NOVEL APPLICATIONS OF TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

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Dedicated to Jill

Declaration

I hereby declare and affirm that this thesis is entirely my own work and composition. Where I have received technical assistance this is indicated in the text.

Signature .....

Abstract

Transoesophageal echocardiography has become a widely used diagnostic imaging technique by virtue of its ability to yield high quality images of the heart and great vessels. This thesis is based on work performed between January 1991 and July 1992 during which novel applications of transoesophageal echocardiography were investigated in the intraoperative and critical care settings.

The mechanism by which closed chest cardiopulmonary resuscitation (CPR) generates forward blood flow has long been debated. Use of transoesophageal echocardiography allowed the physiology of CPR to be elucidated in 18 human subjects with cardiac arrest. These observations supported the cardiac pump theory of CPR and suggested that transoesophageal echocardiography might be utilised to monitor the efficacy of CPR. A preliminary investigation of CPR performed with the active compression-decompression device is described.

The pathophysiology of the fat embolism syndrome (FES) is poorly understood. Transoesophageal echocardiography detected intraoperative fat embolism in 24 patients with traumatic injuries, three of whom subsequently developed clinical evidence of FES. Paradoxical embolism through a patent foramen ovale occurred in one subject with fulminating fat embolism. These results support the mechanical theory of the aetiology of fat emboli, and suggest that transoesophageal echocardiography might be used to identify patients at greatest risk of FES.

The role of transoesophageal echocardiography in monitoring regional and global myocardial function was explored in a study of the cardioprotective properties of acadesine in patients undergoing coronary artery bypass surgery. No differences were observed between the acadesine and control groups in the incidence of new regional wall motion abnormalities or in changes in the area ejection fraction. The strengths and limitations of transoesophageal echocardiography are discusssed.

Transoesophageal echocardiography was used to examine the role of transgastric imaging in the assessment of cardiac haemodynamics. This novel imaging plane facilitates assessment of aortic stenosis and estimation of cardiac output. Use of transoesophageal echocardiography for estimation of pulmonary artery systolic pressure was also examined.

The role of transoesophageal echocardiography in cardiac surgical intensive care was explored. Important clinical information was obtained in the majority of patients when used for emergency diagnosis. Elective monitoring of cardiac function was shown to be feasible and gave valuable information in 12 out of 33 patients.

In conclusion, transoesophageal echocardiography is a valuable imaging technique that has useful applications in a variety of clinical settings. It can provide new insights into long-recognised conditions and might provide new avenues for future research.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS USED IN TEXT AND FIGURES

ACD	Active compression-decompression device
AEF	Area ejection fraction
AO	Aorta
AV	Aortic valve
AW	Anterior left ventricular wall
CABG	Coronary artery bypass surgery
CAD	Coronary artery disease
CI	Cardiac index
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
CVP	Central venous pressure
ECG	Electrocardiograph
FE	Fat embolism
HR	Heart rate
HT	Haematoma
IVC	Inferior vena cava
LA	Left atrium
LAA	Left atrial appendage
LCA	Left coronary artery
LLPV	Left lower pulmonary vein
LPA	Left pulmonary artery
LUPV	Left upper pulmonary vein
LV	Left ventricle
LVOT	Left ventricular outflow tract
LVSWI	Left ventricular stroke work index
MAP	Mean arterial blood pressure
MI	Myocardial infarction
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure

PV	Pulmonary valve
PW	Posterior left ventricular wall
RA	Right atrium
RAA	Right atrial appendage
RCA	Right coronary artery
RLPV	Right lower pulmonary vein
RPA	Right pulmonary artery
RUPV	Right upper pulmonary vein
RV	Right ventricle
RVOT	Right ventricular outflow tract
RWMA	Regional wall motion abnormality
SVC	Superior vena cava
SVR	Systemic vascular resistance

CHAPTER 1

INTRODUCTION

Over the past decade, transoesophageal echocardiography has become a widely used diagnostic imaging technique largely as a result of its ability to yield high quality images of various structures that are poorly imaged by conventional transthoracic imaging. The probe is composed of a miniature ultrasound transducer incorporated into a flexible gastroscope. Most transducers are now capable of supporting two-dimensional and M-mode imaging, pulsed and continuous wave Doppler, and colour flow mapping. The probe is positioned in the oesophagus, where by virtue of its proximity to most cardiac structures, high resolution imaging is obtained. In comparison to transthoracic imaging, the ultrasound beam is not impeded by intervening structures such as lung and bone. This allows the use of higher frequency transducers, and gives superior resolution of such structures as the mitral and aortic valves, and the thoracic aorta. An additional important attribute is the ability to image in a variety of planes, some of which are unique to transoesophageal echocardiography. These include the views of the pulmonary veins, the left atrial appendage, the atrial aspect of the mitral valve, and the thoracic aorta. Although transoesophageal echocardiography has been used in multiple fields, the main applications have been in diagnostic cardiology and in intraoperative imaging. In this thesis, I describe a series of studies that were performed between January 1991 and July 1992, in which novel applications of transoesophageal echocardiography were explored in the perioperative and critical care settings.

Development of Transoesophageal Echocardiography

Transoesophageal echocardiography was first described in 1976 when M-mode images of the heart were recorded in conscious patients (Frazin et al., 1976). This early experience proved of limited practical value, however interest in the technique

grew in the 1980s when flexible endoscopes were fitted with steerable phased array transducers and real-time two-dimensional imaging became possible (Souquet et al., 1982). A further important technological advance during this period was the development of transoesophageal colour flow Doppler that facilitated analysis of blood flow patterns within the heart and great vessels (Takamoto et al., 1985).

In Europe, early investigators explored the role of transoesophageal echocardiography in diagnostic cardiology (Erbel et al., 1987; Erbel et al., 1988; Taams et al., 1988). In contrast, in Japan and the United States transoesophageal echocardiography was developed initially by anaesthetists interested in monitoring intraoperative cardiac function (Matsumuto et al., 1980; Kremer et al., 1982). Subsequently, clinical interest spread rapidly, and transoesophageal echocardiography began to find applications in a wide variety of fields including adult and paediatric cardiology, cardiac surgery, anaesthesia and intensive care.

By the end of 1990, prior to commencing my own studies with transoesophageal echocardiography, the technique had already become established for the diagnosis of various conditions including infective endocarditis (Erbel et al., 1988), left atrial thrombus (Aschemberg et al., 1986), aortic dissection (Erbel et al., 1989) and prosthetic mitral valve dysfunction (Currie et al., 1987). Intraoperative applications included monitoring high risk patients for myocardial ischaemia (Roizen et al., 1984; Smith et al., 1985), planning the precise surgical approach prior to sternotomy, (Sheikh et al., 1990) and assessing the technical quality of the surgical procedure following weaning from cardiopulmonary bypass (Dan et al., 1990; Stumper et al., 1991). Transoesophageal echocardiography had been shown to be particularly valuable in the immediate evaluation of the results of mitral valve repair procedures (Currie et al., 1988) and it had also been used to monitor for the occurrence of air embolism complicating neurosurgical and cardiac procedures (Cucchiara et al., 1984; Meloni et al., 1990).

In addition to these clinical applications, some investigators had also attempted to use

transoesophageal echocardiography to gain novel insights into various aspects of cardiac physiology. It was hoped for example, that analysis of pulmonary vein flow patterns might facilitate investigation of left ventricular diastolic function (Churchwell, 1991). Pulsed Doppler studies of the left anterior descending artery had been described as a possible technique to assess coronary flow reserve (Iliceto et al., 1991). These research applications were at an early stage of development but suggested that transoesophageal echocardiography might become a powerful new investigative tool.

Accordingly, in a relatively short period transoesophageal echocardiography had progressed from experimental prototype, to established diagnostic imaging technique, to potential research tool. However, there appeared to be considerable scope to widen its applications, particularly in the perioperative and critical care environments. This opportunity arose in the Royal Infirmary, Edinburgh at the start of 1991, whilst working as a Research Fellow within the Department of Cardiac Surgery under the supervision of Professor David Hamilton, in collaboration with Dr George Sutherland, Department of Cardiology, Western General Hospital, Edinburgh.

Outline of Thesis

The mechanism by which closed chest compression generates forward blood flow during cardiopulmonary resuscitation (CPR) has been debated since the technique was first described by Kouwenhoven in 1960. The advent of transoesophageal echocardiography made high quality imaging possible for the first time in humans during CPR. In Chapter 2, I describe how the mechanisms of CPR were investigated using transoesophageal echocardiography to study the extent of cardiac compression and patterns of blood flow in the heart and great vessels. These studies suggested a new role for transoesophageal echocardiography in helping assess the effectiveness of conventional CPR, and facilitated preliminary investigation of CPR performed

with the active compression-decompression device.

The fat embolism syndrome was first described by German pathologists in the late nineteenth century, yet much of its pathophysiology remains as obscure today as it did to these early investigators. Two issues, the aetiology of fat emboli and their role in the pathophysiology of the pulmonary and systemic manifestations of the fat embolism syndrome have been disputed for more than one hundred and thirty years. In Chapter 3, I describe how intraoperative transoesophageal echocardiography brought new insights into the pathophysiology of this old, but poorly understood condition.

In the United States, transoesophageal echocardiography had often been used to monitor cardiac function during cardiac and other major surgical procedures. However, at the start of 1991 its role in intraoperative monitoring had not been established conclusively, and it had not been used widely in the United Kingdom. In Chapter 4, I explore the role of transoesophageal echocardiography as a research tool to investigate regional and global left ventricular function in patients undergoing coronary artery bypass surgery.

Despite the development of probes offering spectral Doppler capabilities, transoesophageal echocardiography has found only limited application in the assessment of cardiac haemodynamics. This largely reflects the limitations of the conventional oesophageal imaging planes that prevent parallel alignment with the direction of blood flow in the left ventricular outflow tract and across the aortic valve. In Chapter 5, I discuss the role of transoesophageal echocardiography in assessment of cardiac haemodynamics and explore the applications of the transgastric plane, a novel imaging position that facilitates Doppler interrogation of the left ventricular outflow tract and the aortic valve.

At the outset of these studies, isolated case reports and small series had been published suggesting that transoesophageal echocardiography was particularly suited

to diagnostic imaging in the intensive care environment. Studies are readily performed at the bedside and image quality is not influenced by extraneous factors such as mechanical ventilation, wound dressings, or surgical emphysema. However, no large series had examined the role of transoesophageal echocardiography in cardiac surgical intensive care. In Chapter 6, I explore the contribution that transoesophageal echocardiography can make in this setting in respect of both emergency diagnosis and elective monitoring of cardiac function postoperatively.

