important to get as close to the aortic bifurcation caudally. These two techniques aim to protect those areas at most risk of dilation and subsequent aneurysm formation (Oberhuber 2012). A greater amount of graft in contact with the proximal and distal landing zones produce better graft fixation, a tighter seal, and lessens the risk of migration and secondary endoleak (Hinchliffe 2002). A study by Zarins et al (Zarins 2004) concludes for each millimeter increase in the distance between renal arteries and the top of the stent-graft on post-deployment CT scans, the risk of migration increased by 6%.
- The use of supra-renal fixation with uncovered stent and "barbs and hooks upon a crown" has been developed to prevent migration and also to treat aneurysms with short proximal necks. The supra-renal aorta does not appear to be subject to the same aneurysmal process as the infra-renal aorta so is a more desirable fixation site (Oberhuber 2012, Saratzis 2012, Lawrence-Brown 1998, Malina 1998a, Sonesson 1998). In both the short and medium term, supra-renal fixation has been shown to reduce the incidence of migration and proximal endoleaks with a low incidence of renal complications (Bown 2012, Gonçalves 2012, Moulakakis 2010, Magennis 2002, Lobato 2000, Macieriwicz 1999, Marin 1998).

- The use of endo-grafts that are made of fabric and metal skeleton formations to allow bending with no compromise of lumen diameter permits EVAR repair of the more challenging angulated AAA (previously deemed anatomically unsuitable). (Perdikides 2009, Saratzis 2008, Wang 2008, Albertini 2006, Hinchliffe 2004b).

Anatomical suitability for EVAR

For successful EVAR treatment a number of AAA anatomical criteria need to be fulfilled to allow complete exclusion of the aneurysm. Larger aneurysms (with a greater chance of rupture) have more adverse morphological features that reduce the suitability of EVAR. It is widely reported that approximately 60% of AAAs are treatable by EVAR (Ahanchi 2011, Cross 2011, Donas 2011a, Schanzer 2011, Sweet 2011, Cotroneo 2006, Arko 2004a, Hinchliffe 2002, Whitaker 2001a, Woodburn 2001, Armon 1997, Bayle 1997), and some believe that the majority (80%) are suitable (Nordon 2012,). The remaining 40% usually have unfavorable proximal neck or iliac arteries. However with the growing skill of operators and improvements in technology making devices more versatile and usable, endovascular treatments will be applicable to a greater proportion of patients (Perdikides 2009).

Poor patient selection contributes to many early and late complications seen after endografting. This has been demonstrated in a recent study by Schanzer et al, who has shown in a multicenter study that low compliance with EVAR device guidelines result in a high rate of post-EVAR sac enlargement increasing concerns of long-term rupture rates (Schanzer 2011). Placing endografts outside their instructions for use is associated with an increased incidence of type I endoleak and all cause mortality (Becquemin 2012, Cross 2011, Richards 2009, Hobo 2008), however some units are reporting good results in specific cases (Reijnen 2012, Starnes 2012, Wyss 2012, Léon 2011, Peppelenbosch 2011, van der Steenhoven 2011, Cheong 2010, Power 2010, Hiramoto 2009, Leon 2009, Teijink 2006).

Successful EVAR requires a detailed knowledge of aneurysm morphology to correctly size the endograft and optimize aneurysm exclusion. Contrast-enhanced computerized tomography (CT) is the pre-operative investigation of choice for AAA EVAR suitability (Sun 2009, Iezzi 2006a, Willmann 2001). The previous gold-standard of invasive diagnostic angiography is now rarely used except where pre-EVAR interventions are required e.g. renal

artery angioplasty, internal iliac artery embolization or in complex fenestrated graft placement planning (Papazoglou 2012, Jim 2010).

Important measurements for anatomical suitability and EVAR planning include:

- Diameter of the infrarenal aorta – should be < 70mm
- Length of the infrarenal aorta
- Aortic neck (proximal landing zone) diameter must be <30mm (this is the primary factor for exclusion from endovascular repair (Oberhuber 2012, Cotroneo 2006, Whitaker 2001a, Stanley 2001a, Stanley 2001b); length must be ≥15mm to prevent migration (Scarceilo 2012, AbuRahma 2009, Leurs 2006, Whitaker 2001a, Stanley 2001a, Greenberg 2000); angulation should be <60° (Ishibashi 2012, Hoshina 2011, Hobo 2007, Tonnessen 2004, Chaikof 2002a, Sternbergh 2002, Carpenter 2001b, Dias 2001, Whitaker 2001a, Albertini 2000)
- Common iliac arteries (distal landing zones) diameter must be ≤20mm (Ohrlander 2011, Whitaker 2001a); length and level of bifurcation to internal and external iliac arteries must be ≥7mm with minimal tortuosity (Whitaker 2001a)
- Tortuosity, composition (minimal thrombus and calcium burdens) and length of access vessels (usually common femoral arteries) – if unsuitable and would preclude adequate access and wall apposition, then a conduit onto the iliac vessels can be considered or pre-procedural iliac dilation (typically a 10mm Dacron graft) (Gonçalves 2012, Kaladji 2012, Wyss 2012, Ohrlander 2011, Phade 2011, Wisniowski 2011, Wyss 2011, Fernandez 2009, Peterson 2008, Rockman 2004, Woody 2004, von Segesser 2002a, Tillich 2001a, Whitaker 2001a, Henretta 1999, May 1994)
- To achieve optimal seal of the endograft to the arterial wall, the infrarenal aortic neck and iliac arteries must be smaller than the expanded endograft diameter by 10-15%.

A number of computer software packages have been developed to accurately predict the required size of endograft (England 2012, Setacci 2012, Kauffmann 2011, van Prehn 2008, Yeung 2003, Whitaker 2001b).

Advantages of EVAR

EVAR avoids a number of problems that are associated with conventional open AAA repair, reduces physiological stress and lowers peri-operative morbidity and mortality. Open AAA repair requires a general anesthetic. Due to minimal groin exposure EVAR can be performed under general, regional or even local anesthetic, thus making this technique appropriate for the unstable patient. (Al-Zuhir 2012, Bakker 2012, Karthikesalingam 2012a, Salata 2012, Wang 2012, Edwards 2011, Franz 2011, Geisbüsch 2011, Varty 2011, Asakura 2009, Sadat 2008a, Ruppert 2006, Verhoeven 2005, D'Ayala 2004, de Virgilio 2002, Bettex 2001).

EVAR does not require a laparotomy so problems associated with a large abdominal incision are avoided, such as:

- Third space fluid loss
- Gastrointestinal mobilization and resultant adhesion formation
- Vascular trauma to renal, adrenal, lumbar and gonadal veins during aortic neck dissection
- Post-operative ileus
- Post-operative ventilator impairment and infections
- Urinary retention
- Delayed mobility
- Significant post-operative pain
- Intensive care post-operative monitoring
- Prolonged hospitalization

Another significant advantage of EVAR is that there is no need for aortic cross-clamping so there is less cardiac stress due to a reduced afterload compared to open surgery. There is also less visceral, renal and lower limb ischemia with reduced complications of ischaemia-reperfusion syndrome (Wang 2012, Becquemin 2008, Maldonado 2004, Dadian 2001, Mialhe 1997).

There is increasing evidence that quality of life following EVAR is comparable to or even better than that faced by patients undergoing conventional open repair (Dick 2008, Muszbek 2008, Kolh 2008, Ligush 2002) and a recent prospective study of patient preference has shown that the majority (80%) would prefer to undergo EVAR rather than open repair (Reise

2010). Patient preference differs widely and is highly dependent on how the treatment options are communicated to them by the treating physician (Faggioli 2011b, Lindahl 2011).

Complications of EVAR

EVAR is not a technique without complications. The majority are early and procedure related. Early complications (<30 days) include (May 2010, Jaunoo 2008, Bown 2004):

- Wound complications – infection, hematomas, lymphoceles
- Arterial access complications – arterial perforation, rupture, dissection and plaque embolisation, pseudoaneurysm formation (Phade 2011, Fernandez 2009, Hingorani 2009)
- Deployment and repositioning problems
- Renal ostia coverage and resultant renal infarction (Greenberg 2012, Hamish 2010, Hartshorne 2006)
- Hypogastric artery embolisation complications – buttock claudication, gluteal myonecrosis and renal failure (Papazoglou 2012, Pavlidis 2012, Ryer 2012)
- Ischemic colitis (Kim 2012)
- Testicular ischemia (Hall 2010)
- Endoleaks
- Endograft limb kinking, occlusion or thrombosis (Blom 2012, Karthikesalingam 2012b, Wyss 2012, Wyss 2011, O'Neill 2010, Hingorani 2009, Corbett 2008, Clevert 2007a, Cochennec 2007, Hartshorne 2006, Erzurum 2004, Woody 2004, Fransen 2003a, Conner 2002, Fairman 2002a, Parent 2002a, Aljabri 2001, Amesur 2000, Schunn 2000, Umscheid 2000)
- Systemic complications – (at a lesser rate than open repair) e.g. cardiac and pulmonary dysfunction, renal failure, hepatic failure, urinary tract infections, embolic phenomena, intestinal and spinal cord ischemia (Grant 2012b, Becquemin 2008, Maldonado 2004, Dadian 2001, Mialhe 1997). EVAR can cause an unexpected systemic inflammatory response syndrome (Wong 2012, Hamano 1998, Muckart 1997, Schlag 1996, Bone 1992), known as postimplantation syndrome, and characterized by the presence of fever, leukocytosis and sometimes coagulation disturbances (Wong 2012, Arnaoutoglou 2010, Chang 2009, Gabriel 2008, Akowuah 2007, Gabriel 2007, Gerasimidis 2005, Galle 2000, Velazquez 1999, Blum 1997, Norgren 1997).

Late complications (>30 days post-operatively) are usually diagnosed on graft surveillance imaging studies. Late complications include (Jaunoo 2008, Becquemin 2005):

- Wound complications – lymphoceles, pseudo-aneurysms
- Endoleaks
- Endograft limb occlusion or thrombosis (Polat 2011, Hingorani 2009)
- Rupture (Schlösser 2009)
- Graft migration – rates vary from 0-45% (Cao 2002)
- Neck dilatation
- Sac expansion
- Endotension – an increase in sac pressure without the presence of an endoleak
- Graft infection –significantly lower rates than in conventional open repair (Halak 2012, West 2011, Ducasse 2004, Murphy 2004, Fiorani 2003)
- Aorto-duodenal fistula (Batt 2011, Sharif 2007, Ghosh 2006, Ratchford 2006, Tiesenhausen 2006, Lyden 2005, French 2004, Alankar 2003, Bertges 2003b, Elkouri 2003a, Fanelli 2002, Ohki 2001, Parry 2001, Whitaker 2001a, Hauseggar 1999, Velazquez 1999, Alimi 1998, Norgren 1998)
- Implantation-related complications – hook or bard fractures, modular component separation and fabric erosion (Klein 2012, Lee 2007b)
- Aortic perforation due to suprarenal fixation (Smeds 2012)
- Systemic complications – very rare in the late period, however include contrast induced nephropathy from surveillance imaging using iodinated contrast agents

First and second generation devices are estimated to have a 1% annual risk of rupture (Harris 2000) and frequently suffer from endograft migration (Martin 2011, Becquemin 2005, May 2000, Umscheid 1999, Parodi 1997). Today a number of complications are seen arising from the use of these early devices. Many of these grafts have been withdrawn from the market due to material failure (Nordon 2012, Milner 2011, Ghouri 2010, Mestres 2010, Becquemin 2005, Hiatt 2004, Torella 2004, and Laheij 2000). Since 1996 a national registry (RETA) has recorded endovascular stent-grafts problems and complications. European collaborators have been collecting the European stent-graft technique data to compile the voluntary EUROSTAR registry (Harris 2004, Harris 1999, Harris 1997), and similar reporting

standards have been developed for use in the US (Ahn 1997) and Europe (Boyle 2011), with worldwide series now emerging (Stokmans 2012a, Stockmans 2012b).

Reintervention after EVAR

Several studies have demonstrated that EVAR reduces associated complications and mortality when compared with open repair. This is despite EVAR patients being generally older with more co-morbidities (Schermerhorn 2008, Greenhalgh 2004, Prinssen 2004a). The incidence of secondary interventions post EVAR has decreased significantly when compared with earlier procedures (Black 2009, Dias 2009, Carpenter 2004, Hinchliffe 2004, Leurs 2004). The common indications for reintervention post EVAR are (Desai 2010, Abbruzzese 2008, Szmidt 2007, Brewster 2006, Subramanian 2006, Goueffic 2005, Flora 2003, Sampram 2003, Makaroun 2002, and Cuypers 2000):

- Persistent primary endoleaks
- Significant graft migration
- Late-onset endoleaks
- Graft limb stenosis or thrombosis
- Endotension causing sac enlargement

The procedures required commonly include:

- Placement of proximal/distal extension limbs
- Coil embolisation of branch vessels or external band application
- Relining of failed stent-graft
- Angioplasty and stenting of graft limb kinks
- Conversion to open surgical repair to remove a failed stent graft (Chaar 2012, Newton 2011, Lee 2007b)
- Renal artery repair via angioplasty, re-implantation or bypass
- Graft limb thrombectomy
- Repair of common femoral artery pseudoaneurysms
- Extra-anatomical bypass for limb occlusion
- Thrombolysis

However the frequency of trans-abdominal and extra-anatomical re-interventions has reduced to a lesser degree and these are associated with the highest mortality risk. These findings suggest a continuing need for surveillance for device-related complications.

EVAR is considerably more expensive than conventional open surgical repair, over doubling the expense of initial hospitalization (Becquemin 2012, Brown 2012, Nordon 2012, Fotis 2008, Prinssen 2004, Clair 2000, Sternbergh 2000, Ceelen 1999), confirmed by statistical cost-modeling (Blackhouse 2008, Epstein 2008, Hayter 2005, Biancari 2002, Bosch 2002, Patel 1999). The majority of the cost (58%) is the actual endograft itself (Hayes 2010, Angle 2004, Sternbergh 2000). The total expenses between manufacturers does not differ greatly (Feezor 2008). It has been estimated that the average cost of an open repair graft is $750, much lower than the average cost of an EVAR stent-graft $12,974 (Dryjski 2003). It is unlikely that the cost of stent-grafts will reduce in time due to the huge cost of research and development (Noll 2007, Hayton 2005, Angle 2004) and there has been a noticeable cost escalation since the US FDA approval for their use in 1999 (Kim 2008, Angle 2004). Analysis of mean contribution margin per day nonetheless reflects more profitability for EVAR than for open repair because of shortened hospitalization and higher operative volumes (Dosluoglu 2012, Kim 2008, Kapma 2007, Hayter 2005, Rosenberg 2005, Angle 2004, Krupski 2004, Bertges 2003a, Dryjski 2003, Moore 1999, Seiwert 1999). A recent paper by Mohan et al, has shown that between 2001-2009 total hospital charges for EVAR were lower than charges for open repair, so the technique may be getting cheaper (Mohan 2012).

Endoleaks

Endoleaks are a problem unique to EVAR and are caused by the inability to obtain or maintain a secure seal between the aortic wall and a transluminally implanted intra-aneurysmal graft so there is an incomplete exclusion of blood flow from the aneurysm sac (White 1998a, White 1998b, White 1997, White 1996). An endoleak is the presence of flow out-side the endograft lumen (perigraft) but within the aneurysm sac, transmitting systemic pressure. This can increase the risk of aneurysm rupture because the aneurysmal sac is still being filled, so it continues to expand due to sustained pressure (Wyss 2010, Schlösser 2009, Becquemin 2005, Hiatt 2004, Murphy 2004, Buth 2003, Fransen 2003b, Mehta 2003,

Bernhard 2002, Magennis 2002, Veith 2002, Baum 2001a, Mehta 2001, Vallabhaneni 2001, Baum 2000, Gilling-Smith 2000, Harris 2000, Politz 2000, Schurink 1998, Lumsden 1995).

The presence and detection of endoleaks remain the main reason for post-operative surveillance and has been described as the Achilles heel of EVAR (du Toit 2004). The significance of endoleaks with respects to patient outcome is not well understood (Stavropoulos 2004, Sternberg 2003, Wolf 2002, Veith 2002, Arko 2001, Baum 2001a, Baum 2001b, Chuter 2001, Petrick 2001, Zarins 2000). The rate of endoleak post-EVAR is approximately 14% (Wain 1998) but has been reported to occur in up to 25-50% (Nordon 2012, de Bucourt 2011, Bargellini 2009, Carrafiello 2008, Lee 2007b, Stavropoulos 2007, Golzarian 2005, Becquemin 2004, Kritprach 2004, Pearce 2004, Ouriel 2003, Carpenter 2002, Parent 2002b, Buth 2000, Cuypers 1999, Moore 1996). The EUROSTAR database revealed that 50-60% of the endoleaks present on EVAR completion spontaneously sealed within the first post-operative month and a minority closed after this (Buth 2003, Buth 2000, Makaroun 1999, Matsumura 1998, Broeders 1997). EUROSTAR also showed that 15.7% of endoleaks were present on discharge from hospital, but a further 18% developed new endoleaks during the first year of follow-up (Harris 1999).

The annual incidence of endoleaks may be as high as 5% when including data from multiple endograft designs (van Marrewijk 2005). Each type of leak can be noted during the EVAR procedure or on surveillance imaging. There are five different types of endoleak (**Table 1**):

Table 1: Types of endoleak

Endoleak	Cause
Type Ia	Anastamotic leak at the proximal graft attachment sites due to inadequate endograft to aortic wall seal.
Type Ib	Anastamotic leak at the right or left distal graft attachment sites due to inadequate endograft to aortic wall seal.
Type Ic	Anastamotic leak from an iliac occluder (plug) if an aorto-uni-iliac device is used.
Type II	Collateral branch retrograde back bleeding into the aneurysm sac from a patent aortic side branch (which is not ligated in EVAR). This can be a simple or to-and-fro direction from only one patent branch (Type IIa) or a complex flow-through the sac with two or more patent branches creating a circuit (Type IIb). Usually due to back flow from a patent lumbar (usually the 4th lumbar artery), middle sacral, inferior mesenteric, hypogastric or accessory renal artery.
Type IIIa	Modular dissociation/dislocation due to a junctional leak.
Type IIIb	Graft fabric tear/failure/disintegration due to a graft defect caused by a fabric disruption (mid-graft hole). Can be categorized as minor (<2mm, e.g. suture holes) or major (≥2mm).
Type IV	Graft wall (fabric material) porosity or "sweating" (<30 days after graft placement). These endoleaks appear as an angiographic "blush" on completion angiography, particularly in thin walled devices, and most resolve within one month.
Type V	Termed "endotension". This phenomenon is controversial and occurs when there is evidence of raised intra-sac pressure, usually manifested as aneurysm sac expansion, without radiological evidence of an endoleak.

Not all endoleaks are of equal significance and their presence does not accurately predict outcome. In the setting of aneurysm enlargement Type I, III or persistent Type II endoleaks necessitate a secondary procedure. Secondary procedures occur with a cumulative annual rate of 4.6% and no apparent plateau in incidence (Hobo 2006).

It must be remembered that the proximal, distal and modular attachment sites of stent-grafts are not sutured so the potential for type I and III endoleaks is always present and reliant on adequate seal zones. These are high-pressure endoleaks so should be considered dangerous. They pose a significant risk of late aneurysm rupture and require urgent intervention because of the high short-term risk of sac rupture (Hoshina 2011, Cao 2010, Iezzi 2010, Hartshorne 2006, Biebl 2005a, Becquemin 2005, Sampaio 2004, Buth 2003, Faries 2003a, van Marrewijk 2002, Veith 2002, Harris 2000, Laheij 2000, Karch 1999, Golzarian 1997, White 1997).

Type I endoleaks were the primary cause for stent graft failure in Parodi's initial trial and they can be avoided today by appropriate patient selection, graft design and accurate graft deployment. Type I endoleaks are relatively uncommon, occurring in 0-10% of EVAR (Veith 2002). Laboratory flow model studies by Albertini et al, have shown that neck angulation increases the risk of type I endoleak, principally due to a poor seal, which is often related to the stiffness of the graft (Kaladji 2012, Albertini 2001, Umscheid 1999). Other causes for an unfavorable neck include conical shapes, severe angulation and calcification (Kaladji 2012, Wyss 2012). Londero et al, found that 89.6% of cases with proximal type I endoleaks were due to hostile anatomy (Londero 2011). Even if a satisfactory seal is achieved, the slightest migration poses a risk for proximal leakage. Sampaio et al, show that a short aneurysmal neck and large aneurysm size increase the risk of type I endoleaks (Sampaio 2004). Grafts whose fixation relies on radial force are more prone to caudal migration and thus type I endoleak than grafts that possess hooks and barbs. For this reason the oversizing of the graft diameter by 10-20% larger than the aortic diameter (22-44% larger in area) is useful (Rodway 2008, Zhou 2007, Sternbergh 2004). It has been observed that there is an increase in type I endoleaks if oversizing was <10% (Mohan 2001). More recently the experimental use of endostapling for proximal graft fixation has been evaluated in cadavers and models demonstrating significant increased strength ($p<0.001$) when 4 staples are employed thus reducing type I endoleak (Melas 2012).

Pulsatile blood flow and pressure can generate longitudinal distraction forces in the range of 7-9 Newton's upon the stent-graft main body and sideways force on the curved iliac limbs of 1.5 Newton's (Murphy 2004) which potentially cause migration if overlap and fixation is not adequate.

Distal type I endoleaks occur at the iliac level, usually when the graft limb is too short or migrates upwards under the sac's retraction pressure (Becquemin 2005). Another distal cause for type I endoleaks are the development of common iliac aneurysms distal to the limb of the stent-graft, which may cause graft-arterial wall separation. Using a relatively long limb covering the entire iliac artery may be preventative.

The majority of intraoperative endoleaks can be treated at the time of surgery via an endovascular method, such as an extension cuff if the stent has migrated or landed too low, a giant Palmaz stent to straighten the aortic neck if it is too angulated, or balloon angioplasty if there is poor stent and aortic wall interface (Bown 2012, Arko 2011, Londero 2011, Wales 2008, Stavropoulos 2004a, Hinchliffe 2002, Dias 2001). More recently, type I endoleaks have been embolized percutaneously from a transabdominal or transarterial approach with N-butyl cyanoacrylate, with and without the need for coils (Fatimi 2012, Choi 2011, Rusius 2011, Choi 2010). If an endovascular procedure is unsuccessful then a conversion to an open procedure may be required (Buth 2003). Increased understanding of aneurysm morphology and EVAR suitability has reduced early Type I endoleaks. Late endoleak and graft migration still remain problematic.

Type III endoleaks are rare causing direct repressurization of the aortic sac and are caused by component modular separation or fabric erosion and holes from friction between the metallic frame and graft fabric at seams or sutures (Abbruzzese 2008, Guidoin 2000, Bohm 1999, Riepe 1999, Umscheid 1999). These can be treated by inserting an appropriately sized cuff to restore continuity of the graft elements or relining of the device with another stent-graft (bifurcated or uni-iliac) (Reijnen 2012, Teruya 2003). The newer generation of stent-grafts have modifications to prevent these endoleaks, such as the positioning of metallic stents on the outside of the fabric and thicker polyester modular components with longer limb overlaps. These alterations have reduced the incidence of graft disconnections with first generation devices (Arko 2011, Troisi 2011a, Ghouri 2010, Fransen 2003b). The diagnosis of a type III endoleak is difficult and can often simulate a type II endoleak (Becquemin 2002). It can be missed when the thrombus is tightly attached to the stent wall, thus frequently type III endoleaks are diagnosed at the time of re-intervention.

Type II endoleaks in contrast are generally considered as benign, rarely causing aneurysm expansion and rupture (Karthikesalingam 2012c, Jones 2007, Murphy 2004, Steinmetz 2004, Timaran 2004, van Marrewijk 2004, Buth 2003, Fransen 2003, Lee 2003, Lipsitz 2003, Abraham 2002, Bernhard 2002, van Marrewijk 2002, Hinchliffe 2001a, Politz 2000, White 2000). The occurrence of a type II endoleak depends on a number of factors (AbuRahma 2011, Sampaio 2005, and Velazquez 2000):

- Endovascular graft type
- Presence of mural thrombus
- Number of patent aortic side branch vessels

The incidence of type II endoleaks due to sac reperfusion from lumbar and inferior mesenteric arteries occurs in 5-25% of cases of EVAR and is the most common type of endoleak (Nolz 2012, Beeman 2010, Gelfand 2006, Jonker 2009, Rayt 2009, Silverberg 2006, Drury 2005, Hiatt 2004, Steinmetz 2004, Buth 2003, Rhee 2003, and Veith 2002). The majority of type II endoleaks spontaneously thrombose without treatment, so close surveillance is recommended (Sarac 2012, van der Berg 2012, Beeman 2010, Jonker 2009, Rayt 2009, Jones 2007, Silverberg 2006, Tolia 2005, Steinmetz 2004, Timaran 2004, van Marrewijk 2004, Buth 2003, Maldonado 2003, Bernhard 2002, Veith 2002, Dorffner 2001). It has been estimated that 40-80% disappear in the early months following EVAR (Karthikesalingam 2012c, Jones 2007, Stavropoulos 2007, Becquemin 2005). There is evidence that smoking causes clotting changes and promotes spontaneous small vessel occlusion (Koole 2012, Yarnell 2001). Similarly warfarin may have an adverse effect on type II endoleak closure (Bobadilla 2010, Fairman 2002b). A type II endoleak that has not sealed within six months is termed a persistent endoleak and is unlikely to spontaneously seal after 12 months (Abularrage 2012, Patatas 2012, Jones 2007, Gelfand 2006, and Veith 2002). Steinmetz et al, calculated that the mean global cost for treating persistent type II endoleaks associated (with increasing sac size) was $6695 and the treatment cost of all 35 of the type II endoleaks in their series that persisted more than 6 months was $200000 (Steinmetz 2004,). The observational approach for these types II endoleaks with stable sac sizes is cost-effective (Patatas 2012), however can cause anxiety to both the patient and physician particularly when the AAA is large. Some have advocated a change of the term type II endoleak to “persistent collateral” to reflect its benign nature in the majority, and reduce patient anxiety from the word “leak” (Taylor 2011).

No pre-operative predictors have been found for type II endoleaks or their subsequent thrombosis (Aoki 2011, Back 2003, Walker 1998b). Conversely, delayed type II endoleaks can occur and are believed to develop from spontaneous lysis of thrombus at the orifice of collateral vessels or modifications in intra-sac pressures (Becquemin 2005). There are recorded cases of type II endoleaks causing rupture and it has been shown that sac pressure is high in the presence of these endoleaks and sac shrinkage is less when compared with excluded aneurysms. Original aneurysm size has been highlighted as a predictor for aneurysm growth as well as the number of outflow and inflow channels to the endoleak (AbuRahma 2011, Warrier 2008, Jones 2007, Sampaio 2005, Fritz 2004, van Marrewijk 2004, Haulon 2003, Arko 2001, Fan 2001, Gorich 2001, Velasquez 2000, Broeders 1998). When an inflow channel is present, the likelihood of spontaneous thrombosis is higher, mirroring the behavior of pseudoaneurysms.

In the early years of EVAR, all type II endoleaks were recommended for closure (Karthikesalingam 2012c, Chuter 2001, Holzenbein 2001, Baum 2000a, Görich 2000, Resch 1998, Schurink 1998), but initial treatment failure often results in multiple re-interventions, especially if multiple lumbar arteries are involved (Gallagher 2012, Nolz 2012, van den Berg 2012, Solis 2002). Today type II endoleaks are treated if they are persistent and causing sac size increases, by a variety of methods that include: direct embolisation (transarterial, transcaval or translumbar); thrombin or glue injection; endostapling of graft; laparoscopic clip ligation of the causative vessel; prophylactic packing of the aneurysmal sac with thrombogenic material or open conversion (Abularrage 2012, Chaar 2012, Evans 2012, Fatimi 2012, Gallagher 2012, Hiraoka 2012, Nolz 2012, Sarac 2012, Uthoff 2012, van der Steenhoven 2012, van den Berg 2012, Voûte 2012a, Chughtai 2011, Cornelis 2011, de Vries 2011b, Cao 2010, Choi 2010, Mehta 2010, Nevala 2010, Pilon 2010, Jonker 2009, Rayt 2009, Gorlitzer 2008, Lee 2007b, Stavropoulos 2007, Binkert 2006, Gelfand 2006, Golzarian 2005, Subramanian 2005, du Toit 2004, Stavropoulos 2004a, Steinmetz 2004, Faries 2003a, Stavropoulos 2003, Baum 2002, Schmid 2002, Baum 2001c, Edoga 2001, Ohki 2001, Baum 2000b, Gorich 2000, van den Berg 2000, Wisselink 2000, Karch 1999, Walker 1999, Golzarian 1997). It is also an accepted practice to coil embolize mesenteric, lumbar or iliac vessels prior to undergoing EVAR, to prophylactically avoid type II endoleaks (Papazoglou 2012, Ryer 2012, Jonker 2009, Sheehan 2006, Axelrod 2004, Bonvini 2003, Parry 2002,

Solis 2002, Gould 2001). This practice has associated complications (Gambaro 2004, Miller 1983).

The incidence of Type IV endoleaks was thought to be high in the infancy of EVAR, mainly due to graft porosity of approximately 65% (Guidon 2000). Peri-operative "contrast blushing" can be present, but this usually resolves spontaneously during the post-procedure period (Jaunoo 2008, Stavropoulos 2007) as thrombosis of the graft occurs and these pores are filled by fibrin. Persistent Type IV endoleaks are rare particularly with the newer generation of endografts which are made of very thin ePTFE and woven polyesters.

Type V endoleaks are commonly referred to by the phenomenon of endotension, which is characterized by the continued pressurization of an aneurysmal sac with subsequent enlargement, in the absence of an apparent endoleak. It is often caused by pressure transmission through a sealed or thrombosed endoleak (Kamineni 2004). The EUROSTAR database of information from 6337 patients has demonstrated that <1% of patients in the first 4 years post-stent implantation have EVAR sac enlargements with no detectable endoleaks, or endotension (Koole 2011), but an earlier report by the EUROSTAR collaborative found the incidence to be 5.4% from the same database (Buth 2003). Type V endoleaks were most frequently reported with the use of the Excluder graft where 60% of aneurysm sacs did not shrink (Cho 2004). It is believed that the porosity of the polytetrafluoroethylene (PTFE) content of this graft was the main reason. Some have attempted to classify endotension into subcategories according to pressure characteristics (Gilling-Smith 1999):

- **Grade I** = high pressure and high flow
- **Grade II** = high pressure and low flow
- **Grade III** = high pressure and no flow (which is a true endotension or sealed leak)

Controversy exists about the etiology and clinical sequelae of endotension, but a number of possibilities have been suggested (Desai 2010, Uhlenbrock 2010, Hartshorne 2006, Buth 2003, Matsumura 2001, White 1999):

1. Pressure transmission to the AAA sac around the ends of the graft
    - Layer of thrombus between the graft and aortic wall
    - Graft displacement exposing thrombus layer at aortic neck
    - Endoleak channel sealed by thrombus

- Undetected or missed endoleak
- Intermittent endoleak channel
- Very low-flow endoleak channel

2. Pressure transmission through the graft wall
    - High graft porosity
    - Microleak through graft interstices
    - Transudation/exudation of fluid through graft fabric
    - Graft pulsatiliy/wall movements
3. Pressure transmission from branch vessels
    - Thrombus over orifice of internal mesenteric or lumbar arteries
4. Pressure build-up from fluid accumulation *in situ*
    - Graft infection (Kar 2002, White 2001)
    - Thrombus fibrinolysis/hygroma of the aortic sac (Ryu 2007, Risberg 2004, Gawenda 2003, Risberg 2001)
    - Genetic modulation
    - Enzymatic activity
    - Hyper-osmolarity
    - Others

Interventional procedures to combat endotension include open replacement of the graft, wrapping the endograft with a new graft through laparotomy or laparoscopy (Imamura 2005), endovascular relining of the stent (Lin 2003) and also percutaneous translumbar aspiration of the aneurysmal sac (Cerna 2009). If there is no demonstrable endoleak or the aneurysm is shrinking in size then additional intervention is usually not required (Giles 2009a, Mennander 2005).

Clinical results of EVAR

There is a plethora of non-randomized data, predominantly single center results and individual small series (Al-Zuhir 2012, Bonardelli 2012, Chadi 2012, Gupta 2012, Harris 2012, Pol 2012, Raux 2012, Stokmans 2012a, Wang 2012, Martin 2011, Verhoeven 2011a, Mehta 2010, Mestres 2010, Balasubramaniam 2009, Espinosa 2009, Baril 2008, Bos 2008,

Wales 2008, Aune 2007, Szmidt 2007, Väärämäki 2007, Subramanian 2006, Biebl 2005b, Cronenwett 2005, du Toit 2005, Becquemin 2004, Carpenter 2004, du Toit 2004, Hinchliffe 2004a, Rigberg 2004, Verhoeven 2004, Elkouri 2003b, Maher 2003, Ohki 2001, Schunn 2000). A RCT was required to determine if EVAR was superior to open repair and in which cases. The first randomized trial was conducted by the UK multicentre studies group (EVAR 1) in 1999 to define the role of EVAR in 37 hospitals. EVAR 1 randomized patients for EVAR or open repair who had AAAs ≥5.5cm and were suitable for both procedures (Brown 2012, EVAR trial participants 2005a, Greenhalgh 2004). This study randomly assigned 1,082 patients, with 94% receiving their allocated treatment. Blood product use and length of hospital stay favored EVAR, as did perioperative mortality (1.7% for EVAR vs 4.7% for open surgery; p=0.009) (Greenhalgh 2004). However, the primary end point of all-cause mortality did not show a lasting benefit for EVAR at the 4-year study conclusion. Long-term complication and reintervention rates were also higher in the EVAR group (41% vs 9%, p<0.0001). A reduction in aneurysm-related death was noted (3.5% for EVAR, 6.3% for open surgery; p=0.02), but this came at a higher mean hospital cost (EVAR trial participants 2005a).

A second smaller RCT named the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, randomly assigned 351 patients with asymptomatic AAAs >5cm in diameter with anatomy suitable for EVAR to open or endovascular repair. A strong trend towards a 30-day benefit in mortality favored EVAR (1.2% for EVAR vs 4.6% for open surgery; p=0.10) (Prinssen 2004a). These initial results led the investigators to report that endovascular repair was preferable to open repair in patients with AAAs of at >5cm in diameter. However, two-year follow-up data demonstrated that by 1 year, this trend toward improved survival was lost, with no mortality benefit using EVAR (Blankensteijn 2005). Many have criticized DREAM for being underpowered because the sample size calculation was based on a primary endpoint of short-term mortality and complications.

The early results from these two randomized controlled studies were verified in a Medicare cohort study of 45,660 patients (Schermerhorn 2008). Using administrative data from Medicare beneficiaries, patients undergoing open repair were compared with those undergoing EVAR in the United States between 2001 and 2004. After matching, 22,830 patients were available for study in each cohort. Perioperative mortality was 1.2% after

EVAR and 4.8% after open repair (95% CI, 3.51-4.56; p<0.001), as were reintervention rates related to AAA (9.0% for EVAR vs 1.7% for open repair; p<0.001). However, factors such as appropriate initial patient selection for EVAR, technological advances, and device modifications as well as the frequency and duration of individual patient follow-up cannot be assessed with this type of analysis (Chambers 2010, Eliason 2009).

Since 2002 an interim analysis is ongoing by the American Veteran's Affairs Cooperative Study Group called the Open Versus Endovascular Repair (OVER) (Lederle 2009). Their aim is to assess device and technique evolution effects on mortality rates. The OVER trial procedures were performed from 2002 to 2007, compared with 1999 to 2003 for the DREAM and EVAR 1 trials. The OVER study has randomized 881 veterans and initially found that the perioperative mortality was lower for endovascular repair compared with open repair (0.5% vs 3.0%, p=0.004). At 2 years there was no significant difference in mortality (7.0% versus 9.8%, p=0.13), major morbidity, secondary therapeutic procedures and health-related quality of life. The OVER trial long-term results are eagerly awaited.

The combination of these results supports EVAR over open surgery, leading to the increased use of EVAR in patients with AAAs with suitable anatomy. Encouragingly recent NICE guidance supports the use of EVAR.

Holt et al, analyzed the English NHS administration dataset: Hospital Episode Statistics (HES) data over 5 years until 2008, specifically looking at elective AAA repair with open and EVAR techniques (Holt 2010a). The mean hospital mortality was 5.9% for the 18,060 elective AAAs repaired, 14,141 were repaired open with a mean mortality of 6.5% and 3,919 (22%) were repaired with EVAR with a mortality of 3.8%. EVAR patients were discharged earlier (p<0.001) but had a higher rate of re-intervention (p=0.001). Lastly they found that octogenarians were significantly more likely to undergo EVAR (p=0.001).

Recently the EVAR 1 trial published the first set of long term data for aortic endovascular repair (Brown 2012, Wyss 2011, The UK EVAR Trial Participants 2010a, Wyss 2010). They reported after 8 years follow-up that EVAR is not associated with a long-term survival benefit. The new endograft-related complication rate was higher than for open repair, but there is no trial performa or reporting of open complications such as incisional hernia. Further

worrying evidence is that 25 secondary ruptures after EVAR occurred and the majority (72%) were fatal, compared with no secondary ruptures reported in the open repair cohort. These secondary ruptures explain the reduction of the statistically significant 3% aneurysm-related survival benefit for EVAR vs open repair observed during the first 4 years of follow-up (EVAR Trial Participants 2005a). After 6 years survival curves for EVAR and open repair converge and at 8 years the aneurysm-related survival rate was 93% for both groups (Brown 2012, The UK EVAR Trial Participants 2010a, Wyss 2010).

Similarly the long-term outcomes of the DREAM trial (de Bruin 2010) have shown that the initial survival benefit of EVAR was no longer significant in the second year. At 6 years after randomization, the cumulative survival rates were 69.9% for open repair and 68.9% for EVAR. The cumulative rates of freedom from secondary interventions were 81.9% for open repair and 70.4% for EVAR. Thus the authors have reached the same conclusion as EVAR 1 that there were similar rates of survival between both groups but a significantly higher rate of reintervention for EVAR. A meta-analysis of 42 studies comprising 21,178 patients has also questioned the durability of EVAR (Lovegrove 2008). Despite this the majority of centers worldwide have adopted EVAR and it is considered by many to be the first line treatment for AAA (Brown 2009).

EVAR in high-risk patients

When EVAR was first introduced, it was viewed as an alternative for patients who were considered high risk for open surgical repair (Bonardelli 2012, Chadi 2012, Becquemin 2011, Hiromatsu 2011, Shalhoub 2010a, Porcellini 2007, Jordan 2002). The EVAR 2 trial began in 1999 to identify whether EVAR improved survival compared with no intervention in patients unfit for open AAA repair. 338 patients unfit for open AAA repair but suitable for EVAR, were randomized for no intervention but best medical therapy (BMT) (n=172) or EVAR (n=166) (EVAR trial participants 2005b).

Patients involved in EVAR 2 had significantly worse heath than those enrolled in EVAR 1. Consequently there was a high 30-day mortality rate of 9% in the EVAR group and an overall mortality after 4 years of 64%, there was no significant difference between the 2 groups in all-cause or aneurysm-related mortality. The mean cost per patient over the follow-up period

were significantly higher (mean difference £8,649) in the EVAR group and the authors concluded that EVAR did not improve survival over BMT.

There have been several criticisms of the EVAR 2 trial result and thus its clinical applicability:

- Some critics express the view that there was a possible over-representation of more expert centers producing above average results with no financial constraints. However with the move to centralize vascular services in the United Kingdom, these better results and larger budgets will be a reality.
- The aneurysm-related mortality rate at 30-days of 9% and of 64% at 4 years in the EVAR group was markedly higher than that reported in other high-risk patient cohorts.
- In the EVAR 2 trial, 14 patients (8%) died in the interval between randomization and repair, thus 52% of the perioperative deaths as well as 19% of the total deaths in the EVAR group occurred preoperatively and were counted as having received EVAR.
- 9 patients died from aneurysm rupture before their surgical date, and this accounts for 45% of the 20 aneurysm-related deaths in the EVAR group. The median time for randomization to rupture for these 9 patients was 98 days (range 6-767).
- In a group of patients with a mean aneurysm diameter of 6.4cm, a median wait period of 57 days for the EVAR group does not coincide with standard medical practice and may have falsely inflated the death rate in the treatment arm.
- More than a quarter of patients (47/172) assigned to no intervention subsequently crossed over to undergo EVAR with a mortality of 2%. At least 18 of these patients were intervened upon for late rupture, accelerated growth, or development of symptoms. This clearly reduced the aneurysm-related death in the no-intervention group.

There are 2 large studies in the US comparing EVAR and open surgery for high-risk patients. They are the Society for Vascular Surgery Outcomes Committee analysis of data from 5 multicenter investigational device exemption clinical trials (Sicard 2006) and a study from the Department of Veterans Affairs National Surgical Quality Improvement Program using prospectively collected data (Bush 2007). Neither of these studies had a surveillance arm as in EVAR 2.

The Society for Vascular Surgery Outcomes Committee analysis of data identified 565 EVAR patients and 61 open surgical controls. These EVAR patients were defined as high risk according to the EVAR 2 trial. The 30-day operative mortality was 2.9% in EVAR and 5.1% in the open group (p=0.32). The aneurysm related death rate after EVAR was 3.0% at 1 year and 4.2% at 4 years, compared with 5.1% at both time points for the open group (p=0.58). The overall survival at 4 years after EVAR was 56% vs 66% in the open group (p=0.23). The authors concluded that EVAR in anatomically suitable high-risk patients is safe and provides lasting protection for aneurysm related mortality. However, this study did have a low number of patients in the open groups and the study was underpowered to identify a difference in mortality between the 2 groups.

The Department of Veterans Affairs National Surgical Quality Improvement Program studied a cohort of 788 high-risk EVAR patients and 1,580 patients undergoing open repair. EVAR had a lower 30-day (3.4% vs 5.2%, p=0.047) and 1-year (9.5% vs 12.4%, p=0.038) all-cause mortality than open repair. The risk of perioperative complications was significantly lower after EVAR (16.2% vs 31.0%, p=<0.0001). The authors interpreted these data to conclude that EVAR should be considered the primary treatment for a patient with AAA and considerable comorbidities.

EVAR 2 has recently published the 8 years follow-up results demonstrating a much improved aneurysm-related survival for EVAR (86% at 6 years vs 64% for no intervention), but no clear difference in all-cause survival was observed (The UK EVAR Trial Participants 2010b). In summary they have shown that EVAR can reduce aneurysm rupture (and related mortality) but not improve survival. However it must be noted that only 20% of the patients in the EVAR 2 trial were alive at 8 years and these were very unwell people (Brown 2011, Brown 2010a, The EVAR Trial Participants 2007) so EVAR providing short-term but not long-term benefits may be important and more applicable to this medically unfit cohort.

More medically unfit patients who fulfill the EVAR 2 criteria, who would not be suitable for a conventional open repair are successfully undergoing EVAR. A recent analysis from France by Sobocinski et al, identified that their high-volume centers practice was in opposition to the EVAR 2 conclusions and that this practice was safe and effective if a multidisciplinary approach is undertaken (Sobocinski 2011). This type of practice is being conducted

frequently in many centers with good results for these patients who were conventionally regarded as medically unfit for definitive management of their AAA (Chadi 2012).

EVAR for women

The majority of EVAR studies include predominantly men, mainly due to a lesser incidence of AAA in women. However, AAA disease in women is challenging and rupture may occur more frequently due to several factors including vessel size (Al-Khatib 2012, Becquemin 2012). Few studies have focused on the outcomes of gender and EVAR. Mehta et al, studied outcomes following both endovascular and open AAA repair in women (Mehta 2012). Prospectively 2631 patients were studied over 7 years, 1698 had EVAR and 933 open. Males composed 76% of their cohort and 21.6% elective EVAR and 31.1% emergency EVAR were women.

Their results revealed for women, elective EVAR resulted in significantly greater mortality than men (3.2% vs 0.96%, $p<0.05$), a greater mean blood loss (327ml vs 275ml, $p=0.003$) an increased incidence of aortic neck or iliac rupture (4.1% vs 1.2%, $p=0.002$) and use of Palmaz stents for type 1 endoleaks (16.1% vs 8%, $p=0.0009$). Women also had more perioperative complications: leg ischemia (3.5% vs 0.6%, $p=0.003$), colonic ischemia and colectomies (0.9% vs 0.2%, $p=0.009$) with a longer mean hospital stay (3.7 vs 2.2 days, $p=0.0001$).

There were no gender differences for emergency EVAR, emergency and elective open repair. The authors using logistic regression, concluded that the female gender remains a significant risk even when the effects of AAA size and age are considered (odds ratio 3.4, $p<0.01$). So elective EVAR may benefit men more than women.

More recently Al-Khatib et al, evaluated the selective use of percutaneous EVAR in a small series of 30 women (Al-Khatib 2012). Of this cohort, 24/47 (51%) femoral arteries were appropriate for this technique and compared to open EVAR cut-downs, less wound complications reported ($p=0.02$), including hematomas, wound breakdown and pseudoaneurysms. They concluded that in women selective EVAR cases could be carried out safely with a percutaneous approach.

EVAR for Ruptured AAA

With evidence that elective EVAR reduces morbidity and mortality over open repair, there have been many advocates of using EVAR preferentially for patients with the highest mortality i.e. those with rupture (Biancari 2011), with significant benefits (Dick 2012, Harris 2012, Mohan 2012, Nedeau 2012, Noorani 2012, Salata 2012, Mani 2011, Karkos 2011, Jim 2010, Lyons 2010, Castelli 2005, Greenhalgh 2004, Veith 2003, Hinchliffe 2001b).

The earliest report of using EVAR for ruptured AAA is described by Yusuf in 1994. EVAR for ruptured AAA has shown promise, yielding survival rates comparable with the best single-centre results of open repair for rupture (Dick 2012, Mohan 2012, Nedeau 2012, Ten Bosch 2010a, Eliason 2009, Guo 2009, McPhee 2009, Moore 2007, Lagana 2006, Mehta 2006, Brandt 2005, Alsac 2005a, Hechelhammer 2005). In non-randomized data systematic reviews and meta-analyses EVAR has shown trends towards reduced blood loss, intensive care stay, early complications, and mortality (Al-Zuhir 2012, Dosluoglu 2012, Freyrie 2012, Mohan 2012, Noorani 2012, Wang 2012, Foster 2009, Lovegrove 2008, Rayt 2008, Sadat 2008b, Harkin 2007).

There is single-state administrative data and a single randomized trial (which has now stopped) comparing EVAR with open surgical repair for rupture demonstrating no difference in mortality (Hinchliffe 2006, Leon 2005). Individual reports of conversion to open repair in the setting of EVAR for rupture have yielded a mortality rate of 40% (Coppi 2006, Hechelhammer 2005, Kapma 2005, Larzon 2005, Scharrer-Palmler 2003, van Herzeele 2003, Hinchliffe 2001b).

Caution must be taken when interpreting this ruptured EVAR data with open emergency repair results because the outcome data is heterogeneous with a variety of biases that confound results. In many studies, the use of EVAR is often limited to those patients with hemodynamic stability who can undergo pre-operative imaging. Procedures are undertaken in centers with personnel and technology equipped for EVAR out of hours. It has been estimated that less than half of ruptured AAA have anatomical characteristics suitable for EVAR (Slater 2008). Also the inclusion of symptomatic patients without rupture skews this data set.

A number of RCTs have been attempted but have stopped due to under-powering (Hinchliffe 2006) and early non-significance (Amsterdam Acute Aneurysm Trial Collaborators 2006). Currently there is a United Kingdom RCT called the Immediate Management of the Patient with Rupture: Open Versus Endovascular Repair (IMPROVE) trial, which aims to resolve these issues by randomizing 600 patients (Powell 2009). Until completion of this trial, our knowledge of the use of EVAR for ruptured AAA is limited to single-center experiences and population-based database analysis with systematic reviews of the literature (Hinchliffe 2009).

A potential complication of EVAR for rupture that should be noted is abdominal compartment syndrome, caused by increased intra-abdominal pressures or hypertension, resulting in decreased intra-abdominal organ perfusion and increased airway pressures (Björck 2012, Djavani Gidlund 2011, Mayer 2011, Mayer 2009, and Mehta 2005). A series of 40 cases of EVAR for ruptures from 2002-2004 by Mehta et al (Mehta 2006), revealed 7 cases of abdominal compartment syndrome (18% incidence) with a 57% mortality rate in this subgroup compared with a 9% mortality in the cohort with no compartment syndrome. Other authors report similar abdominal compartment syndrome rates of 20% (Mayer 2011, Mayer 2009) and others have a lower incidence of 9% (Djavani Gidlund 2011), nonetheless it is a complication to be aware of in this group of EVAR patients.

EVAR for ruptured AAA is dependent on the immediate availability of a suitable endograft. To address this issue and make EVAR more available in the emergency setting manufacturers are currently developing “off the shelf” devices which consist of a modular aorto-uni-iliac graft with multiple proximal and distal sizes.

EVAR for small AAA

It is a commonly accepted practice to operate on AAA with diameters ≥5.5cm by conventional open surgical repair and keep patients with smaller AAA under surveillance (Brewster 2003). However, as the outcomes of EVAR continue to improve with low risk of perioperative mortality, some question if the threshold for intervention should be lowered. Intervention for small AAA with EVAR is supported by reports demonstrating freedom from endoleak, late rupture, and aneurysm related death (Peppelenbosch 2004). Golledge et al, prospectively studied the treatment of small AAA (≤5.5cm) in their small single centre series

and found that EVAR in this cohort would be inappropriate because it exposes relatively well patients with a low risk of rupture to an invasive procedure carrying a significant reintervention rate (Golledge 2007).

To answer these questions, two RCTs were established to evaluate early EVAR vs surveillance for small AAA. The first is a European multicenter study named the Comparison of surveillance vs Aortic Endografting for Small Aneurysm Repair (CAESAR). The CAESAR trial randomized 360 patients with AAA 4.1-5.4cm to surveillance or early EVAR (Cao 2011, CAESAR Trial Collaborators 2005). The target recruitment number was 740 patients, but the trial was closed prematurely because of poor recruitment. They found mortality and rupture rates in AAA <5.5cm to be low and no short term advantage for EVAR, however the end points of this study and various other aspects of the method have be criticized (Bicknell 2011). In a separate publication their data analysis has revealed an initial heath-related quality of life advantage in the EVAR group, but this difference is lost at 32 months (de Rango 2011b). However, they predicted that 60% of small aneurysms under surveillance might grow to require repair and that 17% might lose suitability for EVAR, which is agreement with earlier data provided by Thompson et al (Thompson 2006).

The second trial is the 70 site Positive Impact of Endovascular Options for Treating Aneurysms Early (PIVOTAL) trial in the United States. In November 2008 728 patients with small AAAs (4-5cm) were randomly assigned to EVAR or surveillance (Lall 2009, Ouriel 2009a). The interim results at 20 months have shown no difference in rupture, aneurysm-related mortality, or survival between the 2 groups (Lall 2009, Ouriel 2009b).

Until further results from these trials are available, clinicians continues to use the 5.5cm diameter as the threshold for repair.

Future prospects of EVAR

EVAR is currently curtailed by cost, technical limitations and patient selection criteria. Improved technology and endovascular experience with new customized fenestrated and branched devices (Adam 2012, Cross 2012, Parlani 2012, Pua 2012, Resch 2012, Starnes 2012, Wyss 2012, Cross 2011, Donas 2011b, Linsen 2011, Oderich 2011, Peppelenbosch

2011, Phade 2011, Pua 2011, Troisi 2011b, Donas 2010, Ferreira 2010, Nordon 2010a, Zhou 2007, Greenberg 2006, Malina 2006, Chuter 2005, Stanley 2001b, Browne 1999) have extended the technique to patients deemed anatomically unsuitable for EVAR and even in open repair who possess juxtarenal, suprarenal and thoracoabdominal aneurysms with challenging landing zones. Fenestrated devices use the placement of holes within the fabric of the endograft, aligned with renal or visceral arteries, through which balloon-expandable stents are placed. This technique was first clinically described in 1999 (Browne 1999) after preliminary experimentation (Park 1996). Early and mid-term results have been positive with low mortality and endoleak (<5%) rates (Cross 2012, Donas 2011a, Resch 2011, Resch 2010, Greenberg 2009, Sun 2009, Scurr 2008, Verhoeven 2007, Greenberg 2004a).

With increasing experience of endovascular techniques and centralization of vascular surgery services in to high-volume tertiary referral centers, we are seeing excellent surgical results and patient outcomes (Holt 2012, Mell 2012a, Mell 2012c, Nordon 2012, Sobocinski 2011, Thompson 2011, Holt 2010b, Holt 2010c, Jim 2010, Karthikesalingham 2010a, Chaikof 2009, Giles 2009b, Hafez 2009, Holt 2009, McPhee 2009, Schwarze 2009, Dimick 2008, Holt 2008, Egorova 2008, Holt 2007, Young 2007, Mehta 2006). Patients are prepared to travel longer distances for better outcomes (Holt 2010d, Reise 2010). The role of open surgery will diminish but not disappear, in a similar way to which laparoscopic surgery has replaced many open abdominal operations. With a greater emphasis on EVAR, surgeons will be challenged to maintain their skills in open repair. The hope for the future is a less costly, lower profile device with wider applicability, improved stability and fixation, and the elimination of endoleaks providing a durable repair comparable to an open surgical graft.

ENDOVASCULAR STENT GRAFT SURVEILLANCE

Long-term surveillance is essential for EVAR success with frequent monitoring of patients to ensure persistent aneurysm exclusion from the systemic circulation (Nordon 2010b, Szmidt 2007, Hobo 2006, Bown 2004, D'Ayala 2004, Elkouri 2004a, Stavropoulos 2004b, Conners 2002, Thurnher 2002, Tonnessen 2002, Patterson 2001, Laheij 2000, Kalman 1999). FDA assessment of EVAR durability in the 1990's included *in vitro* "bench-top" mechanical fatigue testing, short-term (<1 year) animal implantation testing and industry sponsored human clinical trials with relatively short-term (1-2 years) safety and clinical efficacy end points (Back 2007). The gold standard for surveillance frequency and modality has not been determined.

Open AAA repair does not have the same long-term follow-up requirements because of lesser late graft related complications (Angle 2004, Hallett 1997). The EVAR 1 study (EVAR trial participants 2005a) demonstrated that EVAR was associated with a 20% reintervention rate compared with 6% for open repair after 4 years. The DREAM trial mirrored these findings (Prinssen 2004), however reintervention rates vary widely between different series and can range from 1 to 37% (Nordon 2010b, Stavropoulos 2004b, Verhoeven 2004, Walschot 2002, Baum 2001a, Baum 2000b). Surveillance imaging is critical for the detection of endoleaks, limb kinking or stenosis, limb occlusion, migration and sac expansion. These problems often require endovascular reintervention to maintain aneurysm exclusion, reduce late rupture and subsequent mortality.

During the infancy of EVAR, diagnostic catheter angiography was routinely used for post-EVAR assessment as it could depict flow direction (Stavropoulos 2005). This was not the ideal test as it was invasive, time consuming and demanding on both patients and staff (Hellinger 2005, Seldinger 1953). Other disadvantages are that the images are only 2D and therefore multiple acquisitions with separate contrast medium injections required. Despite this, accurate images are not guaranteed due to overlapping, magnification causing vessel foreshortening (Beebe 1995) and soft-tissue resolution that is required to depict vessel walls, aneurysm thrombus and viscera. It lacks the sensitivity (63%) to reliably detect endoleaks (Armerding 2000). Currently catheter angiography is used as a problem-solving tool following EVAR, when non-invasive modalities cannot be relied upon. Targeted pigtail and

selective vessel injections can directly confirm the origin, flow direction and potential outflow of an endoleak prior to treatment with embolotherapy.

Today contrast enhanced CT angiography remains the "gold-standard" surveillance (Oikonomou 2012, van der Vilet 2011, Carrafiello 2008, Eliason 2008, Back 2007, Hartshorne 2006, AbuRahma 2005, Murphy 2004, Thurnher 2002, Veith 2002, Makaroun 2001, Görich 1999, Karch 1999, Golzarian 1998, Balm 1997, Grimshaw 1992) It is implemented at 1, 3, 6 and 12 months and then annually for the patients' lifetime (Oikonomou 2012, Iezzi 2010, Patel 2010, Go 2008, Zelenock 2006, Eksandari 2001, Vallabhaneni 2001). These surveillance time-lines were based on early recommendations from protocols used in the various FDA trials and by early registries, such as EUROSTAR (Harris 2000) with little change since (Kranokpiraksa 2008). It is estimated that 5.1 CT scans are required with most protocols within the first 2 years of EVAR follow-up, compared with 1.4 scans in the same time period for open repair (Mills 2008). In the EUROSTAR database 84% of patients were followed with CT angiography, 4% with diagnostic angiography, 3% with MRA and 8% with DUS (Buth 2003). There is little evidence regarding technique and frequency of surveillance for the newer EVAR techniques (e.g. fenestrated stents). Life-long surveillance is crucial but not yet defined (Pua 2011b), and varies greatly depending upon the center where the patients original procedure was performed (Milner 2006). This variability may explain the differing detection rates of endoleaks reported in the literature (Carrafiello 2008).

Karthikesalingam et al, studied routine post-EVAR surveillance protocols in the UK (Karthikesalingam 2011b). Their aim was to identify the degree of variation in national practice and see if protocols were in line with the manufacturer's instructions for use. A telephone survey was carried out with 41 centers with more than 10 years EVAR experience. CT was the primary mode of surveillance in 12/41 centers and ultrasound in 14/41, with the remaining 15/41 using a combination of the two. The authors concluded that there was a significant heterogeneity of frequency and modality reflecting uncertainty in surveillance protocols throughout the UK. They concluded that a consensus towards a national surveillance program should be sought.

Surveillance scans of post-EVAR patients contributes to the high costs of the EVAR procedure itself (Karthikesalingam 2011b, van der Vilet 2011, Verhoeven 2011b, Black 2009, Sharma 2009, Hayter 2005, Michaels 2005, Bosch 2002, Patel 1999). The financial outlay required by patients and their families to travel long distances, miss work to attend follow-up appointments, as well as health care resource implications to conduct these examinations should be considered (Go 2008). Long-term surveillance imaging and consequent secondary procedures have been shown to increase the global cost of EVAR by approximately 50% (Kim 2008, Noll 2007), specifically 65% of follow-up costs have been attributed to CT imaging as detailed in the NIHR Health Technology Assessment of EVAR (Karthikesalingam 2011b, Chambers 2009, Prinssen 2004b). Kim et al, demonstrated in an analysis of 360 patients that reinterventions increased costs significantly by 8.3-fold ($p<0.05$) compared with those without secondary procedures (Kim 2008). Typically post-EVAR CT and MRI scans cost approximately £750-£1000 and £1000-£1300 respectively, in comparison with £300-£400 for a surveillance color DUS (Sharma 2009). Outpatient attendance accounts for 7.6% of EVAR costs (Noll 2007). Thus to reduce the overall costs of EVAR, surveillance expenditure must be reduced.

Surveillance is particularly important for patients treated with the early abdominal endografts as these have a high incidence of complications and reintervention requirement (Mestres 2010, Espinosa 2009, Szmidt 2007, Bos 2008, van Herzeele 2008, Väärämäki 2007, Hobo 2006, Lalka 2005, Prinssen 2004, Laheij 2000), compared with second-generation devices (May 2000). A recent single-center study from a high-volume unit conducted by Karthikesalingam et al, analyzed 553 patients over 9 years and found that 69 of them required 86 reintervention procedures (Karthikesalingam 2010b). They concluded that most patients requiring reintervention presented symptomatically and a significant number required an intra-operative adjunct procedure during their index procedure ($p=0.024$). They recommended that this subgroup should undergo a specifically targeted surveillance regime.
A reduced surveillance regime may be appropriate in instances where there is early success with newer devices. This may improve patient compliance with programs, and also improve safety by reducing the effects of intravenous contrast and radiation exposure, whilst reducing health care costs. However this has not been validated in a prospective RCT.

Schlösser et al, identified 270 ruptures detailed in the literature of post-EVAR rupture and found that 35 had no prior abnormalities (such as endoleak, migration, sac enlargements etc) found on follow-up (Schlösser 2009). However, 43 of these patients refused surveillance or re-intervention highlighting the importance of compliance.

Antoniadis et al, recently have published their small single-center study of 42 patients who received a surveillance follow-up booklet to improve compliance (Antoniadis 2012). This simple intervention resulted in all patients fully complying with their protocol instructions. The authors also suggested that this booklet is not only of use for patients finding it difficult to comply with surveillance but also has an important purpose when patients attend different hospitals for various reasons.

Nordon et al, reiterated that a targeted surveillance programme should be implemented for patients that are deemed to be particularly at a high risk of developing complications. They performed a systematic literature review and meta-analysis of re-intervention-free survival post-EVAR (Nordon 2010b). Over a 7 year period (2002-2009) 32 studies were selected including 17,987 patients undergoing EVAR. Crude annual secondary intervention rates were 3.7%/year (range 1.7-4.3%) and the combined re-intervention-free survival estimates demonstrated a linear progression with 89.9%, 86.9% and 81.5% of grafts without secondary procedures at 2, 3 and 5 years respectively. They found that surveillance imaging alone initiated secondary interventions in 1.4-9% of cases and >90% of EVAR cases received no benefits from surveillance scans. Waasdorp et al, have similarly demonstrated that early post-procedural CT imaging has failed to influence treatment in 99% of patients (Waasdorp 2008). Nordon et al, concluded that some form of surveillance was required, but for a specific targeted high risk cohort.

Other authors have called for redefining surveillance. Sternbergh et al, used the US Zenith prospective multicenter pivotal (phase II) and continued-access (phase III) trial data with 739 patients (Sternbergh 2008). They found that patients without early endoleaks at 1 month predictive ($p<0.001$) of reduced aneurysm-related morbidity. They proposed a new EVAR surveillance regime with early patient outcome dictating the intensity and frequency of imaging.

Most AAA ruptures occur within the first 2-3 years after EVAR (Schlösser 2009) and most secondary interventions (85%) were performed within 30 days post-implantation according to the LIFELINE registry (Lifeline registry of endovascular aneurysm repair 2005). The majority of secondary procedures for reduced limb blood flow occur within 90 days of deployment (Black 2009, Moore 2003). Thus EVAR surveillance may be improved if it were focused on patients within the first 3 years post-EVAR (Schlösser 2009).

A number of authors have called for redefined programs the intensity and frequency of which are based on early outcomes (Oikonomou 2012, Verhoeven 2011b, Sternbergh 2008) and a variety of radiological imaging modalities.

Black et al, analyzed 417 consecutive elective EVAR cases with the Cook Zenith device and found that secondary procedures were performed in 31 patients (7.4%), of which 6 (1.4%) were detected by CT surveillance (Black 2009). Of these patients, 12 required reintervention (2.9%), consisting of 10 type I and 2 type II endoleaks. Similarly Dias et al, using the same Cook Zenith device in 279 elective EVAR patients found that less than 10% of their patients actually benefited from yearly surveillance (Dias 2009). Both authors and a growing number of other groups (Go 2008) have questioned the value of prolonged surveillance with reference to their lower reintervention rates and call for surveillance protocol revision.

There appears to be a current paradigm shift in surveillance protocols between centers of excellence employing more sophisticated techniques and others using limited imaging, particularly in Europe (Oikonomou 2012, Blankensteijn 2004). The current intensive programs being undertaken in many units are based on data provided from the early, first generation device failures (Resch 2001, May 2000). These have not been evaluated in relation to greater success rates of later generations of stent-grafts.

SURVEILLANCE IMAGING MODALITIES

a. **Plain Radiography**

Plain abdominal radiography is simple, inexpensive and useful for EVAR surveillance because a number of structural failures, modular disconnections and graft distortions may be observed that are not seen with other imaging modalities (Gray 2012, Oikonomou 2012, Verhoeven 2011b, Stavropoulos 2007, Murphy 2004, Fearn 2003, Whitaker 2001a, May 1997). It cannot be used to detect the presence of endoleak or investigate stent-graft perfusion. CT can also be used to inspect for graft fractures, however it is not as accurate as plain radiography (Roos 2005). Comparing serial radiographs can be useful for the diagnosis of graft migration from the proximal or distal attachment zones, particularly in gross movement (Oikonomou 2012, Murphy 2004, Magennis 2002).

The most useful view to detect migration is a lateral film. Lumbar spines can be seen within the same plane as the stent, providing clear landmarks against which movement can be demonstrated. Oblique views improve the detection of stent-wire fractures. A standardized protocol can be used to limit artefactual migration, by reducing variation in the radiographic centering point, beam direction and focus-to-film distances (Hodgson 2003, Murphy 2003).

It is advised to perform abdominal radiographs prior to same-day CT examinations so that excreted contrast material in the collecting systems do not obscure views (Murphy 2003). Embolization coils are important to note following adjunctive embolisation of aortic side branches or an internal iliac artery.

b. **Computed Tomography**

At the end of the 19th century, the Nobel Prize was awarded for the discovery of X-rays and in 1896 it was used for angiography (Bergqvist 2010). In 1960s, the electrical engineer Hounsfield developed the idea of Computed Tomography (CT) at about the same time that a South African-born physicist, Allen McLeod Cormack, independently described its theoretical basis. The first clinical application of CT took place in 1971 to image brain. Whole body scanning was achieved in 1975 (Hounsfield 1973). CT now makes up 25% of all medical imaging (Bajoghli 2010).

It has been the mainstay of pre-procedural imaging to determine anatomical suitability and post-procedural graft surveillance since the development of EVAR and is the gold-standard imaging modality for post-EVAR follow-up. The preliminary CT scan determines anatomical suitability for EVAR then serves as baseline comparison for subsequent surveillance CTs (Hellinger 2005). CT has been demonstrated to be superior to the more invasive conventional catheter angiography in detecting endoleaks (Armerding 2000, Görich 1999, Rozenblit 1995), and is widely considered to be the most sensitive modality for assessing changes in aneurysm size and identifying endoleaks (Milner 2006). Advantages of CT include quick scan acquisition time, widespread availability and the acquisition of important non-vascular cross-sectional information, high soft-tissue resolution, which may influence treatment decisions, and detect incidental malignancy (Lyons 2009, Indes 2008, McDougal 2006). Disadvantages include radiation exposure and the use of nephrotoxic iodinated contrast (expanded on later).

Originally CT surveillance imaging protocols included thin-section (1-1.5 mm) acquisitions timed to the arterial phase. This has evolved to biphasic (arterial and delayed scans) then to triphasic series (initial non-contrast scan, then arterial, and then delayed scans). There is definitive CT protocols for endoleak detection, with some advocating arterial phase and others championing delayed images. Contrast enhanced spiral CT arterial phase images are said to be the method of choice for detecting the majority of endoleaks (Iezzi 2006b, Magennis 2002). However, slow filling side branch endoleaks may not be seen until a later delayed phase of imaging, after contrast medium injection, typically 70 seconds after administration (Lehmkuhl 2012, Sommer 2012, de Bucourt 2011, Macari 2006, Hellinger 2005, Rozenblit 2003, Golzarian 1998).

Endoleaks are detected on CT by the accumulation of rapidly injected iodinated contrast medium within an aneurysm sac out-side of a stent-graft. As endoleaks have variable flow rates, they can be detected at variable times after contrast medium is injected. Graft related and side branch related endoleaks can be distinguished by the relationship of contrast medium accumulation to the aortic wall and its side branches or the stent-graft and its attachment zones (Görich1999). Endoleaks in the periphery of the aneurysm sac away from contact with the stent may represent a type II endoleak. If this endoleak is anterior then it is probably caused by the inferior mesenteric artery, whilst those posterolateral are due to lumbar arteries. If the endoleak is in communication with the proximal or distal stent then

they may represent a type I. Endoleaks around the graft which spare the sac periphery are usually type III endoleaks (Görich 1999). Different types of endoleak may co-exist where the aortic side branches act as the outflow for an endoleak due to a graft-related problem (Magennis 2002).

Stavropoulos showed that when compared with catheter angiography CT did not accurately detect endoleaks in 14% of cases; reclassification of these endoleaks with angiography changed treatment for 11% of patients (Stavropoulos 2005).

Endoleaks can be confused with areas of longstanding increased density within mural thrombus (e.g. calcification) and termed pseudo-endoleaks (Hellinger 2005, Rozenblit 2003). A non-contrast/unenhanced study can help with distinguishing between the two and thus reduces the number of indeterminate studies (Rozenblit 2003), but further increases the radiation exposure to the patient (de Bucourt 2011, Laks 2010, Iezzi 2008, Iezzi 2006b, Murphy 2004, Farner 2003, Rozenblit 2003, Golzarian 1998).

Triphasic CT surveillance protocols expose patients to a substantial radiation dose and have higher costs than biphasic protocols (Saba 2010, Iezzi 2006b, Rozenblit 2003, Golzarian 1998), but many question the reliability of low flow endoleak detection in these programmes. It is generally accepted that CT allows the easy detection of relatively large endoleaks. However, the detection of low-flow and small endoleaks, particularly those close to high-attenuation components such as metallic portions of stent-grafts and calcification, can be difficult (Wieners 2010, Iezzi 2008, Kramer 2002).

Concerns regarding radiation dose have led some investigators to consider the possibility of eliminating portions of multiphasic surveillance CT protocols. A compromise is with an initial non-contrast CT then perform subsequent biphasic scans, minimizing radiation exposure (Iezzi 2006b). Some have proposed the use of dual-source dual-energy multidetector CT which eliminates the need for unenhanced views because a virtual non-enhanced data set is generated during a single simultaneous helical acquisition by two separate CT scanner at 90-degrees to each other (Laks 2010, Sun 2010, Johnson 2007, Flohr 2006), after contrast administration. After image capture, post-processing algorithms are applied which remove iodine information from the contrast enhanced data depending on the

different attenuation properties of material imaged (Laks 2010, Chandarana 2008, Scheffel 2007). This technique was found to reduce radiation exposure, by removing the routine acquisition of non-contrast data in 22 patients, and significantly detected 6 endoleaks with a higher attenuation ($p<0.03$) than conventional single source triphasic CT (Chandarana 2008). It has been calculated this technique results in a 61% reduction in radiation exposure for each follow-up CT (Laks 2010, Chandarana 2008, Stolzmann 2008). Sun et al, have demonstrated experimentally with an *in vitro* phantom, that dual-source CT significantly ($p<0.0001$) reduces radiation exposure by 26.5% (Sun 2010). Limitations of dual-energy CT that need to be considered prior to widespread adoption (Laks 2010) include the following:

- This technique has been shown to detect type I and II endoleaks, but there is a paucity of data evaluating of type III and IV endoleak identification.
- Over subtraction of calcium in the non-contrast acquisition may lead to false-negative interpretation of an endoleak (Sommer 2010a). This is an intrinsic pitfall of the virtual non-contrast algorithm, but can be overcome by additional post-processing algorithms allowing differentiation of calcium from contrast enhancement.
- In the immediate post-operative period (<1 week), the presence of residual contrast in the aneurysm sac from the original procedure may lead to false-positive endoleak diagnosis, because it will be subtracted in the virtual non-contrast images (Stolzmann 2008).
- Obese patients can have inadequate investigation due to the generation of excessive image noise (Chandarana 2008) producing suboptimal quality data and false-positive endoleak detection (Stolzmann 2008).

Others have advocated eliminating the arterial phase altogether, which contributes to 36.5% of the effective radiation dose delivered as delayed post-contrast imaging will depict endoleaks with a higher sensitivity (Macari 2006). This has been demonstrated by Macari et al, in their study of 85 patients with 28 endoleaks detected on non-enhanced and venous phase imaging compared with the 25 detected by arterial phase. The 3 missed endoleaks were all type II's and were only seen in the delayed images, which agrees with other findings (Iezzi 2006b, Rozenblit 2003). However arterial acquisitions are not obsolete as they allow planning exactly where to access an endoleak during embolisation reinterventions (Dias 2009, Farner 2003).

Sac diameter measurements are important to demonstrate size regression, stasis or increase. There is a significant interobserver variation when measuring aortic diameters using CT, with the image orientation being a key factor, but reliable measurements can be produced if used correctly (Nagayama 2012, Sprouse 2004, Abada 2003, Singh 2003, Tillich 2001b, Rubin 1998). Many AAAs have a non-geometric shape with asymmetrical bulges and thus a number of diameters can be chosen for measurement and can vary depending on the anteroposterior, transverse or oblique plane. Ideally, previous images can also be reviewed at comparable axial levels to produce comparable diameters for surveillance information. However, there can be significant interobserver variation between measurements depending on the slice chosen for measurement and its orientation so standardization with stringent protocols are imperative.

CT data 3D reconstruction can provide volume measurements and eliminate user variation to a certain extent (Hahne 2012, Nagayama 2012, Oikonomou 2012, Boyle 2011, Kauffmann 2011, van Prehn 2008, Lee 2007b, Pollock 2002, Whitaker 2001a, Wever 2000). Views can be seen in any projection including endoluminal, which are superior to single measurements. Traditionally a technique called filtered back projection has been used to transform raw CT data into a final reconstructed image. Recently a more effective statistical iterative reconstruction technique has been adopted (Thibault 2007). There are cases in the literature of stable sac sizes but increasing aneurysm volumes in the presence of an endoleak (Bargellini 2005a, Lee 2003, Prinssen 2003, Czermak 2001, Whitaker 2001a, Singh-Ranger 2000a, Wever 2000), and similarly diameter increases without a total volume increase has been reported (van Keulen 2009a). Fillinger et al, have found that volume measurements depict aneurysm enlargement 18 months earlier than diameter measurements do (Fillinger 2006). Volumetric protocols covering the abdomen (450-550 mm) are time-consuming, and generate a large amount of data with numerous images that are no longer viewed on printed sheets of film. Today they are reconstructed on 3D-workstations which include quantitative analytic tools. Accurate measurements can be obtained in a plane perpendicular to the center line of the vessel that can be defined by multiplanar reformatted software, with a low interobserver variability (England 2012, Kaladji 2012, Oikonomou 2012, Tambone 2012, Voûte 2012b, Kauffmann 2011, van Prehn 2008, Abada 2003, Whitaker 2001a).

Aortic volume analysis has also been obtained with non-contrast CT. This is accurate, highly reproducible and significantly correlates with paired contrast CT images ($p<0.0001$) in a series of 316 cases that advocated sparing contrast exposure to patients (Nambi 2011). Bley et al, have proposed a surveillance follow-up using volumetric analysis derived from a combination of enhanced and unenhanced CT acquisitions that has been shown to reduce radiation exposure by approximately 57-82%, contrast usage and costs (Bley 2009).

Care must be taken when using sac size as an indicator of successful treatment (Gilling-Smith 2000). The aneurysm sac may take many months to shrink, even if the aneurysm has been completely excluded. Some AAA sacs may stop shrinking after 18 months (Resch 2000, Singh-Ranger 2000b). There have been reports of aneurysm rupture where initial sac size reduced then increased again (Greenberg 2004b, Alimi 1998) and ruptured (Schlösser 2009, Becquemin 2005).

A reduction in sac diameter would indicate treatment success. Houbballah et al, have demonstrated in 371 patients undergoing CT surveillance, that significant sac retraction (75% sac size reduction) can accurately predict durable success after EVAR ($p<0.05$) and this cohort may require a less intensive follow-up (Houbballah 2010). However, as explained earlier, the phenomenon of endotension may only be detected by subtle increases in sac diameter in the absence of a demonstrable endoleak (Gilling-Smith 1999). An increase of greater than 5 mm is particularly worrying and may imply impending rupture if occurring within a short period of time.

Intraoperative angiographic CT (DynaCT; Siemens, Germany) is a method of obtaining CT-like images with a c-arm system mounted on a flat-panel detector that rotates 220° around the patient to produce a number of 2D-projections. These are then reconstructed in a cross-sectional format to produce 3D-images. DynaCT occurs on table in an endovascular hybrid suite so unnecessary time wasted in a radiology CT room is avoided during rupture emergencies. This technique has also been demonstrated to be a powerful tool for detecting endoleaks, limb compression and graft thrombosis, and has been shown to be more sensitive than uni-planar angiography in the immediate period post-EVAR deployment (Lehmkuhl 2012, Biasi 2009, Rydberg 2004).

Eide et al, demonstrated in 20 non-consecutive patients that DynaCT allows adequate selection of the appropriate stent graft pre-EVAR, when compared to multi-detector CT (Eide 2011, Eide 2009). Six arterial and nine anatomical regions were measured with both modalities to asses potential ruptured AAA and allow pre-EVAR anatomical suitability measurements. However, they found that there was a significant difference of 1.3mm for aortic diameters ($p=0.043$) and evaluation of iliac arteries were suboptimal due to limited imaging volume size, but visualization of all areas was possible nonetheless. The authors concluded that DynaCT gives sufficient information to determine correct ruptured AAA treatment and proper stent graft selection rapidly in the emergency situation.

There have been no reports to date of DynaCT being employed for post-EVAR surveillance programmes apart from the immediate post-operative period. Biasi et al, used DynaCT to detect and correct a type Ia endoleak on EVAR completion that was missed by conventional angiography (Biasi 2009). The fact that this technique is rapid and offers adequate data could be advantageous but proper assessment of efficacy is required first.

i. **Ionizing Radiation**

Marie Curie died from cancer in 1934 caused by exposure to her discovery, radium, and Thomas Edison who invented the fluoroscope, stopped work when his assistant died of an x-ray overdose. For post-EVAR surveillance, clinicians need the best imaging to detect the most subtle endoleaks and aortic sac changes. Higher CT image quality increases radiation dose (Singh 2012, Entrikin 2011, Moon 2011, Brenner 2010a, Brenner 2010b, Eisenberg 2010, and Brenner 2007). Over the past 30 years the average radiation exposure to US citizens from medical imaging has increased more than six fold accounting for up to 48% of total exposure (Prokop 2005) whereas the average dose from natural background sources has not changed substantially (Brenner 2010c). Other technological advances such as greater imaging speed have increased radiation doses (Smith-Bindman 2010).

Since the 1980's, it is estimated that CT use has doubled almost every year (Prokop 2005). Unfortunately fear of litigation, miscommunication and a general lack of awareness regarding radiation risks among both health care workers and patients has increased CT use unnecessarily (Baerlocher 2010, Lee 2004). Radiation doses from CT scans are 100-500

times those from conventional radiography, depending on what part of the body is being imaged (Singh 2012, Smith-Bindman 2010, Hartshorne 2006), exposure from a thoraco-abdominal CT may total more than 20 mGy (Brenner 2007).

It is easy to become complacent about the dangers of radiation because it is invisible and odorless. The World Health Organization has classified radiation as a carcinogen. It has been estimated that the lifetime attributable risk of death from cancer following an abdominal CT scan in a patient >50 years is 0.02%; a cumulative risk, which can become significant with repeated exposure (Baerlocher 2010, Brenner 2007). It is estimated that 1.5-2% of all cancers in America may be associated with the use of CT (Brenner 2007). There is a lifetime cancer risk of approximately 5.5% for every Sievert (Sv) of radiation exposure (Howells 2012).

Cancer risk varies with patient age and sex (Motaganahalli 2012). Smith-Bindman et al, showed that the estimated risk of developing cancer was 1:330 for a 20 year old woman compared with 1:880 for a man of the same age undergoing CT (Smith-Bindman 2009). This risk decreases with age for a 40 year old woman (1:870) compared with 1:942 for a similar aged man.

Potential adverse sequelae of high dose ionizing radiation include the following (Howells 2012, Motaganahalli 2012, Singh 2012, Rahimi 2011, Bajoghli 2010, Bannazadeh 2009, Ho 2007, Kocinaj 2006, Yin 2005, Zhang 2005, Preston 2003, Shope 1995, Wagner 1994):

- Skin injuries and burns
- Arterial damage
- Tissue necrosis
- Hair loss
- Cataract
- Infertility
- Bone marrow suppression
- Neoplasia (carcinogenesis and teratogenesis)
- Acute radiation syndrome

Endovascular AAA repair exposes patients to significant radiation during the time of the procedure through fluoroscopy screening time, angiographic acquisitions, collimation,

magnification and also subsequent lifelong annual surveillance (Fossaceca 2012, Manstad-Hulaas 2012, Maurel 2012, Kalef-Ezra 2011, Laks 2010, Kalef-Ezra 2009, Aldrich 2006, Alric 2003). Brenner et al, demonstrated that their patients were exposed to high levels of 50-100 mSV and thus a subsequent significant cancer risk through this process (Brenner 2003). It has been shown that the radiation exposure during the implantation of other endovascular stents in the carotid, renal, iliac, femoral and popliteal arteries varies widely (Majewska 2011). The dose exposure increases with the depth of the artery, e.g. renal and iliac arteries; and increases with the complexity of the procedure e.g. multiple stents and fine caliber vessels. EVAR is thought to involve some of the highest radiation doses (Greenhalgh 2004), however the average radiation dose an EVAR patient receives in unclear in the literature ranging from 43-150 Gy/cm^2 (Thakor 2011, Kalef-Ezra 2009, Weerakkody 2008, Geijer 2005).

Jones et al 2010, calculated the radiation doses that 320 elective and 64 emergency EVAR patients were subjected to with a prospectively maintained database based in Belfast. They found the radiation dose to be 11.7 ± 7.1 mSV with a mean screening time of 29.4 ± 23.3 minutes for elective EVAR and 13.4 ± 8.6 mSV with a mean screening time of 22.9 ± 18.2 minutes for emergency EVAR (Jones 2010). The explanation for the lower screening times ($p=0.053$) with a slightly higher radiation dose ($p=0.12$) in the emergency group, who received an aorto-uni-iliac graft with fem-fem crossover bypass, compared to the elective group, who had a bifurcated stent-graft deployed, was due to surgical technique, and independent of aneurysm morphology (Badger 2010, Badger 2006). They also found that during the first post-operative year, surveillance CTs exposed patients to 24.0 mSV, with 8.0 mSV in subsequent years. An additional 1.8 mSV had to be included for each year due to plain abdominal radiograph exposure.

Weerakkody et al, analyzed 96 patients and found that the median entrance skin dose during EVAR exceeded the threshold of 2Gy (Miller 2002a) for possible radiation-induced skin damage in 29% of procedures (Weerakkody 2008). A number of patients greatly exceeded this threshold. The effective dose of radiation in the first year following EVAR was 79 mSv, which was higher than previously thought, and carried a potential risk of radiation-induced skin damage and later malignancy.

Recently Walsh et al showed in their cohort of 111 EVAR patients that radiation exposure-induced skin injuries were very unlikely, mainly because calculated cumulative doses were lower than other studies as they employed ultrasound and less CT for stent-graft surveillance (Walsh 2012).

Bannazadeh et al, from the Cleveland Clinic demonstrated that infrarenal AAA patients had significantly higher doses of radiation exposure when compared with other endovascular procedures, e.g. thoracic aneurysm endovascular repair ($p<0.004$) (Bannazadeh 2009). They showed that complex procedures were associated with longer fluoroscopy times and more radiation exposure, especially if arterial dissection was required. They felt the greater radiation exposure to patients subjected to arthrectomies was due to the greater penetration of the ionized rays with the skin layer separated and thus not protected from radiation exposure. This observation could explain why Jones et al, found the radiation exposure of patients to be greater during emergency EVAR despite shorter screening times, due to more invasive bypass surgery (Jones 2010).

Thakor et al, in agreement with Bannazadeh et al, recently published their results of 123 patients treated with bifurcated-grafts (Thakor 2011). They concluded that exposure from standard EVAR is acceptable, but increasingly complex EVAR is accompanied with additional radiological investigations and procedures, which can significantly increase radiation burden.

Manstad-Hulaas et al, published a prospective feasibility study of 17 EVAR procedures using 3D-elctromagnetic navigation system consisting of electromagnetically-tracked catheters compared to 10 control patients undergoing standard EVAR with fluoroscopy (Manstad-Hulaas 2012). The 3D system in this pilot study provided more spatial information and also reduced the patient radiation exposure and contrast administration. Small steps like the use of this system could help reduce patient radiation exposure if employed in the future, but further evaluations in larger series are required.

Bannazadeh et al, believed that >50% of the total radiation dose of EVAR could be through CT imaging alone (Bannazadeh 2009). They reported that the radiation associated with their CT scans was 15 mSV, which is twice as high as the dose exposure calculated by Jones et al.

Jones et al concluded that EVAR procedures and their subsequent lifelong surveillance imaging involved a substantial amount of radiation which exceeded recommended dose levels and carried a well-recognized carcinogenic risk (Jones 2010). They advised guidelines implemented throughout the UK and the consideration of alternative surveillance imaging modalities would reduce radiation exposure and enhance patient safety from EVAR.

White et al, have evaluated the radiation burden associated with a conventional CT surveillance programme consisting of 1, 3, 6, 12 month and then annually (White 2010). They found that this type of surveillance programme would equate to a total radiation dose of 145-205 mSV over 5 years. They stated that exposure to 145 mSV to a 70-year-old would yield a lifetime attributed cancer risk of 0.42% and for an exposure of 204 mSV, the risk would be 0.6%. If the patient was 50 years-old, then risks would be 0.73% for 145 mSV and 1.03% for 204 mSV. This risk would be equivalent to one cancer per year in a high volume centre. These figures do not factor in the cumulative nature of these exposures or consider other lifetime sources of radiation but are extrapolated from cancer incidences in the survivors of Hiroshima (Amis 2007). This population was statistically normal and healthy prior to exposure with a normal life expectancy compared to the older patient with AAA. However, Motaganahalli et al have used computer modeling to show that cumulative CT surveillance does increase the risk of new solid organ malignancy due to radiation exposure (Motaganahalli 2012).

A number of studies have investigated the effects of lowering CT tube current and reducing voltages, showing significant reductions in radiation exposure and contrast administration whilst maintaining image quality (Schindera 2011, Schindera 2010, Szucs-Farkas 2010, Schindera 2009a, Schindera 2009b, Szucs-Farkas 2009, Szucs-Farkas 2008, Waaijer 2007, Kalva 2006). Tube current, expressed in milliamperes (mA), is a parameter that affects the quantity of photons generated by the X-ray tube. Tube voltage is the energy and quantity of the photons generated by the tube (Entrikin 2011). It has been shown that reduction in tube voltages in thin patients can produce adequate quality diagnostic images (Szucs-Farkas 2010, Biscoff 2009, Szucs-Farkas 2009) resulting in a 31-88% radiation dose reduction (Hausleiter 2010, Halliburton 2009, Abada 2006). These lower energy photons interact more strongly with iodinated contrast, resulting in increased lumen attenuation and increased contrast with surrounding tissues. Thus whilst these images produce more noise (so called “quantum

mottle") the improved image contrast results in net higher contrast-to-noise ratio to maintain diagnostic image quality.

With the evolution of EVAR techniques, more challenging cases are being attempted with increasingly complex devices using fenestrations, chimneys and branches. Widening the applicability of EVAR to a large proportion of patients previously deemed unsuitable for the technique is to be applauded, however one disadvantage is that increased procedure times has led to increased patient and surgeon radiation exposure. The more complex and detailed imaging necessary for procedure planning, device deployment and surveillance of these cases results in greater exposure to radiation (Howells 2012, Majewska 2011, Thakor 2011, Zhou 2011, Bannazadeh 2009, Ho 2007, Stanley 2001b).

EVAR in the young patient is particularly concerning as exposing this group to significant cumulative radiation carries a potentially high carcinogenic risk. The associated latency period of between 10-20 years is not seen in the older aged patients (Badger 2010, Baerlocher 2010, Bajoghli 2010, de Gonzalez 2004). For this reason, many surgeons recommend the traditional open repair of AAA for younger patients, despite higher morbidity and mortality.

In the US, approximately 10% of the population undergoes a CT scan, with a total of 75 million scans performed, this figure grows by 10% annually (Medicare Payment Advisory Commission 2009). It has not been shown directly that CT increases the risk of developing cancer, however it is well known that radiation exposure is carcinogenic, with extensive proof in epidemiological and biologic studies (Smith-Bindman 2010). It has been estimated that >2% of all carcinomas in the US are caused by CT scans (Bajoghli 2010). The National Research Council has concluded that patients exposed to radiation in the range provided by a single CT scan have an increased cancer risk (Board of Radiation Effects Research Division on Earth and Life Sciences 2006). Smith-Bindman et al, calculated the radiation dose for patients having CT's and quantified the associated cancer risk using the NRC's models and found the risk of cancer to be as high as 1 in 80 (Smith-Bindman 2009). Current evidence suggests the radiation dose from CT could be reduced by 50% or more without reducing diagnostic accuracy (Catalano 2007).

There is no professional or governmental organization responsible for monitoring, collecting or reporting patients' CT radiation dose exposure. There are few evidence based guidelines regarding the appropriate use of diagnostic imaging techniques and radiation doses. Practice varies widely between individuals, institutions and manufacturers (Smith-Bindman 2009, Impact of physician self-referral on use of imaging services within an episode 2009, Baker 2008, Investigation of defensive medicine in Massachusetts 2008, Amis 2007). A general principle followed in medical imaging is that dose exposure should be "as low as reasonably achievable (ALARA)", but there is no literature or guidelines to indicate what doses are reasonably acceptable for particular CT imaging.

In February 2010, the FDA launched an initiative to reduce unnecessary radiation from medical imaging. It is expected that overdosing safeguards should be incorporated into equipment design and that radiation dose exposure to be recorded in medical records and tracked over time.

The use of CT has allowed greater diagnostic sensitivity and specificity, which has encouraged its general use. A large proportion of these scans are thought unlikely to enhance the patients care or clinical decision making (Hilman 2010, Smith-Bindman 2010). With this increase often incidental and irrelevant, commonly benign pathology is found which needs regular surveillance and causes unnecessary anxiety. This contributes substantially to costs. As the use of imaging has rapidly increased, so has its cost. It is now estimated to be the fastest-growing physician-directed expenditure in the Medicare program, far outstripping general medical inflation (Hilman 2010, Medicare Part B imaging services 2008, Government Accountability Office 2005). A solution to all of these problems would be to reduce the number of CT scans performed.

The safety of the EVAR physician also needs to be considered. This is an area which has not been well documented. Ho et al, prospectively monitored a team of physicians' radiation absorption over 12 months using mini-thermoluminescent dosimeters attached at various places (Ho 2007):

1. Chest/body (under a lead apron)
2. Forehead at eye level
3. Hand

4. Patients body near the operative site

149 consecutive endovascular procedures were studied, which included 30 EVAR cases. They found that they median yearly effective chest/body 0.20 mSV (range 0.13-0.27 mSV) and eye 0.19 mSV (range 0.10-0.33) were similar, but a hand exposure dose of 0.9 mSV (range 0.29-1.84 mSV) was significantly higher. In particular the highest doses experienced for all procedures were to the principle physician conducting EVAR. The mean radiation absorption of patients undergoing EVAR was 12.7 mSV, similar to the levels measured by Jones et al 2010. However, Ho et al 2007, concluded that the radiation levels that physicians were exposed to were not exceeding the safety limits recommended by the International Commission on Radiation Protection and that a vascular specialist would have to perform over 2500 EVAR procedures per year before they exceeded the annual dose limit of 50mSv (International Commission on Radiation Protection 1991). They felt that this level of radiation exposure was approximately equivalent to the radiation dose that a frequent flyer is exposed to with two to three round trip trans-Atlantic flights! However, they did concede that variations in practice could result in significant discrepancy of radiation absorption between individual surgeons.

Other groups have reported high radiation absorption rates of up to 18.69 mSV in surgeons (Lipsitz 2000). Means to keep exposure levels minimal should be taken e.g. increased use of radiation protective gloves (Stoeckelhuber 2003) and glasses, in addition to exploring new imaging modalities such as magnetic resonance and ultrasound (Ascher 2005a, Raman 2005). A number of equipment-related factors such as collimation, servicing, filter usage, movement capabilities of the X-ray source, fluoroscopic specifications, X-ray photon energy spectra, the position of the projection and potential variations in the skill of the radiologist will alter radiation exposure (He 2012, Kalef-Ezra 2011, Walsh 2008a).

Radiation injuries have been reported following a range of radiologically guided procedures (Koenig 2001), but there are no specific reports of injuries following EVAR. However, this may not be the case for long with the advances of endovascular techniques to tackle more complex cases with longer operations, screening times and consequent higher radiation doses.

ii. **Iodinated Radiological Contrast**

Different tissues of the human body attenuate X-rays, producing images used in clinical practice. If two organs or structures such as blood vessels have similar densities then it is difficult to differentiate between them. A solution is to artificially alter organ density, for example using gas or air, or to use a contrast agent. Approximately 43% of all CT procedures involve the use of an intravenous iodinated contrast agents, which fill blood vessels and can be easily identified because of the contrast's much higher atomic number.

Radiological contrast media are usually water soluble solutions. Most contrast media are based on the element iodine, discovered in the early 1920s. Sodium iodide when treating patients suffering from syphilis, was observed to be radio-opaque and highlighted the urine and bladder (Speck 1983). Iodine has a high atomic number and is able to form soluble compounds with low toxicity. A single dose of contrast media, such as Omnipaque, Isopaque or Visipaque, contains up to 2000 times the quantity of iodine as in the total body content. Its clearance is natural, rapid and with no adverse effects in a healthy patient. Currently used contrast agents are frequently organic (non-ionic), low osmolar compounds which are hydrophilic and less chemotoxic compared to older generation agents (Sharma 2009, Cohan 1997, Dawson 1996, Sovak 1994, Spring 1991, McClennan 1990, McClennan 1987, Huckman 1975).

The rate of adverse reactions to iodinated contrast media is extremely low, but can occur. The adverse reactions can be categorized into:

1. Dose and concentration dependent (due to the physiochemical effects of the contrast, such as osmolality or ionic electrical charge)
   or
2. Dose and concentration independent

Adverse reactions to iodinated radiological contrast include:

- Pain
- Vasodilaton
- Cardiac depression and arrest
- Hypotension
- Nausea and vomiting

- Allergy/hypersensitivity reactions – urticaria, bronchospasm and laryngospasm

Most contrast media reactions are minor and need no treatment. Death following administration varies between 1:10000 and 1:160000, averaging around 1:75000 (Katayama 1990). Patients who are at increased risk of adverse reactions or events include patients suffering from diabetes, asthma, atopy, cardiac or renal impairment, those with previous reactions to contrast media and patient using metformin who have a high risk of lactic acidosis (Nawaz 1998). Increased use of non-nephrotoxic imaging modalities after EVAR allows reduction in surveillance related morbidity (Boyle 2009, Chaer 2009).

One of the most important adverse effects of iodinated contrast media not mentioned above is nephrotoxicity. Repetitive use of iodinated contrast can have a cumulative deleterious effect on renal function; especially in the elderly and those patients with pre-existing renal impairment (Paraskevas 2010, Davidson 2006, Solomon 2006, Goldenberg 2005). Iodinated contrast is the third leading cause of hospital acquired renal injury (Tublin 1998). Patients with renal function impairment (serum creatinine measurements >120 mm/l) should only be given contrast if absolutely necessary. Mitchell et al, demonstrated that contrast nephropathy caused an 11% increase in renal damage and 0.6% mortality rate following CT (Mitchell 2010). A large proportion of the elderly population who suffer from AAAs have undiagnosed chronic kidney disease (CKD), a large incidence of cardiovascular disease and poorly controlled diabetes (Grant 2012b, Collins 2010, Paraskevas 2010, Proceedings of a centers for disease control and prevention expert panel workshop 2009, Walsh 2008b, Azizzadeh 2006, Nakamura 2006, Walsh 2006, Goldenberg 2005, Mehta 2004, Epstein 1996, Barrett 1994a, Bartett 1993, Parfrey 1989).

Iodinated contrast agents cause renal vasculature vasoconstriction, altering renal tubule water and sodium absorption, increasing renal vascular resistance and reducing glomerular filtration rates (Jost 2010, Seeliger 2007, Persson 2006, Persson 2005, Katzberg 1997, El-Sayed 1992). Subsequent renal failure is seen as an increase in serum creatinine and a decrease in creatinine clearance (Reddan 2009) and has been termed contrast-induced nephropathy (Paraskevas 2010, Tepel 2006, Goldenberg 2005, Gleeson 2004). A small minority of patients will require permanent dialysis or kidney transplantation (Brady 1995). The presence of CKD prolongs the half-life of the contrast agent, leading to increased renal exposure and

nephrotoxicity. Several authors have investigated serum biochemical markers to predict those at risk of contrast-induced nephropathy, such as cystatin C, neutrophil gelatinase-associated lipocalin and the more widely used creatinine (Ishibashi 2010, Paraskevas 2010, Shaker 2010).

Mehta et al, retrospectively reviewed preoperative serum creatinine concentrations in 200 EVAR patients. They found a slight but non-significant increase in the risk for renal failure, dialysis and death following the use of intra-arterial contrast during EVAR in patients with preoperative CKD compared with those with normal renal function (Mehta 2004). However, Walker et al, demonstrates that patients with preexisting CKD have a significant mortality of 47% compared to 3% in those with normal preoperative renal functions (Walker 1998a). Mehta et al, found that perioperative hypotension ($p<0.05$) and increased contrast volumes ($p<0.05$) were significant risk factors for postoperative increases of serum creatinine and death (Mehta 2004). They advocate the use of appropriate precautions to prevent perioperative hypotension and limit the volume of contrast agent used, e.g. employing automated volume controllable power injectors, using alternative contrast agents (specifically carbon dioxide, gadolinium) or intravascular ultrasound (Criado 2012, Pisimisis 2010, Surowiec 2004, Bendick 2003, Parodi 2000, Vogt 1997).

Some advocate the use of pre-procedural intravenous hydration, the use of N-Acetylcysteine (an antioxidant), sodium bicarbonate, fenoldopam mesylate (a selective dopamine receptor agonist), low-dose dopamine, adenosine antagonists (aminophylline), endothelin antagonists, prostaglandin E_1, iloprost or forced diuresis with the administration of mannitol or furosemide to promote diuresis. Some think these minimize the nephrotoxic effects of contrast in a cost-effective manner within 48 hours of exposure and are well tolerated (Oikonomou 2012, Paraskevas 2010, Goldfarb 2009, Spargias 2009, Hatswell 2008, Mills 2008, Tepel 2006, Goldenberg 2005, Gleeson 2004, Mehta 2004, Rashid 2004, Tepel 2000, Bakris 1999, Barrett 1994b). There is increasing evidence that statins have a novel reno-protective effect against contrast-induced nephropathy, further emphasizing their importance in EVAR (Kandula 2010, Yoshida 2009, Xinwei 2009, Patti 2008, Zhao 2008, Alnaeb 2006, Khanal 2005, Attallah 2004).

Another alternative to reduce the amount of nephrotoxic agent used during EVAR is by using carbon dioxide as a contrast agent (Criado 2012, Chao 2007, Gahlen 2001, Seeger 1993). Carbon dioxide angiography is a safe alternative that is vastly underused. A unique physical property of carbon dioxide is its extremely low viscosity (<400 times that of iodinated contrast media). This allows effective, high volume injection rates through small spaces such as between the components of the transluminal device.

A study by Criado et al, recruited 18 patients for EVAR using carbon dioxide angiography delivered through the endograft sheath (Criado 2008). All endografting was conducted successfully with carbon dioxide and even though iodinated contrast was used in 15 patients, it did not modify the procedure in any cases. There were no ischemic or systemic complications related to carbon dioxide administration. CT surveillance showed good stent-graft positioning in all patients and no endoleaks. There was no significant deterioration in renal function in any patient. More recently this group has published data from a larger number of 72 patients, using this technique (Criado 2012). These patients were compared with 42 others with iodinated contrast and no difference in post-procedural endoleak detection was found and did not modify the procedure in any case. The carbon dioxide group had shorter operative times (177 vs 194 minutes, $p=0.01$), less fluoroscopy (21 vs 28 minutes, $p=0.002$) and smaller volumes of contrast administered (37 vs 106 ml, $p<0.001$). No complications of carbon dioxide use were recorded and patients with moderate to severely reduced renal function suffered a 12.7% greater decrease in glomerular filtration rates when administered iodinated contrast agents.

Renal function decline mirrors cumulative radiation exposure in post-EVAR surveillance programs through repeated administration of contrast agent (Mills 2008, Parmer 2006, Sun 2006a, Alsac and Zarins 2005, Greenhalgh 2004, Raithel 2005, Surowiec 2004, Böckler 2003, Bove 2000, Kichikawa 2000, Lobato 2000). Alternative methods of surveillance imaging modalities without nephrotoxic agent use are recommended.

Another harmful complication of CT contrast is extravasation into the subcutaneous tissue. This is a frequent occurrence, principally in the arm. Rates of extravasation have been up to 0.7% in chemotherapy patients and 11% in a pediatric cohort receiving intravenous fluids (Sistrom 1991). Initial rates of contrast extravasation were reported as 0.2%, but this figure

has increased to 0.24% with the widespread introduction of rapid bolus injections to radiology in the 1990s (Federle 1998). Also the use of rapid bolus automated unmonitored injections has led to larger volumes of contrast extravasation, 58% involve volumes greater than 50 milliliters (Loth 1988).

The potential sequelae of extravasation are numerous and variable, particularly in those suffering from arterial, venous or lymphatic insufficiency. The most important include (Sbitany 2010, Gothlin 2001, and Vandeweyer 2000):

- Compartment syndrome
- Skin sloughing
- Skin necrosis
- Erythema
- Localized swelling
- Induration
- Hyperesthesia

Extravasation is usually caused by an intravenous cannulae slipping out or penetrating through a vein and lying incorrectly in the extravascular space. It is then used for an infusion or bolus administration. The mechanism of toxicity by these media is multi-focal, but the most important factors are the hyperosmolality of these solutions that can lyse surrounding cells in the skin and subcutaneous tissue, mechanical compression by large volumes of extravasate, local vasoconstrictive effects, direct cytotoxicity and secondary infections (Sbitany 2010, Langstein 2002, Upton 1979)

In the event of such an incident, specific institutional or departmental protocols and guidelines should be adhered to which include: frequent limb pulse and sensory examinations, arm elevation, temporary limb splinting, local tissue massage, negative pressure therapies, saline irrigation, inpatient plastic surgical consultation and plane radiography of the affected limb with cannulae still left in situ (Goon 2006, Khan 2002, Yilmaz 2002, Vandeweyer 2000).

The use of low-osmolality non-ionic contrast media for CT studies has reduced the incidence of severe extravasation injuries (Wang 2007, Cohan 1990, Kim 1990). Sbitany et al, reviewed

102 consecutive cases of extravasation retrospectively over a 6 year period, and found that ionic dye was used in 6% of cases and that in 90% of cases less than 100 milliliters of contrast was injected (Sbitany 2010).

Nonetheless the use of iodinated radiological contrast is not without risk to the patient and should be considered by the clinician when requesting imaging and rationalizing resources.

c. **Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is available in multiple formats (T1, T2, gadolinium-enhanced). It produces images that involve axial (2D), coronal and contrast enhanced views (with arterial and venous phases), similar to CT, but with better tissue definition after 3D reformatting (Back 2007, van der Laan 2006a, Hellinger 2005, Ayuso 2004, Cejna 2002, Haulon 2001, Ludman 2000, Thurnher 1997), particularly for assessing thrombus organization (Merkle 2002a, Engellau 1998, Castruci 1995). Advantages of this technique are that it is free from ionizing radiation, doesn't involve the use of nephrotoxic contrast and provides imaging comparable or superior to CT for low flow endoleak detection and surveillance (Alerci 2009, Harris 2009, van der Laan 2006a, Pitton 2005, Ayuso 2004, Wicky 2003, Cejna 2002, Haulon 2001).

The superiority of MRI over CT has been shown by van der Laan et al, when analysis of 28 patients showed a significant ($p=0.01$) increase in endoleak detection (23/35) when compared with CT (11/35) (van der Laan 2006). 3 of the 11 endoleaks on CT were of indefinable type. MRI defined all endoleaks seen on CT and then 12 more. Alerci et al, published similar results in 43 patients, but with a slightly lower number of indeterminate endoleaks (Alerci 2009). Alerci et al's results did not translate into therapeutic consequences for these patients, because none of the endoleaks undetected by CT were associated with an increase in aneurysm sac size.

Gadolinium is the organic compound used as a contrast agent for MRI. It possesses inherent paramagnetic properties to alter magnetic fields around tissues and thus produce improved vascular structural visualization. However its safety is questionable as there have been reports of gadolinium-associated nephrogenic systemic fibrosis in patients with severe renal

impairment (van der Vilet 2011, Back 2007, Sharma 2009, Medicines and Healthcare Products Regulatory Agency 2007) as well as other adverse events (Murphy 1999, Murphy 1996).

Constraints of MRI are its expense (Milner 2006) and availability therefore it is not employed by many centers (Eliason 2008). However, MRI is being increasingly used for pre-operative AAA assessment (Anbarasu 2002) and thoracic stent-graft surveillance (Stavropoulos 2006a, Lookstein 2004). Another critical disadvantage of MRI are local field inhomogeneities and radiofrequency artifacts arising from the induction of eddy currents from the metal when imaging stainless steel endografts (e.g. the Zenith endograft (Cook, Bloomington, Indiana)), mimicking endograft occlusion or stenosis and possibly posing a risk of stent-graft migration (Cantisani 2011, Stavropoulos 2007). These patients must use alternative imaging techniques. In fact it is only applicable for those with nitinol (a nickel/titanium alloy) or elgiloy (an alloy of cobalt, chromium and nickel) stents which have low magnetic resonance and thus no ferromagnetic or thermal effects (Wieners 2010, Stavropoulos 2006a, van der Laan 2004, Insko 2003, Wang 2003, Merkle 2002b, Engellau 2000, Hilfiker 1999). This same rule also applies to patients with pacemakers, intracranial aneurysm clips and also patients with any other ferro-magnetic implants. Finally some patients suffering from claustrophobia may require sedation or a general anesthesia to undergo MRI surveillance, which aren't without inherent risk.

MRI imaging is limited by lower spatial and temporal resolution compromise and thus calcification detection is less reliable when compared with CT. Endoleaks are usually seen on MRI as hyper-intense regions when contrast-enhancement is used, but these may need correlating with T1-weighted images because methaemoglobin formation within the aortic thrombus could mimic endoleaks (Enggellau 1998).

Engellau et al, have shown that MRI can provide detailed information regarding stent-graft position and integrity, changes in AAA morphology and also high flow endoleaks (Engellau 1998). They have also shown that multiphasic studies can be used to look for late-filling collateral pathways.

Authors have reported reliable measurements for aneurysm sac (Ayuso 2004, Haulon 2001) and endograft dimensions (Weigel 2003), but caution is recommended when measuring endograft luminal diameters because thickness may be overestimated, resulting in sac size underestimation (Hilfiker 1999).

Newer MRI techniques such as blood-pool imaging and time-sensitive techniques may make MRI more sensitive in the future (Cornelissen 2010, Wieners 2010, Stavropoulos 2006a, van der Laan 2006b, Ersoy 2004, Lookstein 2004).

The blood-pool albumin-binding contrast medium, gadofosveset, was used to prospectively assess type II endoleaks in 32 patients with nitinol stents (Wieners 2010). All of these patients underwent paired CT imaging which detected 12/32 (37.5%) of endoleaks and MRI scans which detected an additional nine, 21/32 (65.6%). The majority of endoleaks 14/32 detected by MRI were in the steady-state phase following gadofosveset administration in the first-pass phase. The authors judged the diagnostic accuracy of MRI with gadofosveset to be superior to CT in 66% of examinations. Similar findings to this were demonstrated by Ersoy et al, in a smaller study using the blood-pool agent ferumoxytol to detect four low-flow endoleaks not seen on CT (Ersoy 2004).

Draney et al, have shown that the evaluation of native aneurysm sac wall motion with MRI correlates with the presence of endoleaks (Draney 2004). Similar observations have been made by other groups using cine motion (Lee 2007b, van Herwaarden 2006, Hiatt 2004, Faries 2003b, Vos 2003, Malina 1998b). This is an additional method to evaluate translational aneurysmal movement during the cardiac cycle before and following EVAR to correlate with endoleak types (Floris 2003). This technology is also being evaluated in the thoracic aorta (Clough 2012). Complementing this quantitative assessment, Spatial Modulation of Magnetization (SPAMM) sequences can be applied to qualitatively evaluate aneurysm wall motion, characterize endoleaks and demonstrate direction, quantify flow and velocity (Hellinger 2003).

Other future applications for MRI for EVAR surveillance include the detection of ultra-small superparamagnetic iron oxide particles that accumulate in macrophages within atheromatous

lesions (Sadat 2011). These correspond with AAA growth and would decrease post-repair. This technique is in its infancy at present.

d. **Intra-Arterial Pressure Monitoring**

Implantable sensor technology is in its infancy. It offers a non-imaging, non-invasive remote residual aneurysmal sac systolic and diastolic pressure measurements. This is with wireless pressure sensors that are paper clip sized (Phade 2011, Ricco 2011). In other words these devices provide a physiological assessment of EVAR treatment success. They don't require contrast agents or radiation and depending on the device used, may not require the patient to attend hospital.

Initial experience of this technique consisted of direct percutaneous translumbar catheter puncture of the aortic sac to provide pressure measurements in anatomically suitable aneurysms (de Rango 2011c, Dias 2010, Dias 2007, Mozes 2005, Dias 2004, Chuter 1997). Current devices are less invasive, requiring transcatheter placement through a 14 Fr delivery device into the aneurysm sac after EVAR main body deployment. There are two main sensors available (Milner 2006). A third has only been tested on *in vitro* models and a fourth is currently under development:

1. **Impressure Sensor** (Remon Medical Technologies, Caesarea, Israel) – this is an ultrasound-based technology. The sensor is not dependent on batteries or wires. An external monitoring system acts in a manner similar to an ultrasound probe. The pressure sensor is attached to the endograft prior to its insertion.
2. **CardioMems EndoSure Wireless AAA Pressure Sensor** (CardioMems, Inc, Atlanta, GA) – this technology is radiofrequency-based and the sensor contains a sophisticated external antennae and receiver system within a resonant circuit. The sensor is delivered into the aneurysm sac via its own sheath and remains completely separate from the endograft. This is the only pressure sensor with current FDA approval. Initial demonstration of efficacy for this sensor was performed in a canine model (Ohki 2003).
3. **Telemetric Pressure Sensor** (Helmhotz Institute for Biomedical Engineering and the Institute of Materials in Electrical Engineering, RWTH, Aachen, Germany) – tested only in *in vitro* models and is based on a digital microchip which transfers data to an external monitoring station (de Rango 2011c).

4. **Acoustic Pressure-Sensing** (Commonwealth Scientific and Industrial Research Organization, Australia) – this is a new, non-electronic technology that is currently under development (de Rango 2011c). It is based on previous porcine abdominal aorta non-invasive vibrometry measurements of AAA sac tension generated by modulated ultrasound (Mozes 2005).

Serial pressure recordings within the aortic sac are produced and theoretically these correlate with endoleak development and overall graft stability following EVAR. Kwon et al, have used a computational biomechanical simulation model of vascular growth and collagen stress-mediated remodeling to investigate this hypothesis (Kwon 2011). They found that intrasac pressure had a significant impact on post-EVAR AAA size changes and sac remodeling depended on how pressure time changes. An intrasac pressure of 60 mmHg was proposed as the critical value at which AAA remain stable, values above caused expansion and those below resulted in regression. Additionally it was seen that an initial decrease in pressure helped shrinkage even if there was a later pressure increase.

A systematic review of systemic pressure measurements during and after EVAR has shown that stent-graft deployment does not result in an immediate sac size reduction in the absence of an endoleak and sac pressure is elevated (Hinnen 2007). However, mean pressure indices differ widely between studies in the absence and presence of endoleaks. Hinnen et al, also demonstrates that mean pressure indices were not specific to endoleak type.

Chaer et al, used a canine model with type II endoleak to conduct tests assessing the accuracy of a wireless pressure sensor (Chaer 2006). Close correlation was found between the wireless transducer and the control strain-gauge transducer ($p<0.001$), indicating potential clinical applicability in diagnosis of type II endoleaks. Milner et al, have similarly demonstrated the efficacy of this technology using a sheep AAA model with endoleaks (Milner 2004a, Milner 2004b).

Preliminary short-term human data has been promising but more concrete evidence regarding durability and efficacy is pending (Gandhi 2011, Hoppe 2008, Springer 2008, Ohki 2007, Ellozy 2004, Vallabhaneni 2003). Ellozy et al, initially assessed the Impressure Sensor in a small clinical trial at Mt. Sinai Medical Centre in New York (Ellozy 2004). They measured

follow-up pressures with a remote sensor. In patients with completely excluded AAA a significant difference was found between sac and systemic pressures at the time of operation and at 1 month post-EVAR. However, pressures could only be obtained in 15/21 patients in their series (de Rango 2011c, Ellozy 2004). The ratio between sac and systolic pressure was later found to increase over several months in patients without endoleak and so it was demonstrated that EVAR resulted in a marked reduction of intrasac transducer-sensed pressure in patients with aneurysm shrinkage (Ellozy 2006).

The Acute Pressure Measurement to Confirm Aneurysm Sac Exclusion (APEX) trial, enrolled 70 patients in 9 US centers and 3 centers outside, to demonstrate the efficacy of the EndoSure sensor (Ohki 2007). Most patients with low residual sac pressures were shown to correlate well with exclusion and sac shrinkage in the short-term on follow-up, and those with expanding sac sizes had elevated pressures (Milner 2011). However, results were not reported in 14 of the enrolled patients due to "protocol violations", which were typically missed measurements, which the authors explained was due to the "learning curve" associated with the technique (Ohki 2007). Malposition of the sensors, compression artifact and thrombus pressure or attenuation could have also explained these missed measurements (de Rango 2011c, Dias 2007). The data provided by the APEX allowed FDA approval for acute implantation, but approval has not been gained for long-term surveillance (Milner 2011, Milner 2006).

A number of trials have shown pressure sensors detection of type I and III endoleaks, but definitive proof of efficacy is lacking, specifically for type II endoleaks (de Rango 2011c, Hall 2011). Type II endoleaks have been shown to be associated with different sac pressures that can be elevated or reduced depending on specific configurations of aortic collateral branch in- and out-flow channels, making their clinical relevance questionable (de Rango 2011c, Forbes 2011, Kurosawa 2007, Ohki 2007, Ellozy 2004). In Ellozy et al's series an endoleak caused by a lumbar vessel thrombosed at 6 months, but the intra-sac pressure remained elevated (Ellozy 2004). Similarly the APEX trial, showed a less than 30% reduction in sac pressures in patients without any evidence of endoleak at angiography (Ohki 2007).

Pressure sensor technology is in its infancy for surveillance of the thoracic EVAR (Parsa 2010). Most benefit has been seen when applied to the excluded false lumen of a dissection and may provide long-term confirmation of successful treatment (Milner 2006).

Before this technology replaces current surveillance modalities, a clinical trial is required to assess its safety with long term follow-up. A current trial comparing the EndoSure sensor and CT is ongoing. It is unknown if this surveillance modality is cost-effective in the long-term. The pressure sensor costs $3500 and the device reader is $25000 (de Rango 2011c, Kim 2008), which are comparative to the price of the actual endograft itself. There are financial implications for longer operating times and training required to insert these sensors correctly (Parsa 2010). Evidence is required that pressure sensors identify endoleaks earlier and therefore avoid aneurysm-related complications overall.

e. **Other endoleak detection modalities**

i. **Computer analysis of reconstructed CT and MRI data**

Virtual angioscopy and 3D navigation is a novel technique using detailed analysis of CT scans with reconstruction techniques since 1996 (Louis 2010, Davis 1996). These techniques have been used to assess the aorta pre-operatively and determine EVAR suitability and post-EVAR for surveillance in pilot studies. The majority of work in this area has been for the thoracic aorta, however it has been shown to be effective for infrarenal AAA as well. 64 CT slices are reconfigured using 3D software, applying spatial and volume-rendered thresholds to generate endoluminal views. In a series of 103 patients undergoing thoracic procedures, 46 anomalies were detected including: inadequate stent apposition or overlap, stent kinkage, intimal tears and secondary dissection (Louis 2010). This alternative view of the aorta, which resembles the view of the colon on endoscopy (Haigron 2004, Smith 1998), allows precise localization of abnormalities post-EVAR.

3D reconstructions of CT images have been used by other groups to assess a variety of AAA geometric parameters. Georgakarakos et al analyzed 3D reconstructions to investigate the correlation between peak wall stress and the presence of intraluminal thrombus on AAA (Georgakarakos 2010). In a series of 19 patients, they found significant changes in peak wall

stress that significantly correlated with intraluminal thrombus volume ($p=0.03$). In particular they had significant effects on AAA tortuosity ($p=0.03$) and maximum diameter ($p<0.0001$). Similarly, Helderman et al, used reconstructions of CT images to produce 3D modeling and statistics of AAA geometry. They studied expansion rates and wall stress (Helderman 2010) and found that the use of this technology allowed a high predictive rate of aneurysmal expansion at 30 months ($p<0.01$). Local anatomy contributed in 62% and the risk profile in 38% to the aneurysmal expansion rate. This specific technology hasn't been applied to EVAR, but could provide geometric and statistical data to predict complications and potentially replace surveillance in a proportion.

In an attempt to apply these techniques to EVAR, Molony et al, used computerized 3D AAA modeling of CT scans in 10 patients to specifically study EVAR graft migration and hemodynamic drag forces on stents (Molony 2010). They found that neck angulation was the greatest determinant of drag force magnitude ($p=0.009$) and could predict graft dislodgement.

Analysis of data collected from the EVAR 1 (EVAR trial participants 2005a, Greenhalgh 2004) and 2 trials (EVAR trial participants 2005b) has shown common anatomical variants of 756 patients (Brown 2010b) with graft-related complications (179) and reinterventions (114). It was calculated by multivarient analysis that graft-related complications were significantly increased with

- larger aneurysm diameters ($p<0.001$)
- older age ($p=0.04$)
- Larger common iliac diameters ($p=0.011$).

With the use of computer technology and modeling of CT reconstructs of AAA before and after EVAR, these baseline factors could be used to highlight and specifically target individuals at risk of complications for surveillance.

Another surveillance possibility is the use of dynamic CT of the aorta post-EVAR. Rodway et al, analyzed the progression of aneurysmal disease in patients enrolled in the EVAR 1 trial (EVAR trial participants 2005a, Greenhalgh 2004), two years after EVAR and open repair (Rodway 2008). Using a workstation, three levels of the aortic neck was measured in 67

EVAR and 56 matched open repair patients. The EVAR group had a significantly greater size increase in aortic neck ($p<0.001$) when compared with the open group.

A group from the Netherlands have taken this further, measuring pulsatile distension of the post-EVAR aortic neck with dynamic CT (van Keulen 2010a, van Keulen 2010b, van Keulen 2009b). Van Keulen et al, deduced that the aorta exhibits significant changes morphology throughout the cardiac cycle through a systematic review of 25 articles employing dynamic ECG-triggered CT and MRI simultaneous recorded acquisitions (van Keulen 2009b). These techniques offer a significant advantage over the static images that are routinely used for current surveillance as they provide an insight into aortic shape changes throughout the cardiac cycle. They are mostly used for the thoracic segment but do have a role in the abdominal aorta.

Thirty EVAR patients had dynamic CT reconstructed images analyzed over the cardiac cycle; the aortic area and diameter changes were determined at two defined levels (van Keulen 2010a). The cases were divided into three, depending on EVAR stent-graft type. Their findings were that the aorta expanded significantly and asymmetrically throughout the cardiac cycle post-EVAR, and there was no difference depending on which stent was present. Aortic area increased significantly over the cardiac cycle ($p<0.001$) as did diameter changes, but all three EVAR stent-grafts adapted well to the asymmetric aortic shape.

Further work by van Keulen et al, has demonstrated that pre-operative cardiac cycle aneurysm neck distension is significantly associated with stent-graft migration at 3 years ($p<0.001$) and these patients have significantly higher aortic pulsatiliy (van Keulen 2010b).

Hope et al, have described using time-resolved 3D phase-contrast MRI, in what they term as 4D flow, to characterize a type I endoleak (Hope 2009). This technique combines ECG-gated-MRI with DUS velocity data and does not require the administration of any gadolinium based contrast. This technique is still in its infancy and can only be offered in certain academic centers, but is likely to be widely available in future.

These types of advanced imaging using computer geometric reconstructions and dynamic views of the aorta could play a role with post-EVAR surveillance, however further studies

specifically looking at geometric changes in the stented aorta are required. One consideration is that this type of imaging is extremely time consuming currently requiring a number of days to reconstruct the images of a single patient, particularly with virtual angioscopy. With advances in technology the time issue will decrease, but at present it is impractical, remaining experimental.

ii. **Nuclear medicine**

Despite not being used frequently in practice, nuclear medicine scans have been shown to detect endoleaks. Stavropoulos et al, in a prospective study compared CT with technetium-99m (^{99m}Tc), sulfur colloid scans and ^{99m}Tc-tagged red blood cell scans for the detection of endoleaks in 13 patients (Stavropoulos 2006b). 78% who displayed an endoleak on CT were seen on both ^{99m}Tc sulfur colloid and on ^{99m}Tc-tagged red blood cell scans. However 22% of endoleaks seen on CT were not seen on either nuclear medicine scans. The patients with no endoleak on CT also did not yield a positive result with the other scans. This small study showed that nuclear medicine scans were not as sensitive as CT. Refining of the technique may lead to improved sensitivity.

iii. **Blood testing**

Over a number of years studies have suggested venous blood sampling may be able to detect the presence of an endoleak. This will have enormous implications upon EVAR surveillance imaging. Histo-morphological studies have demonstrated that structural alterations within the aneurysmal wall are caused from degradation of matrix proteins by a group enzyme called the matrix metalloprotinases. These are characterized by an elevation in elastolytic and collagenolytic activity (Abisi 2007, Davis 1998, Knox 1997, Shah 1997, Tamarina 1997, Freestone 1995, Thompson 1995, Dorbin 1994). It has been described over the last decade, that there are higher concentrations of matrix metalloproteinase-3 (MMP-3) and -9 (MMP-9) in patients with AAA that can accurately predict the presence of an aneurysm from aortic tissue or a venous blood sample (Hellenthal 2012a, Hellenthal 2012b, Hinchliffe 2012, Lee 2012, Nakamura 2009, Taurino 2004, Lorelli 2002, Sangiorgi 2001, McMillan 1999, William 1999, Dorbin 1994, Newman 1994a, Newman 1994b, Vine 1991).