Methods and Materials

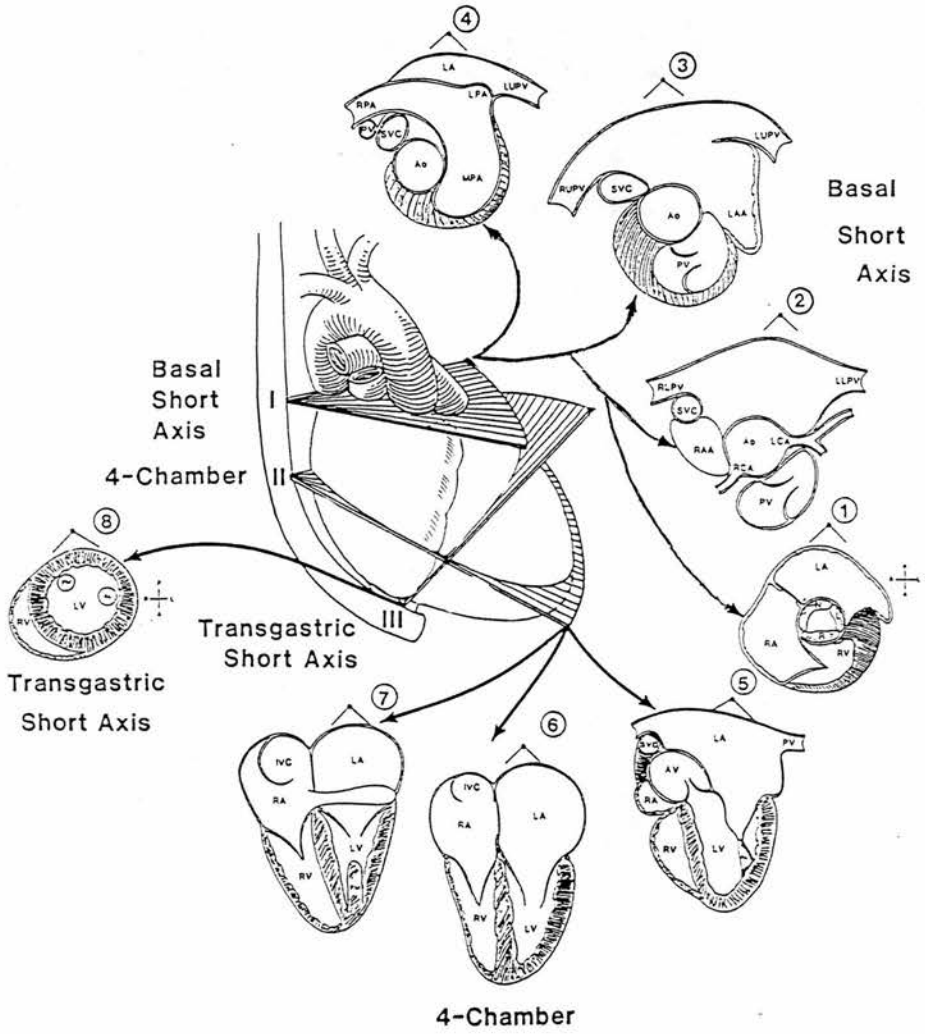
Detailed methodology is described in the specific chapters. Ethical approval was obtained for the individual studies from the Lothian Health Board Ethics of Medical Research Committee. Informed consent was sought from patients prior to each study, with the exception of the study described in Chapter 2. In this study, consent could not be obtained as patients presented to hospital in cardiac arrest and special ethical approval was obtained from the Ethics of Medical Research Committee.

Transoesophageal Imaging Technique: all these studies were performed using a Siemens Sonoline, SI1200 echocardiography machine with a 5 MHz transverse plane transoesophageal echocardiography probe. The capabilities of this system included two-dimensional and M-mode imaging, and pulsed, continuous wave and colour flow Doppler. Echocardiographic studies were recorded on VHS video tape. Quantitative analysis was performed using the tracker ball and analysis package supplied with the echocardiographic machine. Unless otherwise stated in the text, standard imaging planes were utilised (Seward et al., 1988). Three different imaging planes have been decribed for cardiac imaging using transverse plane echocardiography (Figure 1.1):

Basal Short-axis. This is obtained by positioning the transducer 25-30 cm from the incisors and allows the following structures to be imaged: the main and proximal pulmonary arteries, the proximal ascending aorta and aortic valve, the left atrium and atrial appendages, the inter-atrial septum and the superior vena cava. The

Figure 1.1

Standard Imaging Planes Using Transverse Plane Transoesophageal Echocardiography. Modified from Seward et al., (1988) with permission. For abbreviations see page xii.



pulmonary veins can also be imaged and pulsed Doppler can be used to determine patterns of blood flow. Interrogation of pulmonary vein flow was used to advantage in Chapter 2, and allowed the mechanisms of blood flow during CPR to be determined.

Four Chamber. These views are obtained by advancing, or by retroflexing the transducer from the basal short-axis position. In this plane, both right and left heart chambers are well visualised, as are the atrioventricular valves, the left ventricular outflow tract and the coronary sinus. This plane was particularly useful in the studies into the mechanisms of CPR as it allowed the extent of chamber compression and atrioventricular valve function to be investigated. In the studies described in Chapter 3, the four chamber view allowed fat emboli to be visualised within the heart in patients undergoing treatment of long bone fractures. A limitation of this plane is that both the left ventricular outflow tract and the tricuspid valve are imaged obliquely. Accordingly, it may not be possible to achieve parallel alignment with Doppler ultrasound, making quantitative haemodynamic assessment of these regions difficult (Figure 1.2).[1] This problem is addressed in Chapter 5, in which haemodynamic assessment using the transgastric plane is described.

Transgastric Short-axis. By positioning the anteflexed transducer in the gastric fundus, a short-axis view of the left ventricle is obtained. This plane is valuable in the assessment of left ventricular function, and was used in the study of patients

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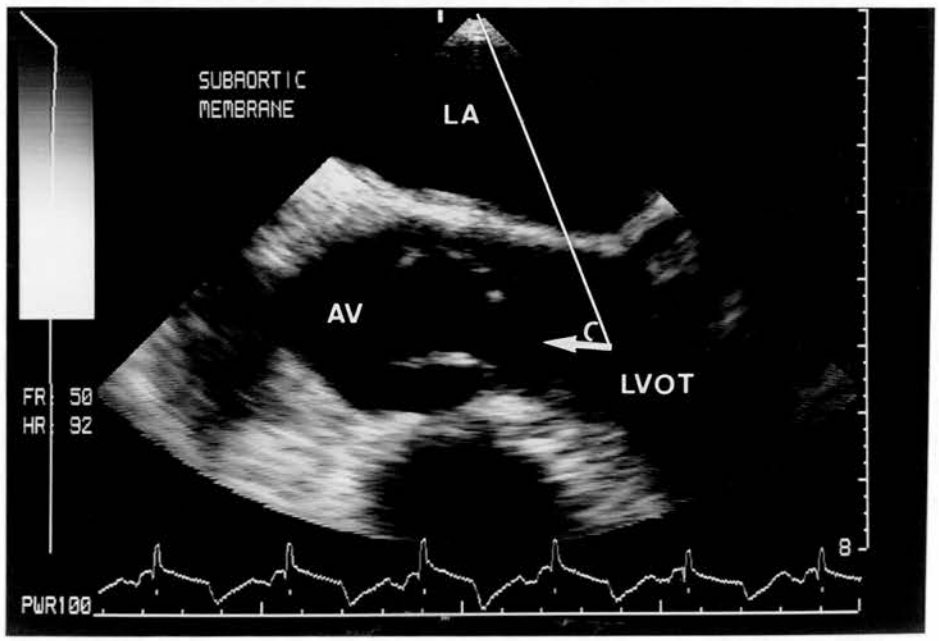
[1]By recording the velocity of intracardiac blood flow quantitative haemodynamic information can be obtained using Doppler ultrasound (Hatle and Angelson, 1984). The velocity (V) of blood flow ($cm.s^{-1}$) can be calculated from the frequency shift (f) of ultrasound signals reflected from moving red blood cells using the following formula: $V = f.c/2F.\cos\theta$, where c is the speed of ultrasound in tissues in $cm.s^{-1}$, F is the frequency of the emitted ultrasound (Hz) and θ is the angle between the ultrasound beam and the direction of blood flow. In clinical practice the value of θ may be difficult to determine and errors are liable to be introduced if estimates are made. As $\cos 0 = 1$, it is recommended that the ultrasound beam should be aligned parallel to the direction of blood flow whenever possible.

Figure 1.2

Subaortic stenosis demonstrated using four chamber view. In this plane, quantitative haemodynamic assessment is difficult as the direction of blood flow (arrow) in the left ventricular outflow tract is not parallel to Doppler ultrasound directed from the oesophagus.



undergoing CABG described in Chapter 5. Regional systolic function is studied by assessment of both systolic wall thickening and radial shortening (Leung et al., 1989). When using transthoracic echocardiography, global left ventricular function is commonly assessed by calculation of the ejection fraction.[2] A limitation of transverse plane transoesophageal echocardiography is that a true long axis image of the left ventricle is rarely obtained from the oesophagus. As a consequence, left ventricular volumes cannot be calculated using the usual algorithms and the ejection fraction cannot be derived readily. However, the fractional area change of the left ventricle in short-axis at mid-papillary muscle level is closely correlated to the global ejection fraction (Clements et al., 1990) and was used as an index of global left ventricular function in Chapter 5.

Unless otherwise stated all studies were performed on anaesthetised patients with an endotracheal tube in position. To insert the probe the subject's jaw was lifted anteriorly and the lubricated probe was passed under direct vision towards the midline of the oropharynx. The tip was then anteflexed and the probe introduced into the oesophagus. If difficulty was experienced a finger inserted towards the back of the oropharynx assisted in guiding the direction of the probe. If this was unsuccessful direct visualisation of the oesophagus with a laryngoscope usually allowed insertion. Additional manoeuvres that sometimes facilitated insertion included neck flexion and temporary deflation of the cuff on the endotracheal tube. The controls were not locked when manipulating the probe within the oesophagus, unless repeated lateral deflection prevented satisfactory passage. The probe could not be inserted in approximately 2% of subjects. The probe was cleaned and sterilised in 2% glutaraldehyde (Cidex) after each study.

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[2]The left ventricular ejection fraction is the difference between the end-diastolic and end-systolic volumes expressed as a percentage of the end-diastolic volume. A variety of algorithms can be used to derive the left ventricular volume from two-dimensional echocardiograms. The majority of these formulas require an accurate measurement of the long axis of the left ventricle. For example, the biplane Simpson's rule method is based on the use of orthogonal planes in the apical four-chamber view (Schiller et al., 1989).