Sangiorgi et al, performed surveillance CT's and MMP-3/MMP-9 measurements by a sandwich enzyme-linked immunosorbant assay (ELISA) (McMillan 1999) on 45 patients

before AAA intervention (open and EVAR) and for surveillance (Sangiorgi 2001). Both MMP-3 and -9 basal levels were higher in patients with AAA than control subjects. Levels decreased after conventional surgery. After successful EVAR, MMP-3 and -9 levels decreased to a level similar to that of patients who had undergone conventional open repair. However, plasma MMP-3 and -9 levels were higher in patients with endoleaks ($p<0.005$). The authors concluded that in those patients who do not show a decrease in MMP levels after EVAR an endoleak may be present with continuous sac pressurization and aneurysm expansion. Similarly, Hackmann et al, have shown raised MMP levels in association with type II endoleaks (Hackmann 2008).

These findings were replicated by Lorelli et al, who measured MMP-9 before and after patients AAA open repair (26) or EVAR (25) (Lorelli 2002). There were no differences between MMP-9 levels pre-operatively. MMP-9 levels significantly increased after open repair ($p<0.05$) and remained elevated at 3 months. EVAR patients showed a significant decrease in MMP-9 levels at 3 months ($p<0.01$) after successful repair. Eight patients had endoleaks detected on CT after undergoing EVAR and these patients did not have a significant MMP-9 level decrease at 3 months.

Similarly Taurino et al (Taurino 2004), have shown in a small study of open repair (12) and EVAR (9) that MMP-9 levels increased post-operatively and remained significantly elevated in the open group but decreased in the EVAR group at 3 months. This group did not comment on the effect of endoleak with respects to MMP levels. They did however demonstrate that at 3 months the MMP-9 decrease was significant for smokers only ($p<0.05$) and that the levels did not change with non-smokers, throwing potential confounders into the equation for consideration.

More recently Nakamura et al (Nakamura 2009), confirmed a significant reduction of MMP-9 in successful EVAR (22) with no endoleak ($p=0.004$) at 3 months, in contrast those with endoleaks did not show a significant decrease in MMP-9. Those patients who were taking an athero-protective calcium-channel antagonist, azelnidipine (Nakamura 2005), and had no endoleak showed a significantly greater post-operative fall in MMP-9 ($p<0.001$). This effect of azelnidipine on MMP-9 levels has been demonstrated previously in a rat model (Yokokura 2007). These results highlight yet another potential confounder.

These results show that the measurement of MMP may have a clinical value as an enzymatic plasma marker for endoleak detection in EVAR surveillance but refinement of the technique and potential confounders of MMP levels must be considered.

f. **Duplex Colour Ultrasound**

Duplex colour ultrasound (DUS) is an established, widely available modality used to assess vascular morphology and function and serves a key role in screening for suspected AAA (Hartshorne 2011, Lindholt 2010, Hellinger 2005, Ashton 2002, Hendrickson 2001, Scott 2001, Miller 1999a, Grimshaw 1992, Horejs 1988, Shuman 1988). It is a technically demanding investigation that requires specific skills and knowledge by vascular scientists/technologists and interpreting physicians (Taylor 1990, Winkler 1990).

DUS led EVAR surveillance programmes have been adopted by a number of centers, since the first single-institution cohort analysis in the late 1990s. The inherent problem of user dependence impacting on variance in sensitivity and specificity of this surveillance modality has produced marked differences in reliability of surveillance findings (Oikonomou 2012, Sharma 2009, Sandford 2006, Sun 2006b, Arko 2004b, Elkouri 2004b, Hiatt 2004, Sprouse 2004, Raman 2003, Golzarian 2002, Greenfield 2002, McLafferty 2002, D'Audiffret 2001, Pages 2001, Fletcher 2000, Wolf 2000, Zannetti 2000, McWilliams 1999, Berdejo 1998, Kronzon 1998, Sato 1998, Thompson 1998, Heilberger 1997).

Advantages of DUS include

- Non-invasive
- Inexpensive
- Relatively portable, can be performed at the bed-side (Miller 1999a, Miller 1999b)
- No nephrotoxic contrast medium or ionizing radiation.
- Demonstrates aneurysm size
- Allows dynamic arterial flow direction
- Demonstrates velocity in real-time to assess aneurysm wall motion, endograft limb kinkage and patency of access vessels (Karthikesalingam 2012b)
- Distant sites away from the endograft can also be examined with DUS, such as wound complications or post-operative collections

However DUS provides limited information for EVAR patient selection and planning as it cannot demonstrate structural relationships in a 3D format.

DUS AAA assessment is more detailed in comparison to the standard protocol used for a gray-scale abdominal ultrasound study. The aorta is initially viewed using B mode in both the longitudinal and transverse planes (unlike the oblique axis measured on CT which can generate larger dimensions (Foo 2011, Hartshorne 2006, Brown 2004, Raman 2003, Sprouse 2003, Chaikof 2002b, Lederle 1995, Lederle 1994)). Color Doppler is then used to provide dynamic flow information, which CT cannot offer (Carrafiello 2008, Palombo 2003, Greenfield 2002, D'Audiffret 2001). The sac contents should be scrutinized and may demonstrate a heterogeneous mix of echoes caused by an organized thrombus or areas of flow corresponding to an endoleak (Hartshorne 2006). Scanning the abdominal and pelvic arterial tree in such detail is time-consuming, particularly if pathology is found.

With ultrasound the proximal end of the stent-graft can be examined and renal perfusion bilaterally checked. Increasing distances between these fixed landmarks, the renal arteries, and the upper end of the stent on serial scans would imply distal stent migration (Magennis 2002).

Both iliac limbs of the stent-graft should demonstrate blood flow through the metal stent skeleton of the device. Hemodynamically significant stent-graft kinkage, which is associated with graft limb occlusion, will be seen on ultrasound as areas of turbulence on colour imaging with increased velocity on spectral Doppler (Karthikesalingam 2012b, Palombo 2003, Greenfield 2002, Magennis 2002). Imaging the iliac vessels is particularly difficult in obese patients, those with bowel gas and when the iliacs are tortuous (Pearce 2004). Elkouri et al, reported >25% technical DUS inadequacy in their series. Nearly 50% were performed pre-discharge in the first week post-EVAR and affected by bowel distension and obesity (Elkouri 2004b). In these cases, the arterial waveforms may be useful to identify occlusive stenosis. Mazzariol et al, have shown that abnormal arterial waveforms were 100% predictive for detecting stenosis greater than 50% (Mazzariol 2000). More recently Karthikesalingam et al, have shown that patients with increases in the peak systolic velocity of stent-graft limbs are predisposed with an increased risk of limb complications, thus DUS could be used as a predictive tool for complications in surveillance protocols (Karthikesalingam 2012b).

More recently Blom et al, have reinforced these findings in a large study of 496 graft limbs in 248 patients. They measured iliac-limb serial peak systolic velocity, demonstrating a 100% sensitivity and 98% specificity for occlusion ($p<0.01$) (Blom 2012).

Colour Doppler ultrasound also confirms vessel patency and demonstrates endoleaks as a Doppler signal within the aneurysm sac or extrastent flow (Arko 2004b, McWilliams 1999). Pulsatile flow can be traced to the site of origin or patent aortic branch in the case of a type II endoleak, defining the source, aiding reintervention or further surveillance.

Of course it is possible for a patient to have more than one type of endoleak. Small fabric defects can lead to perigraft "jets" of blood which can be seen on colour flow and have been termed microleaks (Matsumara 2001). Conformation of an endoleak must be undertaken using spectral Doppler to determine flow pattern and measure velocity and direction. Color Doppler alone may produce false positive endoleak identification due to artefactual colour spill-over/bleed-over from the graft into adjacent anechoic thrombus (Carrafiello 2008, Arko 2004b, Wolf 2000, Sato 1998). Indiscriminate flashes of color (Doppler noise) are produced in the area of interest by this artifact and diminish during diastole. Endoleaks are relatively uniform, reproducible and their color persists into diastole. These false positive diagnoses can be avoided by optimizing machine settings allowing small, low velocity endoleaks can be imaged. This involves reducing the colour scale (P.R.F), or flow rate and colour wall filter (Hartshorne 2006), and subsequent conformation with spectral Doppler.

A further advantage of DUS is that potential endoleaks can be imaged from a number of different positions for confirmation, and also reducing artifact and false positive findings. Some authors conclude that it is better to pick up all potentially dangerous endoleaks, accepting the fact that some may be false positive findings and instigating further unnecessary testing (Bakken 2010).

Chisci et al, compared two different protocols to investigate the number of secondary interventions in asymptomatic cases prompted by surveillance imaging, reported in 1.4-9% of cases (Chisci 2012). The study protocols consisted of group 1: DUS+CT (376 patients) and group 2: DUS+CT initially then DUS+AXR after 6 months (341 patients). Group 1 freedom from rupture (98.3%), freedom from secondary intervention (82%) and asymptomatic

secondary intervention rate at 3 years (8.8%) were not significantly different from group 2: 98.7% (p=0.456), 83.5% (p=0.876) and 8.5% (p=0.49) respectively. However, estimated costs, radiation exposure and contrast administration at 3 years in group 1 vs group 2 showed that group 2 had a significant 3, 4 and 6 fold reduction in overall costs, radiation exposure and contrast used, respectively (p<0.0001). The authors concluded that the rate of asymptomatic secondary interventions is not affected by the type of surveillance and surveillance based primarily on DUS is acceptable.

Recently Harrison et al, have published results from their protocol of performing CT only when problems are detected by using DUS and abdominal radiographs or when these tests are not diagnostic (Harrison 2011b). In 194 patients cumulative freedom from CT was 65%; mean reduction in radiation exposure of 45 mSV at 3 years; and a mean annual cost reduction of €223 per patient, per year. However, some have noted that if their cost comparisons were made with more common protocol of only CT and abdominal radiography, then their cost savings would be smaller (van der Vlietm 2011).

Palombo et al., have successfully used colour Doppler to deploy EVAR in a case report of a patient with CKD, to avoid contrast administration at all costs (Palombo 2003). Similarly Ascher et al, have used DUS alone for the endovascular repair of popliteal aneurysms (Ascher 2010), femoropopliteal occlusive disease (Ascher 2005a) and also carotid stents (Ascher 2005b), thus eliminating the need for iodinated contrast agents (Mazzariol 2000).

DUS is currently being employed by vascular sonographers and screening technicians to measure aortic diameters in the UK national screening programme, using static anterior-posterior images and electronic calipers (Long 2012, Wanhainen 2011, Earnshaw 2010, Martin 2010b, Manning 2009a, Ellis 1991). There is little controversy about DUS being used for pre-operative evaluation and surveillance of small AAA (Arko 2004b). Intraobserver variability for DUS AAA diameters have been reported from 2.3mm to 5-8mm (Akkersdijk 1994b, Ellis 1991). A recent study assessing diameter measurements of 60 images by 24 subjects concluded that inner-to-inner wall measurements were significantly (p=0.016) reproduced when compared with outer-to-outer (adventitia to adventitia) diameters, so standardization could eliminate error (Abbas 2012, Long 2012, Beales 2011, Earnshaw

2011b, Hartshorne 2011, Arko 2004b, Singh 1998), increasing the success of screening programmes.

There is a high degree of correlation between DUS and CT for sac diameter measurements following EVAR (Pearson correlation coefficient range: 0.88-0.96) (Bakken 2010) and there is a consistent observation, with one exception (Wolf 2000), that DUS underestimates size relative to CT (Keefer 2010, AbuRahma 2005, Elkouri 2004b, Raman 2003). Grimshaw et al, have demonstrated that DUS is accurate when compared with CT in assessing AAA size and that repeatability can be achieved within 3mm between observers (Grimshaw 1992). Bargellini et al, also demonstrated a high agreement (k=0.96) between these two modalities with a mean difference of 2.5mm (Bargellini 2009). Han et al, have also shown that DUS diameter measurements after EVAR correlate well and have a better agreement with centerline 3D CT reconstructions than axial CT (Han 2010). However, many authors have the opinion that DUS underestimates measurements when compared with those taken with CT (Earnshaw 2011b, Manning 2009a, Sprouse 2004, Raman 2003, D'Audiffret 2001, Jaakkola 1996, Lederle 1995, Thomas 1994), but still that the two modalities correlate well. Foo et al, analyzed 5 years of DUS recordings in 123 patients and compared them with matched CT investigations (Foo 2011). They found a significant mean difference between modalities of 2.1mm ($p<0.001$) that was significantly higher at 3.9mm for smaller aneurysms measuring 5-5.4cm ($p<0.001$) compared with 10mm for AAA ≥5.5cm ($p>0.05$). Manning et al, similarly demonstrated in 109 consecutive patients that CT produced significantly larger measurements than DUS ($p<0.001$), that significantly differed from each other ($p<0.001$). They found that aneurysm size did not significantly affect these differences (Manning 2009a).

Others believe that DUS misrepresents changes in sac measurements (Elkouri 2004b, D'Audiffret 2001) and have persisted with CT due to the demand for precise, reproducible measurements. Overall image quality and aneurysm measurement with DUS may be less (mean difference of 2.5-6.5 mm) than those generated by CT, depending on measurement errors and the acoustic window, particularly in the obese patient (Hollinger 2005). To minimize intestinal gas which obscures the ultrasound transmission across the acoustic window thus producing shadowing artifact, some recommend a low-residue diet 1 day prior and fasting for 6-8 hours before undergoing a DUS examination to the patient (Gray 2012, Back 2007, Hollinger 2005, Arko 2004b, Hiatt 2004). It is important to compare intra-

modality trends and measurements to determine sac stability. When using CT as the standard reference, DUS may only correctly identify the trend in 73-77% of examinations (Elkouri 2004b, D'Audiffret 2001).

Variable success has been reported to detect and localize endoleak source, depending on technical factors, imaging protocol and image quality. Reported sensitivities for DUS endoleak detection compared with CT range between 12-100%, with specificities of 74-99% (Oikonomou 2012, Verhoeven 2011b, Bargellini 2009, Manning 2009b, Schmieder 2009, Carrafiello 2008, Sun 2006b, Elkouri 2004b, Raman 2003, Golzarian 2002, McLafferty 2002, McWilliams 2002, Parent 2002b, D'Audiffret 2001, Pages 2001, Fletcher 2000, Wolf 2000, Zannetti 2000, Thompson 1998, Sato 1998, Heilberger 1997). The following can contribute to operator dependence and variability:

- Differences in technique
- Technologist experience
- Diagnostic criteria
- Scanning equipment
- Patient population

When compared to CT, the gold-standard for endoleak detection, DUS has been shown in some series to be inferior (Hellinger 2005) and can miss up to one third of CT detected endoleaks (AbuRahma 2005). The first series comparing these two imaging modalities was published in 1998 and evaluated 100 paired studies (Sato 1998) with a sensitivity of 97%, specificity of 74% for DUS, but a low rate (19%) of technical adequacy and a high rate of false positive findings, thought to be because their protocol omitted the delayed-phase. Wolf et al, in their series had a smaller rate of technical inadequacy (7%) producing an 81% sensitivity, but only used delayed-phase CT in 57% of the included cohort (Wolf 2000). Arko et al, similarly had a technically unsuccessful scan rate of 6% (24/407), principally due to obesity and bowel gas (Arko 2004b).

In a study of 117 patients who underwent CT imaging after EVAR, 28 endoleaks were detected (24%) with a sensitivity of 86% and a negative predictive value of 94%, with only 4 minor leaks missed (Manning 2009b). The authors stressed that DUS is user dependent and that individual institutions should validate their own results. Raman et al, in one of the largest

DUS studies consisting of 281 patients, detected 35 endoleaks thus producing 96% specificity and 94% negative predictive value, but 43% sensitivity and 54% positive predictive value, demonstrating only a modest agreement between the two modalities (Raman 2003). This poor sensitivity and correlation with CT was attributed to the use of older equipment and short imaging times. Other authors have shown similar disappointing sensitivities for DUS endoleak detection of 60% (Bendick 2003), 54% (Badri 2010), 48% (Pages 2001), 42.9% (Raman 2003), 35% (Nagre 2011), 25% (Elkouri 2004b) and 12% (McWilliams 2002).

AbuRahma et al, performed a large study involving 367 paired CT and DUS examinations after EVAR and reported an intermediate sensitivity of 68% (AbuRahma 2005). This is in agreement with a meta-analysis of 711 patients (8 published and 2 unpublished studies) of DUS detected endoleaks with a sensitivity of 69% (Ashoke 2005). Ashoke et al, concluded that DUS did not have the diagnostic accuracy to detect all endoleaks but the diagnostic accuracy would be improved if type II endoleaks were ignored. Verhoeven et al, reiterated this in their small series of 62 patients by demonstrating DUS sensitivity of 66.7%, again this was mostly due to type II endoleaks being missed (Verhoeven 2011b). AbuRahma et al's series agreed with this conclusion because there was a greater sensitivity for type I endoleaks (88%) than type II (50%). In further analysis specifically of the outcome of 11 endoleaks missed by DUS, 2 (both type I endoleaks) required reintervention but both displayed sac enlargement (AbuRahma 2006). Sandford et al, reported a similar sensitivity (64%) only missing 1 type I endoleak with DUS but detected a consequent sac enlargement, so concluded that no clinically significant endoleak was missed, despite DUS not being as sensitive as CT (Sandford 2006).

Schmieder et al reported a 64% sensitivity using DUS, but found equivalence between this modality and CT for the detection of type III endoleaks and a trend towards being superior for type I detection (Schmieder 2009). The authors insightfully noted that the true gold-standard for endoleak detection remains unknown and if it were DUS in their series, then CT would have a sensitivity of 44%! DUS would have a high sensitivity for detecting endoleaks requiring intervention.

The downfall of DUS appears to be with type II endoleak detection (Oikonomou 2012, Schmieder 2009, Stanford 2006). However, for the endoleaks detected, DUS characterizes

them with spectral Doppler which other modalities cannot achieve. Some groups have shown that the use of Doppler waveforms and flow velocities can help predict spontaneous endoleak resolution (Arko 2003, Carpenter 2002, Parent 2002b).

Type II endoleaks can be characterized on DUS as biphasic (high resistant) or monophasic (bi-directional) (Pearce 2004). Using this criteria, Carter et al, evaluated 89 patients who had undergone EVAR (Carter 2000). Endoleaks were present in 12 patients and 2 had false-positive endoleaks on CT, probably due to calcium or stent-graft artifact. Of the 12 endoleaks, 10 were branch endoleaks and 2 possessed both attachment system and branched vessel endoleaks. In this series, the persistent endoleaks exhibited biphasic arterial flow and the mono-phasic endoleaks were more likely to occlude.

Beeman et al, evaluated type II endoleaks and sought to predict features of persistence (Endo 2011, Beeman 2010). Their cohort of 278 EVAR patients revealed 38 type II endoleaks (14%) that were divided into 3 groups dependent on outcome:

1. Spontaneous resolution (n=14)
2. Persistence associated with increased sac diameters (n=12)
3. Persistence associated with either stable or decreased sac diameters (n=12)

Neither location nor intrasac flow velocity were predictive of type II endoleak persistence. However, bidirectional Doppler flow pattern and the presence of more than one type II endoleak were predictive of sac enlargement. The authors conclude that bidirectional Doppler flow reflects the absence of an outflow vessel, thus increasing the diastolic pressure within the sac, predisposing to enlargement. It was recommended that more frequent surveillance and potentially earlier intervention should be conducted in the presence of multiple type II endoleaks or bidirectional Doppler flow.

On the contrary to this, Arko et al, have demonstrated that endoleaks which seal in less than 6 months have significantly lower intrasac flow velocities (75.5±78.8cm/s) than those with persistent type II endoleaks (138.2±36.2cm/s) ($p<0.01$) (Arko 2004b). These velocities were directly related to the patency of the inferior mesenteric artery ($p<0.01$) and if more than 2 paired lumbar arteries were patent ($p<0.001$) on the pre-EVAR CT. Intrasac flow velocities decreased to zero in all patients with sealed endoleaks after 6 months and endoleak resolution

was confirmed with CT. Persistent endoleaks with elevated velocities that were >100cm/s on follow-up did not change significantly over time (Arko 2003).

Using this technique, D'Audiffret et al, distinguished between type I and II endoleaks and achieved a sensitivity of 100% and 95% respectively, yielding an overall sensitivity of 96% (D'Audiffret 2001). Parent et al, reviewed 83 patients with 41 endoleaks retrospectively and defined 5 as type I using both CT and DUS, 18 type II with CT and 36 type II with DUS (Parent 2002b). All type II endoleaks seen on CT were identified by DUS with the added advantage that DUS permitted flow characterization and waveform patterns that predicted persistence or resolution.

Arko et al, demonstrated a good correlation between DUS and CT for measuring sac diameter ($r=0.93$, $p<0.001$), and these recordings were 5mm within each other in 92% of scans (Arko 2004b). These findings are in agreement with the results of Elkouri et al ($r=0.9$, $p<0.0001$) and Raman et al ($r=0.65$, $p<0.01$), reiterating the excellent correlation between CT and DUS (Elkouri 2004b, Raman 2003). The sensitivity of DUS was 81%, specificity 95%, positive predictive value 94% and negative predictive value was 90% in Arko et al's study. All of the endoleaks that were identified with CT and missed by DUS were small, posterior and appeared to be associated with lumbar artery flow.

However, the significance of a type II endoleak without associated aneurysm sac size increase is debatable. There is no association between increase AAA rupture risk and conservative management of type II endoleaks (Rayt 2009). Another prompt for conservative management is that the treatment of type II endoleaks have a high risk of failure and may not alter overall outcome (Rayt 2009).

So far 3 series have been published illustrating results of prospective DUS surveillance protocols (Beeman 2009, Chaer 2009, Collins 2007). Collins et al, reviewed 160 EVAR patients over 5 years undergoing bi-annual DUS with CT in the presence of sac enlargement or endoleak (Collins 2007). 41 endoleaks were identified; 14 of these were seen on 35 CT scans; a further 3 endoleaks were detected on CT scans in patients possessing sac enlargements on DUS. Chaer et al, studied 184 patients with no adverse events as a consequence of a DUS protocol, finding no rupture, device failure or limb occlusions (Chaer

2009). Similarly Beeman et al, used DUS exclusively except for the rare minority of extreme obesity, where CT was then employed (Beeman 2009). They reported a 5.5% false-negative rate for CT compared with 2.5% for DUS (p=0.126), with equivalent sensitivities between the two modalities. On cost-analysis, DUS surveillance resulted in a total reduction of $534356, which amounted to a saving of $1595 per patient per year. Arko et al, have estimated the cost difference at their institution to be equally as significant for CT ($4700) compared with DUS ($1000) (Arko 2004b). A recent commentary by Chaudhuri, supports this view that the use of DUS as first-line surveillance reduces cost without compromising accuracy (Chaudhuri 2012, Gray 2012).

Another form of ultrasound which is increasingly used for EVAR is intravascular ultrasonography (IVUS). This technique has been employed as an adjunct for graft selection, deployment and further delineation of aortic branch position. IVUS has been used more extensively in the thoracic segment, particularly for dissection and true/false lumen identification (Stavropoulos 2006). It can help with complex AAA stent alignment, marking of renal and hypogastric arteries, aortic bifurcation level and accurate distance measurements (Phade 2011, Hoshina 2010, Whitaker 2001a, Vogt 1997). Longitudinal measurements with IVUS have been shown to correlate well with CT and have been used successfully to determine endograft size during deployment procedures (Garret 2003, Tutein Nolthenius 2000).

Hoshina et al, studied 33 patients with renal failure, contrast allergy and anatomical difficulties and found the use of IVUS to reduce contrast angiography ($p<0.01$) and fluoroscopy times (Hoshina 2010). Similar results have been obtained by von Segesser et al, showing less contrast media use for conventional EVAR deployment (190mls vs 0mls in the IVUS group) ($p<0.05$) and that the EVAR group also had a greater fluoroscopy time and radiation exposure (24 mins vs 8 mins) than the IVUS group ($p<0.05$) (von Segesser 2002b).

IVUS can also be used to check the entire length of the stent-graft for endoleaks and apposition to the arterial wall (Pearce 2009, Garret 2003), in particular for subtle endoleaks at the boundary between aorta and graft (Whitaker 2001a). Recently there have been a suggestion for the use of IVUS with EVAR, however its invasive nature makes this unlikely (Stavropoulos 2006, Lipsitz 2001).

Despite DUS series producing conflicting endoleak sensitivity, it is believed by some that DUS surveillance post-EVAR along with clinical signs and symptoms may be sufficient (Nagre 2011, Tomlinson 2007), especially when patient advantage is considered. DUS has been shown to capture a significant majority of endoleaks. This sensitivity is likely to be underestimated by comparison the reference standard of CT, because a proportion of true endoleaks are labeled false-positive due to non-visualization with CT.

DUS fulfils these criteria of a cheap EVAR surveillance modality that does not expose patients to radiation or harm. Also DUS performs well in late, secondary re-intervention for endoleak often in the presence of sac enlargement. At present we are unaware of the number of ruptures associated with DUS only protocols. Encouragingly none are reported in the literature to date. Advances in ultrasound technology, including the use of tissue harmonic (Horng 2009), elasticity (Sandrin 2003, Ophir 1991) and contrast enhancement imaging will further improve the diagnostic power of DUS, reducing its current disadvantages.

CONTRAST ENHANCED ULTRASOUND

In 1968 the technique of contrast enhanced ultrasound was first described by Gramiak and Shah (Gramiak 1969, Gramiak 1968), based on the early observations of Claude Joyner (Feinstein 2009). In the 1960s these early echocardiographers recognized by chance that tiny air bubbles accidentally introduced into the circulation after intravenous injections of agitated saline, produced transient echo enhancement of the ascending aorta and right ventricle (Tinkov 2009, Blomley 1997, Fritzsch 1994, Becher 1988, Kremkau 1970). The finding of enhancement was due to the strong echoes produced by acoustic mismatch between free air microbubbles in the saline and surrounding blood. These were of short duration due to bubble instability and diffused in less than 10 seconds, particularly in the pulmonary circulation.

Forty years after these first reports interest, development and refinement of these techniques is expanding rapidly due to the popularity of a new class of imaging pharmaceuticals; stabilized microbubbles with numerous clinical applications available today.

Conventional B-Mode, grey scale and color or power Doppler imaging provides information regarding both flow direction and velocity. Information about slowly flowing capillary blood flow is not obtainable. The main reason for this is because blood is a weak reflector of ultrasound, thus Doppler based techniques are based solely on the movement of red blood cells to differentiate blood flow from tissues. Contrast enhanced ultrasound imaging (CEUS), views specific intravenously administered blood pool contrast agents with conventional ultrasound imaging, at desired specific target sites. It enhances and defines anatomy and also quantifies tissue perfusion, even at the capillary level in vessels measuring less than 100µm diameter (Leen 2004). The ultrasound imaging equipment uses no ionizing radiation and relies only on acoustic energy to produce a real time interactive imaging modality. The technique is portable, cheap, non-nephrotoxic and already widely available. It doesn't require patients to have a normal renal function and has a very low incidence of adverse effects (Piscaglia 2006, Jackobsen 2005).

The ultrasound contrast agents are composed of 1-10µm diameter air-filled microspheres known as microbubbles, which work as intravascular non-diffusible indicators and provide unparalleled imaging of the intrinsic spatial and temporal heterogeneity of tissue perfusion

(Feinstein 2009, Feinstein 2004). These tiny bubbles are capable of surviving transpulmonary passage to recirculate and produce useful systemic ultrasound enhancement, acting as "surrogate red blood cells" unlike larger molecules which are retained in vascular beds (Granada 2008). The echogenicity of the contrast agent allows reflection of ultrasound waves, and is defined by the contained microbubble gas, while the shell provides stability and defines the size of the microbubble. Microbubble size is important, large bubbles are more echogenic but do not traverse through capillaries. Microbubbles of 2-4μm diameter, smaller than red blood cells, appear to function best for imaging and last for a few minutes to produce grey-scale blood vessel enhancement and increased Doppler signal intensity (Iezzi 2010, Cosgrove 2004, Bauer 2003, Burns 2003, Correas 2001, Blomley 1997, Nihoyannopoulis 1996). Typically 1-2ml of contrast agent is required for an examination, which is far less than the patient receives in a contrast-enhanced computerized tomography or magnetic resonance scan (Libbrecht 2002).

a. Contrast specific imaging

Ultrasound waves cause a compressive then expansive effect on microbubbles. Tissues are virtually incompressible (Cosgrove 2006). Specific ultrasound software exists which is based on the cancellation and/or separation of linear ultrasound signals from tissue and utilization of the non-linear response from microbubbles (Phillips 2004, Averkiou 2003, Phillips 2001, Simpson 1999, Burns 1996, Schrope 1993). The non-linear response from microbubbles is based on two mechanisms. The first is the non-linear response from microbubble oscillations at low acoustic pressure, chosen to minimize disruption of the microbubble and the second is the high energy broadband non-linear response arising from microbubble disruption (EFSUMB Study Group 2008).

Tissues may also produce non-harmonic ultrasonic signals themselves, due to a distortion of the sound wave when it propagates through the tissue. The extent of this harmonic response from tissue at a given frequency increases with the acoustic pressure, which is directly proportional to the mechanical index (MI). Low solubility gas contrast agents (e.g. Sonovue, Optison, Luminity) are characterized by the combination of improved stability with favorable resonance behavior at low acoustic pressure. So using a low MI ultrasound setting allows minimal contrast disruption and tissue signal suppression, thus enabling an effective

investigation to last several minutes (Lencioni 2006, Averkiou 2003, Bauer 2002, Lencioni 2002, Tiemann 1999, Simpson 1999). Contrast-specific software eliminates these signals from tissue and detects only contrast-specific signals. Other air filled microbubble agents, such as Levovist, rely on high pressures to disrupt the molecule and cause a "burst-effect" (stimulated acoustic emission), which causes a significant limitation for real time imaging (Villarraga 1997, Walker 1997).

b. Contrast agents

There are a number of microbubble ultrasound contrast agents differing in their gas core and shell structures. In the USA, there are only two FDA approved contrast agents for clinical use: Optison (GE Medical Diagnostics, Princeton, NJ) and Definity (Lantheus Medical Imaging, Billerica, MA). These agents are approved for cardiac left ventricular opacification only. In Europe, there are four contrast agents currently approved and marketed for radiology, transpulmonary and cardiological uses: Levovist (1996), Optison (1998), SonoVue (2001) and Luminity (2006). However, there have been a number of company takeovers and consequent discontinuation of product manufacturing, such as Levovist in part due to the current volatile state of finances. As of late 2009, SonoVue is now the sole commercially contrast agent available for liver and general imaging in Europe. **Table 2** lists the current and past ultrasonic contrast agents and their specific compositions and stages of development (modified from Feinstein 2009).

Table 2: Present and past ultrasound contrast agents (modified from Feinstein 2009)

Contrast agent name	Manufacturer	Composition	Development stage
SonoVue	Bracco	Lipid/Phospholipid shell Sulfur hexafluoride	Approved for clinical use
Definity	Lantheus Medical Imaging	Pentane Octafluoropropane	Approved for clinical use
Optison	GE Healthcare	Sonicated albumin shell Octafluoropropane	Approved for clinical use
Sonazoid	GE Healthcare	Lipid Perfluorocarbon	Approved for clinical use
Echovist	Schering	Lipid Air	Approved for clinical use
Levovist	Schering	Lipid Air	Approved for clinical use
"None"	Accusphere	Polymer Perfluorocarbon	Clinical development
Imavist	Alliance/Schering		Clinical development
Quantison	Andaris	Albumin Low solubility gas	Clinical development
BY963	Byk-Gulden	Lipid Air (BY963)	Clinical development
Bisphere	Point Biomedical	Perfluorocarbon Polymer bilayer	Clinical development
Sonavist	Schering	Polymer Air	Clinical development
Filmix	Cavcon	Lipid Air	Pre-clinical development
Echogen	Sonus	Surfactant Perflurorocarbon	Withdrawn from development

PESDA	Porter MD/University of Nebraska	Sonicated albumin Perfluoropropane	Not commercially available

The “first” generation air based contrast agents required a high ultrasonic MI setting to enable destructive bubble visualization. These agents only lasted a few seconds in circulation because they lacked a stabilization shell and could not pass through capillaries due to their large size (Tinkov 2009). They could not pass into the left heart chamber unless directly injected there. Echovist (Berlin, Germany), is a stabilized form of the bubble and is being used today for cardiac shunt diagnostics.

The “second” generation transpulmonary contrast agents utilized high molecular weight, low solubility gases for protracted *in vivo* presence. A more stable shell composed of protein, polymer or surfactant (Feinstein 2009, Lim 2004, Schneider 1995), permits a prolonged diagnostic window. These agents were proven to be safe, efficient and an economical non-invasive imaging modality. Despite the increased stability of these agents when compared to the “first” generation agents, the unstable gas cores consisted of air, dissolving within blood in <5 minutes. Examples of second generation agents include; Levovist and Albunex. Levovist is a galactose-based general purpose echo-enhancer, stabilized with a very small admixture of palmitic acid as a surfactant (Lindner 2004, Schlief 1997). Albunex, has its air microbubbles stabilized with human albumin which is particularly good for endocardial border delineation and grey-scale chamber enhancement.

The “third” generation contrast agents require more sophisticated harmonic ultrasound imaging with reduced MI imaging for prolonged *in vivo* signal to noise ratios. The air core has been replaced by gases that less soluble in blood and physiologically inert. The half-life of this generation of microbubbles improved >15 minutes. These agents are specifically labeled, and with increased stability provide quantitative physiological localization or molecular imaging of inflammation and other related disease states (Feinstein 2009).

Finally the fourth generation CEUS agents are being designed as ultrasound-directed, site-specific drug/gene therapeutic systems. These are the focus of a number of researcher's worldwide (Tinkov 2009, Pitt 2004, Unger 2001, Shohet 2001, Ishihara 1984).

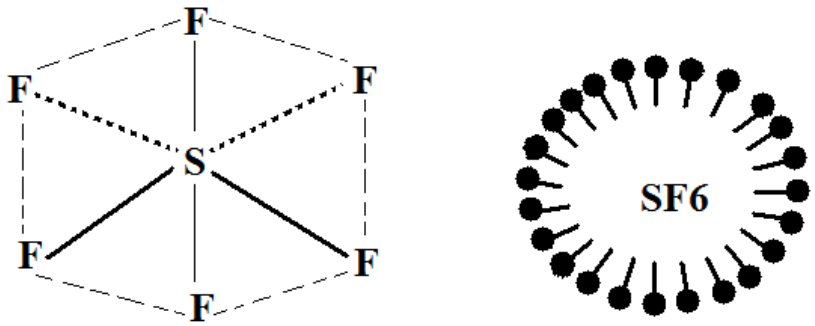
c. **Microbubble contrast pharmacology**

Characteristics and pharmacodynamics of microbubble contrast

Ultrasonic contrast agents are characterized by a microbubble structure consisting of gas bubbles stabilized by a shell to act as blood pool agents (Bernatik 2003, Leen 2003, Bauer 2003, Burns 2003, Basilico 2002). They strongly increase the ultrasound backscatter and the echogenicity of blood flow.

SonoVue is the most widely available CEUS contrast agent available today. It is composed of an innocuous gas sulfur hexafluoride (SF_6) which possesses low blood solubility and is surrounded by a flexible shell, composed of a phospholipid monolayer (Schneider 2000, Schneider 1999, Schneider 1995); **Figure 1** demonstrates the structure of SonoVue. A SonoVue microbubble measures 2.5 microns and in one milliliter of contrast, $5x10^8$ microbubbles may be present (Schneider 1995).

Figure 1: The structure of SonoVue - sulfur hexafluoride (SF_6)



Pharmacokinetics of microbubble contrast

CEUS contrast agents have different pharmacokinetics to CT and MR contrast agents, because the microbubbles are confined to the intravascular space and not cleared from the blood pool into the extracellular space (Piscaglia 2012, EFSUMB Study Group 2008). They have low solubility in aqueous solutions like blood and remain within their phospholipid shells when administered intravenously. The molecules are small enough to pass through the capillary beds, but too large to extravasate into the interstitial spaces (Greis 2004). Thus any echo received from contrast presence during CEUS may be assumed to indicate a vessel (Spinazzi 2001). The lipid composition of these molecules gives elasticity to aid their passage through the microvasculature and to withstand the pulsing pressures generated by ultrasound waves (Greis 2004). During pulmonary passage the microbubble containing gas can diffuse into alveoli and be eliminated by the lungs (Morel 2000).

The active substance of SonoVue is sulfur hexafluoride, which has no known toxic properties. It is an inert medical gas that is rapidly eliminated from the body. It takes 20 minutes for all injected microbubbles to be completely eliminated from the circulation by the lungs. Bolus injection may be repeated after this time (Bokor 2001, Spinazzi 2001, Morel 2000).

SonoVue is stored at room temperature, with a two year shelf life. After reconstitution, a single vial remains stable for six hours. One vial can be used for up to five separate patents, depending on the specific parts being targeted.

The cost to perform a CEUS study includes the cost of the contrast agent (approximately £50 for a 2.5g dose), disposables such as intravenous cannulae, giving sets and needles. In comparison these additional costs for CEUS compared with unenhanced ultrasound differ from CT and MRI investigations, where contrast agent costs are an accepted component of cost already incorporated into departmental budgets. There are also additional time constraints to bear in mind of contrast preparation and administration.

Other disadvantages of CEUS are the short duration of action, extra associated costs, time pressure on already stretched imaging resources. Moreover an inherent reluctance exists to abandon the traditional non-invasive ethos of unenhanced ultrasound.

Safety of microbubble contrast

In general, ultrasound contrast agents are very safe carrying a low incidence of side effects. Unlike other iodinated radiological contrast agents, microbubbles are non-nephrotoxic and do not interact with the thyroid. The incidence of allergic events and severe hypersensitivity is less than current X-ray and comparable to MR contrast agents. The quoted incidence of life threatening anaphylactoid reactions caused by microbubble contrast agents is less than 0.001% (Piscaglia 2006) and 0.01% have been reported to suffer vasovagal or allergy- like reactions a few minutes after administration. In clinical trials, the most frequently reported adverse reactions were headache (2.3%), injection site pain (1.4%), and bruising, burning and parasthesia (1.7%) (Bracco 2005).

However, despite the low risk of adverse events, the use of CEUS should always be considered with the necessary safety mechanisms in place, such as resuscitative equipment and care with "off-label" contrast use. There have been reports of fatal events in a small number of critically ill subjects, who may have a reduced ability to tolerate what are normally considered mild side effects (Piscaglia 2012, EFSUMB Study Group 2008). There are also studies reinforcing the safety of these agents in this group of high risk patients (Jung 2007, Timperley 2005).

In October 2008, the FDA issued an urgent "Black Box" safety restriction warning for ultrasound contrast, specifically those containing Perflutren, following a series of self-reported adverse events in patients with severe cardiopulmonary disease (FDA Alert 10/2007). This included both of the two previously FDA approved agents: Optison (approved in 1997) and Definity (approved in 2001). There has also been safety issues associated with SonoVue in Europe.

There were over 190 post-marketing reports of serious adverse events, including premature ventricular contractions, the release of subclinical myocardial bio-markers (Barnett 2007, Blomley 2007, Vancraeynest 2007) and four deaths shortly following administration of the agents. These adverse events were also identified in animal studies and mirrored the serious cardiopulmonary reactions seen in humans. There was a lack of available pulmonary hemodynamic data in humans and pre-marketing databases generally excluded patients with unstable cardiopulmonary conditions. A theoretical possibility exists that interactions of

diagnostic ultrasound and contrast agents could produce *in vitro* cellular sonoporation, hemolysis and cell death. Small animal and *in vivo* data have demonstrated the interaction between a single gas body and single cell can cause microvascular rupture and petechial bleeding when microbubbles are insonated. This could be particularly worrying when taking place in cerebral and ocular tissues. Nevertheless, under conditions used for diagnosis in humans, such bioeffects have not been observed in the most sensitive tissue of the human body, e.g. heart and brain (Jungehulsing 2008, Cosyns 2005).

Potential toxic effects of contrast agents, such as SonoVue, have been extensively investigated in animals (rats and monkeys), in high doses (up to 20 ml/kg body weight), without toxic effects being found. Sustained high dose administration of 5 ml/kg body weight/day was given over 4 weeks without evidence of chronic toxicity, genotoxicity or reproductive toxicity of clinical relevance.

With this in mind in addition to the lack of a systemic risk assessment, management plan and the failure of the manufacturers to initiate a post-marketing clinical study of product safety, the FDA revised the product label with contraindications.

There was huge concern from physicians, sonographers, nurses and professional guilds (the American Society of Echocardiography and the European Association of Echocardiography) following the FDA's new labeling and limitations for use of ultrasound contrast agents. Clinicians responded with a series of peer-reviewed publications detailing the proven clinical safety record of ultrasound contrast agents. As of May 2009, there were 228611 patient cases cited in publication (Feinstein 2009). Piscaglia et al (Piscaglia 2006), who conducted a large retrospective analysis on a total of 23188 CEUS investigations (the majority were abdominal scans – 92%) performed in 28 Italian centers using SonoVue. They found no fatal events and only four adverse events requiring treatment, giving an overall serious adverse event rate of 0.0086%, which is lower than the reported rates for all other contrast agents, analgesics and antibiotics. These publications and evidence directly influenced the FDA's decision to revise the label changes to reflect the established safety profiles of these agents.

In March 2003, at the EUROSON Congress in Copenhagen a document was proposed to describe essential technical requirements, propose investigator qualifications, suggest study

procedures and steps, guide on image interpretation, establish clinical indications and safety considerations (EFSUMB Study Group 2008, Education and Practical Standards Committee 2006, EFSUMB Study Group 2004). Initially the guidelines were concerned with CEUS liver imaging. Details were finalized at an EFSUMB special consensus meeting in January 2004, Rotterdam, prior to publication in August 2004 in several languages (Xiaoyan 2006, Tranquart 2005). However in 2006, it was proposed that these guidelines be revised to include imaging of additional organs, other than the liver. Hence they were extended and updated for non-hepatic applications (Piscaglia 2012).

d. **Contrast Enhanced Ultrasound Clinical Applications**

Echocardiography

The area where most development of the CEUS technique has been made is in cardiac imaging, specifically echocardiography, allowing direct visualization of the left ventricle and endocardial surfaces. This gives clinical information regarding left ventricular systolic function, filling status and intra-cavitary anatomy. The American Society of Echocardiography and European Association of Echocardiography have both issued position papers and guidelines regarding the use of CEUS (Senior 2009, Mulvagh 2008, Mulvagh 2000). In brief summary the recommendations are that CEUS should be used to improve endocardial visualization, reduce variability and increase accuracy in assessing volumes and ejection fractions. It can also be used to increase reader confidence to confirm or exclude structural abnormalities (Feinstein 2009).

Since the early 2000's, shortly after the initial FDA ultrasound contrast approval, CEUS has been particularly useful in patients who were technically challenging for conventional echocardiography (Yong 2002, Daniel 2001, Reilly 2000). Presently the use of CEUS is incorporated to standard cardiological care for 10-30% of all transthoracic echo imaging, deemed to be technically difficult or uninterpretable.

Kurt et al 2009, reported that the routine use of CEUS for imaging the left ventricle, impacted significantly on diagnostic accuracy and resource utilization, directly benefiting patient management. 14.5% of their cohort (632/4362 patients) required the use of CEUS and its use

prompted a therapy or procedure change for 35.6% of patients, particularly those admitted to the surgical intensive care unit (Kurt 2009).

Vascular Imaging

Following on from the use of CEUS for chamber enhancement in echocardiography, many elements of the vascular tree have been imaged, including aorta, carotid arteries, infrainguinal arteries, bypasses, peripheral venous systems and AV fistula (Clevert 2011a, Clevert 2011b, Young 2010, Clevert 2009a, Clevert 2009b, Clevert 2008b, Clevert 2007b, Clevert 2007c, Kono 2004, Mattrey 1999). In the USA, there is no FDA approval for vascular imaging with CEUS, luckily this isn't the case in Europe, Asia and South America.

The use of CEUS has been identified as a novel imaging technique capable of producing high resolution, real-time images of microvascular perfusion, including angiogenesis. Specifically, imaging of the neovasculature (vasa vasorum) (Doyle 2007, Geiringer 1951) within the carotid artery atherosclerotic plaque has captured world-wide attention (Clevert 2011a, Clevert 2011b, Xiong 2009, Coli 2008, Feinstein 2006, Cosgrove 2004). Neovascularization, defines a critical phase in plaque evolution after which they become more unstable and possibly symptomatic (Cosgrove 2004). Theoretically arterial wall inflammation and hypoxia provide a source of vascular endothelial growth factor (VEGF) generation (Celletti 2001). Neovascularization visible with CEUS occurs (Heliopoulos 2004), from the host arteries to supply the majority of the lipids composing the atherosclerotic plaque (Faggioli 2011a, Fleiner 2004, Moreno 2004, Chen 1999, de Boer 1999, McCarthy 1999). These tiny vessels can be observed as thread-like, moving lines within the plaque. This theory for imaging angiogenesis in carotid plaques is based on the well known concept that VEGF proteins are routinely expressed in a number of disease states such as diabetes, connective tissue diseases, cancer as well as atherosclerosis, where there is inflammatory and hypoxia present (Folkman 1971).

CEUS can be used to image the carotid lumen and wall (independent of blood flow velocity), to identify plaques and ulcers (Clevert 2011a, Clevert 2011b, Faggioli 2011a, Coll 2008, Granada 2008, Chugh 2007, Feinstein 2006, Cosgrove 2004, Feinstein 2004, Macioch 2004, Mattrey 1999), determine intima-media thickness (Feinstein 2009), identify adventitial/intra-plaque angiogenesis of the vasa vasorum (Shah 2007), and for carotid stent surveillance

(Clevert 2011c). CEUS is also now being used to quantify carotid plaque retention of contrast agent, in both symptomatic and asymptomatic patients. The differences between these will be of importance for carotid stenosis stroke risk stratification (Shalhoub 2010b), in conjunction with measurements of internal carotid artery stenosis and presence of focal neurological symptoms.

CEUS can also be used to examine the anterior and posterior cerebral microcirculation, to differentiate between intracranial vessel patency, stenosis, occlusion collateral flow and poor insonation conditions in addition to detection of low blood flow velocities and blood volumes. A reliable diagnosis can be obtained in 90% of acute stroke patients after contrast enhancement with a significantly higher sensitivity and specificity than unenhanced Doppler ultrasound (Piscaglia 2012, EFSUMB Study Group 2008, Nabavi 1998, Baumgartner 1997a, Postert 1997). Several authors conclude that CEUS produces post-stroke information safely, comparable to that of the gold standard of cerebral angiography (Gerriets 2002, Droste 2002, Baumgartner 1999, Kaps 1999, Baumgartner 1997b). Therefore CEUS can provide important, accurate information regarding cerebral vessel patency in the acutely unwell patient. This is critical for treatment regimes, pathways and overall outcomes (Allendoerfer 2006, Baracchini 2000, Kaps 1999, Goertler 1998, Toni 1997).

An important use of CEUS is to monitor the efficacy of thrombin therapy and the recanalization of the obstructed vessel (Alexandrov 2004, Molina 2004, Gerriets 2000, Furlan 1999). Disadvantages of transcranial CEUS are that only the proximal and distal segments of the basilar artery can be visualized, the middle cannot be seen, leaving a diagnostic gap and also the cerebral perfusion and blood flow can only be described, not measured due to bolus shaped variations between subjects.

Hepatic

After the original echocardiological work, the focus changed to the large intra-abdominal organs, with the introduction of contrast specific software to be used in conjunction with the larger ultrasonic probes. The single most important and one of the most common applications of CEUS is hepatic imaging. Conventional ultrasound has poor sensitivity and specificity for focal liver lesions. If a lesion is suspected other contrast using imaging modalities are required for definitive diagnosis. In patients with incidental liver lesions detected on routine

ultrasonography, characterization can be made immediately with CEUS, thus avoiding the wait, anxiety and further costs of further cross sectional imaging modalities (Leen 2006, Bruix 2005). The literature is littered with evidence confirming that CEUS is useful in the characterization of focal hepatic lesions and it shows a strong agreement (Takahashi 2012, Strobel 2008, Konopke 2007, Piscaglia 2007, Nicolau 2006, Wilson 2006, Xu 2006, Dietrich 2006, Bartolotta 2005, Quaia 2004, Wen 2004, Albrecht 2003, Quaia 2003, Solbiati 2003, Jang 2003, Dill-Macky 2002, Beissert 2000, Leen 2002, Harvey 2001, Leen 2001, Tanaka 2001, Kim 2000, Wilson 2000), and some claim superiority (Tranquart 2008, Konopke 2007, Catala 2007, Dietrich 2006, Albrecht 2003, Hohmann 2003, Harvey 2000) when compared with contrast enhanced CT and MR scanning. Some surgeons have also been using CEUS intraoperatively when resecting primary colonic malignancies, to detect spread and also to confirm tumor site prior to hepatectomy. This couldn't be achieved with other imaging modalities (Takahashi 2012, Leen 2006, Torzilli 2005).

Unique to CEUS, when compared to CT and MR scanning, is that it determines lesional vascular patterns, including lesional vessel morphology, distribution, and also their filling pattern, centrifugal, centripetal, or diffuse (Strobel 2008, Wilson 2006). This is achieved by observing the contrast filling of the liver via its unique dual blood supply (25-30% from hepatic artery and 70-75% from the hepatic portal vein) producing three overlapping defined and visible vascular phases:

1) **Initial arterial phase** - mainly used for characterizing focal liver lesions by showing the pattern and degree of vascularity, this starts 10-20 seconds post-contrast administration and lasts 10-15 seconds
2) **Extended portal venous phase** – provides information regarding the washout of contrast compared to normal hepatic tissue, it lasts until 2 minutes after contrast injection
3) **Late washout phase** - mainly used to detect malignancies again by providing details of contrast washout from the lesion in question compared to normal liver parenchyma, this lasts approximately 4-6 minutes post-contrast administration. All of the contrast is cleared from the hepatic parenchyma by either sinusoidal pooling or reticuloendothelial system/Kupffer cell uptake (Yanagisawa 2007, Kono 2002)

The distinction between benign and malignant lesions is made during enhancement in the late phase. Benign lesions retain contrast in the sinusoids and normal capillary beds, leading to a sustained enhancement, whilst malignant lesions rapidly washout contrast in their dense and disorganized arterial beds, appearing hypo-enhanced compared to normal parenchyma. Almost all malignant lesions appear as a conspicuous dark enhancement defect during the late phase.

Disadvantages of CEUS are that very small lesions (<5mm) may be missed, subdiaphragmatic lesions and deep-sited lesions may not be accessible and hypo-echogenicity of the falciform ligament and surrounding fat can cause enhancement defects that may be confused as malignancies (EFSUMB Study Group 2008). Imaging may be very challenging if not impossible in patients with obesity, unfavorable anatomy and also steatotic livers. These contribute to limited ultrasonic wave penetration and compromised image production.

Another novel use of CEUS in the liver has been for pre, peri and post-procedural monitoring of hepatic cell carcinoma treated by percutaneous radiofrequency ablation (Takahashi 2012, Higgins 2006, Vilana 2006, Kiaka 2006, Dill-Macky 2006a, Raut 2005, Tateishi 2005, Sala 2004, Oshowo 2003, Livraghi 2001, Solbiati 2001, Livraghi 2000, Solbiati 1999, Rossi 1996). The real time multi-angle advantages that CEUS offers cannot be matched by any other imaging modalities (Dill-Macky 2006a, Solbiati 2004, Wen 2003, Meloni 2001, Solbiati 1997). It can be used for direct needle/probe placement as it reduces motion artifact and gives a clear image for guidance (Dill-Macky 2006a, Solbiati 2006, Morimoto 2005, Minami 2004, Cosgrove 2004, Choi 2003, Cova 2003, Rhim 2001, Cioni 2001). Often in the initial period after anti-angiogenic treatment, including ablative therapy, lesion necrosis is induced, however, there is no immediate change in the tumor volume. CEUS can demonstrate necrosis, by detecting changes in parenchymal perfusion, and there confers successful ablation (Rehman 2005, de Giorgi 2005, Lassau 2004). Other modalities days or weeks later demonstrate success by showing eventual volume reductions (Vogt 2007, Therasse 2000, World Health Organization Offset Publication 1979). Thus the use of CEUS can eliminate the anxious wait endured by patients to see if their anti-angiogenic ablative therapy has been successful and also gives the treating clinician immediate feedback and an early opportunity to repeat or alter therapeutic strategies to treat residual tumor (Lassau 2006, Solbiati 2004).

Spleen

Contrast studies have been shown to be useful for assessing splenic trauma and also specific focal lesions, such as splenunclus. Similar to the liver, there is a prolonged retention of contrast agents, such as SonoVue, that give a useful late-phase, with even greater intensity than the liver (Cosgrove 2004, Lim 2004, Ota 2004).

Pancreas

CEUS and contrast-enhanced endoscopy has recently well depicted pancreatic vascularity and can be used in the detection and delineation of pancreatic carcinoma, which can easily be confused with chronic pancreatitis (D'Onofrio 2007, Hocke 2006, Masaki 2005, D'Onofrio 2005, Cosgrove 2004, D'Onofrio 2004, Flath 2003, Nagase 2003, Rickes 2002, Koito 1997). Findings correlate favorably with final histological diagnosis (Takeshima 2005, Numata 2005). In the pancreas, uptake of contrast is rapid (25-40 seconds), and produces a bright homogeneous enhancement due to the high vascularity of the organ. It allows delineation of non-vascular pancreatic lesions. However, after injection of contrast, small tumors are actually drowned by microbubbles, so in this situation CEUS is not helpful.

Gallbladder and biliary tree

CEUS applications include gallbladder imaging to assess vascularity for suspected infarction and carcinoma as well as identification of common bile duct filling defects caused by soft tissue masses rather than biliary sludge (Cosgrove 2004).

Renal

In most centers unenhanced grey scale ultrasound is the first line modality for suspected renal disease, such as focal lesions and collecting duct obstructions (Schmidt 2003). There are a number of indications for CEUS imaging in the kidney, including lesion characterization, (benign vs malignant), evaluation of renal perfusion, infarction, hematoma and excretory function in the micro and macrovasculature, which is less accurate with unenhanced ultrasound (Correas 2003).

Once again it should be stressed that CEUS can be used in CKD patients and contraindications to contrast CT or Gadolinium enhanced MRI. Practically, two CEUS contrast doses are required to image both kidneys, and there have been no reports of clinical

side effects in the human kidney to date. CEUS has also been used to investigate renal artery stenosis (Claudon 2000) and as an alternative to nephrostograms (Cosgrove 2004).

Prostate

Prostate cancer is the most commonly diagnosed malignancy and is one of the commonest causes of cancer deaths in men (Greenlee 2001). When CEUS is combined with high frequency transrectal ultrasound probes the prostate can be examined for cancers which is challenging with conventional ultrasound. (Wiijkstra 2004, Halpern 2000). Transrectal unenhanced ultrasound guided prostate biopsies yield positive biopsies in as low as 25% of cores. CEUS can improve this in some operators and reduce the number of biopsies required for a diagnosis (Frauscher 2001, Halpern 2001), but has been also demonstrated to produce a non-significant difference in other operators (Blomley 2001a, Laniado 2001, Kiely 1998). CEUS can be used in the follow-up of hormonal therapy (Paprottka 2010, Eckersley 2002) or to perform local treatment with high-frequency ultrasound (HIFU), radiofrequency ablation or cryotherapy of prostate cancer (Sedelaar 2000). Another novel use of CEUS is with the detection of anastamotic leakage following radical retropubic prostatectomy, limiting the need for conventional retrograde cystography to determine if a post-operative indwelling catheter is safe to be removed (Schoeppler 2010).

Breast and other endocrine tissues

There is evidence that different circulations handle microbubbles in different ways. This is applicable to breast carcinomas, where different types and more advanced stages may enhance for longer when compared to more benign lesions (Zdemir 2004, Uzzan 2004, Martinez 2003, Schroeder 2003, Muradali 2002, Kedar 1996). Some have even advocated that CEUS might be better than histological examination because it covers the whole lesion and so lessens sampling error underestimation (Cosgrove 2004). Another use for CEUS in breast cancer lies with assessing the vascular component of response to systemic anti-tumor and anti-angiogenetic drug regimes.

Recently CEUS has been used for preoperative localization of sentinel lymph nodes after periareolar intraderrmal injection of microbubble contrast in a series of 48 patients with early breast cancer and suspected metastasis (Sever 2009). The breast lymphatics can be visualized by ultrasonography and followed to identify the sentinel draining lymph node and localized

with a deployed guidewire. In this series, this CEUS technique was found to have a sensitivity of 89% when compared with radioisotope (Goldfarb 1998) and blue dye (Govaert 2005). Studies of this same technique using unenhanced ultrasound yielded significantly worse sensitivities (31-63%) in detecting the involved nodes (Alvarez 2006). This technique has also been used in a swine melanoma model to identify sentinel lymph nodes, which produced a similar detection rate of 90% using CEUS (Goldberg 2004).

Other "fringe" applications of CEUS include superficial benign and metastatic lymph node vascularity (Blomley 2004, Bude 2004, Rubaltelli 2004, Moritz 2000), thyroid (Argalia 2002), parathyroid, adrenal glands (Cosgrove 2004) and skin (Rallan 2003) imaging using high frequency and thus high resonance non-linear imaging (Cosgrove 2004).

Exocrine glands

More recently the use of CEUS has been demonstrated for imaging and diagnosis of obstructive and chronic inflammatory salivary gland disease (Zengel 2011, Zengel 2010). The technique of intraductal insertion of CEUS allows visualization of sialolithiasis, duct stenosis, foreign bodies and other rarities to be achieved (Zengel 2011). This technique has been shown in a series of 15 patients with indeterminate pain in one or more salivary glands, offering improved visualization, quicker and more reproducible than conventional radiological imaging and ultrasound (Zengel 2010).

Gynecology

Echovist, is a galactose-based precursor of Levovist that doesn't survive the transpulmonary circulation, like Albunex. Both of these agents have been used in conjunction with transvaginal ultrasound for the assessment of fallopian tubal patency following direct intrauterine contrast injection (hysterosalpingography) (Fleischer 1997, Killam 1997). CEUS has also been used to distinguish between benign and malignant adnexal masses such as ovarian cysts (Cosgrove 2004) carcinoma (D'Arcy 2004) and torsions. The use of CEUS in this scenario could save a number of women unnecessary laparoscopies and laparotomies to investigate solid adnexal masses, (75% of which are benign).

Bladder

CEUS has been given intravesically to children being investigated for vesico-ureteric reflux and hydroureter with voiding ultrasonography (Darge 2007, Papadopoulou 2005, Bosio 2005, Darge 2004, Ascenti 2004, Cosgrove 2004, Berrocal 2001, Darge 1999). The CEUS technique can precisely visualize the urethra, which other examination modalities cannot (Riccabona 2002, Kenda 2001, Darge 2001). Comparative studies between CEUS voiding ultrasonography and traditional radionuclide cystography reveal a significantly higher sensitivity of CEUS in reflux detection (Ascenti 2004, Darge 2004, Vassiou 2004, Galloy 2003, Uhl 2003, Valentini 2002, Radmayr 2002, Berrocal 2001, Kenda 2000, Mentzel 1999, Darge 1999, Bosio 1998). This technique has been in use for over a decade and no adverse side effects have been reported, preventing exposure of children to radioactive substances (Darge 2001).

Transplant and testicular torsion

These agents are indicated in the imaging of parenchymal hypoperfusion, e.g. failed organ transplantation, arterial and venous thrombosis or suspected testicular torsion (Cosgrove 2004, Correas 1999, Schmiedl 1999, Blomley 1997). The lack of nephrotoxicity makes CEUS particularly useful for imaging vascularity and thus viability of transplanted kidneys.

Blunt abdominal trauma

CEUS has been useful in a large sub-group of low energy trauma patients who are hemodynamically stable and suffered blunt trauma. These patients are frequently young and fertile, so the avoidance of high ionizing radiation exposure and iodinated contrast associated with CT is desirable. CEUS has been used to improve the information gained from Focused Assessment with Sonography in Trauma (FAST) scanning, which is usually performed as part of the primary radiology series to detect free peritoneal fluid indicating hemorrhage. CEUS has not been proven to convey more information than CT for trauma, and it is unlikely that it will replace this common trauma investigation. However, a role for CEUS could lie with the routine subsequent follow-up of these young trauma patients with known parenchymal injuries, to avoid repeat radiological examinations.

CEUS has been used to assess hepatic, renal and splenic injuries in a study of 78 patients who were involved with blunt trauma. The results were compared with DUS and CT findings

(Clevert 2008a). In 15/78 patients DUS identified solid organ injuries (8 hepatic, 2 renal and 5 splenic) and CEUS identified 3 additional injuries (2 hepatic and 1 splenic missed using DUS). CT identified 18/78 injuries that corresponded exactly with the 18 that CEUS detected. CEUS revealed active bleeding in real-time on one of the patients further supporting its use in the hemodynamically compromised.

Rheumatoid arthritis

CEUS has been used to prove activity in synovial tissue of patients suffering inflammatory disorders, particularly in rheumatoid arthritis (de Zordo 2007, Rees 2007, Kaiser 2006, Klauser 2005a, Klauser 2005b, Wamser 2003, Carotti 2002, Klauser 2002, Blomley 2001b). Intraarticular synovial membrane inflammation is correlated with disease severity (Taylor 2005, Bodolay 2002, Backhaus 1999, Koch 1998), and CEUS can be used for the assessment of increased microvascularity which correlates with activity. CEUS has been used for these purposes in a number of regions, including; hands, feet, knee and vertebral joints (Klauser 2005a, Klauser 2005b, Wamser 2003, Carotti 2002).

Current & Future Developments

Ultrasound contrast agents were originally developed for diagnostic clinical imaging, and are currently only approved for this purpose. There is a paradigm shift from diagnostics to therapeutic applications on the horizon. The microscopic, gas filled intravascular sphere, that currently serves as a "stealth" agent has the potential to become an ideal vehicle for delivery of site-specific drugs, nucleic acids, proteins and genes to target organs or tumor growth beds abundant in angiogenesis. Thus CEUS could ultimately dramatically improve both the diagnosis and treatment of a number of diseases.

The mechanism of action is at the target site, where ligands attached to the microbubbles, bind to the required organ's specific ligand receptors. A conjugate of therapeutic containing microspheres, under image guidance, are acoustically disrupted with externally applied acoustic energy, provided by high MI ultrasound ("burst-effect"). This results in a disruption of the microspheres and subsequent release of therapeutic contents at the target site (Tinkov 2010, Feinstein 2009, Tinkov 2009, Klibanov 2005, Tsutsui 2004a, Tsutsui 2004b, Klibanov 1999). Ultrasound itself can improve uptake of polynucleotides (Hosseinkhani 2003, Anwer 2000, Huber 2000, Miller 1999c), proteins (Mukherjee 2000)) and drugs (Zderic 2002), by

causing cavitation in the local cell membrane or increasing capillary permeability (Tinkov 2009, Juffermans 2006, Marmottant 2004, Wei 2004, Guzman 2003, Marmottant 2003, Miller 2002b, Miller 2000, Wang 1999, Barnett 1998, Miller 1993), however these effects occur at an impractical, high ultrasound level causing acoustic damage. These applications are termed 'targeted contrast enhanced ultrasound' (tCEUS), and are currently at the preclinical research and development stage to treat inflammation and cancer with gene and drug delivery. Targeting drug delivery to the desired location using microbubble in this way has a number of benefits (Tinkov 2009):

- Minimization of drug side effects and drug interface away from the target site
- Lower the effective dosage
- Improve the therapeutic efficacy in comparison to application of free drugs

tCEUS offers a different approach to drug therapy and allows the microbubble to act as cavitation nuclei. Recently diverse microbubble structure types have been specifically developed to accommodate molecules with a variety of molecular weights and physicochemical properties (Tinkov 2009), such as:

1. Attachment to outer shell surface (via electrostatic or hydrophobic interactions, van-der-Walls forces or merely by physical encapsulation)
2. Intercalation between monolayer phospholipids (amphiphilic molecules)
3. Incorporation in a layer of oil to form acoustically active lipospheres (highly hydrophobic molecules such as paclitaxel)
4. Complexes with smaller particles (secondary carriers)
5. Physical encapsulation in a polymer layer and coating with a biocompatible material
6. Surface loading of protein-shelled microbubbles
7. Entire volume loading of protein-shelled microbubbles

A disadvantage of tCEUS is that the drug loading of microbubbles is restricted because the effective carrying capacity is limited to the shell (surface loading), which comprises only a small proportion of the microbubble volume. tCEUS has been developed to deliver highly potent therapeutics, which can effectively act in the microgram-range, such as oligo- and polynucleotides for gene therapy.

Current areas of research to improve tCEUS have taken numerous forms, which can be summarized by grouping the developments into three simple categories:

1. Improved ultrasound contrast agents
2. Improved ultrasound contrast imaging and detection software
3. Improved tCEUS ligand binding apparatus and receptor targeting strategies

The future of CEUS lies with a combined diagnostic role and delivery role of therapeutics via a non-viral transduction, ultrasound mediated mechanism. Huge financial and time resources are driving this wonderful new development, which will shape medicine in the very near future.

e. **Contrast Enhanced Aortic Duplex UltraSonography Scanning (CEADUSS)**

The introduction of contrast ultrasound has reignited interest in ultrasound use for post-EVAR surveillance and reducing CTs. CEADUSS significantly improves endoleak detection rates compared with DUS, as shown in a number of papers (Giannoni 2012, Cantisani 2011, Verhoeven 2011b, Bakken 2010, Pfister 2010, Clevert 2009e, Clevert 2008d, Giannoni 2007, Bargellini 2005b, Napoli 2004, Giannoni 2003). This is particularly for low flow endoleaks (Iezzi 2010, Henao 2006, Bendick 2003) and less commonly detects aortic rupture (Clevert 2008d, Catalano 2005). Limitations of DUS are overcome by contrast administration e.g. echo reflection by the metallic portion of the stent-graft, presence of calcification, and color signal "spill-over". The addition of microbubble contrast improves the sensitivity of endoleak detection with color Doppler by 33-100% (Gilabert 2012, Cantisani 2011, Clevert 2009e, Iezzi 2009, Karthikesalingam 2009, Clevert 2008c, Clevert 2008d, Napoli 2004, Bendick 2003, Giannoni 2003, McWilliams 2002, Heilberger 1997), but the specificity may decrease by 17-30% (Giannoni 2003, McWilliams 2002). The detection of endoleaks not seen by CT has been demonstrated (Carrafiello 2006, Napoli 2004, Bendick 2003), so a role for CEADUSS as a problem-solving tool in situations of suspected endotension is reasonable. Very recently there have been advocates for elimination of CT completely for EVAR surveillance (Verhoeven 2011b).

CEADUSS is technically very difficult with a steep learning curve. A skilled technologist trained specifically in contrast enhanced imaging should perform the technique to avoid user-

dependent errors to enable an accurate endoleak study. A further problem is that protocols vary widely between institutions. Patient habitus and bowel gas can also interfere with imaging as with DUS.

CEADUSS examinations are performed in the same manner as DUS and it recommended that patients are fasted (Iezzi 2010) with intravenous access established prior to imaging. The aorta and stent-graft are interrogated first by grey-scale and color Doppler, prior to contrast bolus administration. Accurate baseline examinations assessing aneurysm sac morphology (such as high attenuating thrombus), will act as a comparative reference to reduce false-positive diagnosis. Pre- and post-contrast imaging is performed transversely and longitudinally. The required dose of contrast agent for CEADUSS is not yet defined (Iezzi 2010, Henao 2006, Bargellini 2005b, Napoli 2004). Iezzi et al, compared imaging using 1.2 vs 2.4ml to define the optimal dose required for CEADUSS (Iezzi 2009). 2.4ml was preferable as it produced significantly better intensity, duration of enhancement and overall visualization. The phases of CEADUSS can be defined as:

1. Arterial: 10-40 seconds after contrast injection
2. Venous: 40-90 seconds after contrast injection
3. Late venous: 90-300 seconds after injection

In cases of uncertainty or when there is doubt regarding a diagnosis of endoleak, a destruction-reperfusion technique can be used (Iezzi 2010, Carrafiello 2008). This technique involves a brief pulse of high-intensity (high-MI) sound to confirm the presence of contrast media in a suspected endoleak enabling its complete destruction and then reperfusion in real-time (Carrafiello 2008, Clevert 2008d, Dill-Macky 2007, Bargellini 2005b). This provides added hemodynamic information on blood flow and direction. Gorlitzer et al, have used these techniques to successfully assess the post-procedural outcome of translumbar embolisation of type II endoleaks (Gorlitzer 2008) and others have used them as a tool for decision making and treatment planning (Perini 2011, Clevert 2008d, Bargellini 2005b).

Iezzi et al, have published data demonstrating that certain first generation “low-permeable” stent-grafts (e.g. Gore-Excluder) cannot be studied with CEADUSS as well as DUS (Iezzi 2010, Iezzi 2009), at 1 month follow-up, this has been verified by other groups (Cantisani 2011). This is because the durable reinforced ePTFE graft with low-permeability material

layer and nitinol design, preventing stent-graft evaluation until approximately 6 months after deployment.

CEADUSS detected endoleaks appear as areas of high attenuation beyond the graft but within the aneurysm sac, often absent on the baseline unenhanced images. When an endoleak is detected, its origin as well as identification of the inflow and outflow vessels should be characterized. Endoleak enhancement morphology can be either cavity-filling, which is defined as contrast concentration into a pseudocavity within the sac or simple diffuse spreading of contrast agent into the thrombus (Iezzi 2010). Type I endoleaks appear as a huge high-flow leak, synchronous with respect to graft enhancement, spreading from the proximal or distal end of the prosthesis into the thrombus in a cranial or caudal direction. Type II endoleaks are more pronounced in the periphery of the sac with little or no contact with the stent-graft, commonly in a postero-lateral position and occur in delayed time. CEADUSS allows angiodynamic delineation of these leaks and directional flow can be characterized to identify the causative source. Type III endoleaks appear strictly adjacent to the prosthesis, with a delayed contact with margins of the sac and without opacification of collateral arteries, but flow from the graft to the periphery (opposite to type II). Type IV endoleaks appear similar to type II's with CEADUSS, so should be diagnosed by excluding the other endoleaks (Iezzi 2010).

The first description of CEADUSS in the literature, using Levovist, a first-generation agent, was published in 1997, comparing 113 patients with CT (Heilberger 1997). Only 1 endoleak was missed by CEADUSS (attributed to bowel gas), yielding a 97% sensitivity, however 3 type II endoleaks were detected that were not identified by CT. The authors suggested that CEADUSS may have a higher sensitivity for type II endoleak detection than CT.

The advent of second-generation agents has substantially increased the diagnostic accuracy for endoleak detection (Gilabert 2012, Carrafiello 2008, Giannoni 2007, Carrafiello 2006, Dill-Macky 2006b, Henao 2006, Bargellini 2005b, Martegani 2004, Napoli 2004, Bendick 2003, Giannoni 2003). Carrafiello et al, found in a series of 52 patients that CEADUSS with SonoVue detected 4 slow-flow type II endoleaks that were missed with CT (Carrafiello 2008). The author concluded that CEADUSS should be the imaging modality of choice for surveillance in cases where there are type II endoleaks. Previously this group showed that

CEADUSS was able to confirm different endoleak types accurately on series of 10 patients (Carrafiello 2006). This conclusion has been reiterated by Giannoni et al, following their study of 30 patients (Giannoni 2007).

Three subsequent smaller series have produced CEADUSS sensitivities of 100% (Clevert 2008d, Henao 2006, Bendick 2003, Giannoni 2003) and similar positive results have been achieved by others (Gilabert 2012, Motta 2012, Iezzi 2009, Dill-Macky 2007). Bendick et al, in a study of 20 patients using CEADUSS (using the discontinued agent Optison) found 8 endoleaks, of which 2 were type I endoleaks not detected by CT, confirmed by conventional angiography (Bendick 2003). In this series no false positives were found due to the use of digitally encoded tissue harmonic imaging suppressing artifact, described by others (Iezzi 2010, Brannigan 2004, Dill-Macky 2002, Wilson 2001). Similarly Giannoni et al, identified all endoleaks detected by CT in their series of 26 patients using CEADUSS in addition to 16 type II endoleaks missed by CT, displaying unchanged or increasing sac sizes (Giannoni 2003). Napoli et al, showed accurate detection of type I, II and III endoleaks with CEADUSS and identified two endoleaks not seen by CT. Unfortunately these endoleaks were not classified because as they were diffuse sac enlargements only (Napoli 2004).

Iezzi et al, found a false positive rate of 10% in their series of 84 patients (Iezzi 2009). They believed that these four patients with false positive endoleaks detected using CEADUSS >150 seconds after contrast injection were all low flow leaks thus could be missed false negative CT findings, implying increased diagnostic accuracy of CEADUSS. Bargellini et al, have characterized 18 (44.4%) CEADUSS endoleaks that were missed by CT to be hyperdynamic or slow leaks (Bargellini 2005b), these findings have also been confirmed *in vitro* (Schurink 1998).

Henao et al, developed a novel contrast (Optison) infusion technique to increase contrast circulation concentrations as opposed to using a bolus injection as employed by all other CEADUSS investigators (Henao 2006). Their study of 20 men identified 9 endoleaks (1 type I and 9 type II) with this technique of which only 6 were identified with CT. The three endoleaks missed by CT were all type II. This continuous infusion technique improved scanning in obese patients and those with bowel gas but was relatively expensive, because it requires specific equipment and larger amounts of contrast.

Bosch et al, performed 127 paired investigations on 83 consecutive EVAR patients (Bosch 2010b) and found CEADUSS detected significantly more endoleaks (53% of cases), of which the majority were type II, compared with CT (22%). The number of observed agreements was 77/127 (61%), which is a low level (kappa value 0.237), but CEADUSS was as accurate as CT for assessing sac diameters, demonstrated by a low coefficient of variation (8% and 8.6% respectively). Interobserver variability for sac dimension measurements was low using CEADUSS, disproving this common criticism of ultrasound investigations.

Similarly Motta et al, studied 88 consecutive patients prospectively with triple-phase-CT and CEADUSS (Motta 2012). Their results demonstrated a high correlation between these modalities for sac diameter and a specificity of CEADUSS of 100% for both the detection of endoleak and graft patency. However they found the sensitivity of CEADUSS to be 91.89% for endoleak detection and 72% for graft patency and proposed a protocol for surveillance alternating CT with CEADUSS.

Perini et al, have published the largest study of CEADUSS which evaluated 395 patients with CT (Perini 2011), after earlier experience with the technique (Deklunder 2009). The two modalities demonstrated a good agreement in sac diameter evaluation (mean diameter 54.93mm with CEADUSS vs 56.01 for CT) and detection agreement in endoleak was 359/395 (90.89%). The same type I and III endoleaks were detected by both modalities, suggesting equivalence. CEADUSS detected a higher rate of type II endoleak compared with CT, which the authors interpreted as a higher sensitivity for true low-flow endoleaks and not false-positive findings. CEADUSS detected a higher number of endoleaks, but this difference was not statistically significant.

The only comparison in the literature of the four main surveillance imaging modalities; CT, MRI, DUS and CEADUSS, has been performed by Cantisani et al (Cantisani 2011). Their prospective comparative analysis included 108 consecutive patients with 24 endoleaks (22%) identified. These consisted of 22 type II and 2 type III. The results were as follows:

	CT	**MRI**	**DUS**	**CEADUSS**
Sensitivity	96%	100%	58%	93%
Specificity	96%	100%	83%	100%

CEADUSS was found to allow better classification of endoleaks in 10 patients compared with DUS, in 2 patients compared with CT and in 1 patient compared with MRI. The authors concluded that CEADUSS is significantly better than DUS ($p<0.001$), more accurate than CT and possesses a similar accuracy to MRI in detecting endoleaks.

McWilliams et al, remain the only group to report a marginal sensitivity of 50% using CEADUSS in their study of 53 patients (McWilliams 2002). The contrast agent used, Levovist, has since been discontinued and is inferior to the newer generation microbubble agents (Giannoni 2012, Schlief 1996). They demonstrated that DUS endoleak detection was improved with contrast, but still 9/21 type II endoleaks in their series were missed that were detected on CT. CEADUSS produced 19 cases of false positive endoleaks in this series. Earlier data by this group on a smaller series of 18 patients showed CEADUSS to have a sensitivity of 100% after detecting 3 endoleaks that were not seen with CT, compared to only 1 detected using DUS, (sensitivity 33%) (McWilliams 1999).

With a huge amount of mixed results for both DUS and CEADUSS, Mirza et al, conducted a bivariate meta-analysis of available studies to determine the diagnostic accuracy of these modalities to detect endoleaks. CT was taken as the gold-standard (Mirza 2010). Analysis of endoleak sub-type was not conducted during this study (de Rango 2010). 21 studies of DUS in 2601 patients and 7 of CEADUSS in 288 patients were examined. The pooled sensitivity of DUS endoleak detection was 0.77, with a specificity of 0.94 and sensitivity of CEADUSS was 0.98 and specificity 0.88. A high false-positive rate of CEADUSS compared to CT was attributed to possibly represent its higher sensitivity in detecting true low-flow endoleaks, as has also been stated by others (Mirza 2010, Napoli 2004, Bendick 2003).

The authors concluded that whilst DUS has a poor sensitivity, CEADUSS is highly sensitive. Caution was advised with interpretation of these findings due to heterogeneity throughout the analyzed trials, principally with variable operator dependency. CEADUSS studies were more recent than DUS studies, therefore the better results with contrast may be caused by newer technology and better equipment bias. This opinion is partially based on the findings of an earlier systematic review of 19 CEADUSS studies by Sun et al, who found this technique to be promising but required further assessment (Sun 2006b).

CEADUSS false positive endoleaks not detected on CT have huge implications for more invasive investigations, further management, more intensive surveillance protocols and a greater burden to service provisions overall.

Dirk-André Clevert from Munich, is one of the pioneers of CEADUSS and he has published widely regarding the technique (Clevert 2011d, Clevert 2011e, Kopp 2010, Sommer 2010b, Clevert 2009a, Clevert 2009b, Clevert 2009c, Clevert 2009d, Clevert 2009e, Clevert 2009f, Horng 2009, Clevert 2008c, Clevert 2008d, Clevert 2008e, Clevert 2007b, Clevert 2007c, Wein 2007). In 2008 his group published the first report of EVAR solely using CEADUSS and intra-procedural angiographic fluoroscopy without the use of any iodinated contrast media in a patient with CKD (Clevert 2008e). After this, the technique has been evaluated in a further 17 patients (Kopp 2010). The technique uses intra-operative CEADUSS to localize the stent-graft proximal and distal landing zones, occlude endoleaks and delineate vascular anatomy, particularly the lowest renal artery origin. Proximal landing zones were correctly identified in 14/17 (82.4%) and the iliac bifurcation in 21/24 (89.3%). Time for exposure to radiation, contrast media, number of intraoperative angiographies and post-operative CT and MRI surveillance were significantly reduced when compared to a control group of 20 standard EVAR patients. The intraoperative CEADUSS group detected more endoleaks than the conventional EVAR group (8/17 vs 4/20; p=0.08). This technique is technically very difficult but nonetheless extremely promising for the future of EVAR and improving patient safety.

Another novel uses of CEADUSS includes combining the technique with IVUS to offer even greater vessel detail. Ruiz et al, have described contrast-enhanced-IVUS for the assessment of coronary plaque neoangiogenesis and characterization of atherosclerotic plaques, specifically imaging the vasa vasorum microvasculature (Ruiz 2012). The next stage for this technology will be to test stent-grafts and endoleaks.

AIMS OF THESIS

AAA are common and responsible for a substantial number of hospital admissions, carrying a high mortality mostly due to aortic rupture and exsanguination. For these reasons and because AAA can safely be detected with screening, a national programme is being implemented throughout England, to detect the disease and treat when asymptomatic before a patient presents as an emergency.

The treatment of AAA has historically carried a significant morbidity and mortality when conducted with open repair. Newer laparoscopic techniques have lowered complications but EVAR has dramatically altered AAA management and vascular service provision as a whole. EVAR benefits patients in a number of ways and also allows those previously deemed unsuitable for repair to be treated.

However, experience to date has revealed that up to a quarter of patients in some series, need re-intervention to ensure aneurysm sac regression and prevent death from rupture. It is mandatory for all EVAR patients to participate in life-long surveillance programmes. The long-term durability of the technique and ever evolving stent-technology is still being assessed.

Several imaging modalities have been used to detect complications, principally endoleaks and graft migration. There is no consensus for surveillance timings or modality to be used. CT has been the gold-standard, principally due to its use in the early EVAR studies and their follow-up protocols have been widely adopted, but 20 years later we have not really moved on. CT surveillance is expensive, exposes patients to nephrogenic contrast and large amounts of radiation. A solution to reduce the large financial burden on the NHS and the impact on diagnostic provisions caused by EVAR is needed.

A number of investigators have proposed DUS as a primary mode of surveillance, however the literature possess a number of conflicting statistics for this modality with widely varying sensitivities and specificities compared with CT, leading many to doubt its accuracy. More recently, the addition of microbubble contrast enhancement which safe, well tolerated, cheap

and involves no use of radiation or nephrotoxic contrast agents, has been demonstrated to be superior to DUS.

The principle aim of my thesis is to investigate the use of DUS and CEADUSS to detect endoleaks. I intend to study what operator and physical properties have an effect upon endoleak detection. I wish to assess the effect of endoleak plan position, distance from the stent-graft, flow rate and operator experience on detection. My expectations are that endoleaks in the anterior plane position would be more easily detected than those place laterally and those posteriorly detected the least due to greater distance traversed by the ultrasound waves and thus poorer images and identification. I wanted to see if endoleaks positioned further away from the stent-graft were more easily identified than those nearer or superimposed, similarly to Szucs-Farkas et al's findings (Szucs-Farkas 2011). It is well known that the endoleaks often missed are those which are low flow, so I was expecting by analyzing flow rate was the faster ones to be detected more readily than the slower ones. Lastly DUS is well known to be operator dependent and I wanted to see the effect of experience on endoleak detection expecting the novices to be worse at endoleak detection than the more experienced.

My investigations will be conducted by using DUS and CEADUSS in the laboratory setting and then I intend to use CEADUSS clinically to translate the techniques learnt from my experiments. To do this, I aim to construct a laboratory EVAR phantom model with a variable endoleak. I will use the phantom to investigate how endoleak velocity, position or distance from the main stent-graft effects detection. I also want to know how the use of CEADUSS alters endoleak detection when compared with DUS and if the use of microbubble contrast will improve EVAR surveillance protocols. Before conducting any CEADUSS experiments, preliminary experiments will be required to decipher the behavior of microbubble contrast in this *in vitro* system.

Once laboratory experiments are completed, I aim to conduct a pilot study on a small subset of EVAR patients with either known endoleaks, as detected by CT, but who had normal or indeterminate DUS surveillance examinations. I intend to translate the techniques learnt from the laboratory experiments to the clinical setting and see if the addition of microbubble contrast can reveal the missed or indeterminate pathology in these patients.

The ultimate aims of my thesis are to try and explain in what circumstances DUS detects endoleaks best and to try to define when it should be used for surveillance. I also want to further investigate how CEADUSS similarly performs and compare this to DUS, to attempt to define a role for it in post-EVAR surveillance.

SECTION 2

ORIGINAL WORK

CHAPTER 1

A LABORATORY ENDOVASCULAR STENT PHANTOM AND PRELIMINARY CONTRAST EX-VIVO DECAY AND BRIGHTNESS EXPERIMENTS

ABSTRACT

A laboratory EVAR phantom model with a variable endoleak was constructed to assess the limitations of DUS and CEADUSS as a surveillance modality to replace CT imaging. The phantom was constructed in conjunction with Barts and The London departments of Clinical Physics and Vascular Surgery.

The EVAR phantom contained an endoleak with variable velocities (fast/slow), positions (near/far) and planes (anterior/lateral/posterior). Experiments were initially conducted using DUS, then modifications were made to incorporate microbubble contrast administration and implement CEADUSS.

Before implementing CEADUSS contrast studies were conducted to investigate the behavior of microbubbles *in vitro*. Microbubble contrast didn't decay ($p=0.27$) over a period of 16 days. At 2 months it was still detectable within the phantom system. This implies that the sole degrading factor to reduce endoleak detection was ultrasound.

To investigate microbubble brightness and decay I conducted two experiments exposing contrast to continuous ultrasound. The first experiment had an exposure time of 167.18 minutes and showed a significant linear reduction of contrast brightness with time ($p<0.0001$). The second experiment had greater clinical relevance as it represented the exposure time required to test each subject in future studies (62.17 minutes). This showed a non-significant change in brightness. Combining both sets of results show that ultrasound significantly ($p<0.0001$) reduced the brightness of contrast over time with continuous ultrasound exposure.

With this established, the EVAR phantom was ready to determine the capacity of DUS and CEADUSS for endoleak detection, through testing subjects in further studies.

INTRODUCTION

Ultrasound techniques can be evaluated *in vitro* with the aid of laboratory phantoms (Garret 2003, ICRU 1998) or animal models. Animal experiments to evaluate EVAR include canine aneurysm models that reproduce endoleaks (Matsunaga 2012, Tsui 2010, Lee 2007b, Chaer 2006, Trocciola 2006, Mousa 2005, Rhee 2005, Dayal 2004). For example in three dogs, a jugular vein patch was attached around the aorta and iliac arteries, producing an aneurysm amenable to stent graft implantation. Collateral vessels were specifically preserved to produce a type II endoleak (Lerouge 2004). Doppler ultrasound and angiography follow-up were performed to screen for endoleaks, which were confirmed histologically at autopsy. Similarly a porcine model of AAA has been described in the literature (Suk 2012, Bosman 2010, Liu 2009, Whitbread 1996). A type II endoleak after EVAR has been recreated in eight pigs using a Dacron patch, with preservation of the lumbar arteries (Diaz 2004). Indwelling aneurysm sac pressure transducers and CT confirmed satisfactory stent position and the presence of endoleak. Porcine aneurysm model are relevant as their dimensions are similar to that of a human and can accommodate a range of EVAR grafts.

Aortic phantom models predominantly consist of a prosthetic aneurysm placed in an artificial circulation system (de Lambert 2012, England 2012, Hoskins 2008, Mozes 2005, Poepping 2004, Dabrowski 1997, Petrick 1997). Latex bench models of aneurysms with an endovascular stent have been used for investigation of aortic sac pressure, particularly with endotension (Gawenda 2004, Gawenda 2003).

Our unit aims to construct an EVAR phantom model with a simulated, variable endoleak. Variables include flow rates, planes and position of the endoleaks with respect to the stent. The simulated endoleak could represent a type I, II or III endoleak when velocity and plane alterations were considered, and position measurements would give further information regarding to type II endoleak detection. With this model established I want to determine the capacity and limitations of DUS and CEADUS endoleak detection. Prior to this I will evaluate the behavior of microbubble contrast in our *in vitro* phantom model, to see if the actual phantom and its mechanisms for pulsatile flow cause degradation of the contrast that would thus effect my experimental results interpretation.

METHODS

Development and construction of a laboratory EVAR phantom model

In conjunction with physicists, engineers and a senior vascular ultrasonographer at the Clinical Physics department at Barts and the Royal London NHS Trust, a tissue-mimicking phantom model with endovascular stent and simulated endoleak was built. Requirements for the phantom were numerous but included pulsatile flow for DUS assessment and a delivery system for microbubble contrast administration.

We designed two independent flow circuit systems running in parallel. A commercial Doppler fluid (ATS model 707 Doppler Test Fluid, ATS Laboratories, Bridgepoint, USA) composed of glycerine and distilled water represented the phantom's blood flow.

One flow system had a fixed pulsatile flow rate with an EVAR stent-graft. I chose an Endurant aortic stent-graft (Medtronic) for its bare suprarenal fixation anchoring pins and M-shaped laser cut nitinol stent skeleton which was electro-polished for durability. This was highly flexible, adapted without kinking to tortuous anatomy, allowing its incorporation into our flow system network with ease. The stent fabric was a high density multi-filament polyester graft, anchored to the nitinol skeleton by ultra-high molecular weight polyethylene sutures (claimed to be three times stronger than conventional sutures by Medtronic). The outer stent diameter was 24mm.

Pulsatile flow was achieved with a double banded peristaltic pump (Watson Marlow 620U). Each band rotated 45 times per minute, so when combined, the peristaltic flow is comparable to human blood flow at a rate of approximately 90 bpm. The flow of Doppler blood-mimic testing fluid at the EVAR stent was 14.4 cm/second, an average velocity of 3900 ml/minute. This is equivalent to 90bpm. At rest the average adult heart rate is 60-100bpm, usually increasing with age and lesser physical fitness. Thus a pulsatile flow rate of 90bpm was comparable to that of the older AAA patients needing EVAR.

The second circuit was smaller with a variable non-pulsatile flow rate from an IVAC volumetric pump representing an endoleak. The endoleak consisted of a c-flex (thermoplastic

elastomer) tube 2mm in diameter, running diagonally to the main vessel with variable flow rate. I was assured that the ultrasound properties of this 2mm tubing were minimal and would not significantly affect doppler blood mimic fluid or SonoVue microbubble contrast detection after contacting Saint-Gobain Performance Plastics Regulatory Affairs Department who had access to data from the FDA Material Master Files. I was not allowed a copy of this information. Searching the literature I found supporting data that the acoustical properties of this material were similar to human blood vessels (Martin 2009, Martin 2007, Pfaffenberger 2005, Hoskins 2000, Kollmann 1999). C-flex tubing has a density of 886 $kg \cdot m^{-3}$, acoustic velocity of 1,553 $m \cdot s^{-1}$ and attenuation of 28 $dB \cdot cm^{-1} \cdot MHz^{-1}$, compared to 1,000 $kg \cdot m^{-3}$, 1,540 $m \cdot s^{-1}$ and 0.5 $dB \cdot cm^{-1} \cdot MHz^{-1}$ for tissue (Hoskins 2000), thus the effects on my experiments would be minimal so I did not experiment to explore this factor further.

The phantom EVAR stent-graft was contained within Perspex housing filled with an agar-based tissue-mimicking material (Brewin 2008, Zell 2007, Bude 1995, Rickey 1995, Bush 1983, Madsen 1982, Burlew 1980, Madsen 1978). The Perspex housing had an acoustic window filled with distilled water to represent a viewing platform and coupling material to allow ultrasonic imaging of the contained stent-graft and endoleak. Step by step diagrams of the proposed phantom model are shown below as are photographs of its production (**Figures 2-6**).

Figure 2: An initial diagram of the proposed phantom model

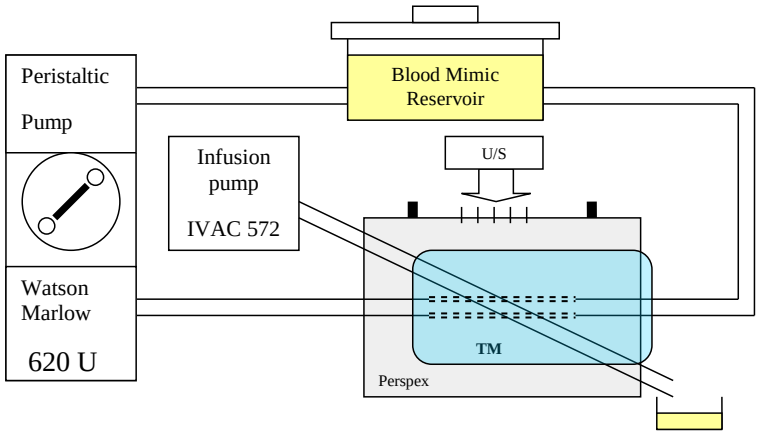


Figure 3: Design plans for the proposed phantom model

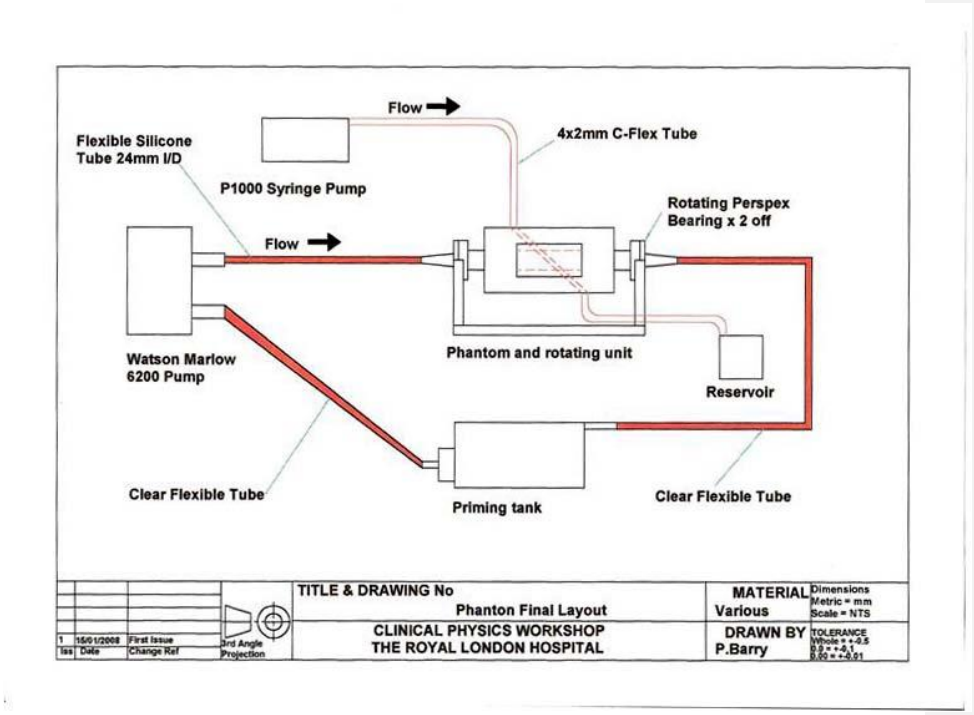


Figure 4: A view of the unfilled phantom housing showing the two adjacent flow systems passing obliquely to each other

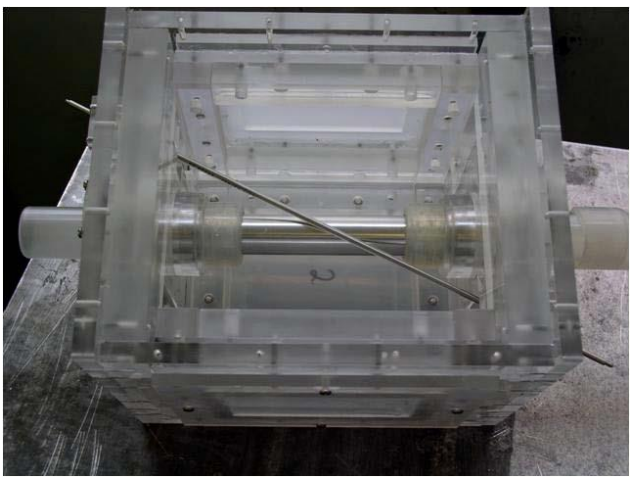


Figure 5: Showing the EVAR stent after incorporation to the large flow system as it passes through the phantom

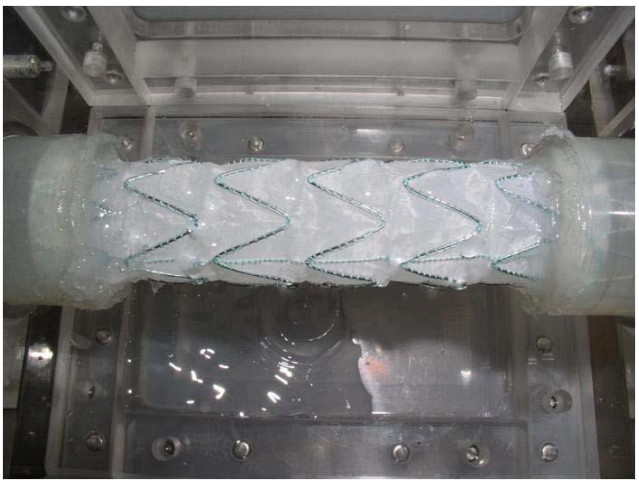
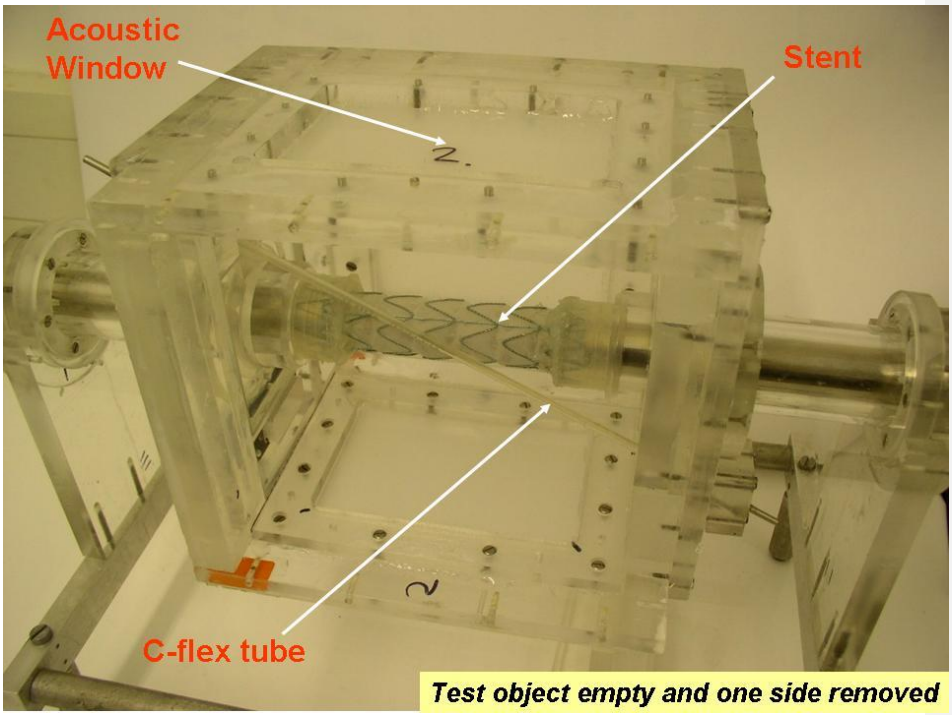


Figure 6: A photograph of the final phantom model unfilled



The following images demonstrate the laboratory set-up with two parallel (large and small) circuits (**Figures 7-25**).

Figure 7: The laboratory set up of ultrasound machine and phantom with two independent flow systems

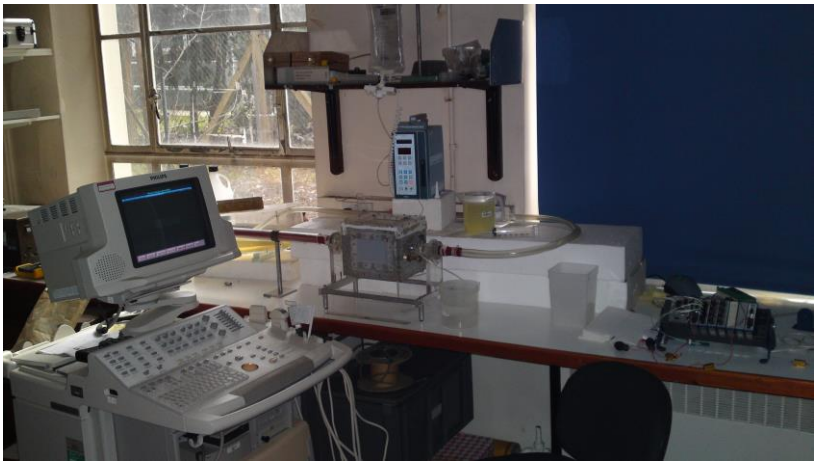


Figure 8: The laboratory set up of ultrasound machine and phantom with two independent flow systems

Figure 9: Doppler blood-mimic reservoir of the large (EVAR stent) flow system

Figure 10: Doppler blood-mimic reservoir of the large (EVAR stent) flow system

Figure 11: Doppler blood-mimic fluid leaves the reservoir and enters the dual band pump, achieving pulsatile flow

Figure 12: Fluid flows from the pump to the EVAR phantom, rate of 90bpm

Figure 13: Proximal entry flow to the EVAR phantom

Figure 14: Birdseye view through the ultrasound viewing window

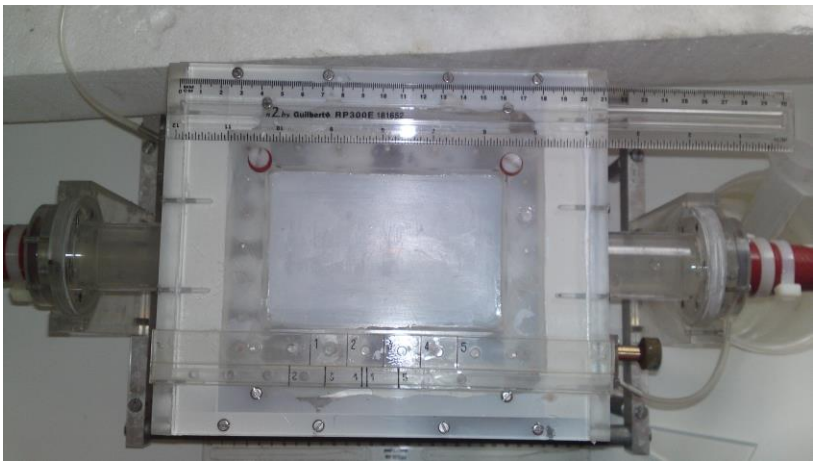


Figure 15: Viewing jig on the EVAR phantom ultrasound window: the probe can be placed at set positions standardizing images between subjects

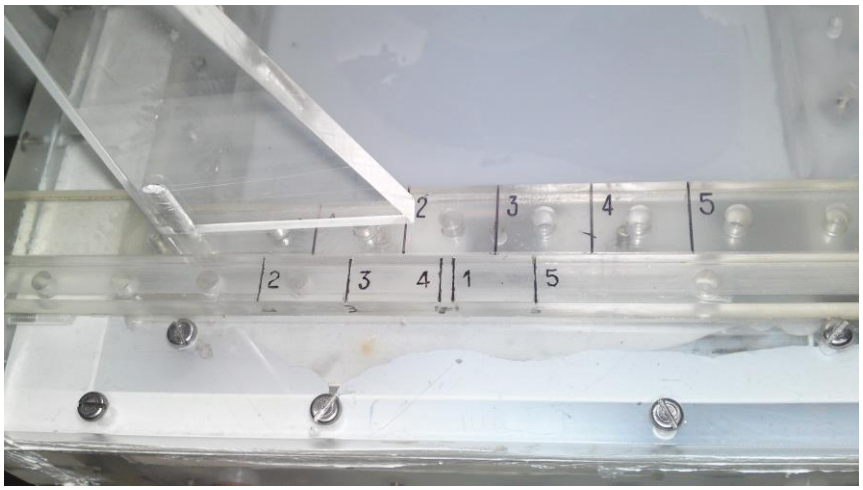


Figure 16: EVAR phantom ultrasound viewing window being filled with water as a coupling medium between probe and phantom surface

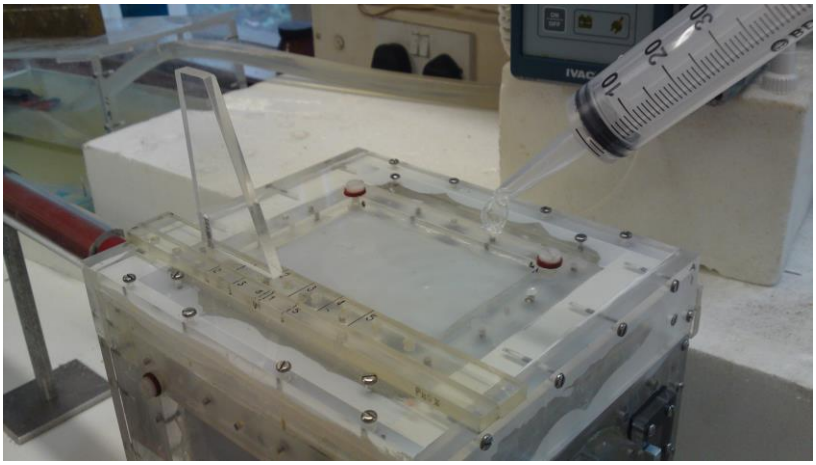


Figure 17: Overview of the completed phantom with large (left to right) and small flow (obliquely from left to empty in a beaker) systems connected

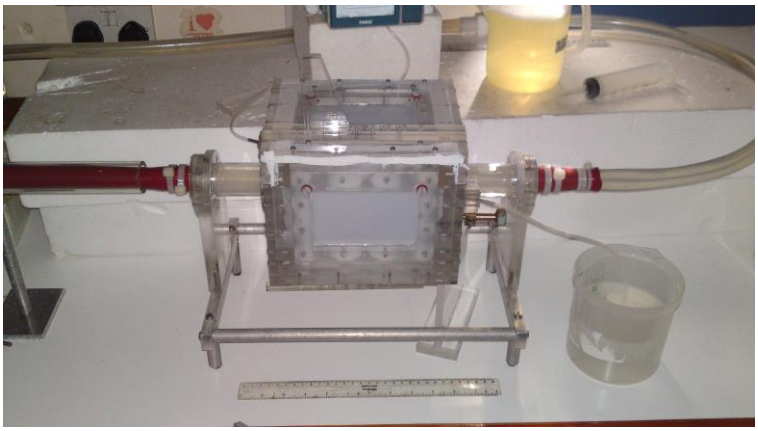


Figure 18: Empty saline bag reservoir for the small flow system that enters a fluid pump to produce the variable endoleak

Figure 19: Saline reservoir bag for the small flow system

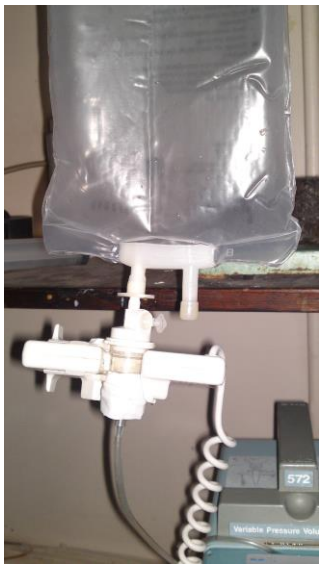


Figure 20: Endoleak flow system variable pump

Figure 21: Small and large flow systems enter the proximal EVAR phantom housing

Figure 22: Superior view of small and large flow systems entering the proximal EVAR phantom housing

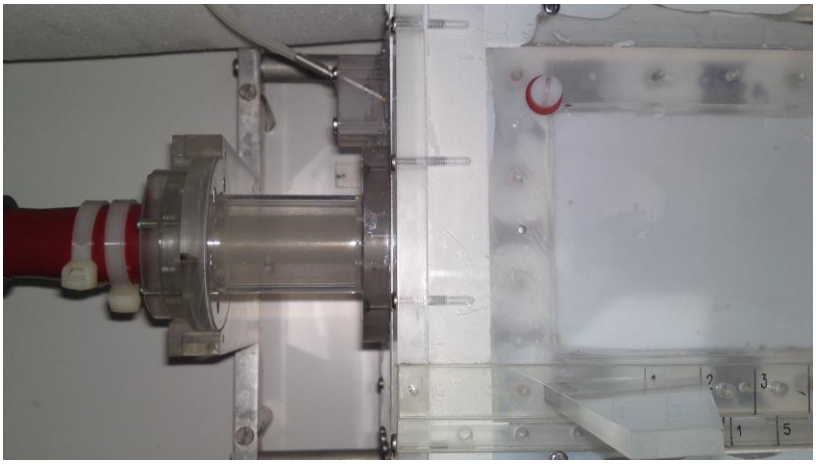


Figure 23: Distal aspect showing the large and small flow systems exiting the housing. The small system collects into the Perspex beaker and is manually used to replenish the small system reservoir in the saline bag

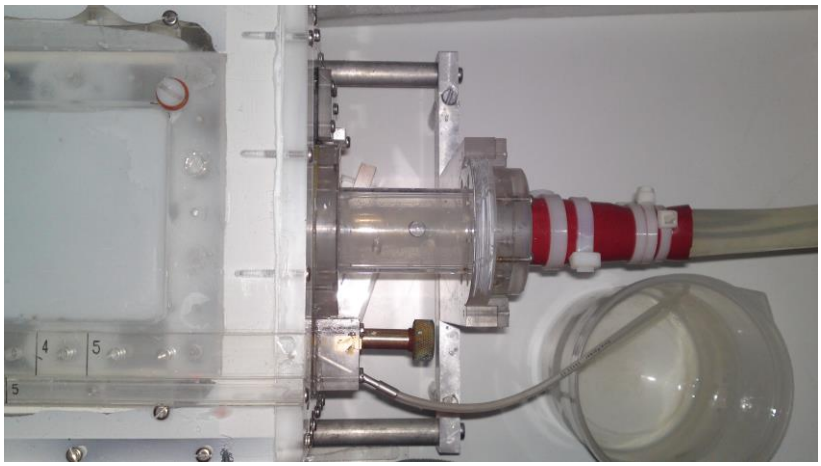
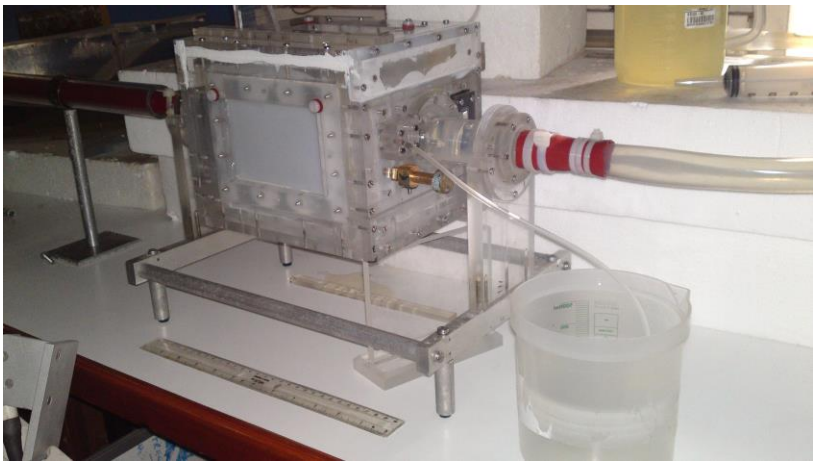


Figure 24: Distal aspect of the phantom showing the large and small flow systems exiting the housing

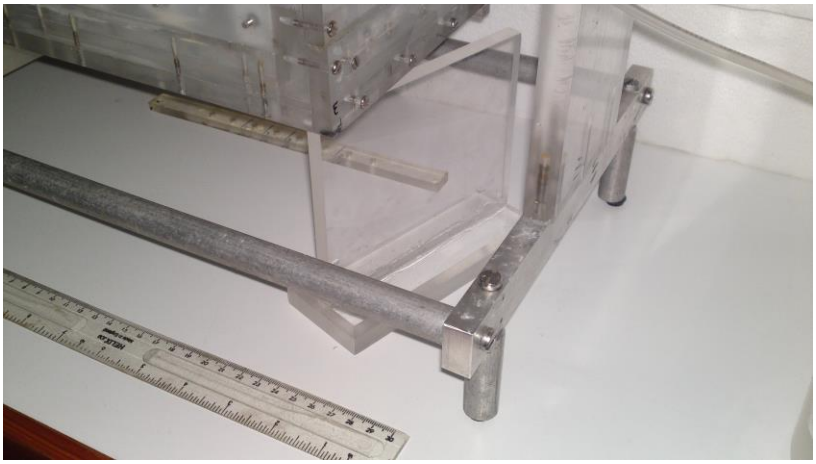
Figure 25: Distal aspect of the phantom showing the large and small flow systems exiting the housing



The infusion pump (IVAC 572) representing the small flow endoleak had variable flow rate settings from 100-900 ml/hr. The position of the endoleak could be altered by viewing along 5 different pre-set viewing positions indicated by a jig to incorporate a curvilinear (2-5 MHz) ultrasonic probe (**Figure 15-16 and 26**). As imaging progressed along the viewing platform, the endoleak position varied from near (superimposed over stent) too far (2cm away) in relation to the EVAR stent. This corresponds with clinical tracking of a type II endoleak. The endoleak plane could be varied by revolving the Perspex housing (**Figure 27**) so that the endoleak plane lay anterior, lateral or posterior to the EVAR stent.

Figure 26: Curvilinear (2-5 MHz) ultrasound probe placed by positional jig, viewing the EVAR phantom and endoleak via the ultrasound viewing window

Figure 27: Removable stopper below the phantom to prevent rotation



The EVAR phantom was a closed system so we had to incorporate a delivery port for administration of microbubble contrast and directly inject the contrast into a saline bag for viewing the endoleak in the second flow system (**Figures 28-32**).

Figure 28: Large flow system curves in a circle after leaving the phantom. Along its course an injectable inlet allowed administration of contrast ultrasound to the system

Figure 29: The injectable inlet for contrast administration to the large system

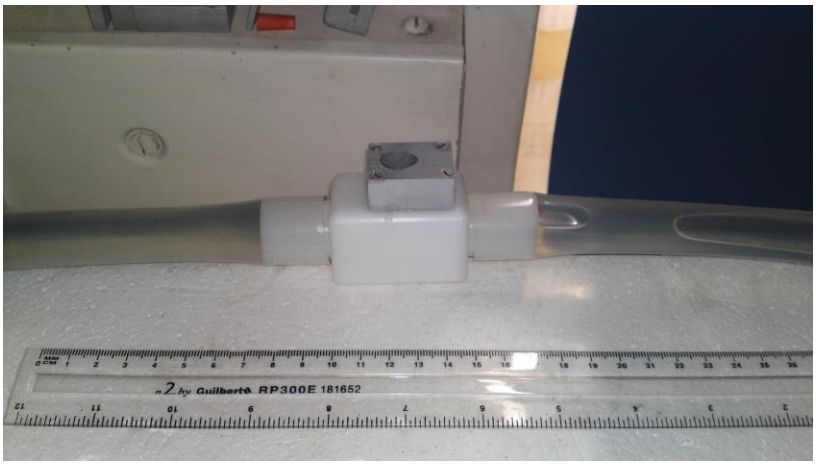


Figure 30: Injectable inlet for large system contrast administration

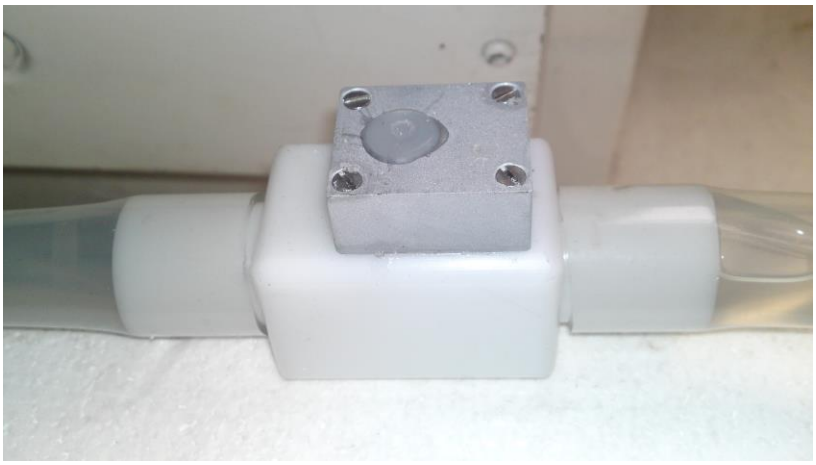


Figure 31: Small flow system reservoir bag cut at one end to refill Doppler fluid from the Perspex beaker and administer contrast

Figure 32: Filling the small flow system reservoir bag with Doppler fluid

We used a Phillips ATL HDI 5000 SonoCT ultrasound machine (Philips, Andover, Massachusetts, USA) with a curvilinear (2-5 MHz) ultrasound probe to image the phantom EVAR stent and endoleak (**Figure 33**). This machine could view the phantom in B-mode (**Figures 34-35**), colour Doppler (**Figures 36-37**) and had Contrast Specific Imaging (CSI) software for microbubble contrast agent enhancement at a low MI.

Figure 33: Phillips HDI 5000 ultrasound machine curvilinear probe used for the EVAR phantom experiments

Figure 34: Transverse ultrasound B-mode image produced of the EVAR stent (large flow system) within the EVAR phantom

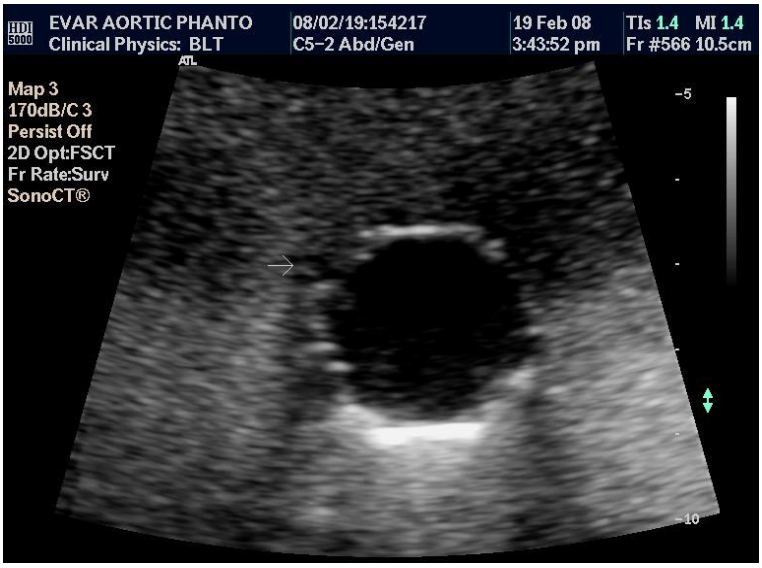


Figure 35: Longitudinal ultrasound B-mode image produced of the EVAR stent (large flow system) within the EVAR phantom

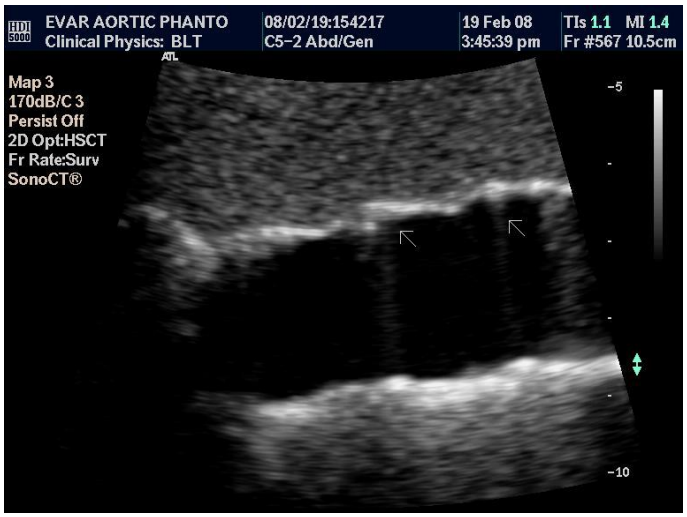


Figure 36: Colour Doppler images produced of the large flow system (EVAR stent) and small flow system (endoleak)

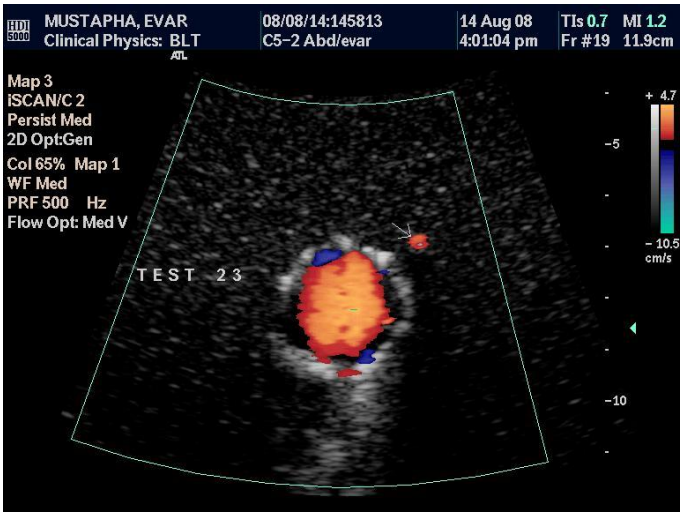
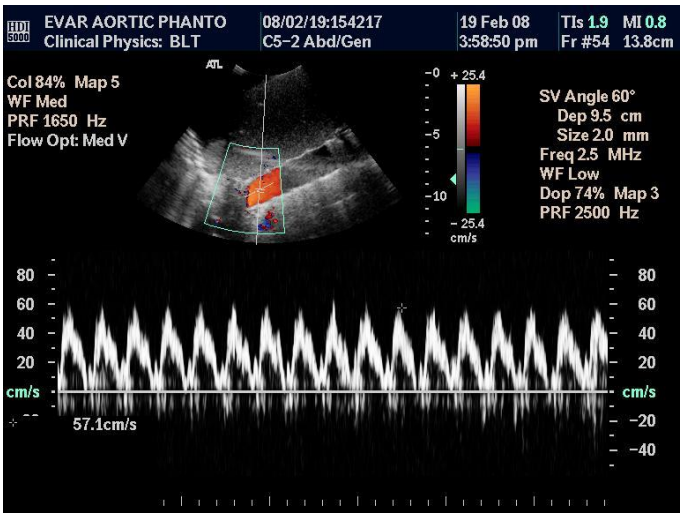


Figure 37: Doppler waveform images of the EVAR phantom stent demonstrating pulsatile flow



Contrast microbubble preliminary experiments

After a detailed assessment of the available ultrasound contrast agents, we chose to use only SonoVue (Bracco, Italy), a widely available third generation microbubble agent containing sulphur hexafluoride. The reason for using SonoVue was that it was the only available contrast agent available for clinical use in the UK at the time of experimentation. Other manufacturers (**Table 2**) had either discontinued production for safety reasons (principally due to containing antigenic proteins that induced anaphylaxis) and other smaller companies that had contrast agents licensed for clinical use had been taken over by larger firms and consequently discontinued production. The only other agent available was Levovist (Schering), but this was only available in Asia, not Europe, and not promoted because it has approximately two years left on patent.