CHAPTER 2

MECHANISMS OF CARDIOPULMONARY RESUSCITATION INVESTIGATED USING TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Introduction

In 1960 Kouwenhoven described the technique of closed-chest compression as a method to maintain myocardial and cerebral perfusion during cardiac arrest (Kouwenhoven et al., 1960). This technique rapidly became accepted as the standard method of maintaining the circulation during cardiopulmonary resuscitation (CPR), and largely replaced the former practice of internal cardiac massage. More than 30 years later, Kouwenhoven's technique remains in widespread use with only minor modifications. That closed chest compression can be effective in maintaining sufficient blood flow to enable successful resuscitation is established beyond doubt (Robertson and Holmberg, 1992). However the precise mechanism by which this technique generates forward blood flow was questioned shortly after its first description (Weale and Rothwell-Jackson, 1962), and even today this remains uncertain and controversial.

Despite the widespread use of this technique there is increasing appreciation that conventional CPR often results in poor cardiac output, and survival after a prolonged period of resuscitation is uncommon (Cummins et al., 1985; Gray et al., 1991). The European Resuscitation Council (ERC) has stated that CPR will not improve the internal milieu of the heart and is unlikely to improve the chances of defibrillation. Indeed, the ERC resuscitation guidelines were revised recently to take account of the fact that successful resuscitation is most likely to be achieved with early defibrillation (ALS Working Party of the ERC, 1992). CPR is unlikely to increase the chances of resuscitation where defibrillation has failed, and immediate, and repeated defibrillation without intervening CPR was advocated. The ERC maintains that the

value of CPR is in maintaining a degree of cerebral perfusion and slowing myocardial deterioration when immediate defibrillation has failed.

A variety of modifications to standard CPR have been described, for example vest CPR, simultaneous compression-ventilation CPR and interposed abdominal counterpulsation CPR (Schleien et al., 1989). These techniques were developed in an attempt to increase cerebral and myocardial blood flow and were based on data aquired from animal studies, or on prevailing assumptions regarding the mechanisms of CPR in humans. In clinical practice no technique has been shown to be superior to conventional CPR and future improvements may depend on a more precise understanding of the mechanisms of blood flow during CPR.

Despite extensive investigation in humans and in animal models, the mechanisms of blood flow during CPR remain disputed. However two case reports published shortly before commencing the studies described in this chapter, described the use of transoesophageal echocardiography during active resuscitation (Higano et al., 1990; Kuhn et al., 1991). High quality imaging was achieved, suggesting that this technique might be used to gain a better understanding of the physiology of CPR.

Historical Perspective

Throughout the history of medicine periodic attempts have been made to promote the circulation of blood in the presence of an arrested heart,[1] however Kouwenhoven is generally credited as the orginator of modern closed-chest CPR (Kouwenhoven et al., 1960). In this short paper, he described how CPR had been performed on 20 patients with cardiac arrest, 14 of whom survived without damage to the central

[1] An extrordinary variety of approaches has been used throughout history in attempted resuscitation amongst the most bizarre of which included placing the subject on a galloping horse. Combined lung inflation and sternal compression was suggested by John Sherwin in 1786. One of the earliest studies was performed by Boehm in 1878 who experimented with closed chest compression in cats. Successful resuscitation of six human patients was reported by Dr Franz Koenig in 1885 (Overbeck, 1969).

nervous system. It is evident from this acccount that he believed that his technique caused direct cardiac compression:

"The heart is limited anteriorly by the sternum and posteriorly by the vertebral bodies. Its lateral movement is restricted by the pericardium. Pressure on the sternum compresses the heart between it and the spine, forcing out blood. Relaxation of the pressure allows the heart to fill."

This became known as "The Cardiac Pump Theory", and although in this first paper Kouwenhoven made no mention of the atrioventricular valves, subsequent authors assumed that unidirectional blood flow occurred because of mitral and tricuspid valve closure in response to raised intraventricular pressure (Jude et al., 1961; Thomsen et al., 1968). The atrioventricular valves open during relaxation and ventricular filling is confined to this phase.

The possibility that closed-chest compression might not result in direct cardiac compression was first raised shortly after Kouwenhoven's original publication (Weale and Rothwell-Jackson, 1962). It was suggested that as the thorax is a relatively rigid box raised intrathoracic pressure resulting from external compression would be transmitted equally to all intrathoracic structures and that:

"...actual compression of the heart itself between sternum and the vertebral column is probably overemphasised as an explanation for the appearance of peripheral arterial pulses."

Furthermore, in light of similar increases in arterial and venous pressure during CPR these authors went on to question the efficacy of closed-chest compression in producing organ perfusion. An early haemodynamic investigation from the Royal Infirmary, Edinburgh in which measurements of the systemic arterial pressure, the right atrial pressure and the cardiac output were made during CPR, also questioned the validity of Kouwenhoven's hypothesis. Although closed-chest compression did generate a cardiac output, it was suggested that this was largely a consequence of a generalised increase in intrathoracic pressure, and not due to cardiac compression

(MacKenzie et al., 1964). This subsequently became known as "The Thoracic Pump Theory".

The landmark paper for supporters of the thoracic pump theory came in 1976 when cough-induced cardiopulmonary resuscitation was described (Criley et al., 1976). These authors described eight subjects who developed ventricular fibrillation during cardiac catheterisation and who were able to generate sufficient cardiac output to maintain cerebral perfusion simply by vigorous coughing. Because of the circumstances of the cardiac arrest, detailed electrocardiographic and haemodynamic records are available which demonstrate conclusively that rhythmical increases in intrathoracic pressure can generate sufficient cardiac output to maintain consciousness during cardiac arrest.

Rudikoff et al. (1980) presented experimental data that lead to the current concept of the thoracic pump mechanism of CPR. Chest compression in dogs resulted in increased pressure in the heart and great vessels that was equal to the rise in intrathoracic pressure. Collapse of the veins at the thoracic outlet resulted in unequal transmission of pressure to the extrathoracic arterial and venous systems, and created the peripheral arteriovenous pressure gradient necessary for forward blood flow. Accordingly, the thoracic pump theory proposes that phasic changes in intrathoracic pressure generates blood flow without direct cardiac compression. Antegrade flow occurs across the open mitral valve during the compression phase, the left ventricle acting as a passive conduit for the passage of blood into the aorta.

Niemann et al. (1981) presented a combined haemodynamic and angiographic study in dogs that also supported the thoracic pump theory. In this study, antegrade flow of blood was observed from the pulmonary veins, through both left heart chambers, and into the aorta during a single chest compression. The heart was not compressed, but appeared to act as a passive conduit for blood flow. These authors also confirmed the existence of functional venous valves at the thoracic inlet that prevented transmission of intrathoracic pressure to the extrathoracic venous system.

Additional evidence that supported the thoracic pump theory was the observation that cerebral perfusion could be augmented in dogs undergoing CPR by enhancing the phasic rise in intrathoracic pressure through abdominal binding (Koehler et al., 1983). Furthermore, an externally applied pneumatic thoracic vest was shown to produce antegrade flow by increasing intrathoracic pressure without causing cardiac compression (Halperin et al., 1986). In humans, haemodynamic evidence for the thoracic pump theory came from a study in which mean arterial pressure and carotid blood flow during CPR were augmented by increased intrathoracic pressures produced by simultaneous chest compression and ventilation at high airway pressures (Chandra et al., 1980). The demonstration that positive pressure ventilation alone could maintain some forward blood flow was also consistent with this model (Forney and Ornato, 1980), as was the finding that duration, rather than rate of compression, is the major determinant of mean arterial blood pressure and flow velocity during CPR in man (Taylor et al., 1977).

Despite the publication of data from animal and human studies supporting the thoracic pump theory, other investigators presented results favouring the cardiac pump mechanism. Direct cardiac compression was reported in small dogs (Babbs et al., 1982). Maier et al. (1984) found that when the force of chest compression was changed, cardiac output increased with low compressive forces, but declined with higher forces. This was contrary to the predictions of the thoracic pump model, and these authors suggested that the cardiac pump mechanism accounted for the major proportion of stroke volume during external chest compression.

Echocardiographic Assessment of CPR

Several studies have used echocardiography to investigate the mechanism of blood flow during CPR. As with the haemodynamic studies, this literature appears contradictory and apparently inconsistent. Two early studies with transthoracic echocardiography in humans concluded that the thoracic pump mechanism was responsible for generating forward flow (Werner et al., 1981; Rich et al., 1981). In

both studies the mitral valve was thought to remain open during chest compression, and no significant left ventricular compression was observed. These findings were thought to be incompatible with the cardiac pump mechanism. More recent experimental studies in animals have yielded different results. Transthoracic echocardiography was performed during external chest compression in immature domestic pigs (Deshmukh et al., 1985 and 1989). Mitral valve closure, a reduction in left ventricular area and antegrade pulmonary artery flow during chest compression were cited as evidence supporting the cardiac pump mechanism. Similar results were obtained in dogs (Feneley et al., 1987). Significant findings in this study included left ventricular deformation, mitral valve closure, and the absence of antegrade transmitral flow during the compression phase.

The first study involving transoesophageal echocardiography used M-mode imaging during external chest compression (Uenishi et al., 1984). The authors claimed that the thoracic pump mechanism was supported by their findings which included mitral valve opening, a decrease in left atrial size and unchanged left ventricular dimensions during compression. However, in light of the development of two-dimensional transoesophageal echocardiographic imaging, it seems unlikely that closure of the mitral valve could be determined with certainty using M-mode imaging, as it is now recognised that both leaflets cannot usually be interrogated simultaneously from the oesophagus. Furthermore, although no shortening was observed in the long axis of the left ventricle, it is unlikely that the authors were able to assess change in the orthogonal axis. The subjects in this study were severely injured, but it is not clear whether they were in cardiac arrest during imaging. Similar reservations apply to a report of a patient with ventricular tachycardia (Clements et al., 1986) in whom tranoesophageal echocardiography was performed during closed-chest massage. More recently however, transoesophageal echocardiography was performed in three subjects in cardiac arrest during CPR (Higano et al., 1990; Kuhn et al., 1991). Both reports supported the cardiac pump mechanism demonstrating mitral valve closure, and left and right ventricular compression during the compression phase, while left ventricular filling was restricted to the relaxation phase.