Bracco kindly donated five packs of SonoVue each containing a 4.8 ml vial for our laboratory experiments. Each vial of SonoVue costs £39.90 excluding VAT, minimum order 10 vials in a box.

SonoVue is provided within a kit (**Figures 38-39**) containing:

- 25 mg vial of dry, lyophilized powder (containing Macrogol 4000, Distearoylphosphatidylcholine, Dipalmitoylphosphatidylglycerol Sodium and Palmitic acid)
- 5 ml prefilled syringe of sodium chloride 9 mg/ml (0.9%) solution for injection
- 1 Mini-Spike transfer system

Figure 38: SonoVue pack: saline in a prefilled syringe, powdered contrast with mixing apparatus

Figure 39: SonoVue pack contents constituted, ready to administer

The microbubble solution was made by injecting 5 ml of sodium chloride 9 mg/ml (0.9%) solution into the vial. The vial was then shaken vigorously for a few seconds until the lyophilisate is completely dissolved and micro-bubbles of sulphur hexafluoride produced. The desired volume is drawn into a syringe at any time up to six hours after reconstitution. Just before drawing into the syringe, the vial was agitated to re-suspend the microbubbles. In clinical practice SonoVue should be administered immediately after drawing into the syringe by injection into a peripheral vein. Every injection is followed by a flush with 5ml of sodium chloride 9 mg/ml (0.9%) solution for injection. The recommended administration dose of SonoVue for vascular ultrasound imaging is 2.5ml.

SonoVue microbubbles have a mean diameter of 2.5µm, 90% have a diameter <6µm and 99% <11µm. Each ml of SonoVue contains 100-500 million microbubbles, 8µl of sulphur hexafluoride microbubbles and on reconstitution as directed by Bracco, is equivalent to 45µg.

The intensity of the signal reflection from SonoVue is dependent on concentration of the microbubbles and frequency of the ultrasound beam. Bracco informed us that at our proposed doses, SonoVue provides significant increase in signal intensity of >2 minutes for B-mode imaging and 3-8 minutes for Doppler imaging.

After an intravenous injection of 0.03ml or 0.3ml of SonoVue/kg (approximately 1 and 10 times the maximum clinical dose) in human volunteers, sulphur hexafluoride is cleared rapidly in the blood and exhaled. Bracco state in their summary of product characteristics for SonoVue, that its mean half-life is 12 minutes (range 2-33 minutes). They also contradictorily state that over 80% of administered sulphur hexafluoride is recovered in exhaled air within 2 minutes of administration, approaching 100% after 15 minutes (Bracco 2005). I did not and could not gain access and find the information and data on which these statements were based in the literature.

There is no information available about the behavior of microbubble ultrasound contrast *in vitro*. Bracco informed me that they do hold information from experiments conducted in their Swiss laboratories but it is restricted and unpublished. They did however concede that our ultrasound equipment and contrast specific software was compatible for use with SonoVue. They did not recommend using the colour Doppler settings as the high power MI would destroy the bubbles very quickly, producing a high percentage of artifacts.

Further useful information from Bracco was the recommended dilutions of 1:2000 to 1:10000 for *in vitro* use. At these dilutions, it was advised that a single 5 ml vial of SonoVue could be used within 6 hours of reconstitution without the need for refrigeration, because within this time period chemical and physical stability is maintained. The recommended shelf life of SonoVue is 2 years. No special storage is required. Bracco confirmed that SonoVue bubbles would be stable in our phantom Doppler blood-mimic fluid, and would behave in exactly the same way if it was in the presence of saline. The osmolality and viscosity of SonoVue is very similar to plasma.

Preliminary ultrasound microbubble contrast decay experiments

A concern was that we didn't know how long the microbubble contrast would persist in our phantom. Consequently, the introduction of contrast to either circuit could pollute the Doppler mimic fluid and this would need to be completely replaced after testing, with high cost. Another consideration was the trauma to the microbubbles themselves by our phantom, e.g. did the mechanical pump revolving belts rupture the actual bubbles impacting on our experiments by contributing to bubble decay?

Contrast volume calculations

Calculations were performed to ensure equivalence in contrast volume administration between our phantom system and the volume used in humans:

It can be assumed that a 70 kg man has a blood volume of 4.7-5L (Taggart 1989). This is less for women and children (Lee 1998). In humans, by weight calculation, men have approximately 40% more blood than females. In a healthy adult, the volume of blood is about one-eleventh of their weight (7% body mass) (Cameron 1999, Lee 1998).

In 1973, the blood volume measurement was calculated in one of two ways. This depends upon putting a known quantity of a substance in the body, and, after it has been distributed uniformly in the whole circulating fluid, measuring the degree of dilution which has taken place. The substances most commonly used then were carbon monoxide, Evans blue dye, and radioactive chromium (Lee 1998).

Small endoleak system volume calculations

- The volume of the small system reservoir is approximately 1L, equivalent to 20% of an average 5L human blood volume
- The volume of fluid in the small system piping was minimal so the total was taken as 1L
- Bracco recommend using a bolus of 2.4ml SonoVue for vascular Doppler imaging in their instructions for use (Bracco 2005)
- Administering 20% of 2.4ml of Contrast = 0.48ml
- 1 pack of SonoVue contrast contains 5mls and can be used for 2 phantom small system experiments

Summary Phantom small system:

0.5ml contrast is equal to 4µl sulphur hexafluoride in the microbubbles which equates to 22.54µg.

Large EVAR stent system volume calculations

The larger system was composed of a series of cylindrical pipes that were connected to the generator pump then passed through the phantom EVAR stent housing. Using the design plans and then measuring the phantom dimensions, I calculated the phantom volume using the following formulae:

Volume of a cylinder = area of pipe x length (height)

$V = \pi r^2 \times h$

1. Volume of pipes in the pump = $9.5\ mm^2 \times (430 + 100 + 100) \times \pi$
   = $178623.10\ mm^3$
   = **$178.62\ cm^3$**
2. Volume of proximal phantom pipes = $12\ mm^2 \times 1070\ mm \times \pi$
   = $484056.60\ mm^3$
   = **$484.06\ cm^3$**
3. Volume of phantom and stent = $11.5\ mm^2 \times 500\ mm \times \pi$
   = $207737.81\ mm^3$
   = **$207.74\ cm^3$**
4. Volume of distal phantom pipes = $10.5\ mm^2 \times 2050\ mm \times \pi$
   = $710039.21\ mm^3$
   = **$710.04\ cm^3$**
5. Volume of primary tank connector = $12\ mm^3 \times 180\ mm \times \pi$
   = $81430.08\ mm^3$
   = **$81.43\ cm^3$**
6. Volume of distal phantom pipes = $12.7\ mm^2 \times 310\ mm \times \pi$
   = $157070.32\ mm^3$
   = **$157.08\ cm^3$**

Total phantom volume

= 178623.10 mm^3 + 484056.60 mm^3 + 207737.81 mm^3 + 710039.21 mm^3 + 81430.08 mm^3 + 157070.32 mm^3

= 1818966.12 mm^3

= 1818.97 cm^3

= **1.89 L**

Therefore if the blood volume for a 70kg man is 5L and an average subject requires 2.4ml of SonoVue for vascular imaging, then the volume of contrast required for the large system with a volume of 1.89 L would be:

0.907ml = which is approximately **0.91ml** of SonoVue when rounded up.

Firstly I administered 0.48ml of SonoVue contrast to the small endoleak system via the reservoir-saline bag to test the specific contrast imaging software. I used the contrast tissue preset for general imaging on the ultrasound machine because at this setting the lowest achievable MI of 0.12 could be achieved using a frequency of 10Hz. Bracco and Phillips both recommend that using the lowest achievable MI possible is advised for imaging vasculature with microbubble contrast to maximize image capture and prevent decay. I didn't continuously agitate the saline bag reservoir but filled it up from the collecting beaker. Images were enhanced. Contrast remained mixed with the Doppler blood-mimic fluid and did not separate, sink or float. Once image and contrast detection were confirmed I administered 0.91ml of SonoVue contrast via our introduction port to the large EVAR flow system.

With contrast flowing through the variable small endoleak system, I varied the flow rate pump, determining the lowest achievable rate detectable using both colour Doppler and ultrasound contrast. Using colour Doppler, knowing the exact position of the endoleak the smallest detectable flow rate was 300 mm/hr, being absent at 100 mm/hr. However the endoleak was visible at the lowest achievable flow rate of 0.1 mm/hr using microbubble contrast.

After I had separately administered contrast to the large or small system, confirmed adequate visibility of the EVAR stent and the endoleak in known positions, I simultaneously

administered contrast to both systems. I demonstrated that the stent and leak can be seen together without pixel overlap. Flow was seen in a pulsatile manner.

RESULTS

Having proven the capacity of the EVAR phantom model to mimic variable endoleaks and calculated equivalent doses of microbubble contrast, the next stage was to assess the behavior of microbubbles in the phantom environment.

The behavior of microbubble contrast in the phantom system

I administered 0.48ml of SonoVue into the small endoleak system on free flow. The pump was turned off and disconnected. With free drainage, the 1L saline reservoir bag emptied over 13 minutes so the flow rate was taken to be 4.62 L/hr. I used the ultrasound machine intermittently to record images of the endoleak (anterior position 5, 2cm from the stent) with free flow contrast at various times for 16 days after administration. At 2 months the contrast was still detected and producing images, however I stopped recordings of brightness at 16 days, as subject experiments were not expected to continue beyond this time. Images were recorded every minute, then hourly and finally over days. I shook the 1L saline bag reservoir containing 0.48ml of SonoVue for 20 seconds between image recordings as per the SonoVue instruction manual for all readings taken hours after administration.

The saved JPEG still images were analyzed using Adobe Photoshop CS5 extended version 12.0x32 to measure pixel brightness and quantify contrast decay in time. I measured two areas within the endoleak lumen at 3 and 9 o'clock to avoid metal artifact and acoustic shadowing pollution. I selected two 50x50 squares of pixels as the area of interest to measure brightness for each image. The data was normally distributed so I calculated the mean for each image corresponding to each time period that the recording was taken (**Table 3**). I used a programme call Graphical pad prism for graphs and statistical analysis of the data (**Graph 1**).

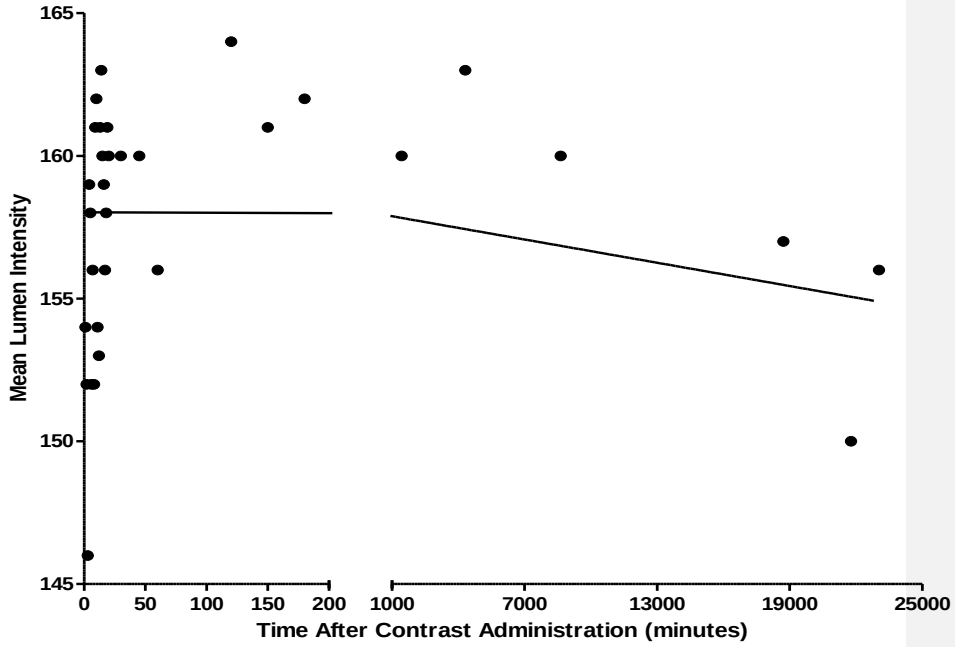
Table 3: Results of brightness measurements for a known endoleak with microbubble contrast and minimal intermittent ultrasound exposure over a variable time period to determine decay rate

Time after contrast administration (minutes)	Lumen Mean Brightness	Standard Deviation
1	154	54
2	152	51
3	146	33
4	159	42
5	158	29
6	152	36
7	156	45
8	152	26
9	161	46
10	162	55
11	154	43
12	153	54
13	161	46
14	163	53
15	160	48
16	159	49
17	156	43
18	158	54
19	161	36
20	160	48
30	160	44
45	160	57
60	156	33
120	164	33
150	161	33
180	162	51

1440	160	63
4320	163	43
8640	160	52
18720	157	66
21780	150	55
23040	156	48

Graph 1: Results of brightness measurements for a known endoleak with microbubble contrast and minimal intermittent ultrasound exposure over a variable time period to determine decay rate

Intermittent Experiment



R square	0.04089
P value	0.2670

These results demonstrate that SonoVue microbubble contrast does not decay when left alone in the phantom system. The manufacturer's advice that a vial of SonoVue should be used within 6 hours of preparation and that nearly all of the contrast is completely eliminated within 15 minutes, were not applicable to our laboratory phantom experiments.

SonoVue doesn't decay over 3 hours, as demonstrated by the flat line plot (**Graph 1**). I expected to perform my phantom subject laboratory experiments within 3 hours so this non-decay was relevant. I demonstrated however that if brightness is recorded over 16 days, that there is a non-significant reduction in brightness ($p=0.27$).

The effect of the phantom casing and mechanics upon the decay of SonoVue microbubble contrast was minimal. Thus the only factor that could affect the bubbles was the ultrasonic waves themselves, necessary for subject testing and endoleak detection.

I used the contrast tissue preset for general imaging on the ultrasound machine because at this setting the lowest achievable MI of 0.12 could be achieved using a frequency of 10Hz. Bracco and Phillips both recommend that using the lowest achievable MI possible is advised for imaging vasculature with microbubble contrast to maximize image capture and prevent decay. To study the behavior of low MI ultrasound upon the microbubble contrast in the phantom system, I again administered 0.48ml of SonoVue to the small endoleak system and 0.91ml to the large system. The phantom was used to detect a range of simulated endoleaks to determined the decay of SonoVue microbubble contrast exposed to a continuous ultrasound beam over a period of 167.18 minutes.

JPEG images were analyzed using Adobe Photoshop CS5 extended version 12.0x32 to measure average pixel brightness and quantify contrast decay over time. I measured two areas of interest within the endoleak lumen at 3 and 9 o'clock to avoid metal artifact and acoustic shadowing pollution. As previously I selected two 50x50 square of pixels as the area of interest to measure brightness for each saved image. The data was normally distributed so I calculated the mean brightness for each time period that the recording was taken (**Table 4**). I used Graphical pad prism for graphs and statistical analysis (**Graphs 2**).

Table 4: Brightness measurements of a known endoleak using contrast enhancement and continuous ultrasound exposure

Time after contrast administration (minutes)	Lumen Mean Brightness	Standard Deviation
3.25	146	33
4.12	150	31
5.05	147	26
5.33	148	27
6.02	167	27
6.26	141	22
6.46	150	32
7.02	156	27
7.13	112	26
7.39	133	23
8.14	151	24
8.26	121	28
8.45	154	27
8.5	138	31
9.25	124	25
9.42	152	29
9.46	132	35
10.12	150	28
10.34	153	28
10.34	153	28
11.07	152	26
11.15	152	24
11.56	158	22
12.33	147	25
12.54	154	30
13.05	155	40
13.09	157	23
13.37	150	27
14.04	149	26
14.14	155	25
14.55	143	27
15.13	124	25
15.32	155	28
15.38	155	26

16.13	153	28
16.43	149	36
16.55	136	27
17.32	125	24
17.55	155	21
18.25	150	25
18.4	137	21
19.08	152	25
19.26	148	30
20.08	137	21
20.27	153	27
20.59	151	25
21.06	138	28
22.15	146	27
22.3	149	31
22.33	154	22
23.05	152	30
23.18	138	23
23.34	152	25
24.26	151	26
24.31	150	24
24.49	125	33
24.55	154	29
25.2	137	45
25.27	156	44
25.36	148	26
26.03	147	34
27.34	147	25
28.06	154	30
28.42	154	27
29.19	154	27
29.46	143	31
30.25	154	22
31.03	138	26
31.44	135	21
33.48	148	27
34.21	140	23
34.46	131	21
35.06	138	21

37.45	158	26
41.02	155	24
41.2	153	23
41.36	156	40
43.1	149	23
43.34	152	29
43.58	151	17
44.13	153	24
45.45	154	25
46.13	152	24
46.15	138	25
46.32	152	22
46.33	130	21
46.54	143	22
46.56	153	18
47.15	123	26
48.18	155	25
48.37	150	30
48.53	134	53
49.12	149	24
49.3	135	23
49.42	154	36
50.03	138	24
51.03	154	26
51.35	152	46
52.14	142	23
52.21	149	43
52.43	132	22
52.49	149	37
53.12	156	24
53.38	135	21
54.07	156	24
54.22	150	26
55	150	24
55.1	148	22
55.19	149	24
55.22	132	20
55.49	134	23
56.22	149	23

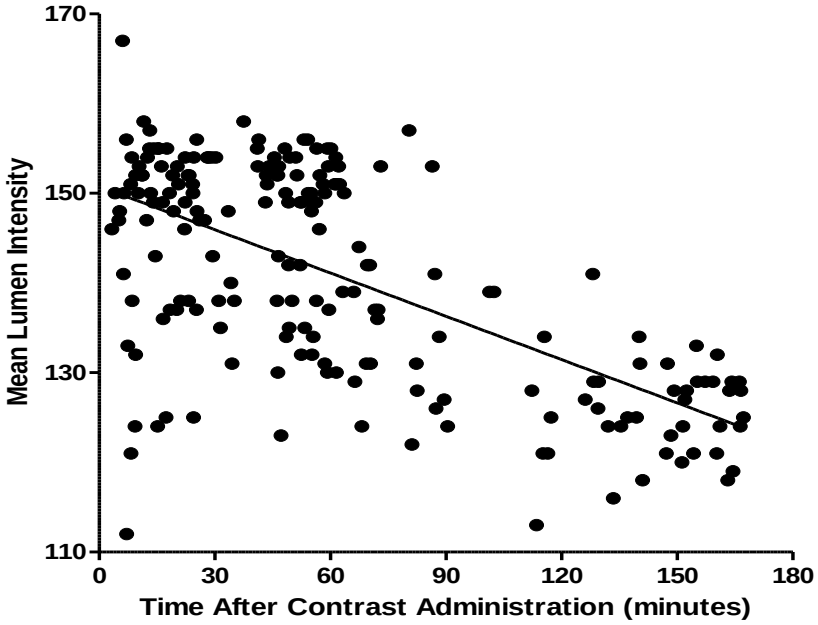
56.35	138	26
56.46	155	24
57.11	146	36
57.27	152	27
58.12	151	23
58.5	150	23
58.52	131	35
59.23	155	27
59.24	130	19
59.46	153	43
59.57	137	22
60.11	155	52
61.19	151	22
61.37	154	21
61.5	151	25
61.52	130	30
62.17	153	21
62.4	151	23
63.22	139	22
63.56	150	25
66.04	139	18
66.38	129	23
67.44	144	38
68.14	124	25
69.28	131	20
69.56	142	23
70.21	142	21
70.44	131	22
71.55	137	18
72.2	136	29
72.38	137	24
73.05	153	23
80.38	157	46
81.19	122	22
82.27	131	18
82.53	128	19
86.43	153	42
87.11	141	23
87.38	126	19

88.22	134	18
89.48	127	19
90.38	124	25
101.31	139	21
102.42	139	23
112.32	128	35
113.52	113	20
115.18	121	25
115.55	134	46
116.41	121	25
117.28	125	17
126.16	127	18
128.07	141	18
128.3	129	22
129.42	126	23
129.59	129	12
132.06	124	19
133.39	116	17
135.38	124	20
137.1	125	21
139.42	125	21
140.1	134	11
140.34	131	27
141.04	118	23
147.18	121	41
147.45	131	22
148.42	123	21
149.18	128	49
151.23	120	15
151.46	124	21
152.03	127	39
152.45	128	37
154.26	121	30
155.01	133	44
155.21	129	35
157.23	129	28
159.28	129	27
160.26	121	20
160.45	132	38

161.1	124	22
163.14	118	15
163.59	128	44
164.17	129	47
164.49	119	51
166.15	129	31
166.37	124	33
166.52	128	33
167.18	125	38

Graph 2: Brightness measurements of a known endoleak using contrast enhancement and continuous ultrasound exposure over a variable time period 1&2 results combined

Continuous Experiment



R square	0.4119
P value	< 0.0001

These experiments exposing microbubble contrast to continuous ultrasound demonstrated that the use of ultrasound on microbubble contrast destroyed it in a linear fashion significantly over time ($p<0.0001$).

DISCUSSION

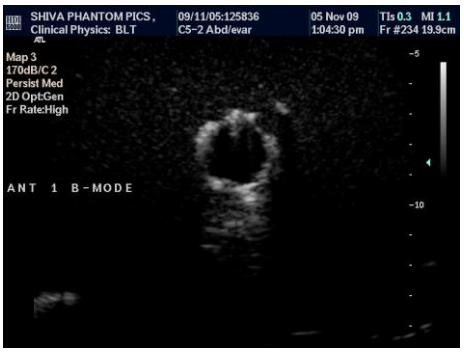
In this chapter I have described the laboratory bench endovascular stent phantom from inception to testing. I will use it to determine the limitations of DUS and CEADUSS imaging in endoleak detection.

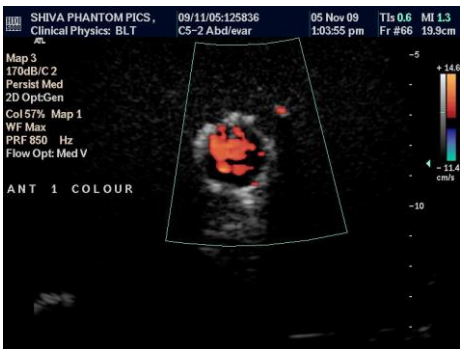
The potential variables to be measured include

- the plane: anterior, posterior and lateral to EVAR stent,
- the distance of endoleak from EVAR stent: near, far or directly adjacent over five separate settings (superimposed, 1cm and 2cm away),
- the velocity of the endoleak flow from 100-900ml/hr.

The following images demonstrate the appearance of the simulated endoleak in all positions that the phantom can achieve using B-mode, DUS and CEADUSS (**Figures 40-51**).

Figure 40: Images of the phantom simulated endoleak in an anterior position 1, using B mode, colour Doppler and contrast enhanced ultrasound





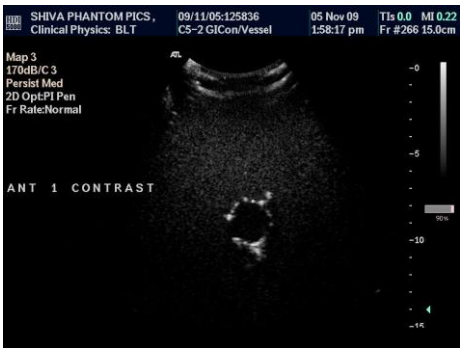
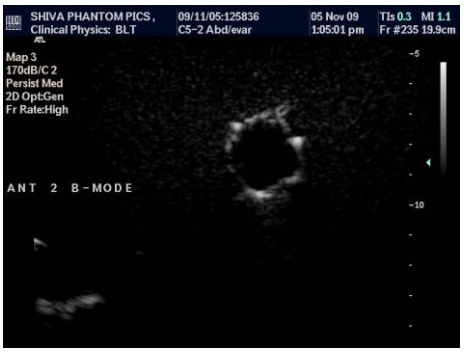
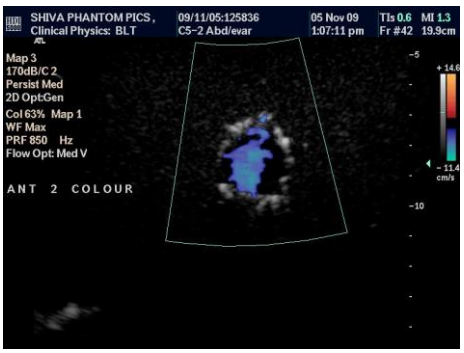


Figure 41: Images of the phantom simulated endoleak in an anterior position 2, using B mode, colour Doppler and contrast enhanced ultrasound





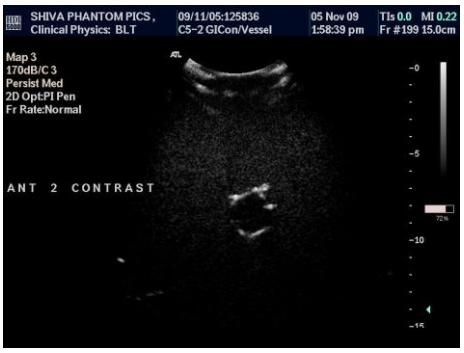
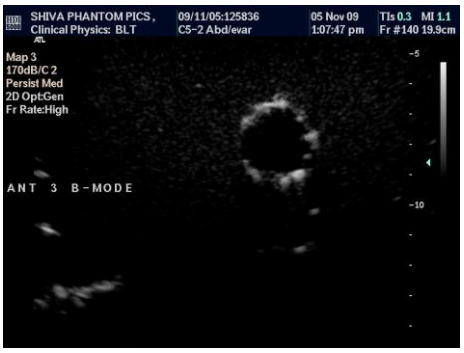
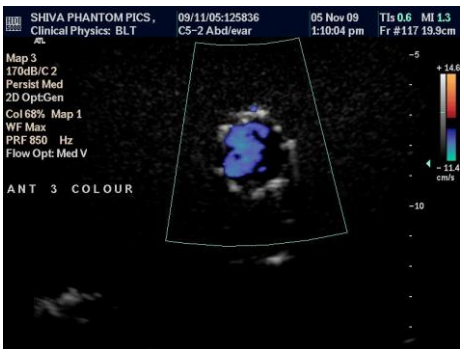


Figure 42: Images of the phantom simulated endoleak in an anterior position 3, using B mode, colour Doppler and contrast enhanced ultrasound





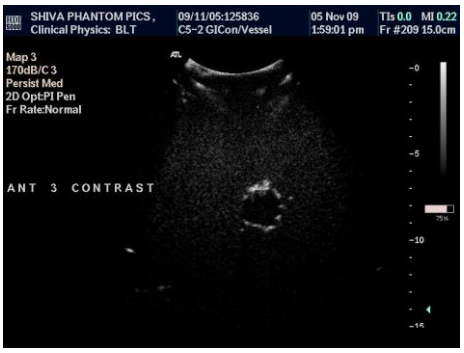
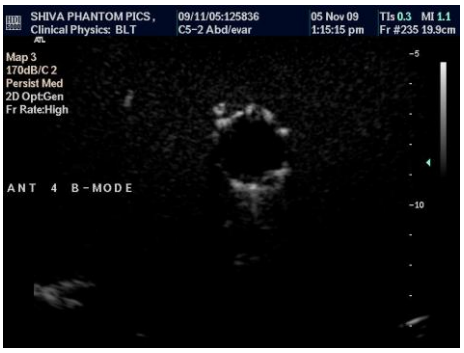
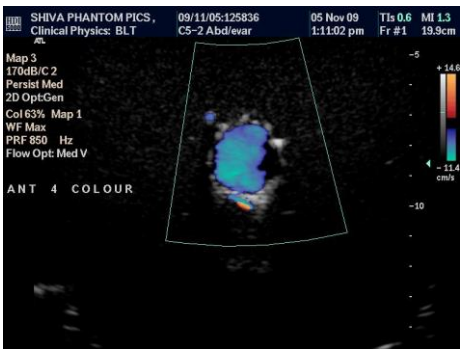


Figure 43: Images of the phantom simulated endoleak in an anterior position 4, using B mode, colour Doppler and contrast enhanced ultrasound





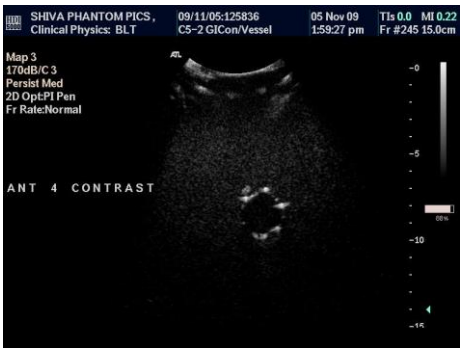
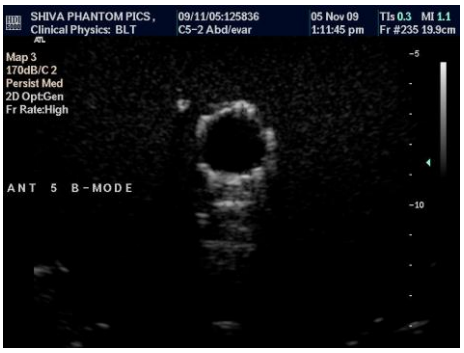
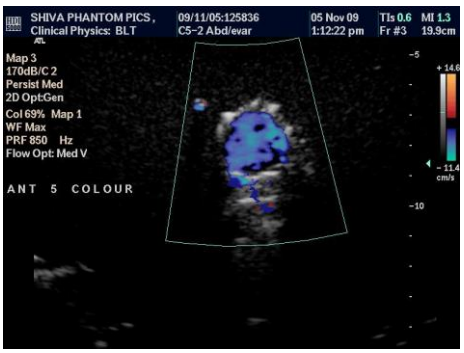


Figure 44: Images of the phantom simulated endoleak in an anterior position 5, using B mode, colour Doppler and contrast enhanced ultrasound





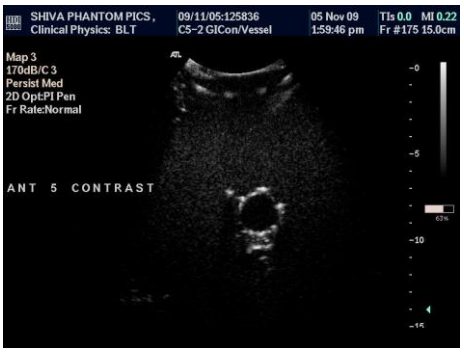
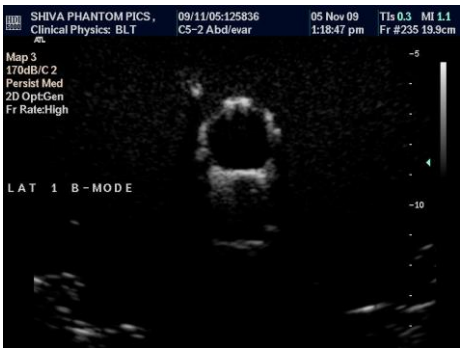
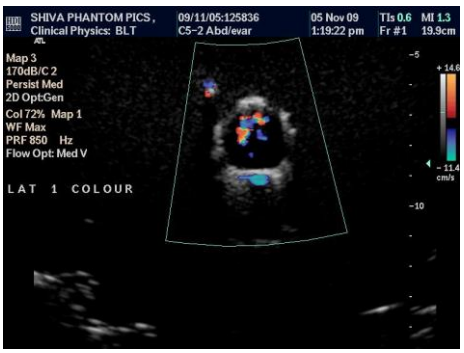


Figure 45: Images of the phantom simulated endoleak in a lateral position 1, using B mode, colour Doppler and contrast enhanced ultrasound





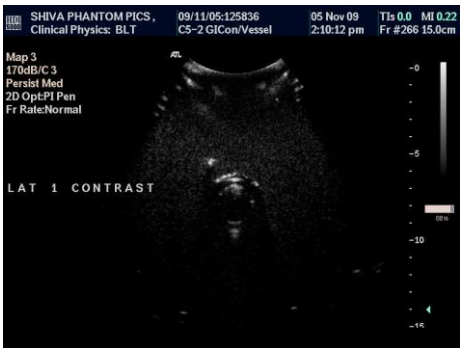
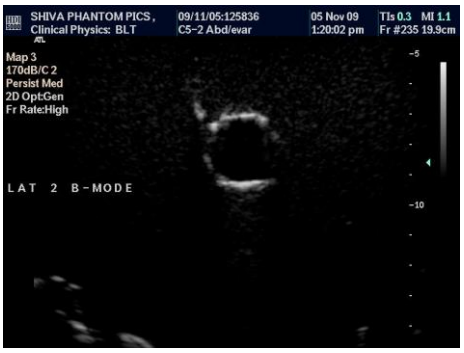
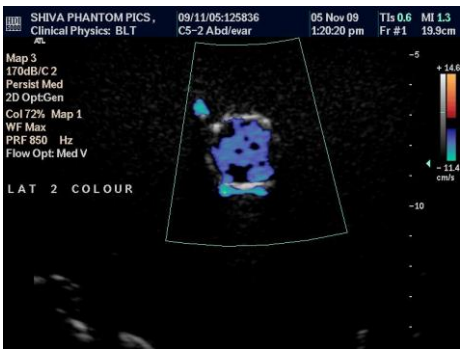


Figure 46: Images of the phantom simulated endoleak in a lateral position 2, using B mode, colour Doppler and contrast enhanced ultrasound





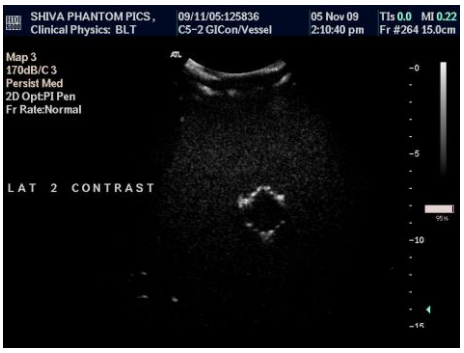
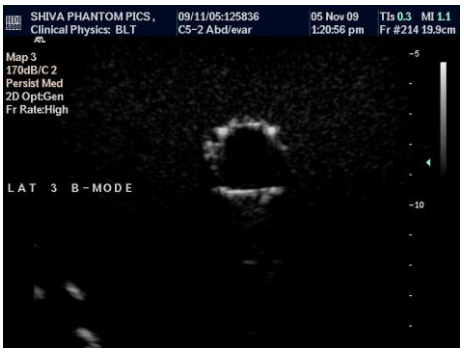
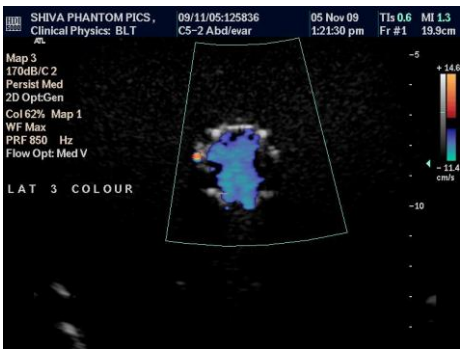


Figure 47: Images of the phantom simulated endoleak in a lateral position 3, using B mode, colour Doppler and contrast enhanced ultrasound





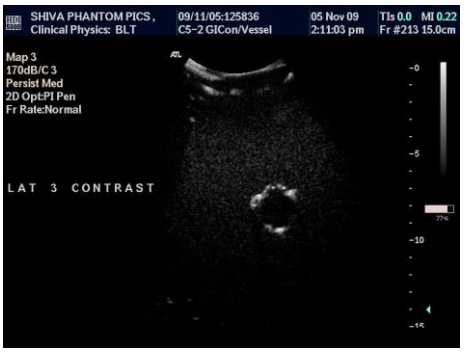
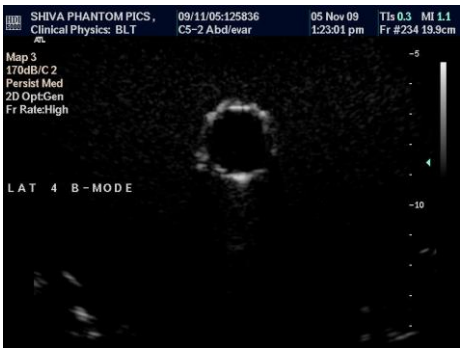
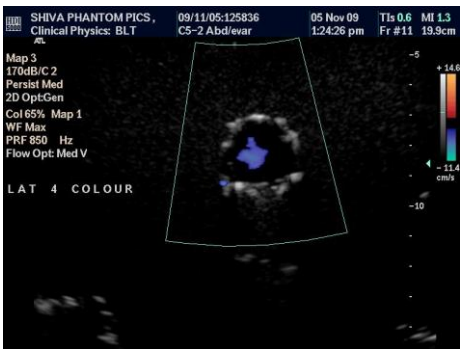


Figure 48: Images of the phantom simulated endoleak in a lateral position 4, using B mode, colour Doppler and contrast enhanced ultrasound





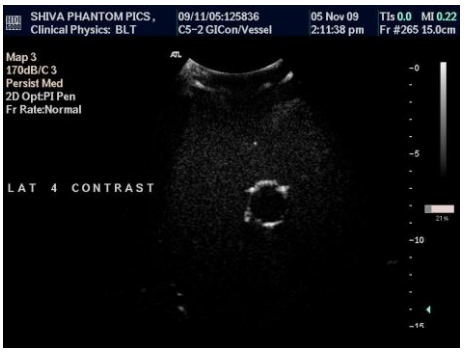


Figure 49: Images of the phantom simulated endoleak in a lateral position 5, using B mode, colour Doppler and contrast enhanced ultrasound

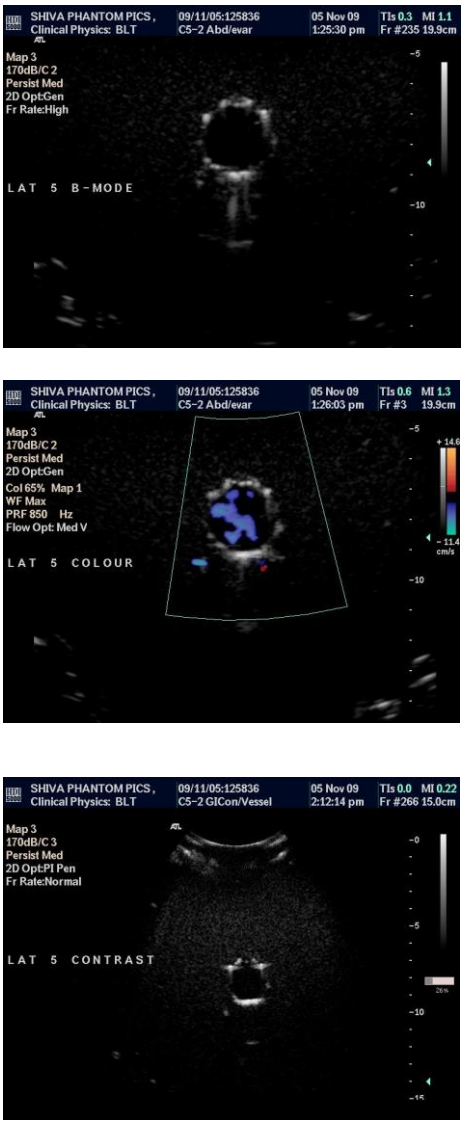
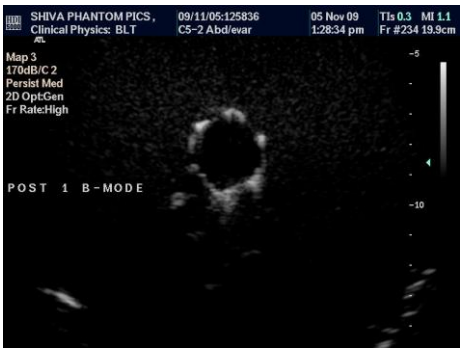
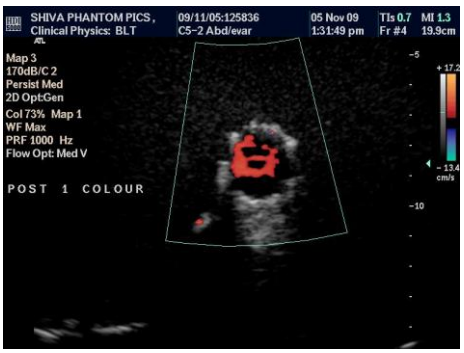


Figure 50: Images of the phantom simulated endoleak in a posterior position 1, using B mode, colour Doppler and contrast enhanced ultrasound





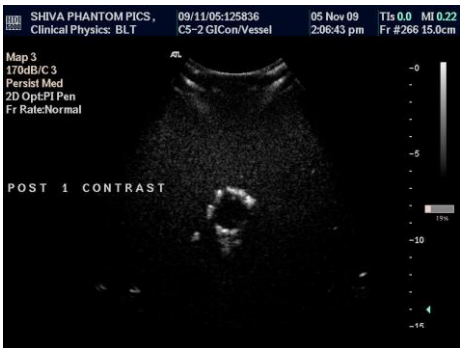
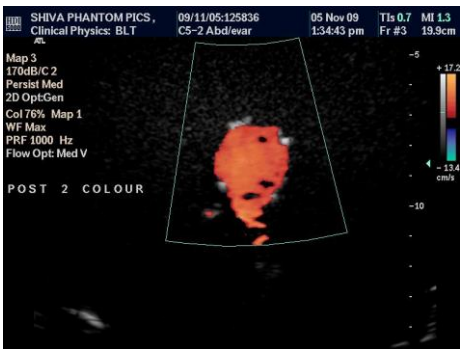


Figure 51: Images of the phantom simulated endoleak in a posterior position 2, using B mode, colour Doppler and contrast enhanced ultrasound



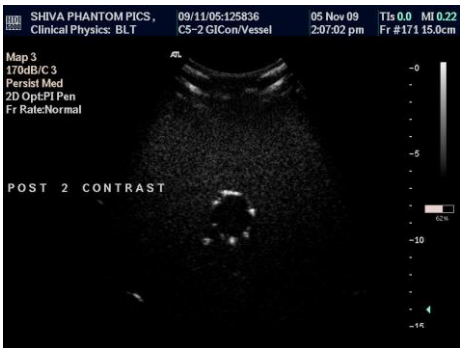
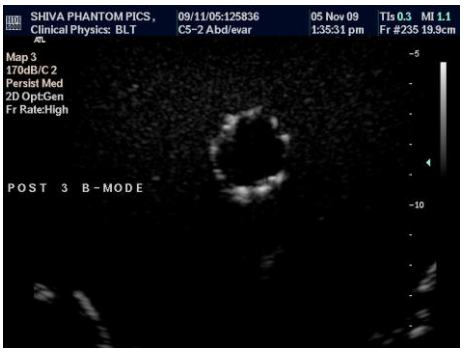
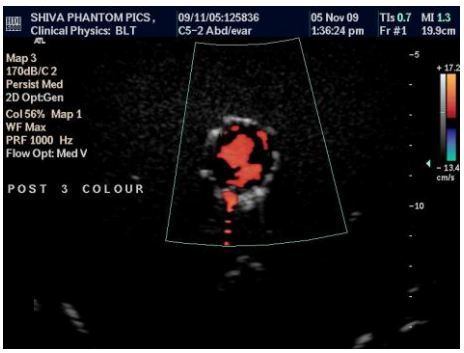


Figure 52: Images of the phantom simulated endoleak in a posterior position 3, using B mode, colour Doppler and contrast enhanced ultrasound





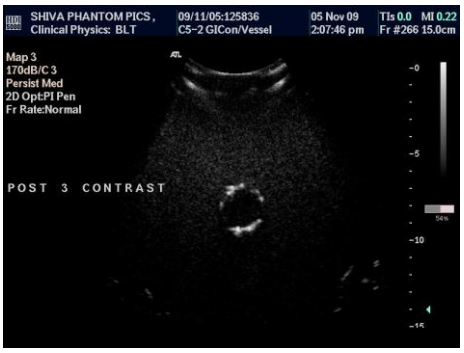
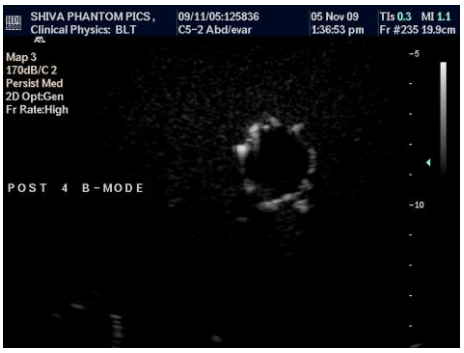
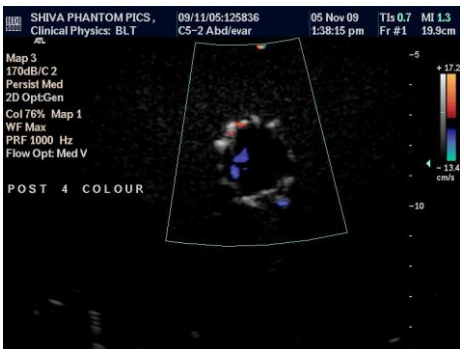


Figure 53: Images of the phantom simulated endoleak in a posterior position 4, using B mode, colour Doppler and contrast enhanced ultrasound





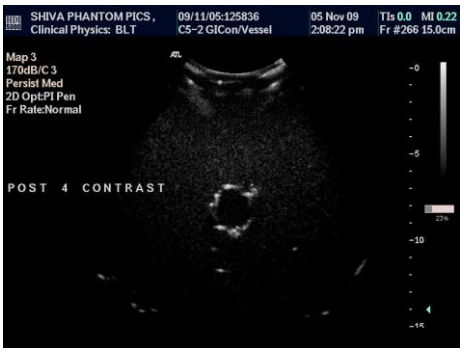
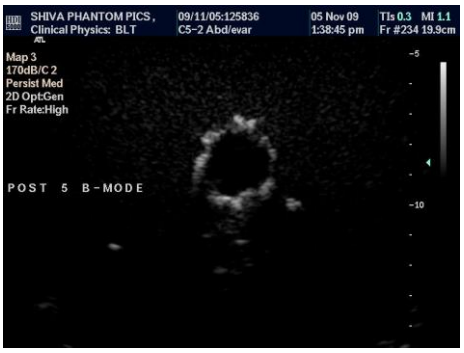
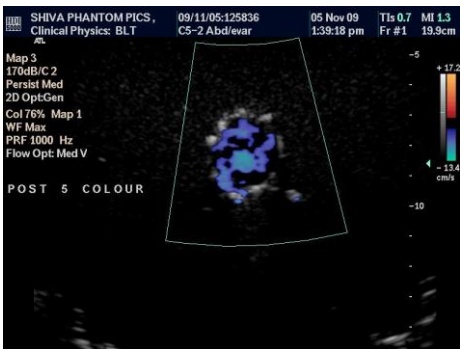
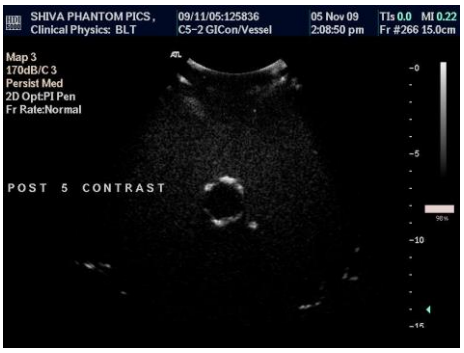


Figure 54: Images of the phantom simulated endoleak in a posterior position 5, using B mode, colour Doppler and contrast enhanced ultrasound

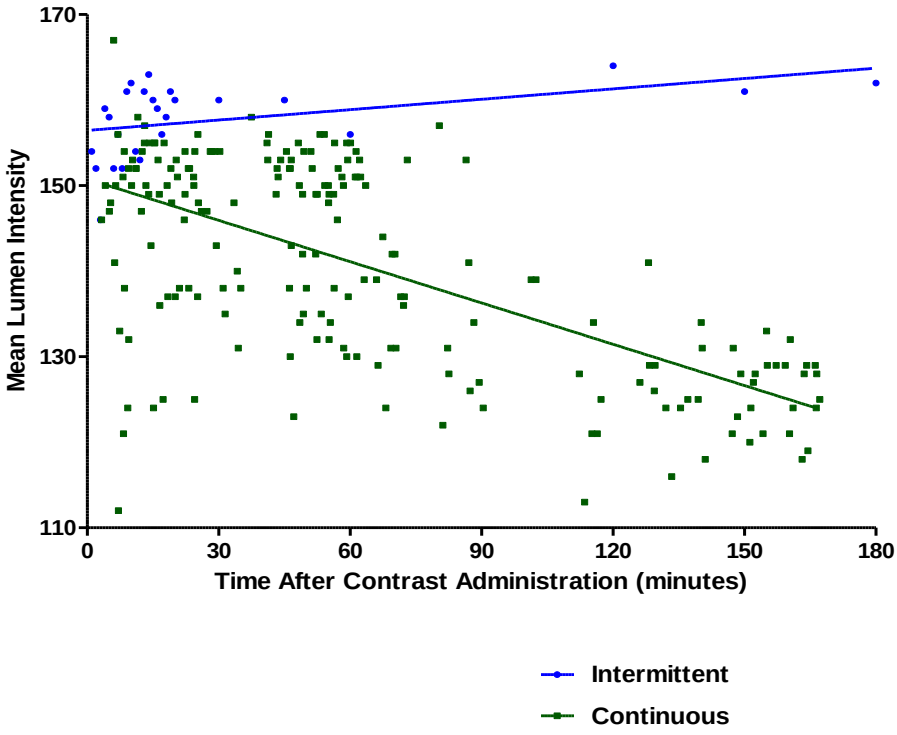






The decay experiments showed that when the contrast was left within the phantom system with minimal intermittent ultrasound exposure, non significant decay (p=0.27) (**Graph 3**) over a period of 16 days and persistence for up to 2 months. This implied that SonoVue microbubble contrast would only be degraded by ultrasound. To investigate this further, I conducted experiments exposing SonoVue to continuous ultrasound to show that ultrasound did significantly (p<0.0001) reduce the brightness of SonoVue over time (**Graph 3**).

Graph 3: Combined results of brightness measurements of a known endoleak imaged using contrast enhancement with both intermittent and continuous ultrasound exposure over time



I added the requirement to top-up or completely replace the phantom testing fluids and microbubble contrast after each subject testing. This avoided later false negatives due to reduced contrast brightness and ineffectiveness.

CONCLUSIONS

With the EVAR phantom model proven and contrast administration possible in equivalent doses to those used *in vivo*, I was ready to conduct subject testing to determine the efficiency and limitations of DUS and CEADUSS in EVAR endoleaks detection.

CHAPTER 2

LABORATORY ENDOVASCULAR STENT PHANTOM EXPERIMENTS COMPARING ULTRASOUND COLOUR DOPPLER AND CONTRAST ENHANCED ULTRASOUND ENDOLEAK DETECTION

ABSTRACT

Stent-graft surveillance is mandatory for all patients undergoing EVAR to detect endoleak and graft migration. CT imaging has been the mainstay of surveillance based on early EVAR protocols from 20 years ago. This convention is costly, exposes patients to cumulative radiation and nephrotoxic contrast and is a burden on limited resources.

A solution is required to reduce cost and harm. Ultrasound has been proposed by several, however skepticism exists due to varying levels of endoleak detection in many studies. Sensitivity has been improved significantly by the introduction of microbubble contrast enhancement.

I constructed an EVAR laboratory phantom with a contained endoleak. The endoleak was variable in terms of velocity (fast/slow), position (near/far) and plane (anterior/lateral/posterior). I aimed to determine which endoleak properties influence detection rates and describe the conditions under which contrast administration might increase sensitivity.

I used DUS in 36 different endoleaks and repeated these with microbubble contrast administration in 6 subjects. There was a significant difference between the endoleak detection rates of CEADUSS and DUS, but further uncertainty was also generated. Low endoleak flow rates and proximity to the main lumen made endoleak detection more difficult. With the introduction of CEADUSS, more junior sonographers were better at spotting anterior endoleaks. Again proximity to the main arterial channel made detection more difficult. The addition of CEADUSS resulted in an 18% (95% CI 9-25) increase in sensitivity for identifying endoleaks over and above DUS. However there was no significant decrease in the overall proportion of inconclusive scans between modalities.

My results give an insight into several factors affecting the ultrasonic detection of endoleaks. With this knowledge, the clinical use of these CEADUSS in EVAR surveillance can be modified as an alternative to current expensive and potentially harmful CT protocols. *In vivo* assessment of DUS and CEADUSS endoleak detection and endoleak characteristics (plane, position and velocity) is needed to improve sensitivity and drive current protocols change.

INTRODUCTION

AAAs are common and aneurysmal rupture is now the 13th commonest cause of death in the developed world (Wilt 2006, Jordan 2002, Bengtsson 1993, Fowkes 1989, Johansson 1986), and tenth amongst men (Wilt 2006, Huber 2001, Gallagher 1999, Lawrence 1999). AAAs are increasingly being treated by EVAR stent-grafts instead of open surgery (Chadi 2012, Chang 2012, Mohan 2012, Mani 2011, Nichols 2011, Schanzer 2011, Kent 2010, Schwarze 2009, Dimick 2008, Szmidt 2007, Anderson 2004). Evidence shows that up to 25% patients undergoing EVAR may require re-intervention to prevent patent, persistently enlarging aortic sacs from rupture (Nordon 2012, Oikonomou 2012, de Bucourt 2011, Bargellini 2009, Carrafiello 2008, Lee 2007b, Stavropoulos 2007, Golzarian 2005, Becquemin 2004, Kritprach 2004, Pearce 2004, Ouriel 2003, Carpenter 2002, Parent 2002b, Buth 2000, Cuypers 1999, Moore 1996).

It is mandatory for all patients with AAA undergoing EVAR to have life-long surveillance, to detect late complications such as stent-graft migration or endoleak (Nordon 2010b, Szmidt 2007, Hobo 2006, Bown 2004, D'Ayala 2004, Elkouri 2004a, Stavropoulos 2004b, Conners 2002, Thurnher 2002, Tonnessen 2002, Patterson 2001, Laheij 2000, Kalman 1999). Traditionally post-operative surveillance programmes have consisted of frequent CT imaging (van der Vilet 2011, Carrafiello 2008, Eliason 2008, Back 2007, Hartshorne 2006, Murphy 2004, Thurnher 2002, Veith 2002, Makaroun 2001, Görich 1999, Karch 1999, Golzarian 1998, Balm 1997, Grimshaw 1992) which have been calculated to contribute 65% of EVAR costs (Karthikesalingam 2011b, van der Vilet 2011, Verhoeven 2011b, Black 2009, Sharma 2009, Hayter 2005, Michaels 2005, Bosch 2002, Patel 1999). This is a large financial burden for the NHS and impacts negatively towards diagnostic provisions.

A cost-effective solution is required and DUS has been proposed as a non-invasive routine surveillance. Clinical results of DUS surveillance protocols have widely varying results (Sharma 2009, Sandford 2006, Sun 2006b, Arko 2004, Elkouri 2004b, Hiatt 2004, Sprouse 2004, Raman 2003, Golzarian 2002, Greenfield 2002, McLafferty 2002, D'Audiffret 2001, Pages 2001, Fletcher 2000, Wolf 2000, Zannetti 2000, McWilliams 1999, Berdejo 1998, Kronzon 1998, Sato 1998, Thompson 1998, Heilberger 1997). Addition of microbubble contrast enhancement has significantly improved endoleak detection rates in the majority of

studies (Giannoni 2012, Cantisani 2011, Verhoeven 2011b, Bakken 2010, Iezzi 2010, Pfister 2010, Clevert 2009e, Iezzi 2009, Karthikesalingam 2009, Clevert 2008c, Clevert 2008d, Giannoni 2007, Henao 2006, Bargellini 2005b, Giannoni 2003, Heilberger 1997), yielding greater accuracies comparable with CT (Carrafiello 2006, Napoli 2004, Bendick 2003).

The literature fails to explain which endoleak type DUS misses and why, tending to blame user technique and patient habitus. Nobody has deciphered the physical properties of an endoleak that reduced DUS sensitivity. Similarly it has not been described which characteristics of an endoleak are enhanced with the addition of microbubbles.

Szucs-Farkas et al, have studied the physical properties of endoleaks detected by CT, using a phantom (Szucs-Farkas 2009). This group has conducted an extensive number of experiments using CT phantoms (Schindera 2011, Szucs-Farkas 2011, Schindera 2010, Schindera 2009b, Szucs-Farkas 2008) as have other investigators (Kalva 2006). Initially investigations were concerned with the effect of CT voltage tube energy and simulated patient size. Only recently it has been demonstrated that endoleak size and position can significantly affect CT detection (Szucs-Farkas 2009).

Endoleak physical properties have not been investigated using DUS or CEADUSS, further study could improve surveillance detection rates. To do this, I successfully developed and constructed an EVAR phantom model with a simulated variable endoleak in conjunction with the department of clinical physics at Barts and The London NHS Trust. After preliminary laboratory study of the *in vitro* behavior of microbubble contrast and its decay within our system, I used the phantom to investigate limitations of DUS in detecting endoleak with variable settings and I also tested ultrasonographers with varying vascular ultrasound experience. I then investigated the effect of microbubble contrast addition and thus factors effecting endoleak detection using CEADUSS which were to be compared with DUS performance findings.

The variables that I wanted to investigate were as follows:

1) The performance of DUS Vs CEADUSS to see if the addition of contrast significantly enhanced the sensitivity of endoleak detection in my phantom as is suggested by

numerous authors in the literature (Giannoni 2012, Cantisani 2011, Verhoeven 2011b, Bakken 2010, Pfister 2010, Clevert 2009e, Clevert 2008d, Giannoni 2007, Bargellini 2005b, Napoli 2004, Giannoni 2003), reduced the proportion of inconclusive tests and to investigate the agreement between these two investigative modalities.

2) The performance of both DUS and CEADUSS when endoleak plane position was varied between anterior, lateral and posterior with respects to the actual EVAR stent, to see the effects on detection rates. It is well documented that body habitus effects ultrasound quality and performance (Arko 2004b, Elkouri 2004b, Pearce 2004, Heilberger 1997). My initial thoughts were that the more superficial the endoleak the easier it was to detect than those deeper where the ultrasound beam has to penetrate more tissue and distance. Thus my hypothesis was that anterior leaks would be detected more easily than lateral and those posteriorly located, which would be imaged the least

3) To assess the effect of endoleak position from variable (2, 1 and 0cm) from the actual EVAR stent on detection using both DUS and CEADUSS. The only study to investigate this physical property of an endoleak, however using CT phantoms, suggested that those further away from the main stent were more readily detected compared with those nearer (Szucs-Farkas 2009). This property of an endoleak has not been previously detected using ultrasound and I believe that detection rates will be similar to Szucs-Farkas et al, and they will be particularly poor when the leak is superimposed over the EVAR stent, where color spillover will be maximum and will have a delirious effect on recognition.

4) It is well documented that endoleak flow rates can vary and those often missed are low (Iezzi 2010, Hartshorne 2006, Henao 2006, Bendick 2003, Matsumara 2001). Picking up low flow leaks is an advantage of CEADUSS and so I want to assess which endoleaks DUS detects more readily and how this performance compares with CEADUSS to try and explain if flow rate is responsible for the documented advantages of using contrast in the literature. It is my belief that high flow leaks will be detected more readily than low flow ones and that CEADUSS will detect more low flow leaks than DUS.