Accordingly, despite numerous investigations the mechanisms responsible for producing forward flow during CPR in humans remain uncertain. Given the anatomical and physiological differences, the relevance of animal studies to human CPR has been questioned (Babbs et al., 1982). There is marked variation in chest wall compliance amongst different animal species. The thoracic pump might be favoured in animals with low compliance as sternal depression may be difficult. In contrast, direct cardiac compression may be readily achieved in animals with high chest wall compliance. The data from human studies is conflicting and although the recent transoesophageal echocardiographic evidence supports the cardiac pump theory, it is at variance with the older transthoracic studies, and was based on observations in only three subjects. Nevertheless, these case reports raised the possibility that transoesophageal echocardiography might be a valuable technique to study the events occurring during CPR and prompted the systematic study described below.

Methods

Transoesophageal echocardiography was performed during CPR in patients presenting with cardiac arrest to the Accident and Emergency Department, Royal Infirmary, Edinburgh. All patients had sustained non-traumatic, normothermic cardiac arrest in the prehospital setting, and had received CPR and defibrillation by ambulance staff, where appropriate, prior to arrival. The resuscitation attempt was led and controlled by a senior clinician (Consultant or Senior Registrar) who remained independent of the echocardiographic study. On admission, patients were treated according to the guidelines of the Resuscitation Council (UK Resuscitation Council, 1984). All patients were intubated and ventilated with 100% oxygen, and closed-chest compression was administered at a rate of 80 compressions/minute, either manually, or mechanically using a Michigan Instruments Thumper, Model 1004, functioning at a ratio of 5 chest compressions to one ventilation (Little et al., 1974). CPR was performed with sufficient force to compress the chest 6-7 cm (36-45 kg) and peak inspiratory pressure was set at 30 cms of H_2O. Electrical DC counter-

shock and anti-arrhythmic agents were used as appropriate.

The transoesophageal echocardiography probe was positioned in the oesophagus following tracheal intubation. Standard imaging planes were used and colour flow and spectral Doppler studies were performed for analysis of blood flow patterns within the heart and great vessels. All studies were recorded on VHS video tape for subsequent analysis. Echocardiography continued until spontaneous circulation was restored or until the resuscitation attempt was terminated.

The video images were studied to determine the extent of chamber compression, the timing and direction of blood flow, and the patterns of valve motion. Frames showing the four chamber view of the heart at end-relaxation and at end-compression were selected, and the area ejection fraction (AEF) was calculated using the analysis package of the echocardiographic machine (Appendix).

Results

Study Population: eighteen patients were studied (12 male, 6 female, age range 26-87 years, median 66 years). The median interval between onset of the cardiopulmonary arrest and initiation of transoesophageal echocardiography was 31 mins (19-71 min). The rhythm on admission was asystole in ten patients, ventricular fibrillation in four patients and electromechanical dissociation in four patients. Spontaneous circulation was restored in two patients. The median duration of the resuscitation attempt in hospital was 18 min (range 7-36 min). Mechanical compression was administered to nine patients, manual compression to one patient, and both mechanical and manual compression to eight patients. Post-mortem findings were available in six patients, and revealed five instances of acute coronary thrombosis and one drug overdose. In the remainder a clinical diagnosis of sudden cardiac death was made.

The transoesophageal probe was inserted in all patients without difficulty and did not compromise the conduct of the resuscitation attempt. There were no complications

associated with echocardiography and none of the subjects examined had evidence of oesophageal trauma at postmortem examination.

General Observations: image quality was good in all patients, and colour flow Doppler analysis of blood flow patterns within the heart and great vessels was possible in every case. However, pulsed Doppler studies were adequate in only four subjects as lateral displacement occurring during chest compression caused movement of the heart out of the plane of the sample volume. Spontaneous echo-contrast[2] developed within the heart when CPR was stopped, and disappeared when CPR was resumed. No differences were observed between manual and mechanical CPR. Large right ventricular thrombi were observed in two subjects. Two patients had small pericardial effusions with no evidence of cardiac tamponade.

Compression Phase: during chest compression, the right atrial and right ventricular free walls were displaced towards the interatrial septum and interventricular septum respectively (Figure 2.1), resulting in a marked reduction in cavity size (Table 2.1). This was accompanied by both tricuspid regurgitation and antegrade pulmonary artery flow. The lumen of the proximal right pulmonary artery was markedly compressed in four patients. These appearances were associated with aliasing[3] of the colour flow Doppler signal.

Chest compression resulted in a moderate reduction in left atrial and left ventricular chamber sizes (Table 2.1), retrograde pulmonary vein flow (Figure 2.2), and

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[2]Spontaneous echo-contrast is the appearance of swirling clouds of "smoke-like" echoes and is commonly associated with low flow states. It has been attributed to increased echo reflection caused by aggregation of red cells, and is a common finding in mitral valve disease, atrial fibrillation and in patients with mural thrombus (Daniel et al., 1988).

[3]The maximum velocity of blood flow that can be recorded using pulsed or colour flow Doppler is limited by the pulse repetition frequency of the system. Aliasing occurs when this velocity is exceeded and can be recognised when using colour flow Doppler as a change in the colour-encoded velocities at a given site. For example, blood flow in the main pulmonary artery moving towards the transducer is normally encoded as red. When aliasing occurs, the colour flow map will demonstrate a change from red to blue.

Table 2.1 Extent of Chamber Compression During CPR

Chamber	Median Area Ejection Fraction (%)	Range (%)
Right Atrium	62	49-85
Right Ventricle	74	39-94
Left Atrium	23	10-43
Left Ventricle	33	19-67

antegrade flow in the left ventricular outflow tract (LVOT). Regional differences in the extent of left ventricular compression were apparent, being greater at the base of the heart than at the mid-papillary muscle level. In five patients the LVOT appeared to be compressed between the interventricular septum and the anterior leaflet of the mitral valve. Aliasing of colour flow Doppler within the LVOT was observed in these subjects (Figure 2.3). The aortic valve leaflets opened early during the compression phase with ejection of blood into the aorta (Figure 2.4). However, with continued compression both the proximal ascending aorta and superior vena cava were compressed and distorted, sometimes with near obliteration of their respective lumina (Figure 2.5).

Mitral valve motion was biphasic. Early in the compression phase there was partial leaflet separation, but with continued compression the two leaflets approximated, although full coaptation was not usually achieved. No antegrade flow occurred across the mitral valve during chest compression, and despite incomplete valve closure mitral regurgitation was observed in only two subjects.

Relaxation Phase: immediately on release of chest compression all four heart chambers re-expanded. Flow into the right atrium from the vena cavae and coronary

Figure 2.1

Four Chamber View During CPR. Appearances at end-relaxation (a), and end-compression (b). The right heart chambers are markedly compressed during CPR.

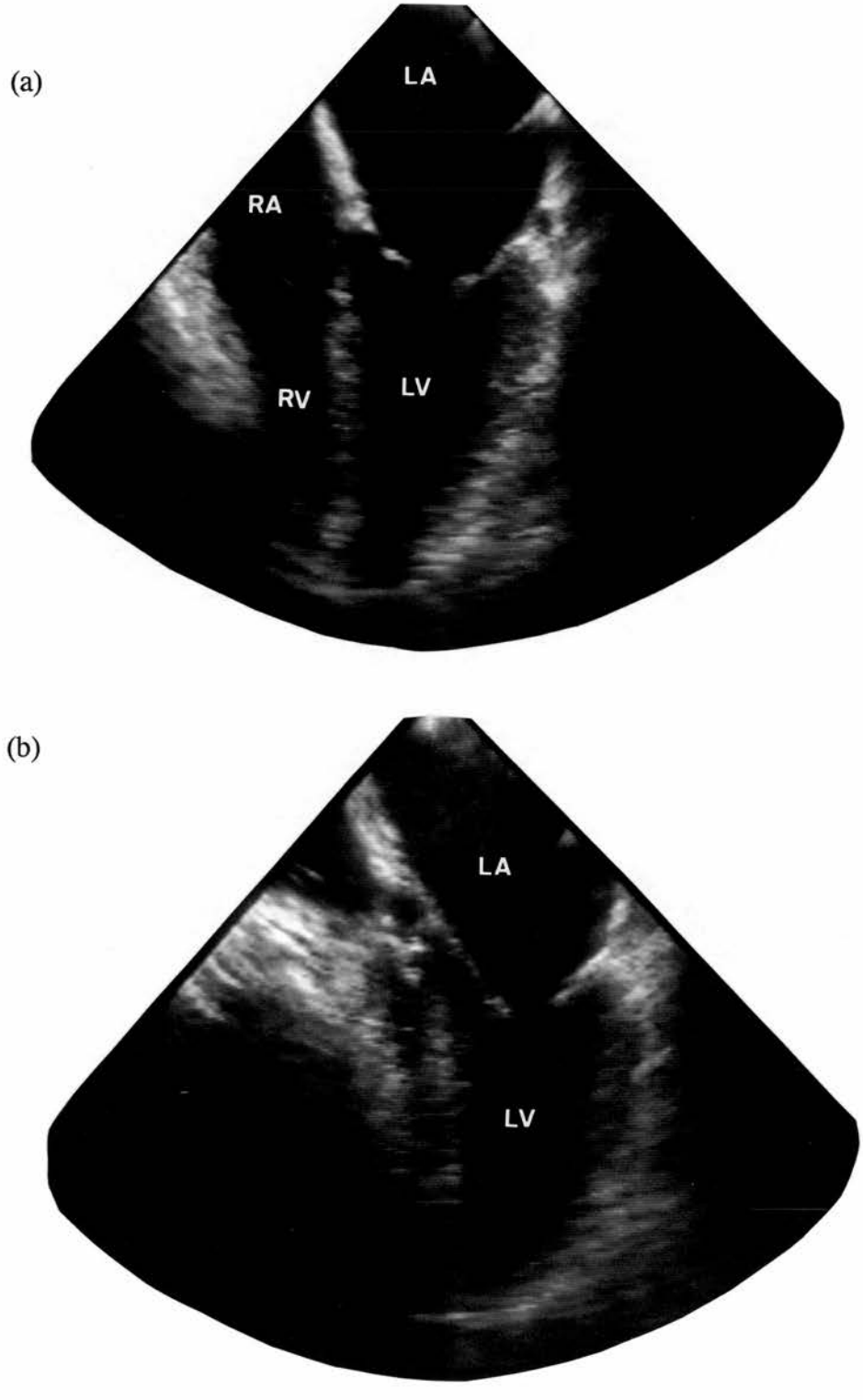


Figure 2.2

Pulsed Doppler of Pulmonary Vein Flow. Antegrade flow in the left upper pulmonary vein (arrowed) occurs in the relaxation phase (**) and retrograde flow occurs during compression (*).

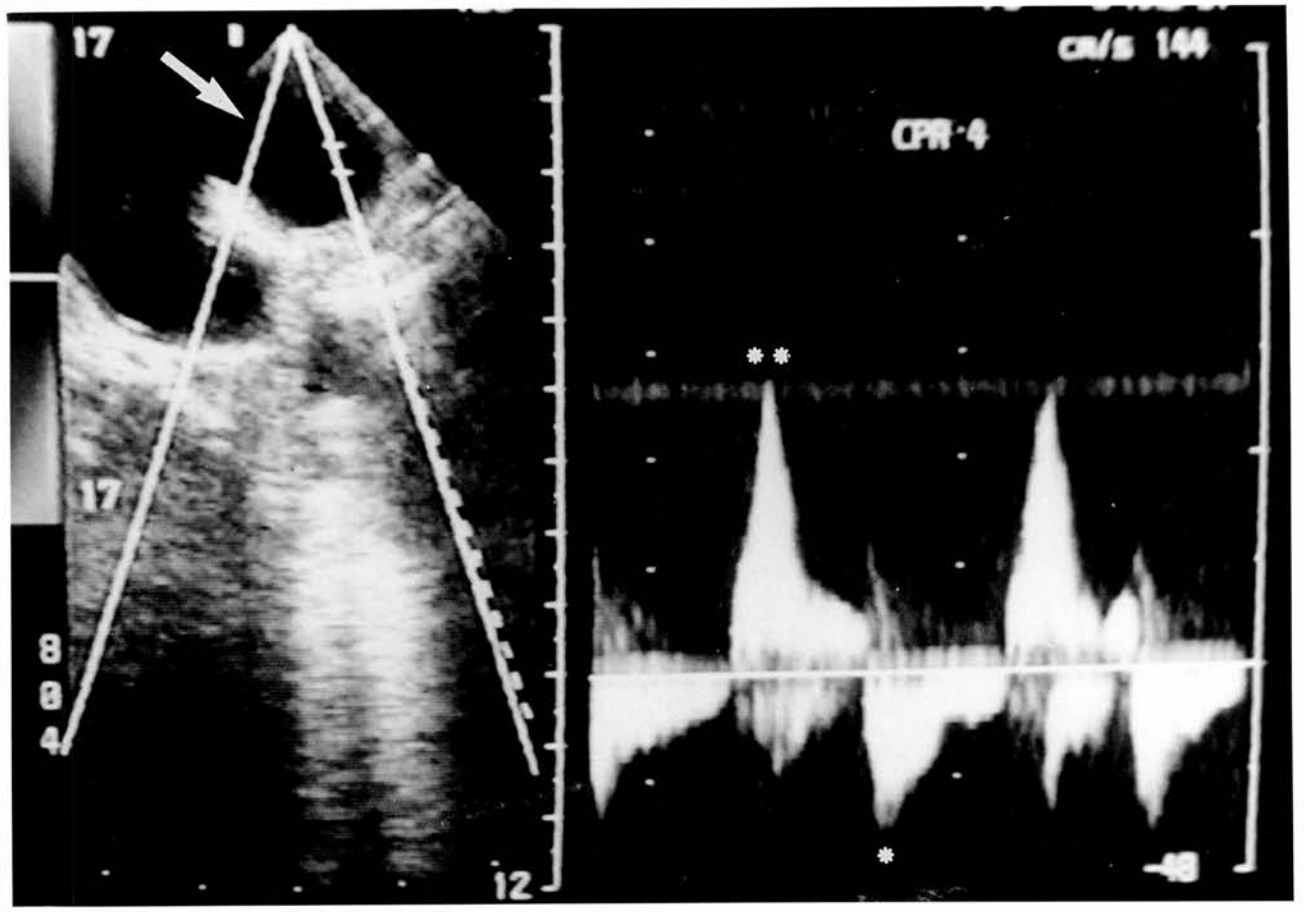


Figure 2.3

Aliasing of Colour Flow Doppler Signal in the Left Ventricular Outflow Tract During Sternal Compression.

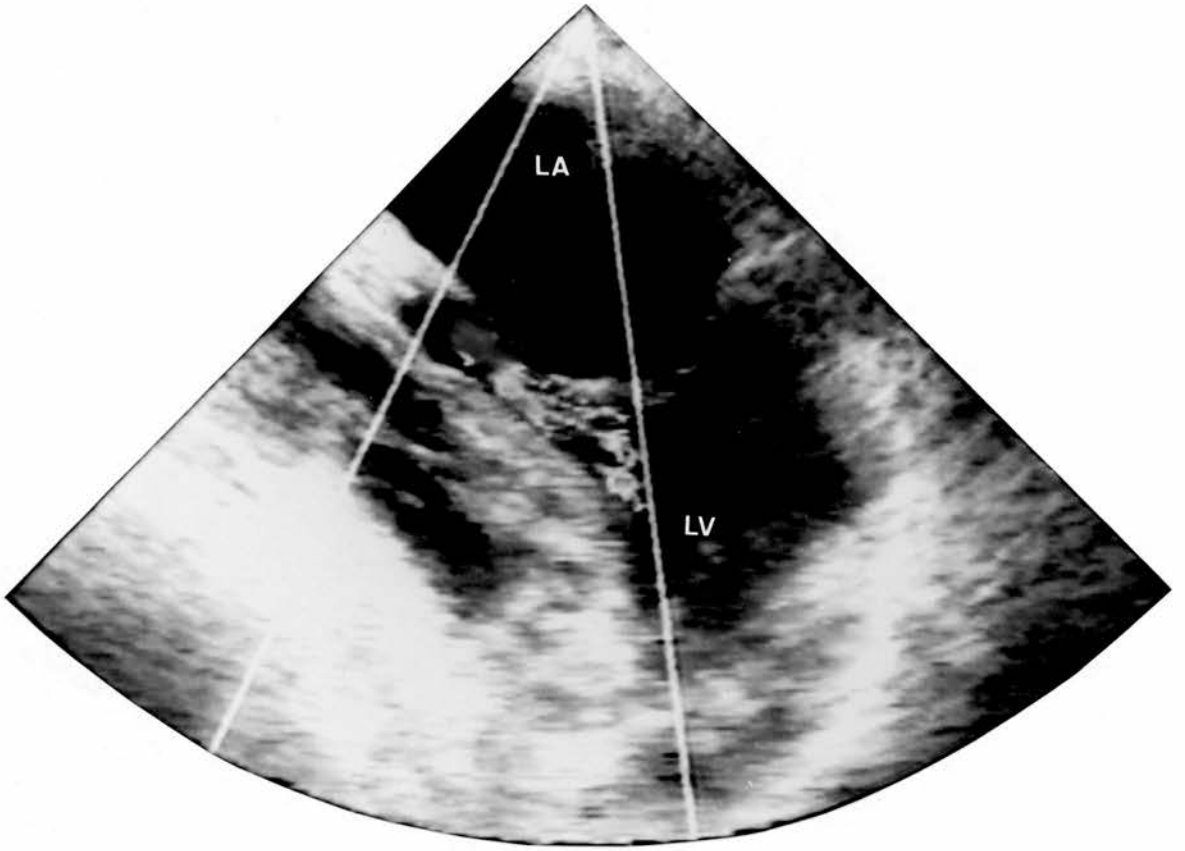


Figure 2.4

Aortic Valve Opening During Compression Phase of CPR.