5) It is well documented in the literature that user experience can have an effect on the sensitivity of ultrasound performance. To investigate this factor, I intend to use a range of ultrasonographers with varying years of DUS experience (23, 11, 7, 2.5, 2 and 0) to see the effect on endoleak detection. Next I will also assess their ability using CEADUSS of which none of them have any prior experience. It is my expectation that those with the most experience will perform the best and detect more endoleaks and have less inconclusive results and perform better with CEADUSS.

It is my ultimate aim from my phantom experiments to see which physical properties of an endoleak (position, plane, flow rate) affect detection and also the contribution that user experience has on the techniques. By assessing these factors, I can compare DUS and CEADUSS to see which has a contributory role in the different pick-up rates of these two modalities, if there is any from my comparison of the two techniques in my experiments.

METHODS

I recruited six vascular scientists from Barts and The London NHS Trust who regularly performed aortic ultrasonography for pre-operative patients and EVAR surveillance. The six subjects had variable clinical experience (**Table 6**). They varied from a very experienced vascular scientist who has published widely in the field of ultrasound with 23 years clinical experience, to four clinical scientists who had been practicing for 11, 7, 5.5 and 5 years respectively to a vascular ultrasound MSc student with 6 months experience. None of the subjects had any prior CEADUSS experience. All subjects were blinded to the EVAR phantom set up and details of its construction were confined to only one person, the Vascular scientist who helped construct the actual model.

Table 6: Showing the variable experience with the clinical use of vascular ultrasound of the six subjects

Subject	Years practicing vascular ultrasound clinically
1	23
2	11
3	7
4	2.5 (plus 3 years as a student)
5	2 (plus 3 years as a student)
6	0 (plus 6 months as a student)

The phantom variables that I wanted to investigate were as follows:

1. Endoleak plane – anterior, lateral and posterior to the EVAR stent
2. Endoleak position – near-far from the stent-graft (transducer positions 1, 2, 3, 4 & 5)
3. Endoleak flow rate – 100, 300, 500, 700 and 900mls/hr
4. Operator experience – 23, 11, 7, 2.5, 2 and 0 years practicing ultrasound experience

I asked the subjects to record if they had seen an endoleak as yes, no or maybe (**Tables 8-9**). I tested the subjects over a range of different endoleak simulations using colour Doppler ultrasound and then repeated the same tests with the addition of contrast enhanced microbubbles.

Statistical advice was sought from the joint research and development office of Barts and The London NHS Trust and Queen Mary University of London prior to planning the phantom study and the study variables were clarified. It was confirmed that this was to be a randomized, single blind, cross-over, case-controlled study that would record results via a categorical variable measured analogue scale as Yes/Maybe/Not seen. Statistical analysis would be based on a logistical regression to predict the probability of outcome. The effect of contrast could be addressed as a dummy variable in the logistical regression. The power calculation for using 5 subjects was appropriate and allowed the positive response to increase from 0 to 80% and it would test for 1% significant level and 80% power. Statistical support was again sought following data collection for re-analysis due to incorrect assumptions being made with the data, to correct it for proper valid conclusions.

I listed and assigned a number to the various different positions, planes and flow rates of the endoleak that could be simulated by the phantom (**Table 7**) and using a random research number generator (www.randomizer.org/form.htm) generated a range of permutations over which to test the subjects. Each subject would be allowed to interrogate the phantom for an endoleak for 1 minute and in total consisted of 36 different endoleaks. After testing 4 endoleaks, I allowed the subject to rest for 3 minutes and to verify that the images were saved correctly, whilst I altered the endoleak plane by rotating the phantom and replenished the water within the viewing window. Total time for testing the phantom lasted 1 hour per subject.

I tested all six subjects in one day, testing with microbubble contrast commenced the next day. The reason for performing tests over two days was to prevent subject fatigue and also once contrast was added, the phantom was contaminated thus colour Doppler testing would not be possible unless fresh Doppler blood-mimic was refilled into a cleaned and drained phantom. This would be time consuming and very costly so was avoided.

Table 7: The final 36 endoleak setting that the subjects tested after randomization

Reading	Plane	Transducer Position	Endoleak (Small) Flow Rate	Time
SET UP ULTRASOUND AND PHANTOM CIRCUITS (Add contrast for 2nd set of experiments) Rotate Phantom so leak lies Lateral prior to start				
1	**Lateral**	**1**	**700mls/hr**	**1 min**
2	**Lateral**	**2**	**500 mls/hr**	**1 min**
3	**Lateral**	**3**	**300 mls/hr**	**1 min**
4	**Lateral**	**4**	**100 mls/hr**	**1 min**
Rotate Phantom so leak lies Anterior				**3 mins**
5	**Anterior**	**1**	**100 mls/hr**	**1 min**
6	**Anterior**	**2**	**300 mls/hr**	**1 min**
7	**Anterior**	**3**	**500 mls/hr**	**1 min**
8	**Anterior**	**4**	**700 mls/hr**	**1 min**
Rotate Phantom so leak lies Posterior				**3 mins**
9	**Posterior**	**1**	**100 mls/hr**	**1 min**
10	**Posterior**	**2**	**300 mls/hr**	**1 min**
11	**Posterior**	**3**	**300 mls/hr**	**1 min**
12	**Posterior**	**4**	**700 mls/hr**	**1 min**
Rotate Phantom so leak lies Anterior				**3 mins**
13	**Anterior**	**5**	**900 mls/hr**	**1 min**
14	**Anterior**	**1**	**900 mls/hr**	**1 min**
15	**Anterior**	**2**	**700 mls/hr**	**1 min**
16	**Anterior**	**3**	**100 mls/hr**	**1 min**
Rotate Phantom so leak lies Lateral				**3 mins**
17	**Lateral**	**5**	**900 mls/hr**	**1 min**
18	**Lateral**	**1**	**100 mls/hr**	**1 min**
19	**Lateral**	**2**	**300 mls/hr**	**1 min**
20	**Lateral**	**3**	**500 mls/hr**	**1 min**
Rotate Phantom so leak lies Posterior				**3 mins**
21	**Posterior**	**5**	**900 mls/hr**	**1 min**

22	**Posterior**	**1**	**900 mls/hr**	**1 min**
23	**Posterior**	**2**	**700 mls/hr**	**1 min**
24	**Posterior**	**3**	**500 mls/hr**	**1 min**
Rotate Phantom so leak lies Anterior				**3 mins**
25	**Anterior**	**4**	**300 mls/hr**	**1 min**
26	**Anterior**	**5**	**100 mls/hr**	**1 min**
27	**Anterior**	**1**	**500 mls/hr**	**1 min**
28	**Anterior**	**2**	**500 mls/hr**	**1 min**
Rotate Phantom so leak lies Lateral				**3 mins**
29	**Lateral**	**4**	**900 mls/hr**	**1 min**
30	**Lateral**	**5**	**700 mls/hr**	**1 min**
31	**Lateral**	**1**	**300 mls/hr**	**1 min**
32	**Lateral**	**2**	**100 mls/hr**	**1 min**
Rotate Phantom so leak lies Posterior				**3 mins**
33	**Posterior**	**4**	**300 mls/hr**	**1 min**
34	**Posterior**	**5**	**100 mls/hr**	**1 min**
35	**Posterior**	**1**	**100 mls/hr**	**1 min**
36	**Posterior**	**2**	**500 mls/hr**	**1 min**

TOTAL = 60 minutes (36 readings /1 min per reading / 3 mins to rotate phantom)

**For 2nd set of experiments – save images after every 4 readings, i.e. just before phantom is rotated and measure image/contrast brightness to record contrast decay and top up etc....*

The phantom test protocol given to the subjects prior to commencing testing of the phantom was as follows:

Phantom Test Protocol

SHORT EXPLANATION

During an EVAR procedure a stent is placed in the aorta, the success of which is monitored with either CT or ultrasound. The stents are prone to leaking. We want to quantify the limitations of ultrasound detection using Unenhanced Colour Doppler imaging i.e. the lowest flow detectable on scan. Then we will repeat the procedure with Contrast Enhanced Ultrasound to see if endoleak detection is altered and to what degree.

In Clinical Physics we have constructed a test object that mimics human anatomy. The test object or phantom has a large stented vessel (EVAR diameter 24mm). The flow in the large vessel remains constant. A second small vessel (endoleak diameter 2mm) has flow which runs diagonally to the main vessel and can lie anterior, lateral or posterior to the main vessel. The flow in this small vessel will have five settings (100, 300, 500, 700 & 900mls/hr). The imaging window has 5 different planes and can show the vessels at variable distances from each other. This permits three variables: the small vessel flow rate, the small vessel position and the distance of the small vessel from the large vessel.

We aim to simulate an endoleak in various flows, planes and positions. The observer will decide whether they can see the leak using a scale of 0-2 where 0 is no leak, 1 is maybe and 2 is definite leak (**Tables 8-9**).

Phantom Variables

1. Unenhanced Colour Doppler (DUS) Vs Contrast (CEADUSS)
2. Ultrasound Endoleak detected = Yes/Maybe/No
3. Endoleak Plane = Anterior/Lateral/Posterior
4. Endoleak Position = 1/2/3/4/5
5. Endoleak Flow rate = 100/300/500/700/900mls/hr
6. Operator experience = 23, 11, 7, 2.5, 2 and 0 years practicing

EVAR TEST OBJECT PROTOCOL (Tester/Controller)

Tests first to be conducted in Unenhanced Colour Doppler Ultrasound then with contrast enhancement in a different session

Set up

- ATL HDI 5000 - Power up scanner. Press "Scan Head" and select correct probe (C5-2) and protocol "Abdominal – EVAR" for the unenhanced colour Doppler tests. For the enhanced colour Doppler tests press "Scan Head" and select correct probe (C5-2) and protocol "Contrast – Gen Imaging Setting".

- SMALL VESSEL - Fill the small vessel drop bag with blood-mimicking fluid (ATS Model 707). Ensure that there are no air bubbles or kinks in the line by releasing it from the infusion pump and undoing pipe clamp. Fluid should flow into blood mimic beaker. Once flow is seen, tighten pipe clamp. Re-attach the line into the infusion pump and close. Turn on the infusion pump. Set the rate to 300 ml/hr. In order to start the pump, press run/hold five times. Should alarm sound, this could be either because there is air in the tube or the drip monitor is not in position.

- LARGE VESSEL – Turn on the aorta pump. Set the rate to 45rpm. Press start. Ensure that there are no air bubbles or visible particulates in the vessel. In order to rid the system of these anomalies, release the pipe join in reservoir and run peristaltic pump at 100rpm with wire gauze held over reservoir outlet/pump inlet pipe. Once blood mimic has been cleared, re-attach the pipe while ensuring not to introduce further air into the system.

EVAR TEST (Observer protocol)

Select the curvilinear (C5-2) probe and rotate phantom so that scan plane 1 is on top. Fill viewing platform with distilled water. Place probe at scan position 3 with probe perpendicular to phantom. Set 2D gain so that tissue background corresponds to middle of grey scale bar. When image is maximized for grayscale, the HD zoom should be used to focus on the area surrounding the stent. It may be necessary to revert to full screen at times in order to check the angling of the probe.

Once the test begins, the colour flow box should be switched on and positioned over the aorta stent vessel with edges of box 2cm box away in all directions. The colour should then be optimized so that the small flow can be visualized using the two controls: Colour gain and colour p.r.f. Start each test with the p.r.f. set high and the colour gain set low. Increase the gain until the point where the colour in the large vessel is not leaking outside its perimeter. Adjust/reduce p.r.f. until small flow can (or cannot) be seen.

You will be asked how well the small vessel is visualized in relation to the big vessel. This should be scored: 0 = no visualization, 1 = possible/maybe visualized and 2 = definite visualization (**Tables 8-9**). One should also note down the gain and p.r.f settings which can be altered for each position.

Plane 1/2/3:

These tests are performed with the probe at right angles to the acoustic window. Use probe guide at pinned positions in order to set the angle and position. We will periodically change the plane of endoleak so please bear with us as we do this.

"PERFORM TESTS"

Empty the well using the large syringe. Wipe excess up with paper towel. Rotate the phantom to scan the 3 different planes. Fill well with distilled water.

Table 8: Subject responses were recorded on the following table for the unenhanced colour Doppler tests

CEADUSS PHANTOM - UNENHANCED COLOUR DOPPLER TEST SHEET

Test __: Time and Date

Subject Name:

Years qualified:

Reading	**Visibility** *0 = no visualization* *1 = maybe visualized* *2 = definite visualization*	**Colour p.r.f**	**Colour gain**
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			

23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			

Table 9: Subject responses were recorded on the following table for the contrast enhanced tests

CEADUSS PHANTOM - CONTRAST ENHANCED TEST SHEET

Test __: Time and Date

Subject Name:

Years qualified:

Reading	**Visibility** *0 = no visualization* *1 = maybe visualized* *2 = definite visualization*
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
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34	
35	
36	

Ethical permission was not required for this study because it was a laboratory phantom experiment without involvement of humans or tissue. This decision was made by the Joint Research and Development Office of Barts and The London NHS Trust and Queen Mary University of London.

RESULTS

Six subjects were tested using DUS on the phantom with 36 simulated endoleaks during one day and retested using the same endoleaks but with CEADUSS the following day:

- 6 testing subjects
- 36 phantom simulated variable endoleaks tested with DUS for each subject
- 36 phantom simulated variable endoleaks tested with CEADUSS for each subject
- 216 observations in total with DUS
- 216 observations in total with CEADUSS

Microbubble contrast produced satisfactory images and endoleak enhancement throughout the duration of experimentation. The results from testing involved a number of variables and generated a large quantity of data. The data was broken down into a variety of subsets for analysis:

1) **The performance of DUS Vs CEADUSS**
   a) Sensitivity of DUS and CEADUSS for endoleak detection
   b) Inconclusive examinations of DUS and CEADUSS
   c) Inter-modality agreement between DUS and CEADUSS for all results combined
   d) Inter-modality agreement between DUS and CEADUSS for each individual subject
   e) Inconclusive examinations amongst sonographers with differing operator experience using DUS and CEADUSS
   f) Sensitivity for endoleak detection with DUS and CEADUSS for sonographers with differing operator experience

2) **The effect of changing variables of an endoleak on DUS detection rates**
   a) Effect of varying endoleak plane position upon detection using DUS
   b) Effect of varying endoleak distance from EVAR stent-graft upon detection using DUS
   c) Effect of varying endoleak flow rate upon detection using DUS
   d) Effect of operator experience upon endoleak detection using DUS

e) Univariate analysis of independent variables in the DUS experiments to see if they were independent
f) Evaluation of independent predictors of endoleak detection using DUS
g) Colour Doppler pulse repetition frequency setting changes between subjects
h) Colour Doppler gain setting changes between subjects

3) The effect of changing variables of an endoleak on CEADUSS detection rates

a) Effect of varying endoleak plane position upon detection using CEADUSS
b) Effect of varying endoleak distance from EVAR stent-graft upon detection using CEADUSS
c) Effect of varying endoleak flow rate upon detection using CEADUSS
d) Effect of operator experience upon endoleak detection using CEADUSS
e) Univariate analysis of independent variables in the CEADUSS experiments to see if they were independent or correlated with each other
f) Evaluation of independent predictors of endoleak detection using CEADUSS

Initially I analyzed my results by combining the results for endoleaks definitely seen (yes) with those possible seen (inconclusive) to form a group of endoleaks that were positive identified to compare with those negatively observed (no). However, by doing this my results were positively biased giving unreliable interpretations of the data. In reality CEADUSS would be used only in the setting where DUS cannot reliably exclude an endoleak. Therefore CEADUSS is only useful if it has a higher sensitivity for endoleak detection than Doppler and therefore reduces the number of inconclusive examinations. Therefore the putative benefits of CEADUSS would be if it reduced the number of inconclusive examinations and if it delivered a higher sensitivity for endoleak detection.

I re-analyzed the data to assess the three independent outcomes independently and particularly focused more on indecision and inconclusive detection of endoleaks to more reliable decipher sensitivity.

For assessing each modality (DUS and CEADUSS) independently and the effects on my measured variables, I had to convert the results into a binary outcome for categorical

observations and Univariate analysis into non-diagnostic (inconclusive) and diagnostic (yes or no) for assessment.

1) The performance of DUS Vs CEADUSS

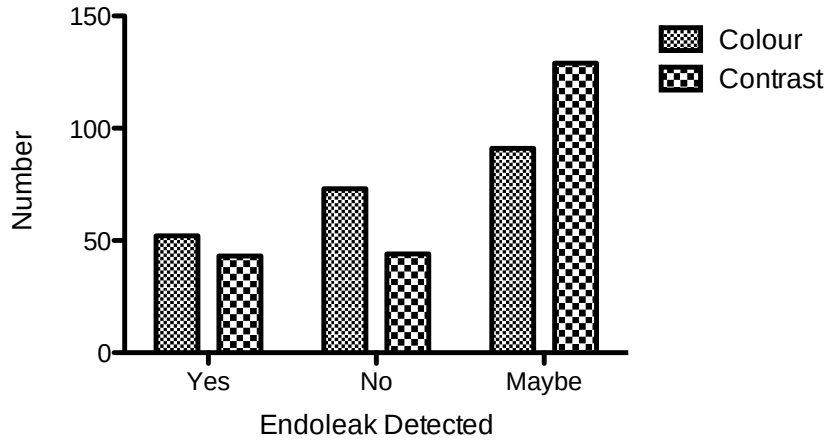
a) Sensitivity of DUS and CEADUSS for endoleak detection

To decipher the sensitivity of both investigative modalities I used the raw data for combined DUS and CEADUSS results in endoleak detection (Yes/No/Inconclusive seen) without simplification. I used a contingency table to determine proportions (**Table 10)** and then plotted them (**Graph 6**). The data was analyzed using Chi-square test and showed a significant difference (p=0.0007) between DUS and CEADUSS for endoleak detection. The addition of microbubble contrast produced more inconclusive decisions than DUS.

Table 10: A contingency table of combined results for endoleak detection using DUS and CEADUSS

Endoleak detection	DUS	CEADUSS
Yes	52	43
No	73	44
Inconclusive	91	129

Graph 6: Combined DUS and CEADUSS data (with inconclusive's considered separately)



Chi-square **p=0.0007**

To compare the sensitivity of these two modalities, the outcomes would have to be changed to a binary outcome to allow me to do a McNemar test for paired categorical observations, which is based on a chi-square test with two modalities on a single case. The data was thus separated into absent or uncertain endoleak (0) and definite endoleak (1). The data is presented in **Table 11** with a McNemar test and also Chi-square test with Yates' continuity correction.

Table 11: A McNemar test for paired categorical observations and Chi-square test with Yates continuity correction for DUS and CEADUSS sensitivity of endoleak detection

McNemar test for paired categorical observations

	DUS positives only		
CEADUSS positives only	**0**	**1**	
0	65	22	87 (40.3%)
1	60	69	129 (59.7%)
	125 (57.9%)	91 (42.1%)	216
Difference	17.59%		
95% CI	9.30 to 24.57		

Chi-square test with Yates continuity correction

Chi-square	16.6951
DF	1
Significance	P < 0.0001

The overall sensitivity of DUS was 91/216 = 42% and CEADUSS was 129/216 = 60%, producing a difference of 18% (95% CI 9-25%) in favor of CEADUSS. There is a statistically significant increase in the sensitivity of CEADUSS for endoleak detection across all observers and conditions of 18% when CEADUSS is added (p<0.0001), which may have clinical significance.

b) Inconclusive examinations of DUS and CEADUSS

The data was again presented depending upon diagnostic outcome and analyzed with a McNemar test and also Chi-square test with Yates' continuity correction, **Table 12**. This time the data were split into diagnostic (0) and inconclusive examinations (1). There were 52/216 = 24% inconclusive examinations with DUS and 43/216 (20%) with CEADUSS demonstrating a difference of 4% (95% CI -3%-11%). There was no statistically significant difference in inconclusive examinations with the addition of CEADUSS (p=0.3135). The percentage proportion of inconclusive and non-diagnostic tests was not changed, there was a marginal benefit but this was not clinically significant.

Table 12: A McNemar test for paired categorical observations and Chi-square test with Yates continuity correction for DUS and CEADUSS inconclusive examinations

McNemar test for paired categorical observations

CEADUSS inconclusive results	DUS inconclusive results 0	1	
0	137	36	173 (80.1%)
1	27	16	43 (19.9%)
	164 (75.9%)	52 (24.1%)	216

Difference	4.17%
95% CI	-3.47 to 11.40

Chi-square test with Yates' continuity correction

Chi-square	1.0159
DF	1
Significance	P = 0.3135

c) Inter-modality agreement between DUS and CEADUSS for all results combined

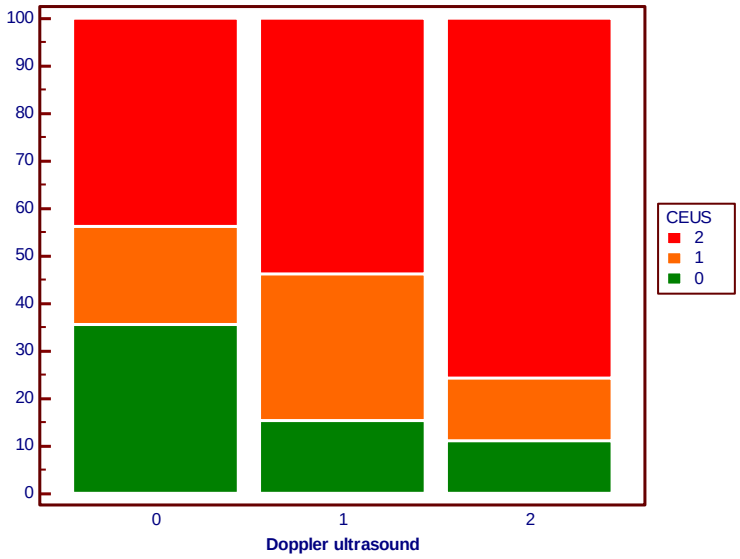
Below in **Table 13** and **Graph 7** data is shown that reinforces the findings of b) Inconclusive examinations of DUS and CEADUSS as presented above. To overcome this problem with statistical comparison that I have because McNemar test for two paired groups only allows a present or absent data format, i.e. no inconclusives, I used kappa for inter-modality agreement, **Table 13**. The 18% increase in sensitivity between using DUS (42.1%) to CEADUSS (59.7%) can again be seen which was significant ($p<0.0001$). The proportions of endoleaks inconclusives' seen with DUS (24.1%) and CEADUSS (19.9%) were approximately the same. Lastly the proportion of endoleaks not seen with DUS (33.8%) was more than those not seen with CEADUSS (20.4%). The kappa value generated was **0.23** which tells us that there is only **fair agreement** between DUS and CEADUSS overall. These findings are graphically represented in **Graph 7** below.

Table 13: The inter-modality kappa analysis of agreement between DUS and CEADUSS for all subjects

	DUS			
CEADUSS	**0**	**1**	**2**	
0	26	8	10	44 (20.4%)
1	15	16	12	43 (19.9%)
2	32	28	69	129 (59.7%)
	73 (33.8%)	52 (24.1%)	91 (42.1%)	216

Kappa	**0.23**
Standard error	0.0495
95% CI	0.133 to 0.327

Graph 7: The inter-modality agreement between DUS and CEADUSS for all subjects



d) Inter-modality agreement between DUS and CEADUSS for each individual subject

To avoid the issue of different ultrasonographers with different scanning experience and modalities, I also performed inter-modality kappa per subject **Tables 14-20** and **Graph 8** below.

The most senior sonographers of 23 years experience results (**Table 14**) revealed that there was more CEADUSS endoleaks detected (yes) 55.6% compared with 44.4% of DUS detected (yes). The proportion of endoleaks inconclusive seen was exactly the same for both modalities (16.7%). The proportion of endoleaks not seen (no) was less for CEADUSS (27.8%) compared with DUS (38.9%). The kappa value generated was **0.55** which tells us that there is a **moderate agreement** between DUS and CEADUSS for the subject with 23 years experience.

Table 14: The inter-modality kappa analysis of agreement between DUS and CEADUSS for subject with 23 years experience

	23 years experience DUS			
23 years experience CEADUSS	**0**	**1**	**2**	
0	9	0	1	10 (27.8%)
1	2	3	1	6 (16.7%)
2	3	3	14	20 (55.6%)
	14 (38.9%)	6 (16.7%)	16 (44.4%)	36

Kappa	**0.55**
Standard error	0.115
95% CI	0.324 to 0.776

The next most experienced sonographers of 11 years results revealed (**Table 15**) that there was a greater proportion of endoleaks seen (yes) with CEADUSS (50%) than with DUS (25%), twice the amount. There were less endoleaks inconclusive seen with CEADUSS (27.8%) than with DUS (38.9%). Lastly there were less endoleaks not seen (no) with CEADUSS (22.2%) than with DUS (36.1%). Overall the Kappa result generated of **0.292** reveals that there was a **slight agreement** between DUS and CEADUSS when used by the sonographers with 11 years experience.

Table 15: The inter-modality kappa analysis of agreement between DUS and CEADUSS for subject with 11 years experience

	11 years experience DUS			
11 years experience CEADUSS	**0**	**1**	**2**	
0	4	3	1	8 (22.2%)
1	6	2	2	10 (27.8%)
2	3	9	6	18 (50.0%)
	13 (36.1%)	14 (38.9%)	9 (25.0%)	36

Kappa	**0.0292**
Standard error	0.108
95% CI	-0.183 to 0.242

The sonographers with 7 years experience results (**Table 16**) revealed that there was also a **moderate agreement** between DUS and CEADUSS, by generating a kappa value of **0.573**. The proportion of endoleaks seen (yes) and not seen (no) were similar for both modalities and the proportions of inconclusive seen were exactly the same.

Table 16: The inter-modality kappa analysis of agreement between DUS and CEADUSS for subject with 7 years experience

	7 years experience DUS			
7 years experience CEADUSS	**0**	**1**	**2**	
0	9	2	0	11 (30.6%)
1	3	4	2	9 (25.0%)
2	0	3	13	16 (44.4%)
	12 (33.3%)	9 (25.0%)	15 (41.7%)	36

Kappa	**0.573**
Standard error	0.110
95% CI	0.357 to 0.789

The results from the sonographers with 2½ years experience (**Table 17**) show that CEADUSS produced more endoleaks seen and inconclusive seen (55.6% and 22.2% respectively) than DUS (38.9% and 16.7%). CEADUSS corresponding produced less

endoleaks not seen 22.2% compared with 44.4% for DUS. The kappa calculation was **0.0571** implying that there was a **slight agreement** between modalities for this subject.

Table 17: The inter-modality kappa analysis of agreement between DUS and CEADUSS for subject with 2½ years experience

	2½ years experience DUS			
2½ years experience CEADUSS	**0**	**1**	**2**	
0	2	1	5	8 (22.2%)
1	3	4	1	8 (22.2%)
2	11	1	8	20 (55.6%)
	16 (44.4%)	6 (16.7%)	14 (38.9%)	36

Kappa	**0.0571**
Standard error	0.128
95% CI	-0.194 to 0.308

The subject with 2 years ultrasound experience produced the following results (**Table 18**). There were more endoleaks identified (yes) using CEADUSS (80.6%) than with DUS (44%). Correspondingly there were less endoleaks inconclusive seen (13.9%) and not seen (5.6%) when compared with DUS (30.6% and 25% respectively). The kappa value of **-0.0435** reveals that there was **no agreement** between DUS and CEADUSS for endoleak detection for the subject with 2 years experience.

Table 18: The inter-modality kappa analysis of agreement between DUS and CEADUSS for subject with 2 years experience

	2 years experience DUS			
2 years experience CEADUSS	**0**	**1**	**2**	
0	0	1	1	2 (5.6%)
1	0	2	3	5 (13.9%)
2	9	8	12	29 (80.6%)
	9 (25.0%)	11 (30.6%)	16 (44.4%)	36

Kappa	**-0.0435**
Standard error	0.0990
95% CI	-0.238 to 0.151

The most inexperienced subject with 0 years experience as she was a student of 6 months had results (**Table 19**) that produced a kappa result of **0.0933** implying that there was **slight agreement** for endoleak detection using DUS and CEADUSS. CEADUSS produced a greater proportion of endoleaks detected (yes) 72.2% than DUS 58.3%. Approximately the same proportion of endoleaks inconclusive seen was produced by both DUS and CEADUSS (16.7% and 13.9% respectively). CEADUSS resulted in less cases of endoleaks not being seen (no) 13.9% than DUS 25%.

Table 19: The inter-modality kappa analysis of agreement between DUS and CEADUSS for subject with 0 years experience

	0 years experience DUS			
0 years experience CEADUSS	**0**	**1**	**2**	
0	2	1	2	5 (13.9%)
1	1	1	3	5 (13.9%)
2	6	4	16	26 (72.2%)
	9 (25.0%)	6 (16.7%)	21 (58.3%)	36

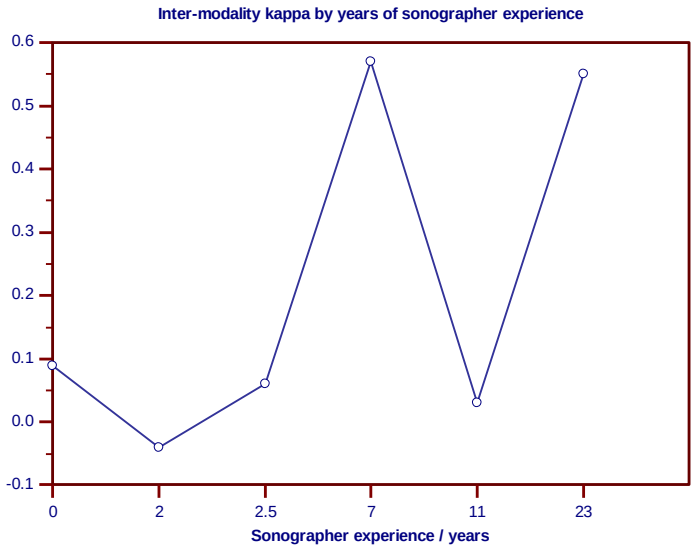
Kappa	**0.0933**
Standard error	0.127
95% CI	-0.156 to 0.343

Below in **Table 20** is a summary table of the overall results for all subjects combined and individuals showing the kappa agreement.

Table 20: Summary of combined results and individual subject's kappa inter-modality agreements using DUS and CEADUSS with years experience

	Ultrasonographer years experience						Overall combined
	23	**11**	**7**	**2½**	**2**	**0**	
Kappa value	0.55	0.0292	0.573	0.0571	-0.0435	0.0933	**0.23**
Agreement	Moderate	Slight	Moderate	Slight	None	Slight	**Fair**

Graph 8: Inter-modality kappa by years of sonographers experience comparing DUS and CEADUSS endoleak detection



Overall there was fair agreement beyond that expected by chance. It was difficult to identify if inter-modality agreement changed with years of experience as the number of sonographers involved was low, making the graph sensitive to outliers (subjects with 11 and 7 years experience).

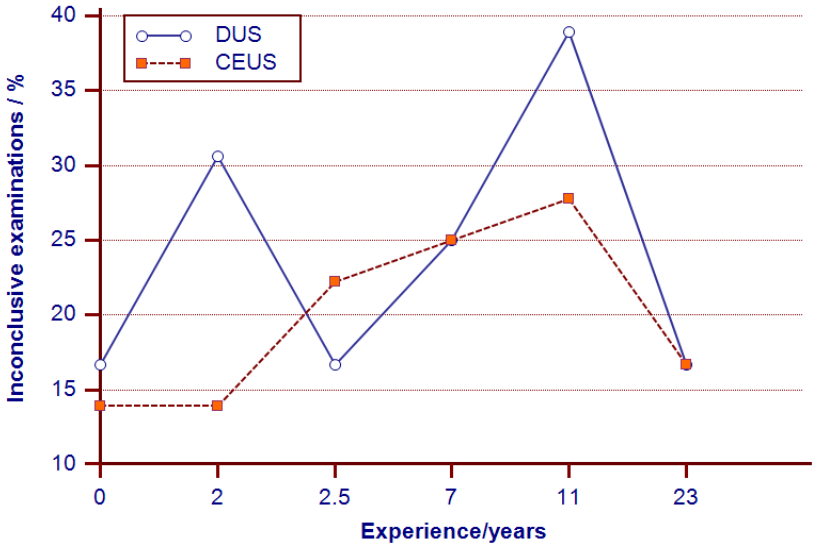
e) Inconclusive examinations amongst sonographers with differing operator experience using DUS and CEADUSS

The data generated from each individual subject (**Tables 14-19**) can be plotted to illustrate proportions of inconclusive examinations using either DUS or CEADUSS against operator experience (**Graph 9**). There were approximately the same number of inconclusive examinations using DUS and CEUS. The sonographers with the most experience (23 years) and those with 7 years experience had exactly the same proportions of inconclusive studies with both modalities. The sonographers with 11 and 2 years' experience both had more inconclusive results with DUS then CEADUSS and the subject with 0 years experience had

only slightly more inconclusive results with DUS. The subject with 2½ years experience was the only one to have more inconclusive results with CEADUSS than DUS.

There was no visual trend for inconclusive examinations for sonographers of differing experience but it appeared that for sonographers of increasing seniority CEADUSS gave more inconclusive examinations. This suggests that in this group of sonographers the diagnostic benefit of adding in CEADUSS was unrelated to experience. It may reflect how comfortable the sonographers were in using or interpreting CEADUSS images, rather than any improvement of the technique over Doppler alone. This may be a function of a learning curve.

Graph 9: Inconclusive examinations amongst sonographers of differing experience using DUS and CEADUSS

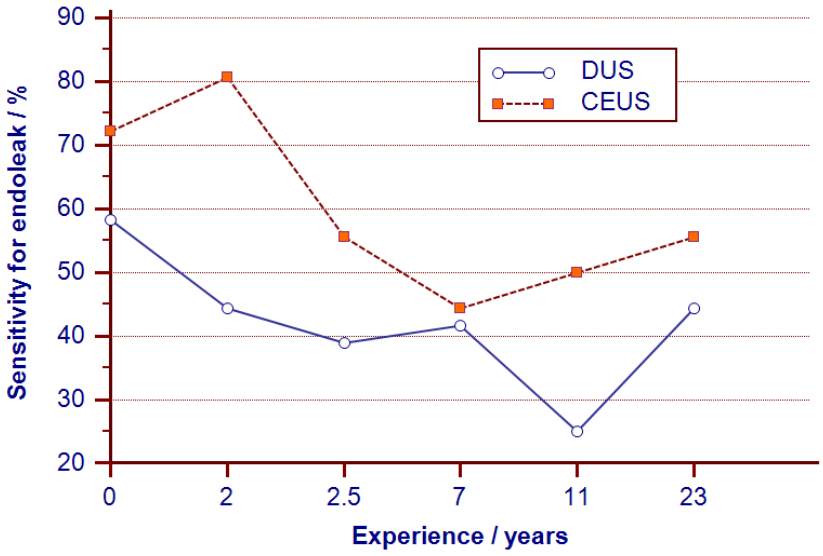


f) Sensitivity for endoleak detection with DUS and CEADUSS for sonographers with differing operator experience

The data generated from each individual subject (**Tables 14-19**) can again be plotted to illustrate sensitivity for endoleak detection using either DUS or CEADUSS for sonographers of differing experience (**Graph 10**). The more junior sonographers appeared to have a higher

sensitivity for endoleak detection and this was consistently enhanced through addition of CEADUSS. Endoleaks were most likely to be detected using CEADUSS by the more junior sonographers with ≤2½ years of experience.

Graph 10: Sensitivity for endoleak detection with DUS and CEADUSS for sonographers of differing experience



2) The effect of changing variables of an endoleak on DUS detection rates

To evaluate the effect of changing various physical properties of an endoleak and the effect on detection with DUS, I performed a Univariate analysis upon the data. In order to do this more reliably, I was advised after statistical consultation to have the data for analysis presented in a binary form. If the data were to be used in its existing form with three outcomes (Yes/Inconclusive/No) then the analysis would not inform us if an individual factor was related to the definite presence of an endoleak (note in this experiment a real endoleak was present every time) or allow multivariate analysis to identify independent factors associated with finding a true endoleak. Thus the data was separated into two categories, endoleak definitely seen and not (everything else).

The four main variables tested for DUS were: endoleak plane position, endoleak distance from midline/EVAR stent-graft, endoleak flow rate and sonographer years of experience. These are all in fact categorical variables, as they cannot have incremental quantities, so the appropriate test for analysis is chi-squared. Below are the separate Univariate analyses for the measured variable to decipher if each one has an effect on endoleak detection.

Once this was established, I next set out to see if these variables were correlated to each other using a Spearman rank correlation analysis. If they were independent then I was to perform a multivariate analysis to assess variables that affect endoleak detection with DUS.

a) Effect of varying endoleak plane position upon detection using DUS

Endoleak plane position was varied so it lay anterior, lateral or posterior to the main EVAR stent-graft. Sonographic testing subjects recorded if they saw the endoleak using DUS as: yes, inconclusive or no. The data was separated into definitely saw the endoleak (Yes) or did not definitely see the endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 21**).

Table 21: A Univariate analysis of DUS endoleak detection with variable endoleak plane position

	DUS endoleak detection		
Endoleak position	**0 (everything else)**	**1 (definite endoleak)**	
1 – Ant	37	35	72 (33.3%)
2 – Lat	45	27	72 (33.3%)
3 - Post	43	29	72 (33.3%)
	125 (57.9%)	91 (42.1%)	216

Chi-square	1.975
DF	2
Significance level	**P = 0.3725**

Chi-square test for trend

Chi-square test for trend	
Chi-square (trend)	1.025
DF	1
Significance level	**P = 0.3112**

There were an equal number of endoleaks positioned anteriorly, lateral and posteriorly. Anterior endoleaks were equally detected as definitely seen (35) and not (37). Less endoleaks were definitely seen than not seen for both the lateral (27 Vs 45) and posterior (29 Vs 43) positions. Endoleak plane position did not significantly affect definite endoleak detection (p=0.3725), and this is also non-significant when analyzed for trend (p=0.3112).

b) Effect of varying endoleak distance from EVAR stent-graft upon detection using DUS

Endoleak distance from the EVAR stent-graft was varied so it lay 2cm, 1cm or superimposed upon the main EVAR stent-graft. Sonographic testing subjects recorded if they saw the endoleak using DUS as: yes, inconclusive or no. The data was separated into definitely saw the endoleak (Yes) or did not definitely see the endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 22**).

Table 22: A Univariate analysis of DUS endoleak detection with variable endoleak distance from the main EVAR stent-graft

Distance of endoleak from EVAR stent-graft (cm)	DUS endoleak detection		
	0	1	
0	30	6	36 (16.7%)
1	64	26	90 (41.7%)
2	31	59	90 (41.7%)
	125 (57.9%)	91 (42.1%)	216

Chi-square	36.303
DF	2
Significance level	**P < 0.0001**

Chi-square test for trend

Chi-square (trend)	33.362
DF	1
Significance level	**P < 0.0001**

During testing of endoleak detection with DUS and varying endoleak distance from the stent-graft, equal proportions of tests for the endoleak lying 2cm and 1cm away were recorded but less tests for the endoleak being superimposed were made. When the endoleak is superimposed, it is detected less (6 Vs 30) and this is similarly seen for endoleaks 1cm away from the EVAR stent-graft (26 Vs 64). However, at 2cm more endoleaks are definitely detected (59 Vs 31). Distance of endoleak from the EVAR stent-graft significantly affects definite endoleak detection ($p<0.0001$) and this is also significant when analyzed for trend ($p<0.0001$).

c) Effect of varying endoleak flow rate upon detection using DUS

Endoleak flow rate was varied from 100, 300, 500, 700 and 900ml/hr. Sonographic testing subjects recorded if they saw the endoleak using DUS as: yes, inconclusive or no. The data

was separated into definitely saw the endoleak (Yes) or did not definitely see the endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 23**).

Table 23: A Univariate analysis of DUS endoleak detection with variable endoleak flow rate

	DUS endoleak detection		
Endoleak flow rate (ml/hr)	**0**	**1**	
100	28	20	48 (22.2%)
300	31	5	36 (16.7%)
500	38	22	60 (27.8%)
700	18	18	36 (16.7%)
900	10	26	36 (16.7%)
	125 (57.9%)	91 (42.1%)	216

Chi-square	26.801
DF	4
Significance level	**P < 0.0001**

Chi-square test for trend

Chi-square (trend)	12.475
DF	1
Significance level	**P = 0.0004**

The slowest endoleaks (100ml/hr), slightly less were definitely detected (20/28 [42%]). At 300ml/hr the majority of endoleaks were not detected (5/36 [14%]) and similarly at 500ml/hr more were not detected (22/60 [37%]). At 700ml/hr equal proportions of endoleak were definitely detected as not (18/36 [50%]). At the fastest rate (900ml/hr) more endoleaks were definitely detected than not (26/36 [72%]). Endoleak flow rate did significantly affect definite detection ($p<0.0001$) and this was also apparent when analyzed for trend ($p=0.0004$).

d) Effect of operator experience upon endoleak detection using DUS

Endoleak detection rates by operators with different experience levels were compared. The subjects had practicing years experience varying from 23, 11, 7, 2½, 2 and 0 years. The six sonographic testing subjects recorded if they saw the endoleak using DUS as: yes, inconclusive or no. The data was separated into definitely saw the endoleak (Yes) or did not definitely see the endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 24**).

Table 24: A Univariate analysis of DUS endoleak detection with operator experience

Commented [TA1]: Other option is to split into <5 years and >5 years

	DUS endoleak detection		
Sonographer experience (years)	**0**	**1**	
0	15	21	36 (16.7%)
2	20	16	36 (16.7%)
2½	22	14	36 (16.7%)
7	21	15	36 (16.7%)
11	27	9	36 (16.7%)
23	20	16	36 (16.7%)
	125 (57.9%)	91 (42.1%)	216

Chi-square	8.526
DF	5
Significance level	**P = 0.1295**

Chi-square test for trend

Chi-square (trend)	3.296
DF	1
Significance level	**P = 0.0695**

Each subject underwent 36 tests for detecting variable endoleaks with DUS. The most experienced subject of 23 years definitely detected slightly more endoleaks than not (21 Vs 15). The subject with 11 years experience definitely detected endoleaks less than not (16 Vs 20). The subjects with 7, 2½ and 2 years experience displayed a similar trend of not detecting endoleaks than definitely detecting them to a lesser degree (17 Vs 21, 14 Vs 22, 16 Vs 20). The least experienced subject with 0 years practicing who was a student of 6 months, detected more endoleaks definitely than not (21 Vs 15).

Commented [TA2]: Give percentages as in section above, i.e. 5/15 [33%]

Operator experience did not significantly affect endoleak detection (p=0.1295) and this was slightly less so for trend analysis (p=0.0695).

e) <u>Univariate analysis of independent variables in the DUS experiments to see if they were independent or correlated with each other</u>

On Univariate analysis it appears that flow rate and distance from the EVAR stent-graft are significantly associated with endoleak detection. To decipher if these independent variables are correlated to each other, I performed a Spearman rank test (**Table 25**).

<u>Table 25: A Spearman rank test of the Univariate analysis of DUS endoleak detection and variables</u>

		Endoleak position	**Endoleak flow rate (ml/hr)**	**Distance of endoleak from EVAR stent-graft (cm)**	**Sonographer experience (years)**
Endoleak position	Correlation Coefficient Significance Level P n		-0.050 0.4622 216	-0.009 0.8968 216	0.000 1.0000 216
Endoleak flow rate (ml/hr)	Correlation Coefficient Significance Level P n	-0.050 0.4622 216		**0.042 0.5422 216**	0.000 1.0000 216
Distance of endoleak from EVAR stent-graft (cm)	Correlation Coefficient Significance Level P n	-0.009 0.8968 216	**0.042 0.5422 216**		0.004 0.9506 216
Sonographer experience (years)	Correlation Coefficient Significance Level P n	0.000 1.0000 216	0.000 1.0000 216	0.004 0.9506 216	

The Spearman rank correlation coefficient interpretation is that the categorical variables are independent of each other so a Multivariate analysis can be performed.

f) Evaluation of independent predictors of endoleak detection using DUS

A Multivariate analysis of the data was performed to investigate the variables that predict endoleak detection (**Table 26**). Candidate variables were entered stepwise into the model starting with the variables with the lowest p-value.

Table 26: A Multivariate analysis of DUS endoleak detection and variables

Dependent Y	**DUS endoleak detection**
Sample size	216

Overall Model Fit

Null model -2 Log Likelihood	294.065
Full model -2 Log Likelihood	228.946
Chi-square	65.119
DF	13
Significance level	P < 0.0001

Coefficients and Standard Errors

Variable	Coefficient	Std. Error	P
Distance_from_midline__cm_=1	1.17431	0.61894	0.0578
Distance_from_midline__cm_=2	2.72650	0.67302	**0.0001**
Flow_rate__ml_hr_=300	-0.34707	0.68438	0.6121
Flow_rate__ml_hr_=500	1.15638	0.55990	**0.0389**
Flow_rate__ml_hr_=700	1.09642	0.53959	**0.0422**
Flow_rate__ml_hr_=900	1.37072	0.52131	**0.0086**
Lateral position=2	-0.56744	0.40598	0.1622
Posterior position=3	-0.31799	0.39146	0.4166
Sonographer_Years=2	-0.75048	0.55330	0.1750
Sonographer_Years=2.5	-1.05567	0.55973	0.0593
Sonographer_Years=7	-0.90197	0.55606	0.1048
Sonographer_Years=11	-1.83684	0.59485	**0.0020**
Sonographer_Years=23	-0.79989	0.55271	0.1478
Constant	-1.5582		

Odds Ratios and 95% Confidence Intervals

Variable	Odds ratio	95% CI
Distance_from_midline__cm_=1	3.2359	0.9619 to 10.8854

Distance_from_midline__cm_=2	**15.2794**	**4.0852 to 57.1470**
Flow_rate__ml_hr_=300	0.7068	0.1848 to 2.7028
Flow_rate__ml_hr_=500	**3.1784**	**1.0608 to 9.5237**
Flow_rate__ml_hr_=700	**2.9934**	**1.0396 to 8.6194**
Flow_rate__ml_hr_=900	**3.9382**	**1.4176 to 10.9406**
Lateral Position=2	0.5670	0.2558 to 1.2564
Posterior Position=3	0.7276	0.3378 to 1.5672
Sonographer_Years=2	0.4721	0.1596 to 1.3965
Sonographer_Years=2.5	0.3480	0.1162 to 1.0423
Sonographer_Years=7	0.4058	0.1364 to 1.2067
Sonographer_Years=11	**0.1593**	**0.0497 to 0.5112**
Sonographer_Years=23	0.4494	0.1521 to 1.3277

Classification table (cut-off value p=0.5)

Actual group	**Predicted group**		**Percent correct**
	0	**1**	
Y = 0	100	25	80.00 %
Y = 1	35	56	61.54 %
Percent of cases correctly classified			72.22 %

ROC curve analysis

Area under the ROC curve (AUC)	0.800
Standard Error	0.0312
95% Confidence interval	0.740 to 0.851

Significant independent predictors of endoleak detection on DUS were distance from midline of 2cm, flow rate 500ml/hr or more. Sonographer 11 was especially poor at detecting endoleaks.

g) <u>Colour Doppler p.r.f setting changes between subjects</u>

The pulse repetition frequency setting changes during the DUS experiments were recorded. There were no significant differences between colour Doppler pulse repetition frequency settings use, except that the subject with 11 years experience changed their settings the most frequently (**Table 27**).

Table 27: Subject pulse repetition frequency setting alterations during DUS experiments

Subject years experience	Number of times pulse repetition frequency settings were altered
23 years	3
11 years	8
7 years	3
2½ years	4
2 years	4
0 years	2

h) Color Doppler gain setting changes between subjects

Color gain setting changes were also recorded during the DUS tests. There were no significant differences between color Doppler gain settings used between subjects (**Table 28**).

Table 28: Subject colour gain setting alterations during DUS experiments

Subject years experience	Number of times colour Doppler gain settings were altered
23 years	14
11 years	17
7 years	18
2½ years	13
2 years	7
0 years	15

3) The effect of changing variables of an endoleak on CEADUSS detection rates

Similarly to my analysis of the six subjects DUS data, in order to perform a Univariate analysis of the variables acting upon endoleak detection, I was advised after statistical consultation to provide the data in a binary form, definitely detected or not. This allowed me to conduct individual Univariate analyses for all of the endoleak variables then a Spearman's correlation test to investigate if the variables were independent or not to ultimately perform a Multivariate analysis using multivariate logistic regression.

a) Effect of varying endoleak plane position upon detection using CEADUSS

Endoleak plane position was varied so it lay anterior, lateral or posterior to the main EVAR stent-graft. Sonographic testing subjects recorded if they saw the endoleak using CEADUSS as: yes, inconclusive or no. The data was separated into definitely saw the endoleak (Yes) or did not definitely see the endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 29**).

Table 29: A Univariate analysis of CEADUSS endoleak detection with variable endoleak plane position

	CEADUSS endoleak detection		
Endoleak position	**0**	**1**	
1 – Anterior	10	62	72 (33.3%)
2 – Lateral	40	32	72 (33.3%)
3 – Posterior	37	35	72 (33.3%)
	87 (40.3%)	129 (59.7%)	216

Chi-square	31.525
DF	2
Significance level	**P < 0.0001**

Chi-square test for trend

Chi-square (trend)	21.046
DF	1
Significance level	**P < 0.0001**

Equal numbers of tests were performed for all three endoleak plane positions. More endoleaks in the anterior position were definitely detected than not (62 Vs 10). Correspondingly less endoleaks are definitely detected in the lateral plane than not detected (32 Vs 40). Endoleaks in the posterior plane are detected in similar proportions as not definitely detected (35 Vs 37). Overall endoleak plane has a significant effect on endoleak detection with CEADUSS.

Commented [TA3]: %
Make bar chart

The detection of lateral endoleaks using DUS and CEADUSS has similarity with respects to proportions but the detection of anterior leaks is better with CEADUSS and there is no similarity in the detection of posterior endoleaks with the two modalities.

b) <u>Effect of varying endoleak distance from EVAR stent-graft upon detection using CEADUSS</u>

Commented [TA4]: %
Make bar chart

Endoleak distance from the EVAR stent-graft was varied so it lay 2cm, 1cm or superimposed upon the main EVAR stent-graft. Sonographic testing subjects recorded if they saw the endoleak using CEADUSS as: yes, inconclusive or no. The data was separated into definitely saw the endoleak (Yes) or did not definitely see the endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 30**).

Table 30: A Univariate analysis of CEADUSS endoleak detection with variable endoleak distance from the main EVAR stent-graft

Distance of endoleak from EVAR stent-graft (cm)	CEADUSS endoleak detection 0	1	
0	20	16	36 (16.7%)
1	57	33	90 (41.7%)
2	10	80	90 (41.7%)
	87 (40.3%)	129 (59.7%)	216

Chi-square	55.210
DF	2
Significance level	**P < 0.0001**

Chi-square test for trend

Chi-square (trend)	37.251
DF	1
Significance level	**P < 0.0001**

During testing of endoleak detection with CEADUSS and varying endoleak distance from the stent-graft, again equal proportions of tests for the endoleak lying 2cm and 1cm away were recorded but fewer tests for the endoleak being superimposed were made. Slightly less endoleaks were definitely detected than not (16 Vs 20) when it was superimposed over the EVAR stent-graft. The difference was not as marked as that shown using DUS. When the endoleak was 1cm away more were not definitely seen than seen (57 Vs 33), in similar proportions to DUS. At 2cm the majority of endoleaks are definitely seen (80 Vs 10), in larger proportions than with DUS. Distance from the EVAR stent-graft significantly affects definite endoleak detection with CEADUSS ($p<0.0001$), as it does with DUS.

c) Effect of varying endoleak flow rate upon detection using CEADUSS

Endoleak flow rate was varied from 100, 300, 500, 700 and 900ml/hr. Sonographic testing subjects recorded if they saw the endoleak using CEADUSS as: yes, inconclusive or no. The data was separated into definitely saw the endoleak (Yes) or did not definitely see the

endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 31**).

Table 31: A Univariate analysis of CEADUSS endoleak detection with variable endoleak flow rate

	CEADUSS endoleak detection		
Endoleak flow rate (ml/hr)	**0**	**1**	
100	9	39	48 (22.2%)
300	20	16	36 (16.7%)
500	29	31	60 (27.8%)
700	18	18	36 (16.7%)
900	11	25	36 (16.7%)
	87 (40.3%)	129 (59.7%)	216

Chi-square	17.189
DF	4
Significance level	**P = 0.0018**

Chi-square test for trend

Chi-square (trend)	1.396
DF	1
Significance level	**P = 0.2374**

When analyzing slow endoleaks (100ml/hr), larger proportions are definitely detected with CEADUSS than not (39 Vs 9), and this is not similar to the detection rate of DUS. At 300ml/hr slightly more endoleaks are not detected than definitely detected (20 Vs 16), there is a more marked difference with DUS. At 500ml/hr there are similar proportions of endoleaks detected as not (31 Vs 29), compared with DUS that detected endoleaks less definitely at this flow rate. Exactly the same proportions for endoleak were definitely detected as not (18 Vs 18) for a flow rate of 700ml/hr, and this was the exactly same finding with DUS. At the fastest flow rate (900ml/hr) the majority of endoleaks were definitely detected than not (25 Vs 11) and this is a similar finding to the proportions of DUS detection at this flow rate. Using CEADUSS, endoleak flow rate does not significantly affect detection (p=0.0018) and the same is true for trend (p=0.2374), these findings are dissimilar to the results from DUS where there was a significance.

d) Effect of operator experience upon endoleak detection using CEADUSS

Endoleak detection rates by operators with different experience levels were compared. The subjects had practicing years experience varying from 23, 11, 7, 2½, 2 and 0 years. The six sonographic testing subjects recorded if they saw the endoleak using CEADUSS as: yes, inconclusive or no. The data was separated into definitely saw the endoleak (Yes) or did not definitely see the endoleak (Inconclusive and No) provide a binary outcome and thus perform a Univariate analysis (**Table 32**).

Table 32: A Univariate analysis of CEADUSS endoleak detection with operator experience

	CEADUSS endoleak detection		
Sonographer experience (years)	**0**	**1**	
0	10	26	36 (16.7%)
2	7	29	36 (16.7%)
2.5	16	20	36 (16.7%)
7	20	16	36 (16.7%)
11	18	18	36 (16.7%)
23	16	20	36 (16.7%)
	87 (40.3%)	129 (59.7%)	216

Chi-square	14.261
DF	5
Significance level	**P = 0.0140**

Chi=square test for trend

Chi-square (trend)	7.405
DF	1
Significance level	**P = 0.0065**

The most experienced subject (23 years) detected marginally more endoleaks definitely than not (20 Vs 16), the opposite findings to using DUS. The subject with 11 years experience definitely detected endoleaks in exactly the same proportions to those not (18 Vs 18), which is not in agreement with DUS which detected less endoleaks definitely. The subject with 7

years experience detected marginally less endoleaks definitely than not (16 Vs 20), in similar proportions as DUS. The subject with 2½ years experience performed the same as the most experienced subject of 23 years, this was the opposite to their detection with DUS. The two least experienced subjects (2 and 0 years experience) detected more endoleaks definitely seen than not (29 Vs 7, 26 Vs 10), these performances are not in agreement with their performance using DUS. Sonographers years of experience does not have a significant effect on endoleaks definitely detected (p=0.0140) and for trend (p=0.0065).

e) <u>Univariate analysis of independent variables in the CEADUSS experiments to see if they were independent or correlated with each other</u>

On Univariate analysis it appears that plane position and distance from the EVAR stent-graft were significantly associated with endoleak detection. To decipher if these independent variables were correlated to each other, I performed a Spearman rank test to assess for collinearity (**Table 33**).

Table 33: A Spearman rank test of the Univariate analysis of CEADUSS endoleak detection and variables

		Distance of endoleak from EVAR stent-graft (cm)	Endoleak flow rate (ml/hr)	Endoleak position	Sonographer experience (years)
Distance of endoleak from EVAR stent-graft (cm)	Correlation Coefficient Significance Level P n		**0.042** **0.5422** **216**	-0.009 0.8968 216	**0.004** **0.9506** **216**
Endoleak flow rate (ml/hr)	Correlation Coefficient Significance Level P n	**0.042** **0.5422** **216**		-0.050 0.4622 216	0.000 1.0000 216
Endoleak position	Correlation Coefficient Significance Level P n	-0.009 0.8968 216	-0.050 0.4622 216		0.000 1.0000 216
Sonographer experience (years)	Correlation Coefficient Significance Level P n	**0.004** **0.9506** **216**	0.000 1.0000 216	0.000 1.0000 216	

The Spearman rank correlation coefficient demonstrated that these categorical variables were independent of each other and thus a Multivariate analysis could be performed.

f) Evaluation of independent predictors of endoleak detection using CEADUSS

A Multivariate analysis of the data was performed to investigate the variables that predict endoleak detection (**Table 34**). Candidate variables were entered stepwise into the model starting with those with the lowest p-value.

Table 34: A Multivariate analysis of CEADUSS endoleak detection and variables

Dependent Y	**CEADUSS endoleak detection**

Overall Model Fit

Null model -2 Log Likelihood	291.221
Full model -2 Log Likelihood	149.194
Chi-square	142.026
DF	13
Significance level	P < 0.0001

Coefficients and Standard Errors

Variable	Coefficient	Std. Error	P
Distance_from_midline__cm_=1	-0.73787	0.64791	0.2548
Distance_from_midline__cm_=2	3.54466	0.84546	**<0.0001**
Flow_rate__ml_hr_=300	-0.92707	0.79309	0.2424
Flow_rate__ml_hr_=500	-1.61841	0.83474	0.0525
Flow_rate__ml_hr_=700	-1.91908	0.79368	0.0156
Flow_rate__ml_hr_=900	-2.49826	0.94084	0.0079
Lateral Position=2	-3.71618	0.64795	**<0.0001**
Posterior Position=3	-3.25639	0.62172	**<0.0001**
Sonographer_Years=2	0.79101	0.73333	0.2807
Sonographer_Years=2½	-1.51486	0.73531	**0.0394**
Sonographer_Years=7	-2.47670	0.76334	**0.0012**
Sonographer_Years=11	-1.84502	0.74934	**0.0138**
Sonographer_Years=23	-1.56151	0.74151	**0.0352**
Constant	4.6565		

Odds Ratios and 95% Confidence Intervals

Variable	Odds ratio	95% CI

Distance_from_midline__cm_=1	0.4781	0.1343 to 1.7024
Distance_from_midline__cm_=2	**34.6281**	**6.6032 to 181.5929**
Flow_rate__ml_hr_=300	0.3957	0.0836 to 1.8727
Flow_rate__ml_hr_=500	0.1982	0.0386 to 1.0178
Flow_rate__ml_hr_=700	0.1467	0.0310 to 0.6953
Flow_rate__ml_hr_=900	0.0822	0.0130 to 0.5199
Lateral Position=2	**0.0243**	**0.0068 to 0.0866**
Posterior Position=3	**0.0385**	**0.0114 to 0.1303**
Sonographer_Years=2	2.2056	0.5240 to 9.2845
Sonographer_Years=2½	**0.2198**	**0.0520 to 0.9290**
Sonographer_Years=7	**0.0840**	**0.0188 to 0.3751**
Sonographer_Years=11	**0.1580**	**0.0364 to 0.6864**
Sonographer_Years=23	**0.2098**	**0.0491 to 0.8975**

Hosmer & Lemeshow test

Chi-square	8.1798
DF	8
Significance level	P = 0.4161

Classification table (cut-off value p=0.5)

Actual group	**Predicted group**		**Percent correct**
	0	**1**	
Y = 0	65	22	74.71 %
Y = 1	14	115	89.15 %
Percent of cases correctly classified			83.33 %

ROC curve analysis

Area under the ROC curve (AUC)	**0.922**
Standard Error	0.0178
95% Confidence interval	**0.878 to 0.954**

Independent predictors of endoleak detection on CEADUSS include distance from midline of 2cm. Factors which lessened the chance of endoleak detection include non-anterior position and sonographers experience >2 years.

DISCUSSION

I successfully tested 6 vascular ultrasonographers of varying clinical experience with my laboratory EVAR phantom simulated variable endoleak. Initially they were tested over 36 different endoleaks with varying plane (anterior/lateral/posterior), distance (near-far) and flow rate (100-900mls/hour) using DUS then repeated with the same endoleaks using CEADUSS. Microbubble contrast produced satisfactory images and endoleak enhancement throughout the duration of the CEADUSS experiments.

Initially I analyzed my results by combining the results for endoleaks definitely seen (yes) with those possible seen (inconclusive) to form a group of endoleaks that were positively identified to compare with those negatively observed (no). However, by doing this my results were positively biased giving unreliable interpretations of the data. In reality CEADUSS would be used only in the setting where DUS cannot reliably exclude an endoleak. Therefore CEADUSS is only useful if it has a higher sensitivity for endoleak detection than Doppler and therefore reduces the number of inconclusive examinations. Therefore the putative benefits of CEADUSS would be if it reduced the number of inconclusive examinations and if it delivered a higher sensitivity for endoleak detection.

I re-analyzed the data to assess the three outcomes independently and particularly focused more on indecision and inconclusive detection of endoleaks to more reliable decipher sensitivity. For assessing each modality (DUS and CEADUSS) independently and the effects on my measured variables, I had to convert the results into a binary outcome for categorical observations and Univariate analysis into non-diagnostic (inconclusive) and diagnostic (yes or no) for assessment.

The results data was broken down into a variety of subsets for analysis; the performance of the two imaging modalities and the effects of changing a variable endoleaks properties using DUS then CEADUSS.

There was a significant difference ($p=0.0007$) when comparing the raw data for all of the DUS recordings with the CEADUSS results. CEADUSS produced more inconclusive results overall. These combined data did not standardize the physical properties of the endoleak but

the same 36 DUS tests were exactly the same as the 36 CEADUSS tests. The 36 tests had varying endoleak plane positions, distances from the stent-graft and flow rates and the operators had varying ultrasound experience. An explanation for why CEADUSS produced more inconclusivity may be that none of the subjects had ever used microbubble contrast or the specialized software for imaging. Thus unfamiliarity and being at the start of the learning curve for this technique may have enforced caution with endoleak identification with the majority not firmly committing to what they saw, as opposed to their opinion with the more familiar DUS that they use regularly.

To compare the sensitivities of the two modalities, the outcomes were converted to binary form to demonstrate that DUS sensitivity was 42% Vs 60% for CEADUSS. CEADUSS was 18% more sensitive for endoleak detection overall, across all observers and conditions and this difference was statistically significant ($p<0.0001$). This result showed that there may be a benefit and thus advantage of using CEADUSS over DUS for endoleak detection.

Again the data was analyzed depending upon diagnostic outcome and DUS produced 24% inconclusive examinations which was similar to the 20% of CEADUSS tests. The difference of 4% was not statistically significant ($p=0.3135$), despite CEADUSS showing a very marginal benefit. CEADUSS may have produced more inconclusive results in this part of the analysis for reasons I have already mentioned. Re-analysis of the subjects after they have gained more experience and familiarity with CEADUSS may confirm or disprove if there is actually a difference or similarity between proportions of inconclusive examinations of these two techniques.

There was only fair agreement between the two imaging modalities, with CEADUSS being more sensitive (60% Vs 42%) and DUS having a greater proportion of endoleaks not seen (34% Vs 20%), there were a similar proportion of inconclusive endoleak detection (24% DUS Vs 20% CEADUSS) when looking at overall inter-modality agreement. Inter-modality agreement was next looked at for each subject separately to assess operator dependency and if years of experience had an effect. The most experienced operator (23 years) demonstrated a moderate agreement, detecting a greater proportion of endoleaks with CEADUSS (56% Vs 44%), more endoleaks not detected with DUS (39% Vs 28%) and the same proportions of inconclusive tests for each modality (17%). The next most experienced subject (11 years)

demonstrated a slight agreement between modalities, CEADUSS detected more endoleaks (50% Vs 25%), DUS had less endoleaks not seen (36% Vs 22%) and CEADUSS had less inconclusive tests (22% Vs 36%). The sonographer with 7 years experience demonstrated a moderate agreement between CEADUSS and DUS with similar proportions for all three outcomes of endoleak detection. The subject with 2½ years experience showed a slight agreement between modalities, with CEADUSS producing more endoleaks seen (56% Vs 22%) and inconclusively seen (39% Vs 17%) and less endoleaks not detected (22% Vs 44%). No agreement between modalities was shown by the subject with 2 years experience, CEADUSS detected more endoleaks (81% Vs 44%) and less inconclusive (14% Vs 31%) and endoleaks not seen (6% Vs 25%). The least experienced subject (0 years) showed slight agreement overall, with CEADUSS producing more endoleaks detected (72% Vs 58%) and less not seen (14% Vs 25%) with similar proportions of inconclusive tests (14% Vs 17%). Overall there was fair agreement beyond that expected by chance. It was difficult to identify if inter-modality agreement changed with years of experience as the number of sonographers involved was low, making the graph sensitive to outliers (subjects with 11 and 7 years experience).

Comparing the proportions of inconclusive examinations for each individual sonographer with each other using both imaging techniques showed no visual trend. It did appear that for sonographers of increasing seniority, CEADUSS gave more inconclusive examinations. This suggests that in this group of sonographers, that the diagnostic benefit of the addition of CEADUSS was unrelated to experience. This may again reflect how comfortable the sonographers were in using or interpreting CEADUSS images, rather than any improvement of the technique over DUS alone. This may be a function of a learning curve.

Sensitivity for endoleak detection using both modalities for each individual sonographer with differing experience showed the more junior subjects had a higher sensitivity for endoleak detection that was enhanced through the addition of CEADUSS. It appeared that for sonographers of increasing seniority CEADUSS gave more inconclusive examinations. However as noted earlier there were approximately the same number of inconclusive examinations using DUS and CEUS. Thus endoleaks were most likely to be detected using CEADUSS by the most junior sonographers with <2½ years of experience.

Next to assess the effects of changing the variables of an endoleak on DUS detection, I looked at the effect of endoleak plane position, distance from the stent-graft, flow rate and operator experience. Again I was advised after statistical consultation to have the data for analysis presented in a binary form. If the data were to be used in its existing form with three outcomes (Yes/Inconclusive/No) then the analysis would not inform us if an individual factor was related to the definite presence of an endoleak (note in this experiment a real endoleak was present every time) or allow multivariate analysis to identify independent factors associated with finding a true endoleak. Thus the data was separated into two categories, endoleak definitely seen and not (everything else). The variables being assessed were all in fact categorical variables, as they cannot have incremental quantities, so the appropriate test for analysis is chi-squared.

I then performed a separate Univariate analyses for the measured variables to decipher if each one has an effect on endoleak detection. Endoleak plane position did not significantly affect definite endoleak detection ($p=0.3725$), nor did operator experience ($p=0.1295$). Distance of the endoleak from the EVAR stent-graft significantly affected definite detection ($p<0.0001$) as did flow rate ($p<0.0001$).

Once this was established, I next set out to see if these variables were correlated to each other using a Spearman rank correlation analysis, which showed that the categorical variables were independent of each other. As they were independent I then performed a multivariate analysis to assess variables that affect and thus predict endoleak detection with DUS. The multivariate analysis showed that endoleak distance from the stent-graft of 2cm and flow rate of 500ml/hr or more were significant independent predictors of endoleak detection using DUS. Of particular interest, the performance of the subject with 11 years experience was particularly poor.

During DUS testing, colour Doppler p.r.f. and gain setting changes were recorded and no significant differences between subjects was found, except that the subject with 11 years experience changed their p.r.f. settings more frequently than the others, but this was a non-significant difference. Perhaps the fact that this subject changed his settings the most and also

had the poorest performance of all may be related. He may have had sub-optimal images due to altering settings thus producing poor endoleak detection or may have found the tests difficult and felt altering the settings may have helped him. The only way to really know is to review his tests, preferably if they were recorded and interview him on how he found them. This would be an additional part of the experiment that could be included in the future.

The overall findings from the multivariate analysis that demonstrated that endoleak distance from the stent-graft of 2cm and flow rate of 500ml/hr or more were significant independent predictors of endoleak detection using DUS can be explained by the fact that one would expect greater detection of an endoleak further from the main stent-graft where there would be less overlap and spillover of color Doppler. Szucs-Farkas et al, also found that endoleaks further away were more readily detected than those closer (Szucs-Farkas 2011). The faster the flow rate of the endoleak meant its detection was better once they were ≥500ml/hr. Low flow endoleaks are commonly missed clinically as they flow within them is not as obvious than if they were faster and thus brighter and more persistent, this finding is what I expected it would be for these experiments.

I assessed the same variables effecting endoleak detection for the CEADUSS tests in the same manner to the DUS analysis. Endoleak plane position had a significant effect on endoleak detection ($p<0.0001$) as did position from the stent-graft but flow rate ($p=0.0018$) and operator experience ($p=0.0140$) did not have an effect. Univariate analyses of the independent variables were assessed with a Spearman's rank correlation that demonstrated that these categorical variables (plane and distance) were independent of each other, thus a Multivariate analysis was performed. Independent predictors of endoleak detection on CEADUSS included distance from the midline of 2cm. Factors which lessened the chance of endoleak detection included non-anterior positions and sonographers experience >2 years.

The fact that endoleaks further away were detected better is again in keeping with what I expected because there will be more separation and less overlap of the two flow systems, similar to the findings of Szucs-Farkas et al (Szucs-Farkas 2011), thus easier identification. Anterior endoleaks were detected the best compared with if they were lateral or posteriorly positioned. The explanation for this is that anterior leaks are the most superficial and so less penetration of the ultrasound waves is required thus detection would be easier due to better

images. Endoleaks lateral and posterior will require the ultrasound beams to travel and return from further away and so images will not be as good as those anterior thus detection not as easy. The last finding is that the least experienced subjects (<2 years) performed better with CEADUSS. An explanation for this may be that with greater experience of DUS using a new technique such as CEADUSS may be more difficult, "it may be more difficult to treat an old dog new tricks"! The less experienced due to not using DUS for such a long time had less habits ingrained so were open to using alternative imaging. Also the most experience operators may have produced images of higher quality due to experience and familiarity with DUS that they regularly use that they may have found CEADUSS, a new technique difficult to detect endoleaks in comparison. A way to determine why experience had an effect with CEADUSS could be found by assessing subject's decision making after image recordings and interviews if I were to repeat the study.

A limitation of my study is that there the endoleaks physical properties were not standardized for the 36 tests. Throughout all of the tests, there were varying plane position, distances from the stent-graft, flow rates and the operators had varying ultrasound experience. For this reason the data wasn't broken into further subsets because numbers become too small and analysis futile. In practice there are several variables present at any time e.g. distance, plane, position and velocity. Dissecting each variable doesn't reflect realistic practice. Assessing the data with a multivariate analysis attempted to decipher if the variables were independent and had an effect on endoleak detection with each modality respectively.

To improve on the study design, more tests could be performed with independent variables standardized thus comparisons and analysis of each variable separately could be performed. More tests and standardization of variables would address the fact that this study is limited by the lack of data on specificity, negative predictive value and positive predictive value. Negative predictive value is important because the role of DUS and CEADUSS is essentially to safely reassure those with no endoleak, rather than being 100% predictive for the presence of endoleak. Ideally these could be used to generate a diagnostic odds ratio for each technique.

The only disadvantage of this would be that each subject would have to perform more tests for longer durations to allow the sheer number required to achieve satisfactory numbers for fruitful analysis. During my study planning I aimed to keep testing to 60 minutes to remain bearable to the subjects, however arranging more testing sittings could achieve more tests if the subjects were willing and their clinical duties allowed.

Another consideration would be the inclusion of instances where there was a control and no endoleak present. This was not included in my current study because with no flow at all in the endoleak, its presence could still be detected due to the outline of the c-flex tubing. It was physically not possible to have no endoleak present unless another phantom without endoleak and only and EVAR stent-graft embedded in agar was made, which would carry its own inherent expense.

Each subject made a static recording of the endoleak seen, maybe seen or did not see during experiments. Reviewing the images recorded was challenging because of the dynamic nature of ultrasound, pictures can't accurately represent what the ultrasonographers were viewing. Without the subjects present it wasn't possible to determine their opinion of the endoleak presence or location. It was therefore impossible to further compare DUS missed endoleaks with CEADUSS misses. I knew the location and would contribute a bias. A solution to this would be to record video cini-loops for comparison and post-testing analysis. I did not record clips during the phantom testing due to limited hard-drive storage of our Phillips ATL HDI 5000 SonoCT ultrasound machine. A newer Phillips iU22 machine now in clinical use does have a greater storage capacity.

Video recordings would also allow independent scrutiny of imaging quality. Other studies have asked subjects to mark endoleak positions on a diagram for analysis (Szucs-Farkas 2009), a grid technique which could easily be employed in further experiments. With this simple measure DUS misses detected by CEADUSS and DUS detected endoleaks missed by CEADUSS could be compared to rationalize the disparities.

Another factor which I could address with video recordings of each subjects tests could be the reasons for their diagnostic decision making. I could ask the subjects post-testing on review analysis or at the time of testing the confidence they had with endoleak identification.

CEADUSS generated more inconclusive results overall and a reason for this could be unfamiliarity with the technique that none of the subjects have ever used. Asking how comfortable they were with interpreting CEADUSS in particular would answer this question and help explain diagnostic uncertainty or reluctance to commit to a concrete diagnosis. This questionable decision making could be explored further by testing and comparing physicians and the subjects with images of known clinical endoleaks using the same yes/no/maybe scale. The inclusion of randomized non-endoleaks within testing the variable endoleak would allow further analysis of decision making and also act as a control, a strategy recently employed by other authors (Szucs-Farkas 2011).

Szucs-Farkas et al, have studied a CT phantom model for several years to determine optimum x-ray tube current and voltage modulation and so reduce radiation exposure without compromising image accuracy and quality (Schindera 2011, Szucs-Farkas 2011, Schindera 2010, Schindera 2009a, Schindera 2009b, Szucs-Farkas 2009, Szucs-Farkas 2008). They have simulated different patient size (small/intermediate/large) by placing their phantom in different cylindrical water containers (Szucs-Farkas 2011, Schindera 2010, Szucs-Farkas 2008). Their work is not unique. Other groups have used water-filled phantoms to study the effects of CT radiation attenuation for aortic imaging (Kalva 2006).

However, Szucs-Farkas has concentrated on the physical properties of an iodinated endoleak detection (Szucs-Farkas et al 2009), similar to my study. They are the only group to investigate parameters that have an effect on endoleak detection with CT imaging. All other studies, both clinical and experimental have concentrated on endoleak presence and have not explained why leaks are missed. Their cylindrical plastic AAA phantom contained a Medtronic stent-graft, embedded in epoxy resin. I used the same stent-graft surrounded by agar for ultrasound imaging. Their study involved 36 simulated endoleaks with varying diameters, densities and distances from the graft. They demonstrated that endoleak diameter, position, phantom dimension and tube voltage all had a significant effect ($p<0.0001$) on the number of detected leaks. I used the same number of simulated endoleaks but did not vary endoleak diameter, density or the effects of detection in different sized phantoms to mimic habitus. My subjects were blinded to the tests and repeated scanning 1 day later with the microbubble contrast.

The most relevant findings of Szucs-Farkas et al, was that more endoleaks were detected the further from the endoleak the stent-graft was positioned ($p<0.001$). This is in agreement with my study where I showed that endoleak distance from the stent-graft had a significant effect on endoleak detection when using either DUS ($p<0.0001$) or CEADUSS ($p<0.0001$). Multivariate analysis demonstrated that distance from the midline of 2cm was a significant independent predictor of endoleak detection using either DUS or CEADUSS. The positions of the endoleak used in their tests were smaller (0-1cm) when compared with my endoleak positions (0-2cm). Lastly my phantom allowed dynamic pulsatile flow adding a further dimension unlike their static phantom images. My experiments were more realistic, mirroring clinical practice more closely.

Originally when designing the EVAR phantom, the endoleak was a type II. After further thought, consultation with surgeons and publications the need to concentrate on the more relevant and dangerous type I and III was evident. Type II leaks were easier to simulate and it wasn't possible to produce a variable type I or III endoleak in my phantom system. However, the variable endoleak of the phantom could represent features of a type I or III endoleak with variation of velocity, position and distances, particularly testing with the endoleak near the stent. Thus my results of endoleak detection characteristics are relevant for all types and not exclusively type II.

A variable that I did not investigate was the size of endoleak. Larger endoleaks are easier to detect than smaller ones as demonstrated experimentally with CT (Szucs-Farkas 2009). Larger endoleaks have also been shown to be associated with greater aneurysm expansion (Timaran 2004), highlighting the importance of this variable. The phantom can be modified to alter endoleak diameter. Szucs-Farkas et al, investigated the effects of patient habitus on endoleak detection by placing their phantom within different sized water cylinders. I did not do this however it would be possible to do so by building larger and smaller agar filled Perspex housings within which the EVAR stent-graft is embedded.

Other variables that could be investigated include different stent-graft sizes to determine if endoleaks around larger or smaller grafts are detected differently, the incorporation of a bifurcated graft as well as investigating a variety of stents from different manufacturers to see

if graft composition effects surveillance. Another variable could be the administration of microbubble contrast into the phantom. Henao et al, developed an infusion technique to increase contrast circulation concentrations as opposed to using a bolus injection as employed in this study (Henao 2006). This continuous infusion technique improved scanning but was relatively expensive, because it required specific equipment and larger amounts of contrast. The phantom could be modified to include it. Lastly surveillance imaging also measures AAA sac size and success is indicated by regression or stability. Expansion indicates a problem. My phantom experiments did not simulate an aortic sac, therefore there are no sac size measurements. There are no studies directly comparing DUS and CEADUSS sac size measurements, however further phantom studies will benefit from simulating a variable aortic sac for measuring.

Low endoleak flow rates and proximity to the main lumen made endoleak detection more difficult. With the introduction of CEADUSS, more junior sonographers were better at spotting anterior endoleaks. Again proximity to the main arterial channel made detection more difficult. The addition of CEADUSS resulted in an 18% (95% CI 9-25) increase in sensitivity for identifying endoleaks over and above DUS. However there was no significant decrease in the overall proportion of inconclusive scans between modalities, suggesting that around 1 in 5 patients who attend for surveillance with either DUS or CEADSS would still require a further investigation, e.g. computed tomographic angiography.

It appears that the benefits of CEADUSS are greater for junior sonographers and help overcome the problem of finding low flow endoleaks.

CONCLUSIONS

An abundance of information regarding endoleak detection was obtained though testing 6 subjects with both DUS and CEADUSS in my EVAR phantom.

There was a significant difference between the endoleak detection rates of CEADUSS and DUS, but further uncertainty was also generated. Low endoleak flow rates and proximity to the main lumen made endoleak detection more difficult. With the introduction of CEADUSS, more junior sonographers were better at spotting anterior endoleaks. Again proximity to the main arterial channel made detection more difficult. The addition of CEADUSS resulted in an 18% (95% CI 9-25) increase in sensitivity for identifying endoleaks over and above DUS. However there was no significant decrease in the overall proportion of inconclusive scans between modalities.

These results give an insight into several factors altering the detection of endoleaks using ultrasound. With this information, there is scope for improvement of EVAR surveillance in the clinical setting, reducing the use of current CT protocols and hence reducing cumulative radiation, nephrotoxic contrast agent exposure, and high costs. Clinical assessment of DUS and CEADUSS endoleak detection noting endoleak characteristics (plane, position and velocity) will improve detection rates and should be considered for inclusion in current protocols.

CHAPTER 3

CLINICAL TRANSLATION OF CONTRAST ENHANCED ULTRASOUND FOR ENDOVASCULAR STENT SURVEILLANCE

ABSTRACT

A small pilot project was conducted to assess the clinical use of CEADUSS to detect endoleaks in a highly selected group of 10 patients. These patients had an endoleak on CT but not detected or categorized by DUS. Patients were also included who had an undefined endoleak type and source or a sac size enlargement with no obvious cause found.

CEADUSS was successfully used without any patient harm and we became familiar with the technique of administration as well as capturing EVAR surveillance imaging. There was no obvious observed universal agreement between investigative modalities. Results were not analyzed due to such small numbers and also the fact that patients were not randomized and highly selected.

Extrapolations of these findings towards the clinical use of CEADUSS must be taken with extreme caution. A larger study with randomized patients is required to define the exact clinical efficacy of CEADUSS to define a role and to establish its appropriate place within EVAR surveillance.

INTRODUCTION

After gaining competency in DUS and CEADUSS techniques with my laboratory EVAR phantom, I wanted to use the technique in human subjects to attempt to demonstrate the clinical relevance of my experiments and define a role of CEADUSS.

I intended to consult the Barts and Royal London EVAR surveillance database and extrapolate data of the number of EVAR's performed and number of endoleaks detected with outcomes. The practice within our department is to follow-up all endoleaks with CT and DUS. I wanted to use CEADUSS in a subset of patients with confirmed endoleaks on CT which were undetected or undefined by DUS to evaluate if contrast enhancement makes these leaks detectable or not, to attempt to define a role for CEADUSS in post-EVAR surveillance.

METHODS

I consulted the Barts and The London NHS Trust EVAR surveillance database in October 2009 to perform a single center prospective study. The database started in August 2001, with the first EVAR procedure at the Royal London Hospital. Barts and The London NHS Trust is a tertiary vascular referral unit for the catchment area of North East and Central Thames in London and Essex. The database includes EVAR procedures performed by 8 consultants, 2 of whom had retired by October 2009, the other 6 were regularly performing procedures. The database patient summary in October 2009 is shown below (**Table 35)**.

Table 35: The Barts and The London NHS Trust EVAR database patient surveillance details as at 1st October 2009

Surveillance category	Patient numbers
On current surveillance	97
Had reintervention and now on current surveillance	11
Having surveillance/follow-up at another unit	3
Converted to open procedures	9
Deceased	33
Total EVAR performed by Barts and The London NHS Trust	153
Under active surveillance by Barts and The London NHS Trust	**108**

All patients at Barts and The London NHS Trust undergo a pre-procedural triphasic CT from the supra-celiac aorta to the femoral arteries. A Siemens Somatom Sensations 64 (Siemens Medical Solutions, Forchheim, Germany) consisting of 32 x-ray detectors with a flying focal spot is used. The pre and post contrast CT slices were of 5mm thickness. Post-contrast fine/thin images (1mm) were used for aortic reconstructions in the coronal and sagittal planes on our Leonardo workstation. This was linked via our WebSpaceServer to the trust picture archiving computer system (PACS). This CT protocol was used both for pre-EVAR and for post-EVAR surveillance imaging. The contrast agent used for these scans was 100ml of Visipaque injected at a rate of 5ml/s.

Peri-procedural imaging during EVAR is with intra-arterial angiography. Immediate post-procedure deployment angiogram is performed. The trust's surveillance protocol includes a pre-discharge synchronous CT, DUS and AXR, then repeated at 3, 6 and 12 months. Patients then have annual surveillance with synchronous CT, DUS, AXR and an outpatient appointment. If an abnormality is detected on surveillance, including sac size increase, stent migration or endoleak, then following discussion at the Barts and The London Vascular Multidisciplinary weekly meeting, imaging protocol is altered. This meeting involves vascular surgeons, radiologist and vascular scientists. Clarification of the abnormality is made and a corresponding revised surveillance schedule for that particular patient or date for reintervention if necessary.

The rationale for synchronous CT, DUS and AXR was its inclusion in a pilot project between the department of clinical physics and a vascular clinical research fellow, investigating DUS and AXR as surveillance modalities previously.

I included patients who possessed endoleaks, of any variety, on surveillance CT imaging but conflicting or undefined on DUS imaging. I excluded those being followed-up in other units, those converted to open and those who were deceased. I also included patients with known undefined endoleaks or sac size enlargements with no identified source.

Radiological imaging for the selected patients was reviewed and reported by two separate Barts and The London NHS Trust Interventional Radiologists. They were blinded to the patient's identification details and previous imaging reports. They were informed of the patient's history at presentation and allowed to review the original EVAR procedure images and details. They were allowed to look at all past radiological imaging for comparison. Neither of the radiologists had reported the previous imaging for these patients. They were unaware of the DUS or CEADUSS findings.

The aim was to confirm CT findings of endoleak or sac enlargement on recent CT, confirm that DUS was normal i.e. missing the abnormality or did not define the problem as detected by CT. Then we were to perform CEADUSS to determine if microbubble contrast highlighted the pathology and thus enhanced surveillance.

The patients were invited to The Royal London Hospital vascular ultrasonography laboratory for a DUS (unenhanced) and CEADUSS. They had a CT and AXR a maximum of 6 weeks previously. Ultrasound imaging was performed by the vascular ultrasonographer, Kate Adams. She has experience of the CEADUSS technique from Kings College Hospital. The rationale for this was to eliminate user dependency and maintain consistency. The vascular scientist was not blinded to patient's details and previous imaging, allowing us to specifically target our CEADUSS imaging.

Dr P Sidhu (Kings College Hospital's ultrasound department) taught me and updated Kate with CEADUSS technique. Our local Phillips technician demonstrated the contrast settings of our ultrasound machine and how to record images, prior to scanning subjects. Finally a SonoVue representative working for Bracco was present during all of the CEADUSS imaging studies performed to teach me how to prepare, administer and optimize our contrast imaging. Bracco kindly provided ten vials of SonoVue for this project.

Initially ethical approval was sought and applied for via the Integrated Research Application System (IRAS). After consultation with Barts and The London NHS department of Research and Development, I was directed to consult Dr AT Tucker. Dr Tucker was chairman of the East London research committee of the National Research Ethics Service and he also was a National Research Ethics Advisor to the UK and sovereign countries in Asia. He advised me to submit this pilot project to the East London and The City Research and Ethics Committee via the Barts and London NHS Trust Clinical Effectiveness Unit application system and so I did so in September 2009 with his help.

They concluded that the proposed activity was an audit of planned clinical practice based on clinical need and did not require ethical review by a NHS Research Ethics Committee or approval from the NHS research and development office as it was not defined as a research project. Patients were being subjected to investigations that were currently available in other centers and this modality (CEADUSS) was to be audited prior to implementation in our unit at Barts and The London NHS Trust to assess suitability. This project was thus formally registered with Barts and The London NHS Trust research and development department (registration number **09/141**). Permission was granted to conduct this CEADUSS study in October 2009 as an audit. Written informed consent was obtained in writing for all patients

for agreement to investigations. As this was an audit project our vascular scientist were not blinded to patient's details and previous imaging, allowing us to specifically target our CEADUSS imaging and evaluate its efficacy.

All patients underwent both colour duplex and contrast enhanced ultrasonography using a Phillips iU22 machine (Phillips, Andover, Massachusetts, USA) and all scans were performed by the same accredited vascular scientist. The ultrasound protocols that were used were as follows:

Barts and the London NHS Trust Vascular Laboratory Protocol for CEADUSS EVAR (Unenhanced and Contrast Enhanced Ultrasound)

Unenhanced EVAR Surveillance Duplex Scan

Patient Preparation:

Check patients identification

Explain test procedure

Obtain verbal consent

Take relevant history from patient

Ask patient to undress as appropriate

Scanner Preparation:

The probes should be cleaned with T – Spray between patients. After scanning an infectious patient, the room should be deep cleaned (order though the helpdesk) and the scanner cleaned according to the manufacturer's protocol.

Procedure:

1) Using B-mode, image the aorta and iliac arteries in longitudinal and transverse planes to determine the proximal and distal limits of the graft.

2) Using B-mode, image the aorta in different planes (transverse, longitudinal), and take several diameter measurements of the aortic sac during systole. Report the maximum aortic sac diameter.

3) Using colour Doppler try to image the renal arteries and report how many renal arteries are visualized and whether they are patent.

4) Using colour Doppler set at a P.R.F appropriate to eliminate aliasing or confirm occlusion where necessary, image the stent, the common iliac arteries and the external iliac arteries down to the level of the inguinal ligament.

5) Report any occlusion, significant stenosis or kinking of the stent and iliac arteries.

6) Using colour Doppler set at a P.R.F of approx 10-13cm/sec and colour gain set just below the level where background noise appears as colour on the screen, image the entire length of the stent in longitudinal and transverse planes:

- Pay particular attention to the posterior aspect of the sac for lumbar artery origins, and the anterior aspect of the distal sac for the IMA.
- If any colour is displayed outside the stent, within the aneurysm sac, use PW Doppler to determine if this colour represents artefactual noise, or if it is pulsatile.
- Spectral Doppler analysis of an endoleak can reveal a to and fro waveform similar to that demonstrated in a pseudoaneurysm when the entry and exit is through the same vessel. A monophasic waveform would be suggestive of multiple entry and exit vessels.
- There are currently 5 different types of endoleaks. Any endoleaks identified should be classified and reported:
    - Type I endoleaks have flow originating from the attachment sites. These can be further divided into Type IA, proximal attachment leaks and Type IB, distal attachment leaks.
    - Type II endoleaks occur from retrograde aortic branch flow into the aneurysm sac (lumbar, IMA etc).
    - A type III endoleak is when there is a structural failure with the graft, for example a hole in the graft fabric, a stent graft fracture or a junctional separation.
    - Although unable to diagnose with ultrasound, Type IV endoleaks occur due to graft wall porosity and endotension, or as sometimes referred to as Type V endoleak, is the exertion of tension on the aneurysm wall with or without the presence of an endoleak.
- If the aneurysm sac is increasing in diameter the relevant vascular team should be informed.

Contrast enhanced EVAR Surveillance Duplex Scan

Patient Preparation:

Check patients identification

Explain test procedure

Obtain written consent

Take relevant history from patient

Ask patient to undress as appropriate

Insertion of green cannulae to anti-cubital fossae, secure and flush with 5mls of normal saline

Check patient does not have any contraindications to Contrast/SonoVue and warn of undesirable effects

Special precautions for administration

Before use examine the product to ensure that the container and closure have not been damaged. SonoVue must be prepared before use by injecting through the septum 5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection to the contents of the vial. The vial is then shaken vigorously for twenty seconds after which the desired volume of the dispersion can be drawn into a syringe as follows, depending on the presentation:

The recommended doses of SonoVue for Vascular Doppler imaging is 2.4ml as stated by Bracco in their instructions for use (Bracco 2005). However, after consultation with a representative from Bracco who was present during clinical testing of CEADUSS, we were advised to use a smaller dose of 1ml which could be repeated and would produce better images of endoleaks. This practice of using 1ml of SonoVue has been widely adopted subsequently since the publication of Bracco's instructions for use in 2005.

After reconstitution, a homogeneous white liquid is obtained. If solid parts of the lyophilisate are seen or the suspension is not homogeneous, the product should be discarded. If SonoVue is not used immediately after reconstitution the microbubble dispersion should be shaken again before being drawn up into a syringe. Chemical and physical stability of the microbubble dispersion has been demonstrated for 6 hours. The vial is for a single examination only. Any unused dispersion remaining at the end of an examination or waste material must be discarded in accordance with local requirements.

Scanner Preparation:

As DUS preparation.

Procedure:

Using Contrast mode (General Contrast setting), repeat steps 1-6 of procedure above

End of examination:

Dress patient and remove cannulae, replace with dressing

Report:

For inpatients, a report should be put in the patient's notes the day of the scan including details of the unenhanced followed by the enhanced scan findings. All patients will have the report saved under clinical documents. All patients scanned were presented and discussed at the January 2010 Barts and The London NHS Trust multidisciplinary vascular radiology meeting, where surveillance and treatment decisions were made.

RESULTS

I consulted the Barts and The London NHS Trust EVAR surveillance database in October 2009 and scrutinized the 108 patients under active surveillance (70.6% of 153 EVAR procedures in the trust). 11 patients (10.2%) fulfilled my selection criteria. These patients either had an endoleak on CT not detected by DUS, an undefined endoleak type and source or a sac size enlargement with no obvious cause found using DUS.

The patients were invited for their surveillance CT, AXR and DUS as per the Barts and The London NHS Trust protocol with an additional CEADUSS. All agreed to participate in the scans over three days. One patient was unable to attend due to being admitted to another hospital, thus was excluded from the study. The 10 participating patients' surveillance findings and CEADUSS results were as follows:

Patient 1

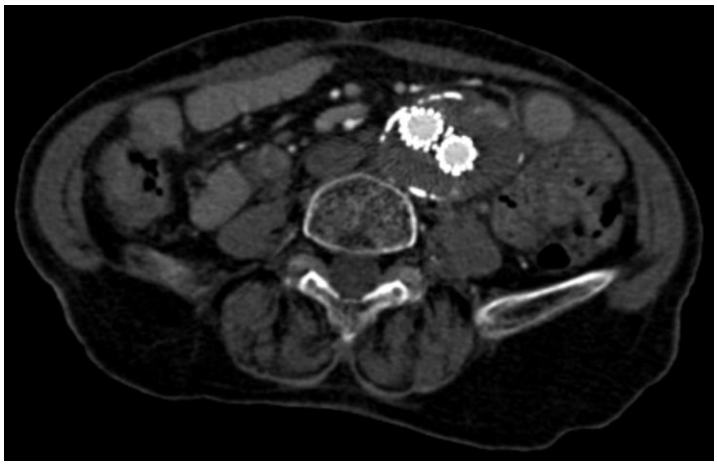
Background

A 74-year-old Chinese lady with an asymptomatic infrarenal AAA of 5cm, found incidentally during an ultrasound investigation for a benign caecal polypoid lesion. Comorbidities include chronic renal disease, hypertension and depression. The AAA measured 6.5cm on CT and was anatomically suitable for EVAR, thus a bifurcated Cook Zenith device was deployed on 8th December 2006. No endoleak was demonstrated on completion angiography.

CT surveillance

- 3 months - no sac size change but a posterior type II endoleak was visualized behind the proximal end of the iliac limbs, secondary to a lumbar vessel.
- 6 months - the type II leak was still persistent at but sac size had reduced to 6cm.
- 12 months – persistence of type II endoleak and sac measured 4.8cm
- 2 years – stable type II endoleak with a sac size of 5.2cm
- 3 year - stable sac size of 5.2cm and a stable type II endoleak was persistent posterior to the left iliac limb origin at the stent bifurcation (**Figure 55**). Both radiologists confirmed the findings.

Figure 55: A persistent stable type II endoleak originating posteriorly from the left iliac limb origin distal to the stent bifurcation, from a left lumbar artery in patient 1



DUS surveillance

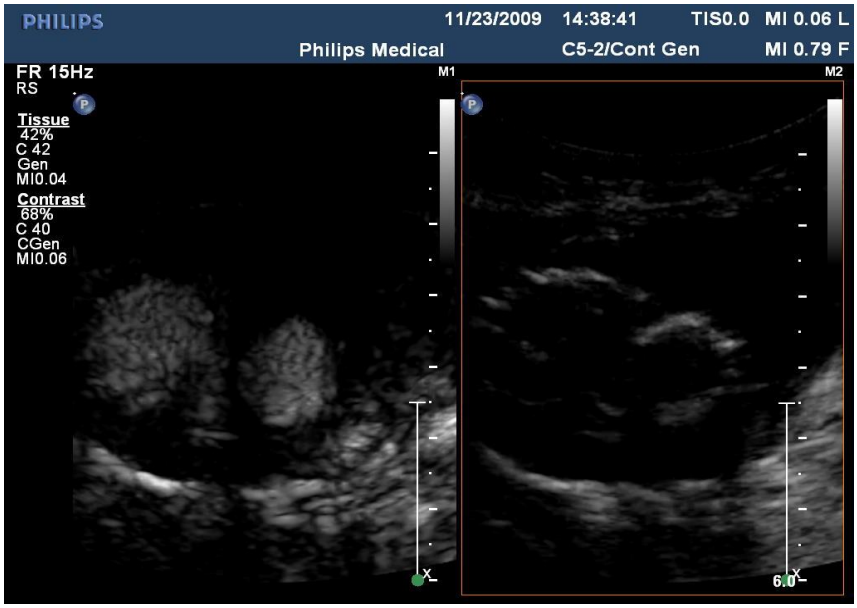
- 3 months - EVAR stent was patent and no endoleaks were seen. Poor views were obtained of distal iliac limbs due to stent overlapping.
- 6 months - the sac had reduced to 6cm and no endoleak was seen. Poor views were obtained of distal iliac limbs due to stent overlapping.
- 12 months – sac reduced in size to 5.3cm and no endoleaks were present. Poor views were obtained of distal iliac limbs due to stent overlapping.
- 2 years – no endoleak and sac size 5cm. Poor views were obtained of distal iliac limbs due to stent overlapping.
- 3 years - no endoleak and sac size 5cm. The distal sac could not be imaged due to acoustic shadowing from stent or calcification of anterior wall of the sac.

CEADUSS surveillance

- 3 years – 1ml of SonoVue microbubble contrast was administered. There were contrast bubbles suggesting evidence of a small posterior sac endoleak to the left hand side, just distal to the graft bifurcation (**Figure 56**). The source of the leak was likely

to be a left lumbar artery. Another 1ml of SonoVue was administered to confirm the above findings after previous contrast washout, the left lumbar type II endoleak was directly visualized feeding the sac in a retrograde fashion.

Figure 56: CEADUSS on the left demonstrating the type II endoleak originating posteriorly from the left iliac limb origin distal to the stent bifurcation, from a left lumbar artery in patient 1 (note the images are reversed from conventional views as were scanning cranially facing caudally for positional purposes in this lady). The right image shows a B-mode unenhanced synchronous image where no leak can be identified



Patient 2

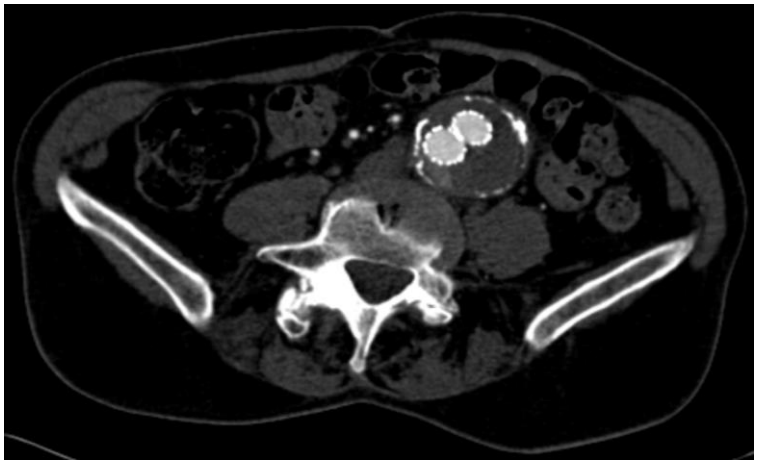
Background

A 72-year-old lady was incidentally found to have a 6.2cm asymptomatic infra-renal AAA during a pre-operative CABG abdominal ultrasound. Her comorbidities include significant cardiovascular disease, hypertension, smoking and rheumatoid arthritis. She underwent an EVAR on 22nd June 2009 after recovering from cardiac surgery, using a bifurcated Gore stent-graft device. On completion angiography there was a small late bottom end leak. This leak was reduced further by ballooning leaving a very small late endoleak on final angiography.

CT surveillance

- 3 months – Type II endoleak at the right posterior inferior aspect of the sac coming from a lumbar vessel. No change in sac size was noted.
- 6 months – The sac size is static and a there is a persistent amount of contrast posteriorly on the right within the lower sac reflecting a type II lumbar endoleak (**Figure 57**).

Figure 57: CT of patient 2 showing a right posterior sac type II endoleak originating from a left lumbar artery coursing down the left side of the sac



DUS surveillance

- Pre-discharge – An endoleak in the proximal sac consistent of a 3mm channel of flow through the proximal sac running from the right to the posterior sac wall. The source of this endoleak could not be identified so the type of leak could not be determined. Poor iliac limb views due to the presence of bowel gas.
- 3 months – A proximal right sac endoleak is noted but the causative source and thus type is not defined.
- 6 months – No change in sac size and undefined endoleak visualized as a tortuous channel of flow through the sac, no source could be identified.

CEADUSS surveillance

- 6 months – 1ml of Sonovue was administered and contrast bubbles suggesting evidence of a tortuous leak present in the right posterior sac originating from a left lumbar artery coursing down the left side of the sac was visualized. There was no reduction in sac size, it remained static at 6.1cm. Another 1ml of SonoVue was administered to confirm the above findings after previous contrast washout, the left lumbar type II endoleak was directly visualized feeding the sac in a retrograde fashion coursing down the left side of the sac to the right posterior side of the sac

Patient 3

Background

An 80-year-old man was incidentally found to have a 6cm asymptomatic infra-renal AAA and was referred from another unit after a period of surveillance. His comorbidities included hypertension, hypercholesterolemia and he was an ex-smoker. It was felt that the distal neck of the AAA was too tight to accommodate two separate iliac limbs without compromising distal flow, so an aorto-uni-iliac device was used. He underwent an aorto right uni-iliac EVAR on 5th February 2008, using a Cook Zenith stent-graft. An Amplatzer plug was inserted into the left common iliac artery and a right to left femoro-femoral cross over bypass was performed. On completion angiography there was no endoleak.

CT surveillance

- 6 weeks – Maximum sac size measures 6cm and there is evidence of a small type II endoleak arising from a lumbar vessel in the region of the native aortic bifurcation. There may be another second type II endoleak proximal to the Amplatzer plug. The right to left femoral crossover graft is patent.
- 6 months – Stable sac size of 5.9cm and a tiny type II endoleak still noted at the distal aorta. No other leaks are noted. The crossover graft is patent.
- 9 months – A small type II endoleak again from a lumbar artery is seen within the sac and the sac size measures 5.8cm. No other abnormalities are noted.
- 18 months – Stable sac size of 5.94cm and again a small type II endoleak originating from a lumbar artery is persistent.
- 2 years – A small type II endoleak originating from a lumbar artery is again noted on the anterior right side of the sac distally travelling up the sac. There is no increase in sac size (**Figures 58-59**).

Figure 58: Lumbar artery entering the sac in Patient 3

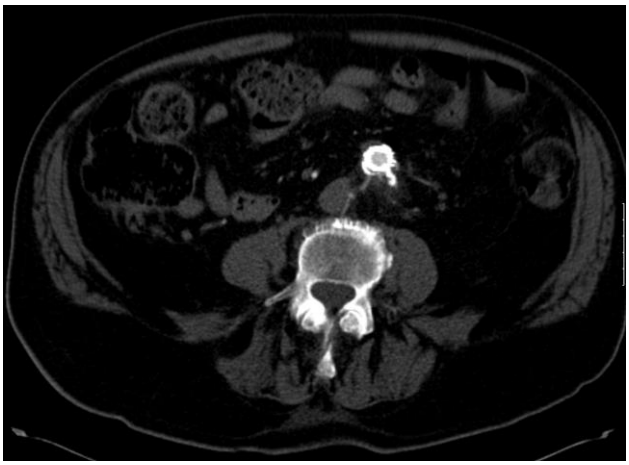
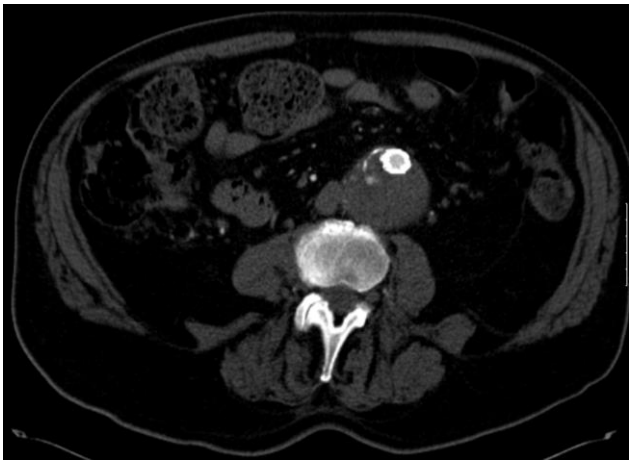


Figure 59: Contrast in the right anterior lower sac consistent with a type II endoleak from a lumbar artery in patient 3



DUS surveillance

- 6 weeks – The EVAR stent is patent with no significant stenosis or kinking. There is a type II lumbar endoleak present resulting with small flow in the right side of the distal aortic sac. The crossover graft is patent.
- 6 months – The EVAR stent-graft is patent and the small type II endoleak previously seen was still present in the right side of the distal aneurysm sac. The sac measured 5.5cm. The left common iliac artery was occluded and the bypass graft was patent.
- 1 year – The graft is patent and the small type II endoleak previously seen is still present in the right side of the distal aneurysm sac, but the causative source was not defined. The sac measures 5.1cm.
- 18 months – Patent aorto-uni-iliac stent-graft with a type II endoleak of undefined source. The size of the aortic sac is unchanged and measures 5.1cm.
- 2 years – The aneurysm sac measures 5.6cm and there appears to be a tortuous channel of flow through the sac from distal to mid sac consistent with an endoleak. The blood flow pattern is typical forward reverse false aneurysm flow, suggesting only one entry and exit vessel. The source of the endoleak could not be identified.

CEADUSS surveillance

- 2 years –1ml of Sonovue was administered and contrast bubbles suggesting evidence of a tortuous leak in the anterior and right of the sac. The endoleak appears to be a type II from a lumbar artery. Another 1ml of SonoVue was administered to confirm the above findings after previous contrast washout, the lumbar type II endoleak was directly visualized feeding the sac.

Patient 4

Background

A 79-year-old man with a 5.5cm infrarenal AAA was repaired on 22nd December 2008 using a Gore bifurcated stent-graft. Completion angiography showed late filling from a small type II endoleak.

CT surveillance

- Discharge – A significant type II endoleak from lumbar vessels was noted.
- 3 months – The previously noted type II endoleak from a lumbar artery is again noted but of a smaller size. The sac size is stable measuring 5.57cm. There is a small infarct at the lower pole of the right kidney noted which is new.
- 6 months – There is a stable type II endoleak caused by a lumbar artery adjacent to the proximal end of the stent-graft (**Figure 60**). The sac size is stable and measures 5.4cm.
- 1 year – The previously noted type II endoleak has now resolved and the sac size is 5.3cm. There is however a very small "fleck" of calcium seen posteriorly at the aortic bifurcation. The Hounsfield unit of this calcium deposit was measured at 658 confirming it was calcium and not radiological contrast (**Figures 61-62**).

Figure 60: Surveillance imaging at 6 months showing a large type II endoleak caused by a lumbar artery in patient 4

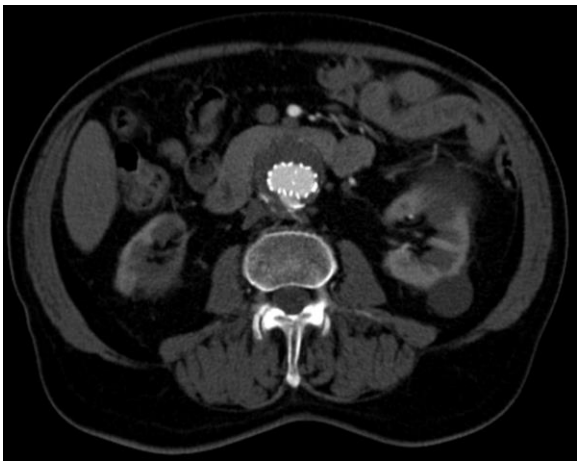


Figure 61: Demonstrating a "fleck" of calcium at the posterior aspect of the aortic bifurcation and not an endoleak in patient 4 at 1 year surveillance

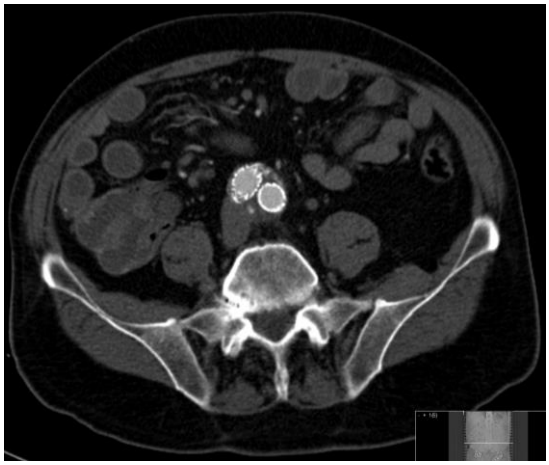
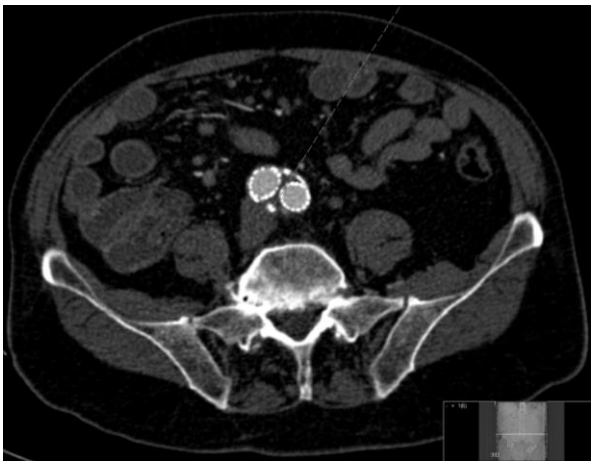


Figure 62: This is the same image as figure 61. The Hounsfield unit of the calcium measuring 658 confirms it wasn't radiological contrast and thus not an endoleak at 1 year surveillance



DUS surveillance

- 3 months – The sac measures 4.9cm and there is no evidence of an endoleak.
- 6 months – The graft is patent and the sac measures 4.7cm. There is no evidence of an endoleak. There were poor views of the iliac limbs due to obscuring bowel gas.
- 1 year - The graft is patent and the sac measures 5.0cm. There is no evidence of an endoleak.

CEADUSS surveillance

- 1 year – 1ml of Sonovue was administered and contrast bubbles suggesting evidence of a leak in posterior of the sac adjacent to the stent bifurcation was seen in continuation with a region outside of the sac wall, which would suggest a type II leak from a lumbar artery. The blood flow pattern is typical forward reverse false aneurysm flow, suggesting only one entry and exit vessel.

Patient 5

Background

A 77-year-old lady had EVAR repair on 23rd June 2003 using a percutaneous Medtronic Talent bifurcated stent-graft of a 6cm AAA. Both internal iliac arteries were embolized. She was admitted one month later with an ischemic right leg. There was an occlusion of the right distal limb of the graft, originating from a kink distal to the modular insertion. Limb salvage was successful after an embolectomy and the graft kink was ballooned.

At 5 year follow-up the graft was found to be migrating inferiorly with consequent sac size enlargement. EVAR reintervention occurred on 18th August 2008 with the deployment of a Cook proximal end cuff extension to seal and stabilize the migrating proximal end. There was endoleak seen filling the sac on completion angiography.

At 6½ years a large left endoleak from the iliac limb was detected on surveillance. The endoleak was categorized as a type III due to left iliac limb modular separation (**Figure 63**). On 25th January 2010 a further Medtronic iliac limb was deployed within the existing left iliac limb to reline it. Post-reintervention no endoleak was demonstrating on completion angiography (**Figure 64**).

Figure 63: The endoleak at 6½ years post-original EVAR. Contrast extravasation seen at the proximal left iliac limb (a type III endoleak) due to modular separation. Note the right and left iliac limb cross-over of "ballerina legs" technique

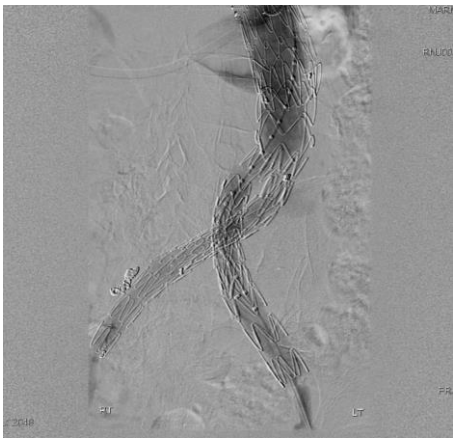
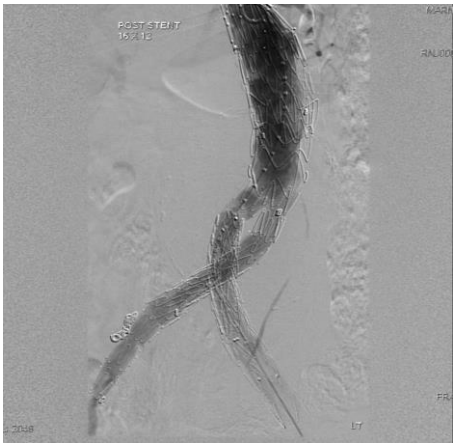


Figure 64: Cessation of the endoleak seen at 6½ years post-original EVAR after the second reintervention with the insertion of a relining left iliac limb



CT surveillance

- 3 months – No endoleak seen.
- 6 months – No endoleak seen and the sac measures 6.1cm.
- 1 year – No endoleak present and the graft and sac size are satisfactory.
- 2 years – Satisfactory graft appearance and no evidence of endoleak.
- 3 years – Satisfactory graft appearance and no evidence of endoleak.
- 4 years – The proximal end of the infra-renal stent graft has migrated slightly inferiorly but remains in an adequate position. There is no evidence of an endoleak, but the aneurysm sac size is 6.4cm.
- 5 years – The proximal end of the graft has almost certainly migrated inferiorly and probably a little further since last year. There has been a significant enlargement of the sac.
- 5½ years (3 months post-reintervention EVAR) – The aneurysm sac size has again increased from 6.5 to 7.1cm. There is no obvious endoleak to account for this and the proximal and distal seals are intact = ?endotension..
- 6 years (1 year post-reintervention EVAR) – There has been an interval increase in the size of the aneurysm sac size to 7.6cm. There is no obvious endoleak to explain this = ?endotension..
- 6½ years (1½ years post-reintervention EVAR) – There is a large left sided endoleak seen arising from the left iliac limb (**Figures 65-66**). Both internal iliac arteries have been embolized. There is a continued growth of the sac which now measures 10cm. No rupture is identified.

Figure 65: Contrast seen leaking out of the left iliac limb to feed the sac in patient 5 at 6½ years post-original EVAR surveillance; significantly expanding sac size

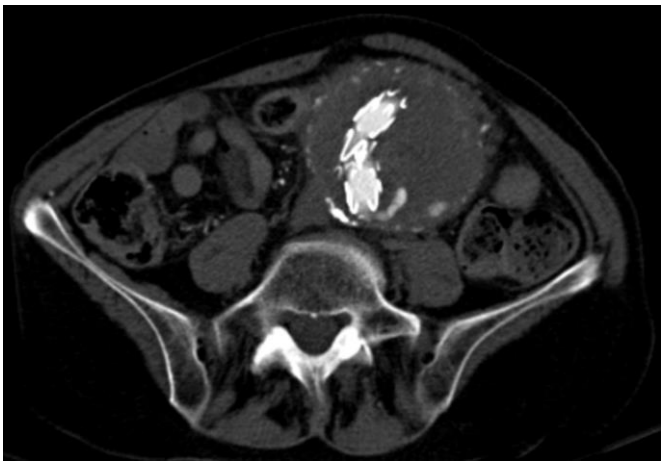
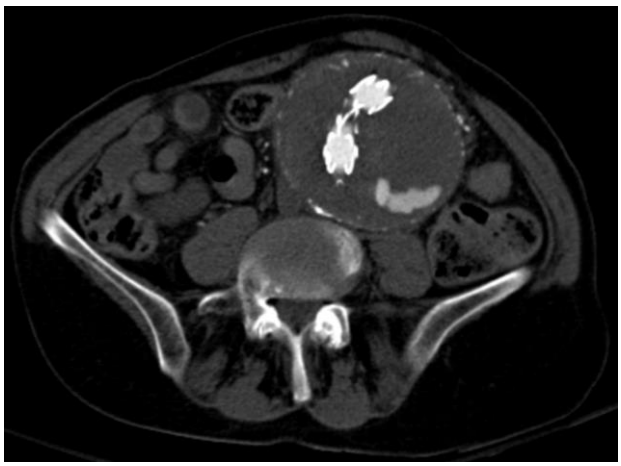


Figure 66: Contrast seen leaking out of the left iliac limb to feed the sac in patient 5 at 6½ years post-original EVAR surveillance; significantly expanding sac size



DUS surveillance

- 4 years – No evidence of an endoleak and the sac measures 6.3cm.
- 5 years – No evidence of any endoleak. The aortic aneurysm sac size has increased from 6.3cm last year to 7.3cm one year on! = ?endotension.
- 5 years (reintervention EVAR discharge scan) – Sac measures 7.3cm and there are no endoleaks = ?endotension..
- 5½ years (3 months post-reintervention EVAR) – The sac measures 7.3cm and there is no evidence of endoleak = ?endotension.
- 6 years (1 year post-reintervention EVAR) – No evidence of endoleak and the sac size is 7.2cm = ?endotension.
- 6½ years (1½ years post-reintervention EVAR) – The aneurysm sac measures 7.7cm and there is no evidence of an endoleak seen = ?endotension.

CEADUSS surveillance

- 6½ years (1½ years post-reintervention EVAR) – Three consecutive 1ml doses of SonoVue contrast agent were administered. There were faint echoes with the appearance of contrast bubbles in the right lateral side of the sac suggesting a very slow endoleak. No source of leak could be seen, but after a delay it collects on the right side of the sac.

Patient 6

Background

A 77-year-old man was found to have a 5.6cm incidental asymptomatic AAA on ultrasound. His comorbidities included asbestosis and consequent chronic obstructive pulmonary disease so an endovascular solution was desired. He was deemed anatomically suitable for EVAR and was offered enrolment with the EVAR II trial but declined because he was not keen on randomization and wanted intervention. On 24th January 2005 he underwent an EVAR using a Gore bifurcated stent-graft device.

At 2 years post-EVAR he underwent reintervention for a type II endoleak caused by a large lumbar vessel fed from an ileo-lumbar branch of the right internal iliac artery, which was embolized. Post-procedure the endoleak was not completely obliterated, but was left alone due the stable aneurysm sac size.

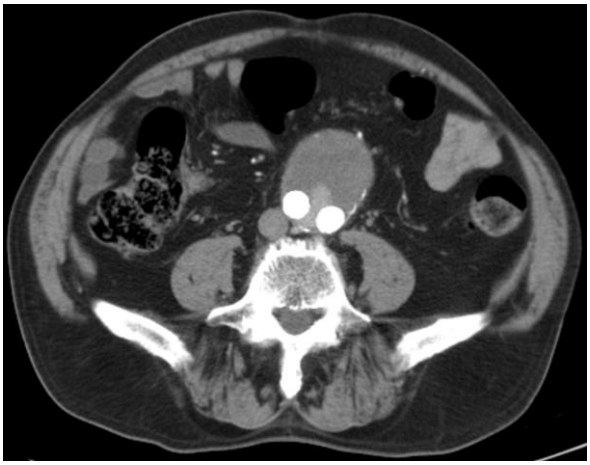
At 3¼ years post-original EVAR procedure he underwent a second reintervention with a Gore iliac extension device deployed into the right common iliac artery immediately above the right internal iliac artery and then ballooned. No endoleak was visualized on post-procedural angiography.

CT surveillance

- Discharge – No endoleak seen and satisfactory stent position.
- 3 months – No endoleak.
- 6 months – Reducing sac size despite the presence of a type II endoleak.
- 1 year – A type II endoleak with a stable sac size.
- 2 years – A persistent type II endoleak with a stable sac size.
- 3 years (1 year post-reintervention) – A type II endoleak is noted from a lumbar vessel just above the aortic bifurcation. A distal type Ib endoleak is also seen from the right common iliac artery. Maximum sac size measures 6.08cm.
- 3½ years (6 months post-second reintervention) – Stable post-EVAR appearance and the distal right type Ib endoleak has sealed after the insertion of an extension graft but the type II endoleak is again noted. The sac size is stable measuring 6.1cm.

- 4 years (1 year post-second reintervention) – The type II endoleak is again seen and unchanged. The sac size is stable at 6.24cm.
- 4½ years (1½ years post-second reintervention) – There is still a type II endoleak seen low in the sac between the limbs. There has been minimal sac expansion to 6.4cm. There is no evidence of migration or strut failure.
- 5 years (2 years post-second reintervention) – No evidence of migration or iliac limb failure. The type II endoleak between the two limbs of the graft distal to the aortic bifurcation into the sac is again noted and unchanged (**Figure 67**). The sac dimensions remain unchanged and stable at 6.8cm.

Figure 67: Persistent type II endoleak from a lumbar artery in patient 6 after unsuccessful embolisation but successful resolution of a right type Ib extension limb



DUS surveillance

- 6 months – Reducing sac size despite the presence of a type II endoleak.
- 1 year – A type II endoleak with a stable sac size.
- 2 year – A persistent type II endoleak is seen with a stable sac size.
- 2½ years (6 months post-reintervention) – Type II endoleak present and arises from a lumbar artery. The sac measures 5.3cm.

- 3 years (1 year post-reintervention) – The previously reported type II endoleak persists. It curves around the lateral edge of the right limb of the graft, filling into the anterior portion of the sac. Flow from the endoleak also courses anteriorly between the two limbs of the stent. The endoleak appears to originate from a lumbar artery. The aortic aneurysm sac measures 5.79cm and has increased in size over 6 months.
- 3½ years (6 months post-second reintervention) – The previously reported endoleak is still present around the lateral edge of the right limb of the graft filling into the anterior sac. There is also flow coursing anteriorly between the two stent limbs. Unable to decipher the type of endoleak II or III. The sac size measures 5.77cm.
- 4½ years (1½ years post-second reintervention) – A channel of flow was seen to course through the aneurysm sac and appeared to originate from the right posterior sac. The exact origin could not be identified. The sac measures 5.7cm.
- 5 years (2 years post-second reintervention) – The previously reported endoleak is still present in the same positions and course. Still unable to determine the type (II or III) and causative source of leak. Sac size is 6.1cm.