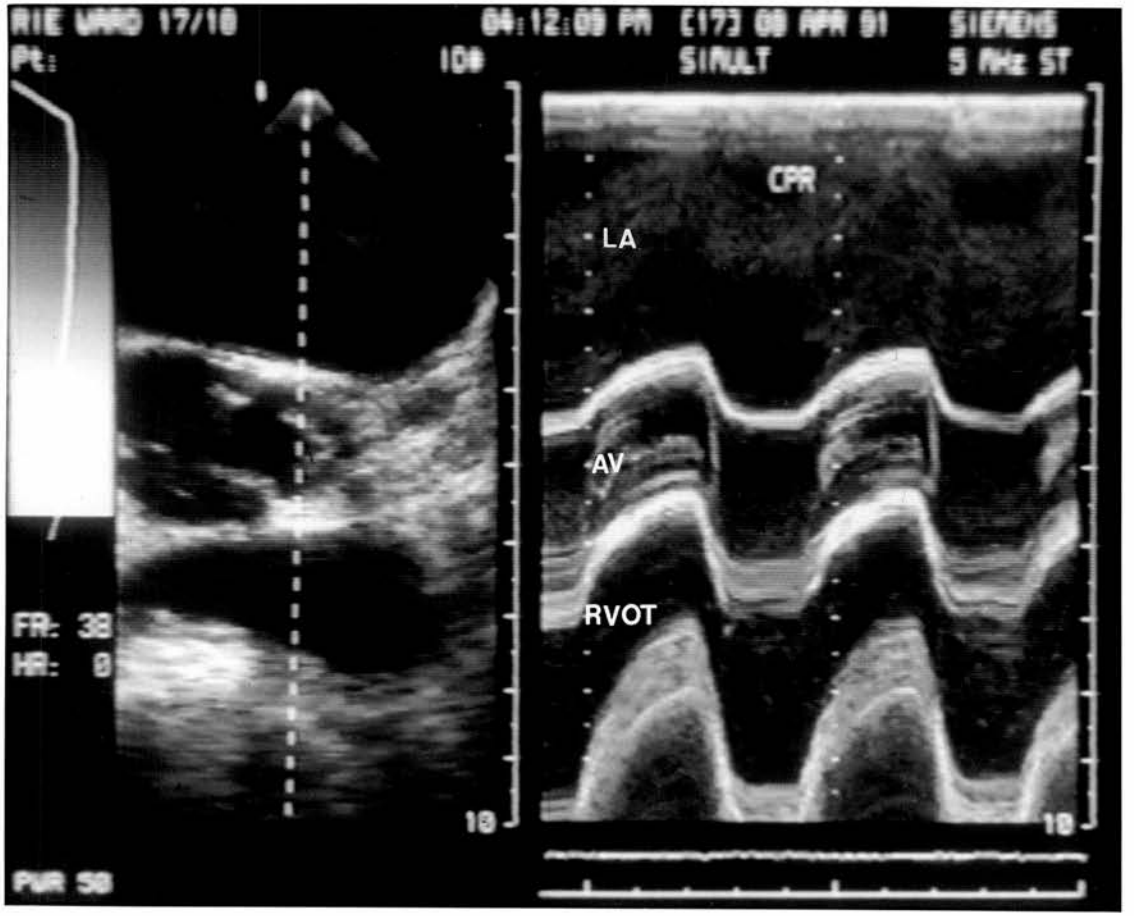
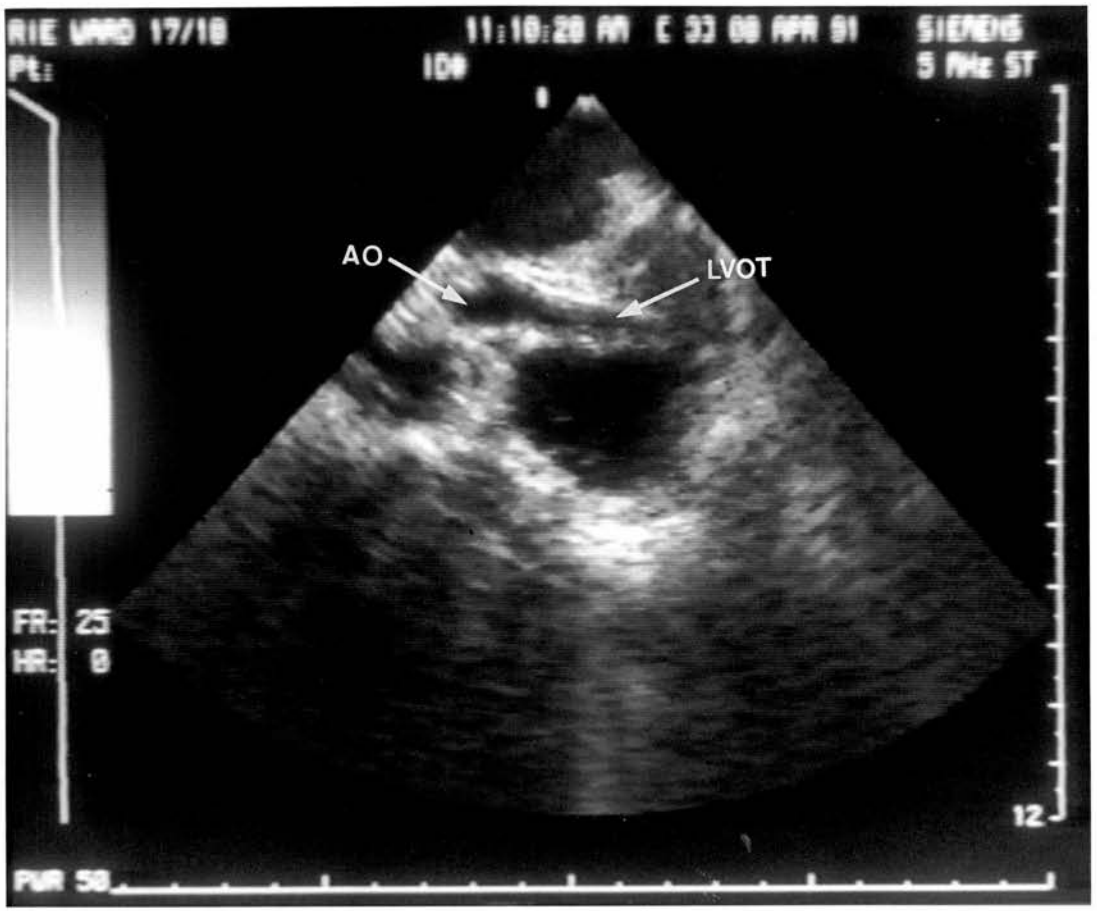


Figure 2.5

Compression and Distortion of the Aortic Root and Left Ventricular Outflow Tract During Sternal Compression.



sinus appeared to be turbulent,[4] and the right ventricle filled through the open tricuspid valve. Antegrade flow occurred from the pulmonary veins, into the left atrium, and through the mitral valve into the left ventricle. Mitral valve motion was also biphasic during the relaxation phase. The valve opened initially, but partial leaflet coaptation occurred later in the phase. Aortic valve closure occurred and the ascending aorta and superior vena cava re-expanded. Mild aortic incompetence was seen in two patients. Although retrograde pulmonary artery flow was apparent, the pulmonary valve and right ventricular outflow tract were poorly visualised and it was not possible to determine patterns of flow within these regions during CPR.

Influence of Underlying Rhythm: Weak contractions of both ventricles and low amplitude movements of the atrioventricular valves were observed when the underlying rhythm was electromechanical dissociation. Systolic wall thickening and change in endocardial area associated with these contractions were minimal, and colour flow Doppler revealed no effective forward flow. No spontaneous contractions occurred in ventricular fibrillation or asystole.

Ineffective CPR: the left ventricle appeared markedly hypovolaemic in five patients (Figure 2.6) and chest compression caused little change in left atrial and left ventricular areas. No flow was evident with colour flow Doppler in these patients and persistence of spontaneous echo-contrast during chest compression suggested ineffective CPR (Figure 2.7). Post-mortem results on two of these subjects failed to reveal an explanation for the hypovolemia.

Conclusions

This study confirmed previous reports that transoesophageal echocardiography might be used to investigate the events occurring during CPR (Higano et al., 1990; Kuhn et al., 1991). Unlike precordial echocardiography, it can be performed continuously

[4]Encoded as a mosaic of colours using colour Doppler.

Figure 2.6

Hypovolaemia of Left Heart Chambers. These appearances were often associated with ineffective CPR.

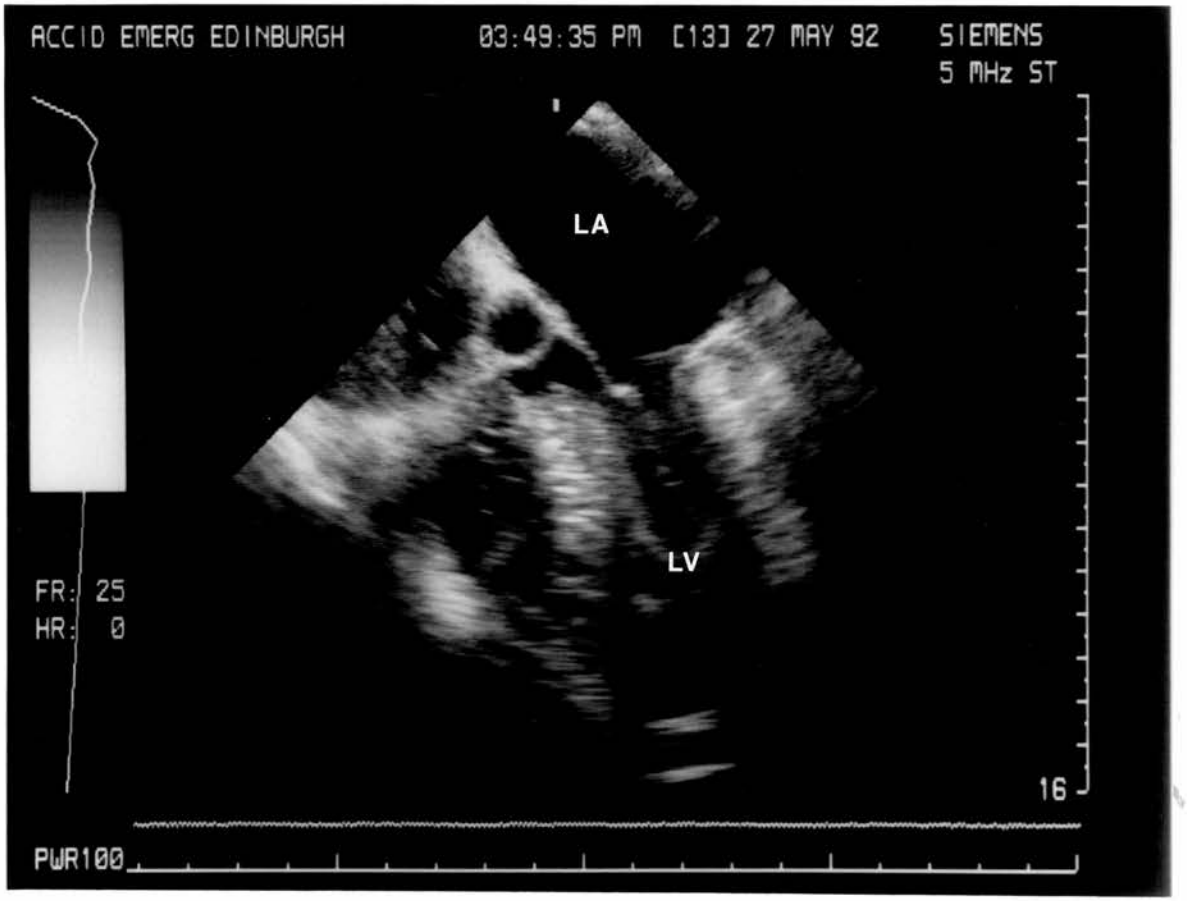
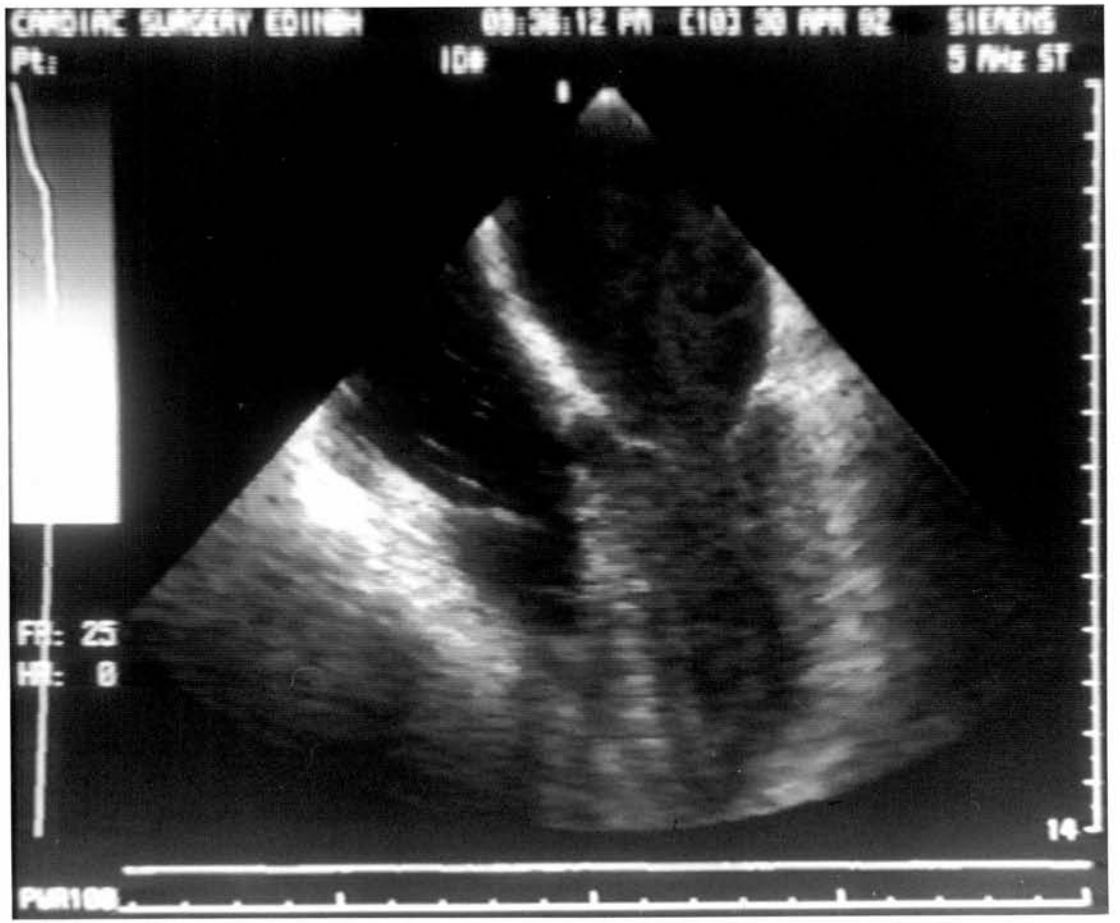


Figure 2.7

Spontaneous Echo-Contrast Within the Left Heart Chambers.



without compromising the resuscitation attempt. The transducer is optimally positioned for visualisation of both atria, the atrioventricular valves, the left ventricular outflow tract and the aortic valve. Furthermore, blood flow patterns are readily demonstrated with colour flow Doppler. In this study, transoesophageal echocardiography was shown to be a powerful tool allowing new insights into the mechanisms of CPR.

These results support the cardiac pump model as the mechanism responsible for generating forward blood flow during CPR. Sternal depression caused direct compression of all four cardiac chambers and resulted in ejection of blood into the aorta and main pulmonary artery. Chamber compression was most marked on the right side of the heart, but the left atrium and left ventricle were also compressed to a variable extent. In subjects with little left ventricular compression, no effective forward blood flow appeared to occur. Whilst the thoracic pump mechanism can operate under certain conditions (Criley et al., 1976), there was no evidence that it was responsible for the generation of forward flow in these subjects. This theory stipulates that the heart is not compressed, but that increased intrathoracic pressure is transmitted equally to all intrathoracic structures. As a result there is antegrade flow in the pulmonary veins and across the mitral valve throughout the compression phase. The evidence from transoesophageal echocardiography does not support this model. In particular, the presence of retrograde pulmonary vein flow and the absence of flow into the left ventricle during compression are incompatible with this mechanism.

The cardiac pump theory postulates that retrograde flow during chest compression is prevented by mitral valve closure. In this study, incomplete valve closure was observed in most subjects, yet mitral incompetence occurred in only two patients. This suggests that the pressures within the left atrium and the left ventricle may rise equally during the compression phase, and that both left heart chambers may behave as a single chamber during CPR. Accordingly, compression of this "common chamber" will result in both ejection of blood into the aorta and retrograde

pulmonary vein flow. There is limited published data on left atrial pressure changes during CPR to elucidate this issue. Similar pressures were recorded from the left atrium and femoral artery during CPR in subjects with mitral valve disease (Thomsen et al., 1968). In contrast, a pressure gradient was demonstrated between the left ventricle and left atrium during CPR in dogs (Feneley et al., 1987).

A limitation was the median delay of 30 minutes between the onset of the cardiac arrest and initiation of transoesophageal echocardiography. It has been suggested that the amplitude of mitral valve movements may diminish in prolonged resuscitation (Deshmukh et al., 1985 and 1989) and the possibility that different mechanisms may operate during the initial stages of CPR cannot be excluded. Nevertheless, the effectiveness of CPR was demonstrated by the eventual restoration of sinus rhythm after prolonged resuscitation in two subjects in whom the cardiac pump mechanism was clearly responsible for ejection of blood into the aorta during resuscitation.

Return of spontaneous circulation in CPR has been correlated with the pressure gradient between the aorta and the right atrium during the relaxation phase (Paradis et al., 1990). The right atrium re-expanded rapidly during this phase and the colour flow Doppler signal suggested turbulent inflow. Right atrial inflow is normally laminar during sinus rhythm and turbulent filling might reflect a rapid fall in right atrial pressure that could contribute to the coronary perfusion pressure by increasing the aortic-right atrial pressure gradient.

These results may help resolve some of the apparent inconsistencies in previous studies that utilised precordial echocardiography during CPR. Earlier authors equated mitral valve motion with blood flow and concluded that the cardiac pump mechanism was supported by valve closure (Deshmukh et al., 1985 and 1989; Feneley et al., 1987), or that the thoracic pump was supported by valve opening (Werner et al., 1981; Rich et al., 1981) during the compression phase. In this study, left ventricular filling occurred exclusively during the relaxation phase, yet mitral valve movements were biphasic. Accordingly, leaflet motion could occur without transmitral flow. The

echocardiographic observations suggested that mitral valve motion during CPR might be dependent primarily on displacement of adjacent structures rather than changes in intraventricular pressure. The anterior mitral annulus is in fibrous continuity with the aortic annulus, and early in the compression phase both structures appeared to be displaced posteriorly to a greater extent than the mitral subvalvar apparatus. As the mitral cusps are tethered by the chordae tendineae a hinge mechanism may operate causing the anterior mitral leaflet to open. Later in the compression phase the subvalvar apparatus is also displaced posteriorly and the mitral valve leaflets approximate.

Marked distortion of the left ventricular outflow tract, the aortic root and the right pulmonary artery commonly occurred during the compression phase. These appearances were associated with aliasing of the colour flow Doppler signal, raising the possibility of obstruction to outflow. Poor alignment from the oseophagus prevented spectral Doppler interrogation of flow at these sites, and it was not possible to ascertain whether a significant outflow gradient resulted. Experimentally, arterial collapse occurs when intrathoracic pressures and compressive forces are high, and this results in a reduction in carotid flow, a decreased stroke volume and the generation of a gradient between the left ventricle and the aorta (Rudikoff et al., 1980; Niemann et al., 1981; Maier et al., 1984). Whether the effectiveness of CPR in man is limited by similar mechanisms is unclear. Indeed, compression of the ascending aorta might even contribute to forward flow if it occurred at a time when left ventricular emptying had been completed. Distortion and compression of the superior vena cava was also frequently observed during CPR. The presence of venous valves in the internal jugular veins is well recognised (Rudikoff et al., 1980; Fisher et al., 1982), however compression of the superior vena cava might represent an additional mechanism by which pressure gradients are generated between the intrathoracic and extrathoracic venous systems during CPR.

Transoesophageal echocardiography identified five subjects with left ventricular hypovolaemia in whom CPR appeared to be ineffective and resuscitation was

unsuccessful. Left ventricular size decreases in ventricular fibrillation (Mashiro et al., 1978) and the volume of the left ventricle may be profoundly reduced at post-mortem examination. The pathophysiology of profound hypovolaemia is unexplained, and although it has been attributed to the position in the cardiac cycle at which the left ventricle arrests (Hutchins and Anaya, 1973), extreme vasodilatation is an alternative explanation (Pearson and Redding, 1965). Swenson et al. (1988) noted wide variations in the effectiveness of CPR as judged from direct haemodynamic measurements in human subjects. The reason for this variability was unexplained although they speculated that it might relate to the volume of blood in the arteries. The findings in the present study support the concept that ineffective CPR may occur in a subgroup of patients in association with apparent hypovolaemia. Identification of subjects in whom conventional CPR is ineffective might allow new therapeutic techniques to be developed to optimise cerebral and myocardial perfusion during resuscitation, for example by fluid loading, or use of the active compression-decompression device (see page 32).

In conclusion, in this study forward blood flow during CPR occurred as a result of the cardiac pump mechanism. Competence of the mitral valve did not appear to be necessary for successful CPR, suggesting that the left atrium and left ventricle may act as a single chamber, compression of which results in forward flow. Patterns of flow within the pulmonary veins and across the mitral valve were incompatible with a thoracic pump mechanism. The possibility that flow limitation may result from outflow tract compression deserves further study, and might permit the development of more efficient methods of closed chest compression.[5]

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[5]Following completion of this study a recent report has appeared in which transoesophageal echocardiography was also used to investigate the mechansims of CPR (Redberg et al., 1993). The authors' conclusions are broadly similar to those presented here and support the cardiac pump theory as the mechanism responsible for generating forward blood flow during CPR in humans.

Assessment of Active Compression-Decompression CPR

As previously discussed, transoesophageal echocardiography led to new insights into the mechanisms of CPR. Reports describing the active compression-decompression device (ACD), a novel mechanism designed to improve the effectiveness of closed chest CPR, appeared whilst these studies were being undertaken (Cohen et. al., 1992a & b). The ACD (Ambu CardioPump, Ambu International A/S) consists of a rubber suction cup, bellows, and handle which incorporates a scale that allows both the force and depth of compression to be monitored (Figure 2.8). The device is placed in the centre of the sternum and allows active manual compression of the chest, in addition to active chest wall expansion (decompression) during CPR. Pulmonary and systemic haemodynamics during CPR have been improved by use of the ACD in both experimental models (Cohen et al., 1991), and in humans (Cohen et al., 1992a). In this study, transoesophageal echocardiography was used to compare conventional CPR, with CPR performed with the ACD (ACD-CPR).

Methods

The methodology used in this investigation was identical to that used in the earlier study, with the exception that chest compression was performed according to a predetermined sequence: mechanical thumper, ACD device, manual compression. Each technique was performed for five minutes. For all these methods, chest compression was performed at a rate of 80 compressions/minute, with a ratio of 5 chest compressions to one ventilation. Acquisition and analysis of echocardiographic images were performed as before. Four of the echocardiographic studies were performed by Dr Stuart Pringle, Senior Registrar, Department of Cardiology.

Results

Seven patients were studied (four male, three female, age range 58-83 years, median 70 years). The median interval between the onset of the cardiac arrest and initiation

Figure 2.8

The Active Compression-Decompression Device.

of transoesophageal echocardiography was 49 minutes. The initial rhythm was asystole in two patients, ventricular fibrillation in three patients, and electromechanical dissociation in two patients. No subject survived to discharge from the Accident and Emergency Department.