CEADUSS surveillance

- 5 years (2 years post-second reintervention) – 1ml of SonoVue was administered. There are contrast bubbles in the posterior distal sac with evidence of bubbles outside the posterior sac suggesting that the leak is a type II from a lumbar artery. In addition the contrast collection in the sac is delayed which may exclude a type III leak. This investigation was repeated after a washout period with another 1ml of SonoVue to clarify the delayed sac filling and that it was truly a lumbar vessel causing a type II endoleak.

Patient 7

Background

A 76-year-old man was incidentally found to have a 6cm AAA amenable to endovascular repair on a CT scan. This was requested to investigate the cause of differing upper limb brachial blood pressures detected during a treadmill test following a myocardial infarction 2 months prior. He had previous suffered another myocardial infarction and had a CABG. Other comorbidities included chronic obstructive pulmonary disease hypercholesterolemia, hypertension and he was an ex-smoker. He underwent EVAR on 2nd September 2005 with a Medtronic Talent bifurcated device.

CT surveillance

- 3 months – No evidence of endoleak and maximum sac size remains stable at 5.9cm.
- 1 year – Sac size is stable and there are no endoleak is seen.
- 2 years – Sac size is stable at 5.9cm and there is no evidence of an endoleak.
- 3 years – No endoleak and stable sac size of 5.9cm.
- 4 years – No endoleak is identified and the sac size has increased slightly over the last year to 6.2cm. There is some renal atrophy noted.
- 4½ years – No endoleak is present and there is a stable sac size of 6.2cm.

DUS surveillance

- 3 months – No evidence of endoleak and maximum sac size remains stable at 5.5cm.
- 1 year – Stable sac size and no endoleak is seen.
- 2 years – Sac measures 5.7cm and no endoleak is seen.
- 3 years – A very tiny endoleak is detected at the anterior of the sac which may possibly be a type II. The sac measures 5.4cm.
- 4 years – A small endoleak is detected in the left anterior aspect of the sac, however type could not be determined but could possibly be a type II? Sac measurement is 6.2cm which is larger than previous recordings.

- 4½ years – The aneurysm sac size is stable and measures 6.2cm. Colour flow imaging suggests a small endoleak in the anterior left aspect of the sac. Type of endoleak was not determined and thus remains uncertain, but could possibly be a type II?

CEADUSS surveillance

- 4½ years – 1ml of SonoVue was administered. There was no evidence of contrast bubbles within the aneurysm sac outside the stents. This may suggest that the leak seen with normal colour flow imaging was possible a movement artifact causing a shadow. A further 2ml dose of SonoVue was administered to confirm that there was no endoleak present.

Patient 8

Background

A 77-year-old man was found to have a 4.7cm infrarenal AAA found incidentally when being investigated for a collapse. His comorbidities included a previous myocardial infarction, hypertension, renal impairment and fibromyalgia rheumatica which restricted his mobility. He was followed up in the vascular outpatient clinic with yearly ultrasound surveillance imaging.

1 year later he was admitted with acute back pain and had a tender AAA on examination. A CT scan showed his AAA to be 5.1cm without signs of rupture, which was anatomically suitable for EVAR. Despite his AAA diameter measuring < 5.5cm he was offered earlier intervention because his AAA was deemed to be symptomatic with documented aneurysmal tenderness. On 16th April 2007 he underwent EVAR with a bifurcated Medtronic stent-graft. Post-procedural completion angiography revealed that the graft was in a satisfactory position and there were no endoleaks present. His renal function deteriorated slightly following his procedure.

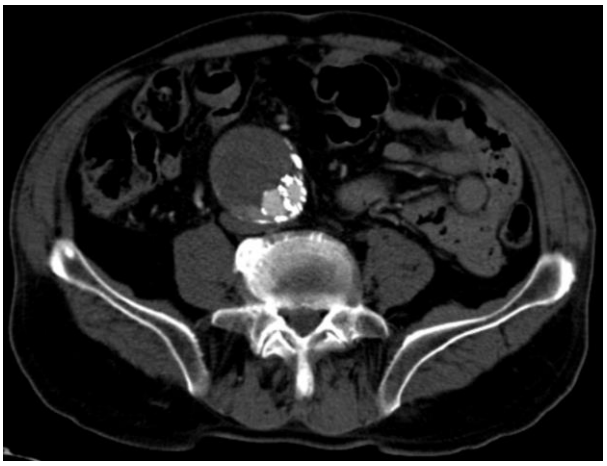
A diagnostic angiogram was performed two weeks after the original EVAR procedure on 25th April 2007 showing an endoleak to the right of the stent's main body and proximal to the right iliac limb. The leak was small and appeared early so was felt to be either a small proximal type I or a fabric tear in the main body. The leak appeared to be draining via a lumbar artery. After discussion at the weekly vascular and radiology multidisciplinary meeting, the decision was made to manage this leak conservatively.

His renal function deteriorated further and the decision was made on 14th August 2008 to undertake his EVAR surveillance with duplex ultrasound only and reserve CT imaging if the appearance of his endoleak worsened or sac size increased. However, he again presented as an emergency with back pain and underwent a further CT scan on 5th September 2008.

CT surveillance

- Pre-discharge – There is a small endoleak at the level of the aortic bifurcation, which extends superiorly for 3.7cm. There is a possible connection of the distal aspect of the endoleak with a lumbar artery, however the endoleak is larger more proximally at the point of the limb bifurcation.
- 3 months – The previously noted small endoleak at the level of the aortic bifurcation is not now present.
- 6 months – No endoleak is identified and the sac size remains stable at 5.4cm.
- 1 year – A small endoleak is seen adjacent to the right iliac limb, just above the aortic bifurcation suggestive of a type II endoleak. The sac has reduced in size to 5.1cm.
- 1½ years – No endoleak seen and no increase in sac size.
- 2 years – There is a type II endoleak adjacent to the aortic bifurcation. The sac size remains stable at 5.1cm.
- 2½ years – There is a stable type II endoleak originating from a small caliber right lumbar artery entering the sac laterally at the level of L5 (**Figure 68**). The sac size is stable.

Figure 68: CT surveillance imaging 2½ years post-EVAR showing a type II endoleak originating from a small caliber right L5 lumbar artery entering the sac laterally. Contrast can be seen filling the aneurysm sac in patient 8



DUS surveillance

- Pre-discharge – There is an endoleak which is either a type I or III. The leak is either coming from an incomplete join between the modular iliac limb and the stent main body or a defect in the proximal end of one of the iliac limbs. The leak is adjacent to the proximal end of the iliac limb which lies on the right side of the sac. The aneurysm sac measures 4.5cm. Persistent extensive bowel gas made this investigation difficult and provided limited views.
- 2 months – No endoleak was seen and the sac diameter measures 4.5cm.
- 3 months – There is an endoleak which appears to be a type III coming from the posterior aspect of the right iliac limb just above the level of the aortic bifurcation. Flow from the endoleak appears to exit the sac via the inferior mesenteric artery. The AAA sac measured 4.5cm.
- 6 months – There is a type III endoleak coming from the posterior aspect of the right iliac limb just above the level of the aortic bifurcation. Flow from the endoleak appears to exit the sac via the inferior mesenteric artery. The AAA sac measured 4.4cm.
- 11 months – There is a type III endoleak from the right iliac limb of the graft. The sac measures 4.5cm. Segments of the iliac limbs and arteries were obscured by bowel gas.
- 1 year – The previously reported endoleak is still present but appears to be a type II endoleak from a right lumbar artery. There is a relatively large amount of flow in the aneurysm sac which measures 4.5cm.
- 2 years – Type II endoleak is still present and originates from a lumbar artery. The sac size is 4.7cm.
- 2½ years – There is an endoleak in the region of the distal sac originating posteriorly possibly from a lumbar artery? However due to the close proximity to the right iliac limb of the graft a type III cannot be ruled out. The aneurysm sac size has increased to 5.4cm.

CEADUSS surveillance

- 2½ years – Two 1ml doses of SonoVue contrast agent were administered. There was an endoleak originating in the region of the distal sac, coursing along the posterior aspect of the right sac to the left sac anteriorly. This is a type II endoleak originating

from a lumbar artery, with typical high velocity forward and reverse flow. Also the presence of microbubbles seen within the endoleak were delayed compared with the contrast seen within the stents, so a type III endoleak can be excluded.

Patient 9

Background

An 86-year-old man presented as an emergency with a 7.2cm leaking infrarenal AAA on 19th May 2008 on transfer from different hospital. His anatomy was deemed suitable for EVAR and underwent stent-grafting with a Medtronic Talent aorto-uni-iliac device, insertion of a left common iliac Medtronic excluder device and then a right to left femoral-femoral crossover bypass grafting. Post-procedural completion angiography demonstrated a type I endoleak which did not improve with ballooning. A Palmaz stent was inserted proximally which resolved the leak. Post-procedure he suffered an acute myocardial infarction on the intensive care unit.

CT surveillance

- Pre-discharge – No endoleak is seen and the maximal sac size is 7.2cm. The stent-graft and bypass are both patent.
- 3 months – Stable sac size. There is flow seen in a lumbar vessel at L4 entering the sac causing a type II endoleak.
- 6 months – The sac size remains stable at 7.1cm. There is filling of the sac from a lumbar vessel consistent with a type II endoleak.
- 1 year – There is no endoleak seen and the sac size measures at 7.7cm.
- 1½ years – No endoleak is noted but the sac size has increased to 8.3cm (**Figures 69-70**).

Figure 69: Surveillance CT imaging of Patient 9 demonstrating an enlargement of sac diameter to 8.3cm, no endoleaks could be detected

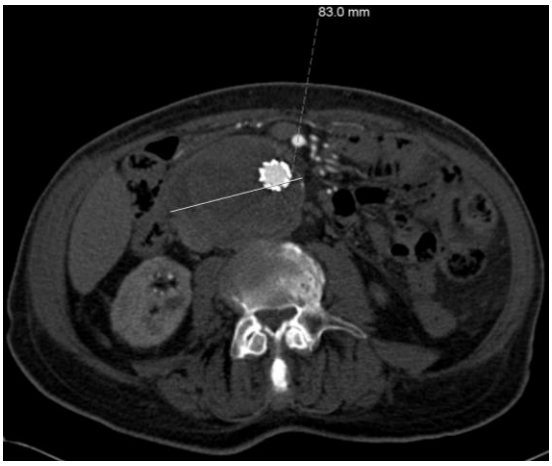
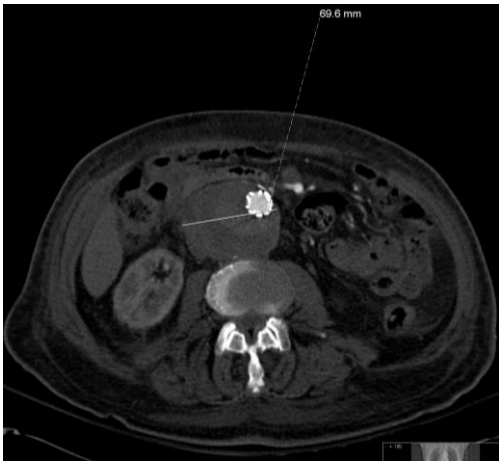


Figure 70: Surveillance CT imaging of Patient 9 performed 1 year prior to Figure 69 showing a smaller sac size of 6.9cm before subsequent increase



DUS surveillance

- Pre-discharge – No endoleak
- 3 months – Very limited views proximally and distally due to extensive bowel gas. No evidence of endoleak was seen. The maximum aneurysmal sac diameter was 6.4cm. The stent and bypass were both patent.
- 6 months – Very limited views due to extensive bowel gas. The stent and bypass were both patent. No evidence of endoleak was seen and the maximum aneurysmal sac diameter was 6.4cm.
- 1 year – Very limited views due to extensive bowel gas. No endoleak seen and the sac measured 6.3cm.
- 1½ years – The aneurysm sac has enlarged and measures 7.0cm. There is no evidence of an endoleak. The proximal and distal ends of the sac could not be imaged due to bowel gas.

CEADUSS surveillance

- 1½ years – 1ml of Sonovue was administered. An area of contrast bubbles could be seen in the region of the proximal anterior right sac. However it is difficult to determine what type of endoleak this is. A further 2mls of Sonovue was administered for confirmation. The type of endoleak could not be classified, but one was present.

Patient 10

Background

An 84-year-old schizophrenic lady was found to have a large AAA when being examined after complaining of constipation. Her comorbidities included angina, atrial fibrillation and hypertension. She was entered into the EVAR-2 trial and randomized to receive endovascular repair of her 9.5cm AAA. On 24th May 2004 she underwent an EVAR using a bifurcated Gore device. The right limb of the graft was extended to the right external iliac artery, thus requiring embolisation of the right internal iliac artery. Post-operatively she complained of right buttock intermittent claudication due to the embolisation of her right internal iliac artery.

Due to illness and also caring for her husband she frequently failed to attend hospital outpatients and surveillance imaging appointments.

She was admitted on 6th June 2005 for a diagnostic angiogram after surveillance imaging suggested a suspected endoleak. No leak was demonstrated.

3½ years after her original EVAR, surveillance imaging detected an enlarging aneurysmal sac with no detectable endoleak. The decision was made to for reintervention. On 14th December 2007 she underwent relining of her EVAR with the deployment of Gore stents within the previous stent. This procedure was performed percutaneously under local anesthesia.

A type Ia endoleak was detected post-relining reintervention to her EVAR and it was decided that this should be treated despite no change in sac size of 12.2cm. On 18th July 2008 she underwent a third EVAR procedure percutaneously. An extension cuff was deployed proximally but on completion angiography there was a persistent late leak. It was decided to insert a Palmaz stent but this was abandoned due to inability to traverse a kinked sheath on the right hand side.

CT surveillance

- Post-procedure – No endoleak seen and satisfactory graft position.

- 6 months – A posterior endoleak is seen.
- 1 year – No endoleak was demonstrated.
- 2 years – No evidence of endoleak.
- 2½ years – Increased sac size measuring 10.2cm.
- 3 years – No endoleaks are identified but the sac size has further increased to 12.1cm. These findings are suggestive of endotension.
- 3¾ years (3 months after reintervention EVAR) – There is an endoleak seen proximally on the right which represents a type Ia endoleak, which has not been previously seen. The maximum sac diameter is stable since the relining reintervention of her EVAR at 12.2cm.
- 4½ years (6 months after second reintervention EVAR) – The type I endoleak is smaller than before the second reintervention EVAR when a proximal extension cuff was inserted. There is also a further type II endoleak from bilateral large lumbar arteries at the level of the stent bifurcation. It is likely that this is the outflow of the type I endoleak. The sac size has increased and measures 12.9cm.
- 5 years (1 year after second reintervention EVAR) – No obvious migration of the proximal stent graft. The aneurysm sac has enlarged since previous imaging and now measures 13.2cm. A type Ia endoleak is seen in the arterial phase originating from the right anterior aspect of the proximal stent (**Figures 71-72**) and has an outflow via a left lumbar artery at L3.

Figure 71: A type Ia endoleak is seen collecting anteriorly at the right proximal side of the stent on a coronal CT image in patient 10

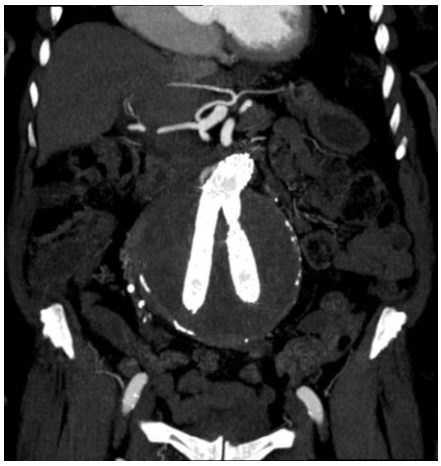
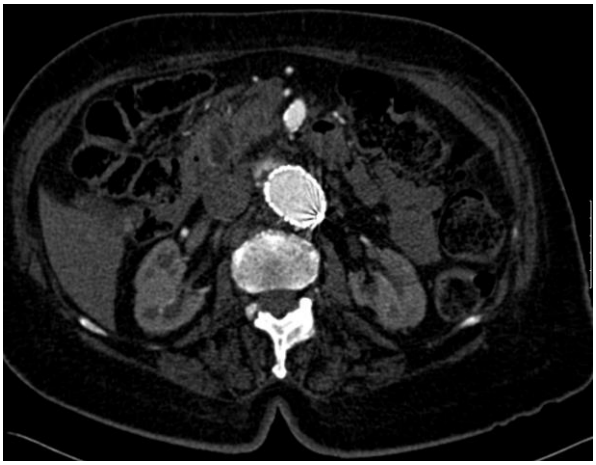


Figure 72: A type Ia endoleak is seen collecting anteriorly at the right proximal side of the stent on an axial CT image in patient 10



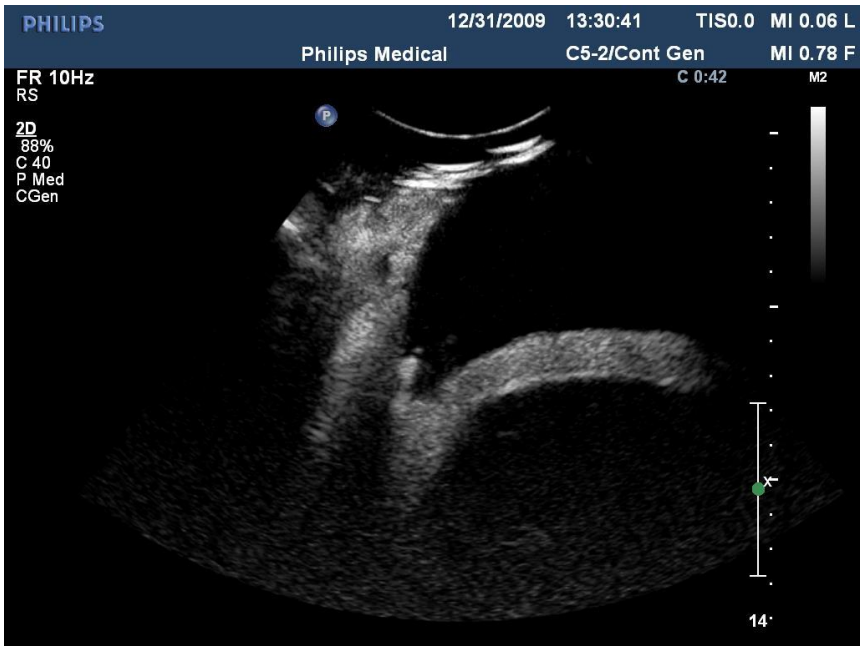
DUS surveillance

- 1 year – No endoleak was demonstrated.
- 3 years – Evidence of an endoleak was seen within the proximal to mid aneurysm sac. A source of the endoleak could not be identified. The aortic sac had increased and measured 10.5cm.
- 3½ years (pre-discharge after reintervention EVAR) – No evidence of an endoleak and the sac measured 10.5cm.
- 4 years (pre-discharge after second reintervention EVAR) – No evidence of endoleak. The aneurysm sac measured 11cm. Poor views due to obscuring bowel gas.
- 5 years (1 year after second reintervention EVAR) – The aneurysm sac measures 12.3cm. There appears to be a small endoleak in the proximal sac, with a forward/reverse flow pattern suggesting a single entry and exit point. The endoleak appears to originate from the proximal stent region, however it was not possible to determine the endoleak type. It was not possible to image the distal aspect of the sac and stents due to bowel gas.

CEADUSS surveillance

- 5 years (1 year after second reintervention EVAR) – 1ml of SonoVue was administered. There are contrast bubbles present suggesting evidence of an endoleak which course up the stent to collect in the proximal anterior sac. The leak is a type III originating at the stent bifurcation at the iliac limb modular insertion (**Figure 73**). The leak also courses up between the relining of the old and new stents to fill proximally on the right mimicking a type Ia endoleak. Another 1ml of Sonovue was administered to confirm the endoleak at the stent bifurcation and to visualize the proximal filling endoleak coursing in a retrograde fashion from the bifurcation up in the space between the two sets of relined stents. These findings were confirmed on diagnostic angiography prior to reinterventions.

Figure 73: A type III endoleak can be seen at the bifurcation of the EVAR stent in patient 10. This leak also traverses up the stent in a retrograde fashion to collect at the right proximal aspect of the graft to mimic a type Ia endoleak



CEADUSS was successfully performed and well tolerated by all 10 patients, there were no side effects.

The results of the 10 patients were as follows:

1. **Patient 1**, 3 years post-EVAR had a type II endoleak originating from a left lumbar artery on CT, was not seen with DUS but confirmed by CEADUSS.
2. **Patient 2**, 6 months post-EVAR had a type II endoleak originating from a left lumbar artery on CT, endoleak type and source was not defined with DUS but was with CEADUSS.
3. **Patient 3**, 2 years post-EVAR had a type II endoleak originating from a lumbar artery. The endoleak type was defined by DUS but source was unidentified. CEADUSS confirmed CT findings by defining type and source.
4. **Patient 4**, 1 year post-EVAR did not have an endoleak on CT having previously demonstrated a type II endoleak which had resolved. DUS agreed with these findings, but CEADUSS demonstrated that the leak was still persisting and had not resolved.
5. **Patient 5**, 6½ years post-EVAR had a type III endoleak originating from the left iliac limb due to modular separation on CT. DUS revealed sac size expansion in the presence of no endoleak (endotension) and CEADUSS revealed a slow endoleak with no identifiable source.
6. **Patient 6**, 5 years post-EVAR had a type II endoleak originating from a lumbar artery. The endoleak type was and source was not defined by DUS. CEADUSS confirmed CT findings by defining type and source.
7. **Patient 7**, 4½ years post-EVAR did not have any endoleak on CT and CEADUSS was in agreement, unlike DUS which identified an endoleak with no type or source identified which could possibly be a type II.
8. **Patient 8**, 2½ years post-EVAR had a type II endoleak originating from a lumbar artery on CT. This was visualized with DUS but remained undefined and the possibility was raised that it was a type II from a lumbar or a type III from the right iliac limb. CEADUSS was in agreement with CT findings.
9. **Patient 9**, 1½ years post-EVAR displayed sac size expansion without the presence of an endoleak (endotension) on CT in agreement with DUS. CEADUSS visualized an endoleak but type and source was not defined.

10. **Patient 10**, 5 years post-EVAR had a type Ia endoleak on CT which was seen using DUS, however type and source was not defined. CEADUSS demonstrated a type II endoleak originating from the aortic bifurcation, filling proximally, confirmed with angiography.

Table 36 presents a summary of the final surveillance findings for all 10 patients using CT, DUS and CEADUSS imaging.

Table 36: Summary of final surveillance findings

Patient	Surveillance time period post-EVAR of most recent imaging	CT	DUS	CEADUSS
1	3 years	Type II endoleak originating from a left lumbar artery	No endoleak	Type II endoleak originating from a left lumbar artery
2	6 months	Type II endoleak originating from a left lumbar artery	Endoleak visualized but undefined because source not identified	Type II endoleak originating from a left lumbar artery
3	2 years	Type II endoleak originating from a lumbar artery	Type II endoleak with undefined source	Type II endoleak originating from a lumbar artery
4	1 year	No endoleak present, previously there was a type II lumbar artery endoleak which has now resolved	No endoleak	Type II endoleak from a lumbar artery
5	6½ years	Type III endoleak from left iliac limb modular separation	No endoleak but serial sac size increase detected = ?endotension	Slow endoleak present but source not identified.

6	5 years	Type II endoleak originating from a lumbar artery	Endoleak visualized but undefined because source not identified. Possibly a type II from a lumbar or type III from the right iliac limb	Type II endoleak originating from a lumbar artery BUT NOT type III as DUS suggests
7	4½ years	None	Endoleak visualized but undefined because source not identified. Possibly Type II?	None
8	2½ years	Type II endoleak originating from a lumbar artery	Endoleak visualized but undefined. Possibly a type II from a lumbar or type III from the right iliac limb	Type II endoleak originating from a lumbar artery BUT NOT type III as DUS suggests
9	1½ years	None but sac size increase - ?endotension	None but sac size increase - ?endotension	Endoleak visualized but undefined
10	5 years	Type Ia endoleak	Endoleak visualized at the proximal aspect of the stent but undefined	Type III endoleak originating at the aortic bifurcation filling proximally

DISCUSSION

Ten patients with confirmed endoleaks on CT but failed identification or definition using DUS were successfully investigated using CEADUSS, with no side effects. If an endoleak was present, then the aim was to define endoleak type and to delineate its origins, this was not possible in all cases. A summary of these findings is presented in **Table 36**.

CT is defined by a number of authors as the "gold-standard" imaging modality for post-EVAR endoleak detection (Oikonomou 2012, van der Vilet 2011, Carrafiello 2008, Eliason 2008, Back 2007, Hartshorne 2006, AbuRahma 2005, Murphy 2004, Thurnher 2002, Veith 2002, Makaroun 2001, Görich 1999, Karch 1999, Golzarian 1998, Balm 1997, Grimshaw 1992) It is implemented at 1, 3, 6 and 12 months and then annually for the patients' lifetime (Oikonomou 2012, Iezzi 2010, Patel 2010, Go 2008, Zelenock 2006, Eksandari 2001, Vallabhaneni 2001). My results from this pilot assessment of CEADUSS and the existing performance of DUS on a small highly selected sub-set of patients from our EVAR surveillance database shows a widespread variability in endoleak detection using these 3 imaging modalities. There is no obvious glaring agreement between any of them.

The data could be analyzed to investigate imaging modality agreement (using Cohen's kappa coefficient), whether findings were positive or negative or if findings would prompt further management including more invasive investigation or reintervention.

DUS agreed with CT in 20% of studies (2/10), however endoleak was visualized but not defined in 60% (6/10) leaving only 2 conflicting studies. CEADUSS fared better and agreed with 60% (6/10) of CT studies. Only a solitary study (10% (1/10)) visualized an endoleak seen on CT but failed to define type and source and there were 3 conflicting studies (30%).

However, due to the fact that there are only 10 patients assessed in this pilot and they are very selected, this would be futile to accept as gold. Small differences between detection rates of the imaging modalities are magnified by analysis due to small numbers. The patients selected all have an abnormality on CT or suggested by DUS which is why they were chosen. Examining the actual patients included reveals that 4/10 (40%) are female which is not representative of the pattern of inheritance aneurysm disease, also females have been shown

to suffer more complications and worse outcomes with EVAR than males (Mehta 2012). Further assessing the patients included in my small series, they are composed of symptomatic patients, a ruptured AAA and two patients that received non-bifurcated devices that are not the normal standard EVAR patient that one encounters more so in clinical practice. These patients are known to be more complicated to manage and thus also provide an additional challenge when detecting complications post-EVAR. Consequently a number of my pilot project patients required reinterventions, that included embolizations, relining of stents, extension cuffs which would further contribute to making surveillance imaging and interpretation of findings difficult.

In summary the patients I have chosen for my pilot project to assess the clinical use of CEADUSS was highly selective and not representative of the majority of patients that have EVAR. Caution must be taken when applying statistical analysis to the outcomes and agreement of the small number of patients used for this pilot project. This further contributes to the validity of the results achieved and provides additional caution to the interpretation of them for clinical translation.

The aim of this study was to use CEADUSS clinically and familiarize ourselves with the technique. We successfully used the technique in all cases to gain adequate images using minimal contrast doses. The patients chosen were a small highly selected subset from our database with known abnormalities on previous surveillance.

There is an abundance of results in the literature demonstrating CEADUSS detected endoleaks not seen by CT which are labeled as false-positives (Mirza 2010, Iezzi 2009, Carrafiello 2006, Napoli 2004, Bendick 2003), because CT is commonly taken as the 'gold-standard'. They are usually low flow endoleaks (Iezzi 2010, Henao 2006, Bargellini 2005b, Bendick 2003, Schurink 1998). CEADUSS and DUS correctly highlighted patients in need of further angiogram characterization, raising the questionable need for CT. In my group of 10 patients CEADUSS did reveal findings that conflicted with CT, further evaluation is required before labeling these as false-positive findings.

It has been suggested that there is a reasonable role for CEADUSS as a problem-solving tool in situations of suspected endotension. In cases of uncertainty or when there was doubt

regarding a diagnosis of endoleak, we used a destruction-reperfusion technique (Iezzi 2010, Carrafiello 2008). This involved a brief pulse of high-intensity (high-MI) sound to confirm the presence of contrast media in a suspected endoleak enabling its complete destruction and then reperfusion in real-time (Carrafiello 2008, Clevert 2008d, Dill-Macky 2007, Bargellini 2005b). This provided added hemodynamic information on blood flow and direction which CT could not offer. My pilot project did not provide enough information to advocate the use of CEADUSS in these circumstances.

There are a number of considerations that a unit unfamiliar with CEADUSS should consider before its introduction. The extra cost of microbubble contrast, each vial of SonoVue costs £39.90 excluding VAT and the minimum order is 10 vials in a box. Each vial can be used for a maximum of 5 patients if a dose of 1ml is used for each examination. Additionally equipment for venous cannulation and cardiac resuscitation are necessary and require inclusion in any business plan. An appropriate ultrasound machine with capabilities for contrast imaging is also mandatory, not all manufacturers offer software capabilities for this so this may be an area of extra financial outlay.

During my CEADUSS clinical studies, I was advised to use 1ml of contrast per investigation, which goes against the recommended doses of SonoVue for Vascular Doppler imaging is 2.4ml as stated by Bracco in their instructions for use (Bracco 2005). This dose of 1ml was chosen after consultation with a representative from Bracco who was present during clinical testing of CEADUSS, we were advised to use a smaller dose of 1ml which could be repeated and would produce better images of endoleaks. This practice of using 1ml of SonoVue has been widely adopted subsequently since the publication of Bracco's instructions for use in 2005.

Another important issue concerns training ultrasonographers with the CEADUSS technique. Initially I learnt the technique with hepatic imaging in a high volume liver unit. Liver patients are plentiful and thus are ideal to learn contrast ultrasound techniques. The volume of EVAR surveillance patients is not comparable to this so gaining adequate experience and patient numbers is important. It is ideal for a single ultrasonographer to practice CEADUSS in a unit and it may be appropriate to centralize EVAR surveillance services, similar to vascular reconfiguration, offering greater patient numbers and experience and a more accurate and

focused imaging service. A change in surgical culture and attitude is needed regarding the ownership of patients, however times are changing and realization that patient care is a priority may be the catalyst for this.

I administered microbubble contrast and cannulated patients in our series. Ultrasonographers are not familiar with cannulation and also do not administer intravenous contrast. Also in the case of a serious side effect such as cardiac arrest, cardiopulmonary resuscitation will be required, so certification is required. I was present throughout the imaging of all of the patients in this pilot project, making it a two person technique. This may have major implications in the implementation of CEADUSS unless the extended role of a 'willing' ultrasonographer is explored. This problem is not encountered if CEADUSS imaging is performed by a radiologist as they are trained in cannulation and permitted to administer drugs.

To make more concrete conclusions, this study needs to be performed on a larger number of patients than the selected subset I have used in this pilot. My qualitative observations are that CEADUSS is a very promising imaging modality for surveillance. It is easy to use and administer once trained correctly and harmless to patients in our small trial. With experience, sensitivity and confidence will improve. CEADUSS should be considered for routine EVAR surveillance or as an adjunct to other imaging modalities after proper evaluation by a large randomized study prior to incorporation into protocols. There may be a role for the use of CEADUSS in difficult cases where there is unexplained sac expansion or undefined endoleaks but again only after proper evaluation.

CONCLUSIONS

This small pilot study investigating the clinical use of CEADUSS in a highly selected specific subset of patients has successfully been conducted with no patient harm. Analysis has revealed promising image capture using CEADUSS but no definitive conclusions can be drawn from them. A larger study with more randomized patients is required to define the clinical role of CEADUSS and assess it potential to be included as a solitary imaging modality or adjunct for post-EVAR surveillance.

SECTION 3

GENERAL DISCUSSION AND CONCLUSIONS

SUMMARY OF THESIS FINDINGS

The principle aim of my thesis was to investigate the use of DUS and determine the characteristics of an endoleak influencing detection sensitivity and specificity. I wanted to conduct investigations using DUS and CEADUSS in both laboratory and clinical settings.

Chapter 1: A laboratory endovascular stent phantom and preliminary contrast ex-vivo decay and brightness experiments

I designed and constructed a laboratory bench endovascular stent phantom to determine the limitations of DUS and CEADUSS for the detection of variable endoleaks. The EVAR phantom can produce an ultrasound detectable endoleak in three different planes: anterior, posterior and lateral to an endovascular stent. Also the distance of the endoleak from the EVAR stent can be varied from near, far or directly adjacent to the EVAR stent over five separate settings (Superimposed, 1cm and 2cm away from the stent). The third variable was that the velocity of the endoleak flow, from low (100 mm/hr) to high flow (900 mm/hr) over five different speed settings.

I then investigated the unknown behavior of SonoVue microbubble ultrasound contrast within the phantom system in anticipation of subject testing. I conducted volume calculations for the phantom to determine the dose of contrast required for administration, correlating to that used in human testing. Once these values were calculated, I carried out several decay and brightness experiments using the microbubble contrast exposed to intermittent and continuous ultrasound. These showed that when the contrast was left within the phantom system with minimal intermittent ultrasound exposure, it did not significantly decay over a period of 16 days ($p=0.27$). At 2 months it was still detectable. This implied that SonoVue microbubble contrast did not decay within the phantom and that the only factor that would alter its presence and use in endoleak detection would be the presence of ultrasound.

Next investigations of the effects of ultrasound upon microbubble decay and brightness were conducted in experiments exposing SonoVue to continuous ultrasound. The results demonstrated that continuous ultrasound exposure to microbubble contrast did significantly reduce the brightness of SonoVue over time ($p<0.0001$) in a linear fashion.

With the EVAR phantom model established and administration of contrast tested in doses reflecting those used in a human subject, I was now ready to conduct subject testing to determine the effectiveness and limitations of both DUS and CEADUSS in EVAR endoleaks detection.

Chapter 2: Laboratory endovascular stent phantom experiments comparing ultrasound colour Doppler and contrast enhanced ultrasound endoleak detection

I successfully tested 6 vascular ultrasonographer subjects with different clinical experience using a laboratory EVAR phantom with a simulated variable endoleak. Initially they were tested with 36 different endoleaks over varying plane (anterior/lateral/posterior), position (5 settings near-far) and velocity (100-900mls/hour) using DUS then repeated with the same endoleaks using CEADUSS.

There was a significant difference ($p=0.0007$) when comparing the raw data for all of the DUS recordings with the CEADUSS results. CEADUSS produced more inconclusive results overall. To compare the sensitivities of the two modalities, the outcomes were converted to binary form to demonstrate that DUS sensitivity was 42% Vs 60% for CEADUSS. CEADUSS was 18% more sensitive for endoleak detection overall, across all observers and conditions and this difference was statistically significant ($p<0.0001$). Again the data was analyzed depending upon diagnostic outcome and DUS produced 24% inconclusive examinations which was similar to the 20% of CEADUSS tests. The difference of 4% was not statistically significant ($p=0.3135$), despite CEADUSS showing a very marginal benefit. CEADUSS may have produced more inconclusive results in this part of the analysis for reasons I have already mentioned. Re-analysis of the subjects after they have gained more experience and familiarity with CEADUSS may confirm or disprove if there is actually a difference or similarity between proportions of inconclusive examinations of these two techniques.

There was only fair agreement between the two imaging modalities, with CEADUSS being more sensitive (60% Vs 42%) and DUS having a greater proportion of endoleaks not seen (34% Vs 20%), there were a similar proportion of inconclusive endoleak detection (24% DUS Vs 20% CEADUSS) when looking at overall inter-modality agreement. Inter-modality agreement was next looked at for each subject separately to assess operator dependency and

if years of experience had an effect. The most experienced operator (23 years) demonstrated a moderate agreement, detecting a greater proportion of endoleaks with CEADUSS (56% Vs 44%), more endoleaks not detected with DUS (39% Vs 28%) and the same proportions of inconclusive tests for each modality (17%). The next most experienced subject (11 years) demonstrated a slight agreement between modalities, CEADUSS detected more endoleaks (50% Vs 25%), DUS had less endoleaks not seen (36% Vs 22%) and CEADUSS had less inconclusive tests (22% Vs 36%). The sonographer with 7 years experience demonstrated a moderate agreement between CEADUSS and DUS with similar proportions for all three outcomes of endoleak detection. The subject with 2½ years experience showed a slight agreement between modalities, with CEADUSS producing more endoleaks seen (56% Vs 22%) and inconclusively seen (39% Vs 17%) and less endoleaks not detected (22% Vs 44%). No agreement between modalities was shown by the subject with 2 years experience, CEADUSS detected more endoleaks (81% Vs 44%) and less inconclusive (14% Vs 31%) and endoleaks not seen (6% Vs 25%). The least experienced subject (0 years) showed slight agreement overall, with CEADUSS producing more endoleaks detected (72% Vs 58%) and less not seen (14% Vs 25%) with similar proportions of inconclusive tests (14% Vs 17%). Overall there was fair agreement beyond that expected by chance. It was difficult to identify if inter-modality agreement changed with years of experience as the number of sonographers involved was low, making the graph sensitive to outliers (subjects with 11 and 7 years experience).

Comparing the proportions of inconclusive examinations for each individual sonographer with each other using both imaging techniques showed no visual trend. It did appear that for sonographers of increasing seniority, CEADUSS gave more inconclusive examinations. This suggests that in this group of sonographers, that the diagnostic benefit of the addition of CEADUSS was unrelated to experience. This may again reflect how comfortable the sonographers were in using or interpreting CEADUSS images, rather than any improvement of the technique over DUS alone. This may be a function of a learning curve.

Sensitivity for endoleak detection using both modalities for each individual sonographer with differing experience showed the more junior subjects had a higher sensitivity for endoleak detection that was enhanced through the addition of CEADUSS. It appeared that for sonographers of increasing seniority CEUS gave more inconclusive examinations. However

as noted earlier there were approximately the same number of inconclusive examinations using DUS and CEUS. Thus endoleaks were most likely to be detected using CEADUSS by the most junior sonographers with <2½ years of experience.

I then performed a separate Univariate analyses for the measured variables to decipher if each one has an effect on endoleak detection. Endoleak plane position did not significantly affect definite endoleak detection ($p=0.3725$), nor did operator experience ($p=0.1295$). Distance of the endoleak from the EVAR stent-graft significantly affected definite detection ($p<0.0001$) as did flow rate ($p<0.0001$).

Once this was established, I next set out to see if these variables were correlated to each other using a Spearman rank correlation analysis, which showed that the categorical variables were independent of each other. As they were independent I then performed a multivariate analysis to assess variables that affect and thus predict endoleak detection with DUS. The multivariate analysis showed that endoleak distance from the stent-graft of 2cm and flow rate of 500ml/hr or more were significant independent predictors of endoleak detection using DUS. Of particular interest, the performance of the subject with 11 years experience was particularly poor.

During DUS testing, colour Doppler p.r.f. and gain setting changes were recorded and no significant differences between subjects was found, except that the subject with 11 years experience changed their p.r.f. settings more frequently than the others, but this was a non-significant difference.

I assessed the same variables effecting endoleak detection for the CEADUSS tests in the same manner to the DUS analysis. Endoleak plane position had a significant effect on endoleak detection ($p<0.0001$) as did position from the stent-graft but flow rate ($p=0.0018$) and operator experience ($p=0.0140$) did not have an effect. Univariate analyses of the independent variables were assessed with a Spearman's rank correlation that demonstrated that these categorical variables (plane and distance) were independent of each other, thus a Multivariate analysis was performed. Independent predictors of endoleak detection on CEADUSS included distance from the midline of 2cm. Factors which lessened the chance of endoleak detection included non-anterior positions and sonographers experience >2 years.

These results give an insight into the variety of factors influencing the detection of endoleaks using ultrasound. With this knowledge, I conducted a pilot clinical study to investigate the clinical use of CEADUSS for EVAR surveillance.

Chapter 3 = Clinical translation of the use of CEADUSS for endovascular stent surveillance

Ten patients with confirmed endoleaks on CT not identified or defined using DUS were investigated using CEADUSS, with no side effects. If an endoleak was present, the aim was to define endoleak type and to determine the source. This was not possible in all cases.

My results from this pilot assessment of CEADUSS and the existing performance of DUS on a small highly selected sub-set of patients from our EVAR surveillance database shows a widespread variability in endoleak detection using these 3 imaging modalities. There is no obvious glaring agreement between any of them. The data could be analyzed to investigate imaging modality agreement (using Cohen's kappa coefficient), whether findings were positive or negative or if findings would prompt further management including more invasive investigation or reintervention.

DUS agreed with CT in 20% of studies (2/10), however endoleak was visualized but not defined in 60% (6/10) leaving only 2 conflicting studies. CEADUSS fared better and agreed with 60% (6/10) of CT studies. Only a solitary study (10% (1/10)) visualized an endoleak seen on CT but failed to define type and source and there were 3 conflicting studies (30%).

However, due to the fact that there are only 10 patients assessed in this pilot and they are very selected, this would be futile to accept as gold. Small differences between detection rates of the imaging modalities are magnified by analysis due to small numbers.

In summary the patients I have chosen for my pilot project to assess the clinical use of CEADUSS was highly selective and not representative of the majority of patients that have EVAR. Caution must be taken when applying statistical analysis to the outcomes and agreement of the small number of patients used for this pilot project. This further contributes

to the validity of the results achieved and provides additional caution to the interpretation of them for clinical translation.

The aim of this study was to use CEADUSS clinically and familiarize ourselves with the technique. We successfully used the technique in all cases to gain adequate images using minimal contrast doses. The patients chosen were a small highly selected subset from our database with known abnormalities on previous surveillance.

CEADUSS should be considered for routine EVAR surveillance or as an adjunct to other imaging modalities after proper evaluation by a large randomized study prior to incorporation into protocols.

STRENGTH AND WEAKNESSES OF WORK

My laboratory EVAR phantom successfully produced a variable simulated endoleak with real-time dynamic flow that could be assessed with DUS and CEADUSS. Previous authors have assessed the characteristics that influence endoleak detection using static non-dynamic images in CT surveillance (Szucs-Farkas 2009).

Laboratory investigations concerning the behavior of SonoVue microbubble ultrasound contrast *in vitro* have not been reported. The manufacturer Bracco informed me that they held such information from experiments conducted in their laboratories in Switzerland but this was restricted and unpublished. They recommended that SonoVue should be used within 6 hours of reconstitution without the need for refrigeration. Within this time period chemical and physical stability is maintained. My preliminary brightness and decay experiments surprised of the manufacturer and have contributed important evidence regarding the performance of microbubble contrast for future work.

To my knowledge my phantom experiments are the only study to attempt to:

- define the physical characteristics of an endoleak that alter detection,
- investigate the influence of operator experience,
- to compare the enhancement of contrast administration on ultrasound.

I have shown the effects of contrast enhancement upon endoleak plane, position and velocity in addition to subject decision making. However, in reality there several variables present at one time e.g. distance, plane, position, velocity which are all unknown. Individual variable analysis does not reflect real clinical practice.

When designing the EVAR phantom, a type II endoleak was originally simulated. After consultation with surgeons and literature the need to concentrate on the more dangerous type I and III became apparent. The type II leak was easier to simulate and it would not be possible to produce a variable type I or III endoleak in my phantom system. However, the phantom could simulate features of a type I or III endoleak with velocity, position and relative distances variations. Thus my results of endoleak detection characteristics are relevant for all types and not exclusively type II.

A limitation of my study is that there the endoleaks physical properties were not standardized for the 36 tests. Throughout all of the tests, there were varying plane position, distances from the stent-graft, flow rates and the operators had varying ultrasound experience. For this reason the data wasn't broken into further subsets because numbers become too small and analysis futile. In practice there are several variables present at any time e.g. distance, plane, position and velocity. Dissecting each variable doesn't reflect realistic practice. Assessing the data with a multivariate analysis attempted to decipher if the variables were independent and had an effect on endoleak detection with each modality respectively.

To improve on the study design, more tests could be performed with independent variables standardized thus comparisons and analysis of each variable separately could be performed. More tests and standardization of variables would address the fact that this study is limited by the lack of data on specificity, negative predictive value and positive predictive value. Negative predictive value is important because the role of DUS and CEADUSS is essentially to safely reassure those with no endoleak, rather than being 100% predictive for the presence of endoleak. Ideally these could be used to generate a diagnostic odds ratio for each technique.

The only disadvantage of this would be that each subject would have to perform more tests for longer durations to allow the sheer number required to achieve satisfactory numbers for fruitful analysis. During my study planning I aimed to keep testing to 60 minutes to remain bearable to the subjects, however arranging more testing sittings could achieve more tests if the subjects were willing and their clinical duties allowed.

Another consideration would be the inclusion of instances where there was a control and no endoleak present. This was not included in my current study because with no flow at all in the endoleak, its presence could still be detected due to the outline of the c-flex tubing. It was physically not possible to have no endoleak present unless another phantom without endoleak and only and EVAR stent-graft embedded in agar was made, which would carry its own inherent expense.

During testing, each subject made a static recording of the endoleak that they saw, maybe saw or did not see. Reviewing each subject's recorded images was challenging due to the dynamic nature of ultrasound. Pictures do not reliably represent what the ultrasonographer is viewing. Without the subjects present it was impossible to determine where they thought the endoleak was present, if they felt it was there at all. For this reason it was not possible to investigate the results further to compare DUS with CEADUSS missed endoleaks. I already knew the location and would be contributing a bias.

Video recordings would also allow independent scrutiny of imaging quality. Other studies have asked subjects to mark endoleak positions on a diagram for analysis (Szucs-Farkas 2009), a grid technique which could easily be employed in further experiments. With this simple measure DUS misses detected by CEADUSS and DUS detected endoleaks missed by CEADUSS could be compared to rationalize the disparities.

Another factor which I could address with video recordings of each subjects tests could be the reasons for their diagnostic decision making. I could ask the subjects post-testing on review analysis or at the time of testing the confidence they had with endoleak identification. CEADUSS generated more inconclusive results overall and a reason for this could be unfamiliarity with the technique that none of the subjects have ever used. Asking how comfortable they were with interpreting CEADUSS in particular would answer this question and help explain diagnostic uncertainty or reluctance to commit to a concrete diagnosis. This questionable decision making could be explored further by testing and comparing physicians and the subjects with images of known clinical endoleaks using the same yes/no/maybe scale. The inclusion of randomized non-endoleaks within testing the variable endoleak would allow further analysis of decision making and also act as a control, a strategy recently employed by other authors (Szucs-Farkas 2011).

Variables not investigated include endoleak diameter, density and the effects of detection in different sized phantoms representing patient habitus. Other variables that warrant investigations include different stent-graft sizes to see if endoleaks around smaller and larger grafts are detected differently, the incorporation of a bifurcated graft as well as investigating a variety of stents from different manufacturers to see if graft composition affects surveillance. Another variation could be the administration of microbubble contrast into the

phantom itself. Henao et al, developed an infusion technique to increase contrast circulation concentrations as opposed to using a bolus injection (Henao 2006). Lastly surveillance imaging also measures AAA sac size and success is indicated by stability or regression. Expansion indicates a problem. My phantom experiments did not simulate an aortic sac.

I used CEADUSS clinically on a highly selected subset of patients without harm or any side effects. I transferred the techniques that I learnt in my laboratory experiments to scan 10 patients with confirmed endoleaks on CT surveillance but not identified or defined using DUS. My results from this pilot assessment of CEADUSS and the existing performance of DUS on a small highly selected sub-set of patients from our EVAR surveillance database shows a widespread variability in endoleak detection using these 3 imaging modalities. There is no obvious glaring agreement between any of them.

The data could be analyzed to investigate imaging modality agreement (using Cohen's kappa coefficient), whether findings were positive or negative or if findings would prompt further management including more invasive investigation or reintervention. However, due to the fact that there are only 10 patients assessed in this pilot and they are very selected, this would be futile to accept as gold. Small differences between detection rates of the imaging modalities are magnified by analysis due to small numbers. The patients selected all have an abnormality on CT or suggested by DUS which is why they were chosen. Examining the actual patients included reveals that 4/10 (40%) are female which is not representative of the pattern of inheritance aneurysm disease, also females have been shown to suffer more complications and worse outcomes with EVAR than males (Mehta 2012). Further assessing the patients included in my small series, they are composed of symptomatic patients, a ruptured AAA and two patients that received non-bifurcated devices that are not the normal standard EVAR patient that one encounters more so in clinical practice. These patients are known to be more complicated to manage and thus also provide an additional challenge when detecting complications post-EVAR. Consequently a number of my pilot project patients required reinterventions, that included embolizations, relining of stents, extension cuffs which would further contribute to making surveillance imaging and interpretation of findings difficult.

In summary the patients I have chosen for my pilot project to assess the clinical use of CEADUSS was highly selective and not representative of the majority of patients that have EVAR. Caution must be taken when applying statistical analysis to the outcomes and agreement of the small number of patients used for this pilot project. This further contributes to the validity of the results achieved and provides additional caution to the interpretation of them for clinical translation.

The aim of this study was to use CEADUSS clinically and familiarize ourselves with the technique. We successfully used the technique in all cases to gain adequate images using minimal contrast doses. The patients chosen were a small highly selected subset from our database with known abnormalities on previous surveillance.

To make more concrete conclusions, this study needs to be performed on a larger number of patients than the selected subset I have used in this pilot. My qualitative observations are that CEADUSS is a very promising imaging modality for surveillance. It is easy to use and administer once trained correctly and harmless to patients in our small trial. With experience, sensitivity and confidence will improve. CEADUSS should be considered for routine EVAR surveillance or as an adjunct to other imaging modalities after proper evaluation by a large randomized study prior to incorporation into protocols. There may be a role for the use of CEADUSS in difficult cases where there is unexplained sac expansion or undefined endoleaks but again only after proper evaluation.

COMPARISON WITH PREVIOUS WORK

Previous authors have examined the characteristics that influence endoleak detection using static non-dynamic images in CT surveillance (Szucs-Farkas 2009). My laboratory EVAR phantom successfully produced a variable simulated real-time dynamic flowing endoleak that could be assessed with DUS and CEADUSS.

My laboratory investigations concerning the behavior of SonoVue microbubble ultrasound contrast *in vitro* have not been previously reported. The information gained is restricted and unpublished by the manufacturer. It is recommended that SonoVue should be used within 6 hours of reconstitution because within this time period chemical and physical stability is maintained (Bracco 2005). My preliminary brightness and decay experiments surprised the manufacturer and have contributed important information about the behavior of microbubble contrast for future work.

My phantom experiments are the only study, to my knowledge, to attempt to define the physical characteristics of an endoleak that influence detection, investigate the influence of operator experience and to compare the actual enhancement with microbubble contrast using ultrasound. Szucs-Farkas et al, have constructed a CT phantom model with several years of data (Schindera 2011, Szucs-Farkas 2011, Schindera 2010, Schindera 2009a, Schindera 2009b, Szucs-Farkas 2009, Szucs-Farkas 2008). Their work is not unique as other groups have previously used similar water-filled phantoms to study the effects of CT radiation attenuation for aortic imaging (Kalva 2006). However, one of their studies concentrated on the physical properties of an iodinated endoleak detection (Szucs-Farkas 2009), similar to my study. They are the only group to investigate characteristics affecting endoleak detection with CT imaging. All other studies in the literature, clinical and experimental have simply concentrated on endoleak presence and have not actually attempted to explain why missed detection occurs.

Their study involved 36 simulated endoleaks with varying diameters, densities and distances from the graft and they demonstrated that these all had a significant effect ($p<0.0001$) on the number of detected endoleaks. I used the same number of simulated endoleaks (36) but did not vary endoleak diameter, density or the effects of detection in different sized phantoms

representing patient habitus. However, my subjects were also blinded to the tests and also repeated them after 1 day with the addition of microbubble contrast. Their most relevant findings were that more endoleaks were detected the further from the endoleak the stent-graft was positioned ($p<0.001$) compared with those superimposed ($p=0.049$). This is in agreement with my study where I showed that endoleak distance from the stent-graft had a significant effect on endoleak detection when using either DUS ($p<0.0001$) or CEADUSS ($p<0.0001$). Multivariate analysis demonstrated that distance from the midline of 2cm was a significant independent predictor of endoleak detection using either DUS or CEADUSS. The positions of the endoleak used in their tests were smaller (0-1cm) compared with my endoleak positions (0-2cm). Lastly my phantom allowed dynamic pulsatitile flow, allowing my experiments to be more realistic and mirror clinical practice more accurately.

My small pilot study investigated the use of CEADUSS clinically on a subset of patients. I used the technique with no patient harm or side effects at all which is in agreement with the safety profile of microbubbles in the majority of the literature (Piscaglia 2012, Feinstein 2009, Jung 2007, Piscaglia 2006, Timperley 2005).

My results from this pilot assessment of CEADUSS and the existing performance of DUS on a small highly selected sub-set of patients from our EVAR surveillance database shows a widespread variability in endoleak detection using these 3 imaging modalities. There is no obvious glaring agreement between any of them. However, due to the fact that there were only 10 patients assessed in this pilot project and that they were very selected, meant analysis of results would be futile.

There is an abundance of results in the literature demonstrating CEADUSS detected endoleaks not seen by CT which are labeled as false-positives (Mirza 2010, Iezzi 2009, Carrafiello 2006, Napoli 2004, Bendick 2003), because CT is commonly taken as the ‘gold-standard’. They are usually low flow endoleaks (Iezzi 2010, Henao 2006, Bargellini 2005b, Bendick 2003, Schurink 1998). CEADUSS and DUS correctly highlighted patients in need of further angiogram characterization, raising the questionable need for CT. In my group of 10 patients CEADUSS did reveal findings that conflicted with CT, further evaluation is required before labeling these as false-positive findings.

It has been suggested that there is a reasonable role for CEADUSS as a problem-solving tool in situations of suspected endotension. In cases of uncertainty or when there was doubt regarding a diagnosis of endoleak, we used a destruction-reperfusion technique (Iezzi 2010, Carrafiello 2008). This involved a brief pulse of high-intensity (high-MI) sound to confirm the presence of contrast media in a suspected endoleak enabling its complete destruction and then reperfusion in real-time (Carrafiello 2008, Clevert 2008d, Dill-Macky 2007, Bargellini 2005b). This provided added hemodynamic information on blood flow and direction which CT could not offer. My pilot project did not provide enough information to advocate the use of CEADUSS in these circumstances.

Thus comparison of findings with other larger less selected studies in the literature was not made as my patients were highly selective and not representative of the majority of patients that have EVAR. This further contributes to the validity of the results achieved and provides additional caution to the interpretation of them for clinical translation.

SUGGESTIONS FOR FUTURE WORK

If I were to repeat my phantom experiments I would include a number of developments to improve my study. Increasing the subject number and tests with more standardization of variables would provide more concrete data for comparison. This would address the fact that this study is limited by the lack of data on specificity, negative predictive value and positive predictive value. Negative predictive value is important because the role of DUS and CEADUSS is essentially to safely reassure those with no endoleak, rather than being 100% predictive for the presence of endoleak. Ideally these could be used to generate a diagnostic odds ratio for each technique. Also the use of non-ultrasonographers, radiologists and vascular surgeons may provide an insight into ultrasound technique and user variability.

To investigate the increased level of uncertainty generated by CEADUSS, whether it was due to technical inexperience or a reluctance to commit to a firm diagnosis, comparison could be made with physicians in subjects with known clinical endoleaks and the same yes/no/maybe scale. The inclusion of randomized non-endoleaks within the test-group would allow further analysis of decision making and also act as a control in future tests, this strategy has been employed recently by other authors (Szucs-Farkas 2011). Repeating the same measurements again could provide data regarding the validity of subject endoleak detection and operator dependency.

Originally when designing the EVAR phantom, the endoleak was a type II. After further thought, consultation with surgeons and publications the need to concentrate on the more relevant and dangerous type I and III was evident. The type II leak was easier to simulate and it was not be possible to produce a variable type I or III endoleak in my existing phantom system. However, the endoleak of the phantom could represent features of a type I or III endoleak with variation of velocity, position and distances in relation to them, particularly testing with the endoleak near the stent. Thus my results of endoleak detection characteristics are relevant for all types, not exclusively type II. To improve this, the phantom could be redesigned to simulate type I and III endoleaks through consultation with the engineering department from Barts and The London Clinical Physics department.

A variable that I did not investigate was endoleak size. Clinically larger endoleaks are easier to detect than smaller ones and demonstrated experimentally with CT (Szucs-Farkas 2009). Larger endoleaks have also been shown to be associated with greater subsequent aneurysm expansion (Timaran 2004), so investigating this factor is important. The phantom could be modified to incorporate different diameter endoleaks. Szucs-Farkas et al, investigated the effects of patient habitus on endoleak detection by placing their phantom within different sized water cylinders. I did not do this during my studies, however building a larger and smaller agar filled Perspex housings within which the EVAR stent-graft is embedded would allow the investigation of this variable. Other variables that could be investigated include different stent-graft sizes to see if endoleaks around larger or smaller grafts are detected differently, the incorporation of a bifurcated graft as well as investigating a variety of stents from different manufacturers to see if graft composition affects surveillance. Another variation could involve the administration of microbubble contrast into the phantom, Henao et al, developed an infusion technique to increase contrast circulation concentrations as opposed to using a bolus injection (Henao 2006). This continuous infusion technique improved scanning but was relatively expensive, requiring specific equipment and larger amounts of contrast. The phantom could be modified for inclusion. Lastly surveillance imaging also measures AAA sac size. Success is indicated by regression or stability, expansion indicates a problem. My phantom experiments did not include an aortic sac. There are no studies directly comparing DUS and CEADUSS sac size measurements, however further phantom studies may benefit from simulating a variable aortic sac for measuring.

I translated the techniques learnt in the laboratory experiments to clinical practice. Ten patients with confirmed endoleaks on CT surveillance but not identified or defined using DUS were successfully investigated with CEADUSS. Caution must be taken when applying statistical analysis to the outcomes and agreement of this small number of patients used in this pilot project. The aim of this study was to use CEADUSS clinically, familiarizing ourselves with the technique. We successfully gained adequate images using minimal contrast doses in all cases. The patients chosen were a highly selected subset from our database with known abnormalities on previous surveillance and the volume used were small. There is only a small difference between detection rates of these imaging modalities, but due to the small number of subjects, these are magnified in analysis.

To make more significant conclusions, this study needs to be performed on a larger number of patients. With increased experience of CEADUSS, as with all other imaging modalities, sensitivity and confidence will improve and better results will be achieved. Perhaps centralizing EVAR CEADUSS surveillance in cities, similar to other specialist services, will increase accuracy and benefit patients. These refinements will provide further evidence to encourage the incorporation of CEADUSS into EVAR surveillance protocols, particularly for cases where there is unexplained sac expansion or undefined endoleaks.

Currently CEADUSS is being used experimentally intraoperatively (Kopp 2010, Clevert 2008e) to deploy EVAR stent-grafts with fluoroscopy, eliminating the need for iodinated contrast and also providing on-table procedural assessment for endoleaks. Other groups have used contrast-enhanced-IVUS (Ruiz 2012) which is being considered for use with stent-graft assessment and endoleak detection. Further experiments to assess the use of this evolving technique should be contemplated in the future.

Lastly the next generation of contrast ultrasound is concerned with targeted microbubble technology. The future of CEADUSS lies with a dual diagnostic and delivery role of therapeutics via a non-viral transduction and ultrasound mediated mechanisms to detect endoleak. Significant time and money is driving this wonderful new development, which will shape medicine in the near future and should be included in further studies.

FINAL CONCLUSIONS

AAA are common, responsible for a substantial number of hospital admissions and carry a high mortality mostly due to aortic rupture and exsanguination. The less invasive aneurysm management by EVAR has led to the parallel requirements for comprehensive and cost-effective non-invasive imaging for long-term surveillance. Currently many department protocols employ CT imaging which is costly, exposes patients to cumulative radiation and nephrotoxic contrast exposure, exerting a burden on already limited resources.

DUS has been proposed as a less costly solution for surveillance as it is cheap, readily available and harmless to patients as it does not involve radiation or nephrotoxic contrast exposure. However, mixed results using this technique are commonly reported. Attempts have not been made to explain these observations and improve DUS surveillance.

My study has demonstrated the strengths and limitations of DUS surveillance by investigating the physical properties of an endoleak that enhance detection. I have also shown the effects of contrast enhancement. CEADUSS is a challenging technique but significantly improves the performance of DUS to detect endoleaks. Clinically I have shown that CEADUSS can be used to detect abnormalities successfully with no patient harm. Further investigating CEADUSS clinically will provide evidence required to incorporate it into current EVAR surveillance protocols.

SECTION 4

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