The mechanisms responsible for generating forward blood flow were identical for all three techniques of cardiac compression and were consistent with the cardiac pump theory of CPR. In the compression phase direct compresson of the right and left ventricles was seen and this resulted in ejection of blood into the pulmonary artery and aorta respectively. Ventricular filling occurred only in the relaxation phase.

The extent of ventricular compression varied according to the compression technique used. All three methods produced relatively greater compression of the right heart chambers than the left. ACD-CPR produced a longer compression phase than manual or mechanical CPR. In three patients, ACD-CPR was associated with a greater degree of right heart chamber compression than when mechanical or manual compression was used. The extent of left heart chamber compression achieved was similar irrespective of the compression technique.

Colour flow Doppler imaging was of sufficient quality in four patients to allow analysis of blood flow patterns. Higher velocity blood flow was observed in two subjects with ACD-CPR, in comparison to manual or mechanical compression in the same subjects. Persistence of spontaneous echo-contrast within the left ventricle, suggestive of ineffective CPR, was observed during manual and mechanical chest compression in three subjects. In one of these subjects ACD-CPR resulted in disappearance of the echo-contrast from the left ventricle.

Left ventricular hypovolaemia was pronounced at the outset of CPR in three subjects. These appearances persisted despite mechanical chest compression. As a consequence, minimal compression of left heart chambers resulted and little effective

forward flow was evident with colour flow Doppler. Following ACD-CPR, increased left ventricular filling occurred in two of these subjects, and improved forward flow patterns were evident from colour flow Doppler.

Although spontaneous circulation was not regained in any of these subjects, transoesophageal echocardiography clearly demonstrated the return of spontaneous ventricular contractions in three subjects during ACD-CPR. In these patients asystole had persisted throughout mechanical CPR. However, these contractions were of low amplitude and did not result in effective blood flow as determined by colour flow Doppler or a palpable pulse.

Conclusions

The observations reported from the earlier study had suggested that ineffective CPR might be recognised echocardiographically by the persistence of spontaneous echo-contrast, left ventricular hypovolaemia, diminished chamber compression, and absent, or low velocity colour flow Doppler signals. There is no "gold standard" method of measuring cardiac output during CPR, against which these echocardiographic observations might be compared. Accordingly, these criteria are unvalidated, although a recent study has also suggested that the absence of a colour flow Doppler signal implies ineffective CPR (Wright 1993).

When assessed by these echocardiographic criteria, this study suggests that ACD-CPR is at least as effective as manual or mechanical CPR. The degree of left heart chamber compression was similar with all forms of CPR. Right heart compression however appeared greater with ACD-CPR in three patients. The velocity of blood flow was observed to increase on changing from mechanical CPR to ACD-CPR in some cases and in one subject spontaneous echo-contrast that had persisted throughout mechanical compression cleared with ACD-CPR.

The mechanisms responsible for these differences between conventional CPR and

ACD-CPR are unclear. Active decompression presumably generates increased negative intrathoracic pressure and this might augment venous return and right ventricular filling. In two subjects right and left ventricular filling appeared to be improved by ACD-CPR and this might have resulted in a greater cardiac ouput in response to chamber compression. In dogs the coronary perfusion pressure is increased by changing from conventional CPR to ACD-CPR (Cohen et al., 1992). It is possible that the return of spontaneous ventricular contractions in three subjects in this study, following a period of asystole, reflected improved coronary perfusion with ACD-CPR.

Whilst these preliminary observations are encouraging, experience with ACD-CPR is limited. However, recent evidence published following completion of these studies suggests that ACD-CPR may improve survival following in-hospital cardiac arrest (Tucker et al., 1993; Cohen et al., 1993). Further studies are warranted to determine the role and clinical efficacy of ACD-CPR.

Transoesophageal Echocardiography and CPR: Conclusions

The evidence from these studies strongly supports the cardiac pump mechanism of CPR. However further research is required to determine whether this is always the mechanism responsible for generating forward blood flow, or whether the thoracic pump mechanism can operate under different conditions. There is a need for an effective method of monitoring the adequacy of CPR for both clinical and research purposes. These studies have shown that transoesophageal echocardiography can readily be performed during CPR without compromising the resuscitation attempt. Further studies are required to validate the suggested echocardiographic criteria for ineffective CPR. However, this research suggests that transoesophageal echocardiography is a promising method of monitoring the effectiveness of CPR, and might be used to guide resuscitation attempts, and ultimately assist in the development of new, more effective methods of CPR.

CHAPTER 3

INTRAOPERATIVE TRANSOESOPHAGEAL ECHOCARDIOGRAPHY I: NEW INSIGHTS INTO THE POST-TRAUMATIC FAT EMBOLISM SYNDROME

"Fat embolism has always given rise to debate and controversy and even now, a hundred years after its first description there is a lack of agreement and, dare I say it, even confusion as to its frequency, aetiology, pathogenesis, clinical significance and its clinical effects"

Sevitt S, (1962) *Fat Embolism*

Introduction

More than thirty years after Sevitt's introduction to his classic monograph the pathophysiology of the post-traumatic fat embolism syndrome remains controversial, and modern day authorities continue to exercise the same arguments that their predecessors first disputed in the late nineteenth century. Few now would dispute the existence of this syndrome as a clinical entity, and the characteristic triad of respiratory insufficiency, a petechial rash and cerebral dysfunction are well recognised (Table 3.1). However, both the origin of fat emboli and their causative role in tissue damage remain contentious issues. There is no specific treatment and no diagnostic test. The disease is unpredictable, and can occur in the patient with a simple long bone fracture whilst sparing the patient with multiple injuries. Little additional progress has been made in our understanding of the fat embolism syndrome since Sevitt's studies, reflecting the difficulty in making an early diagnosis, the lack of an appropriate animal model and continuing uncertainty regarding the fundamental pathophysiology of the condition.

In the studies described in this chapter, the advent of transoesophageal echocardiography permitted the use of a new imaging technique in this condition and

Table 3.1 Diagnosis of the Fat Embolism Syndrome (Gurd & Wilson, 1974).

Major	**Minor**
Respiratory Insufficiency	Pyrexia
Neurological Dysfunction	Tachycardia
Petechial Rash	Retinal involvement
	Jaundice
	Renal involvement
One major + four minor criteria + fat macroglobulinaemia is diagnostic	

brought new insights and understanding of basic mechanisms. Furthermore, preliminary results suggest a role for transoesophageal echocardiography in helping predict which patients are most at risk of developing the fat embolism syndrome following traumatic injury.

Historical Perspective

The association of fat embolism with traumatic injury was first described in the latter half of the nineteenth century. This newly recognised syndrome generated extraordinary interest to the extent that at least 177 cases had been recorded in the literature by 1880 (Scuderi, 1938), and over 600 references had been published on the subject by 1944 (Wilson and Salisbury, 1943-44). Much of the early literature is by German authors and is largely inaccessible to the English reader, however comprehensive reviews were made by Warthin (1913), Scuderi (1938) and Sevitt (1962).

Zenker is credited with the first description of post-traumatic fat embolism in 1862, when he described pulmonary fat emboli in a patient who died following a crush injury to the chest and abdomen (Scuderi, 1938). Erroneously he thought that embolism was secondary to aspiration of fatty gastric contents through gaping hepatic veins. The importance of bone injury was first recognised by Wagner in 1865, who performed post-mortem examinations on 48 cases of fat embolism. The association of fat embolism with bone injury was supported by early experimental work. In 1866 Busch injected a mixture of olive oil and vermillion into the marrow of a rabbit's long bone. The bone was then fractured, and within a few minutes of injury dye-stained emboli could be demonstrated in the lungs (Sevitt, 1962). The first clinical diagnosis of fat embolism during life was made in 1873 by von Bergman in a patient with a femoral fracture. The patient succumbed shortly afterwards and the diagnosis was confirmed at autopsy (Sevitt, 1962).

Many writers have questioned the clinical significance of fat embolism. Scriba, for

example, concluded in 1888 that although pulmonary fat embolism occurred after every injury to bone, in most cases it was subclinical (Sevitt, 1962). Similarly, Cohnheim (1889) cited experimental work in which massive fat embolism in animals caused no discernible clinical abnormality. Whitson (1951) claimed that the symptoms and signs of fat embolism syndrome were unrelated to fat emboli, but were probably due to hypoxaemia and circulatory shock. However, contrary views were expressed by other authors who claimed that fat embolism was an important clinical entity. The significance of the petechial rash was recognised by Benestad and Grondahl in 1911 (Sevitt, 1962). Gaus (1924) identified three distinct presentations of fat embolism: pulmonary embolism that was associated with dyspnoea, tachycardia, cyanosis, restlessness, cough and production of sputum; coronary artery embolism that resulted in symptoms of dyspnoea, tachycardia, and hypotension; and cerebral embolism that was marked by neurological dysfunction.

Accordingly, although not universally accepted, the circumstances and clinical features associated with fat embolism were recognised at an early stage. Ironically, many of the issues that caused debate amongst the early writers, have continued to provoke disagreement and controversy in the past 50 years. Various aspects of the syndrome remain poorly explained and in many respects our knowledge of its pathophysiology has advanced little since Gaus's paper in 1924.

Two topics have aroused particular debate since the earliest reported cases of fat embolism syndrome: the aetiology of fat emboli, and their role in the pathophysiology of the pulmonary and systemic manifestations of the fat embolism syndrome.

The Aetiology of Fat Emboli

The classical school of thought, dating from the early German writers, is that fat emboli originate at the site of trauma. This "mechanical hypothesis" proposes that intramedullary fat fragments enter ruptured veins at the site of a fracture, embolise

to the lungs and lodge in pulmonary capillaries. Intravasation of fat is promoted by transient increases in intramedullary pressure caused by movement or manipulation of the fracture site (Young and Griffith, 1950). Evidence supporting this hypothesis includes the observation that experimentally induced pulmonary fat emboli have a similar lipid profile to that of bone marrow (Hallgren et al., 1966), the fact that bone marrow particles can be demonstrated in the lung following trauma (Mason, 1959), and that a tourniquet proximal to an injured bone will prevent fat droplets from reaching the systemic venous circulation (Peltier, 1956a).

The alternative, "biochemical (or physicochemical) hypothesis" was first proposed by Lehman and Moore (1927), and has continued to receive support from a variety of sources (Johnson and Svanborg, 1956; Bergentz, 1961; Evarts, 1970; Xue and Zhang, 1992). Proponents suggest that fat globules are formed within the circulation from the coalescence of chylomicrons, and point to the association of fat embolism with non-traumatic conditions such as diabetes mellitus, severe infections, chronic alcoholism, burns, cardiopulmonary bypass, osteomyelitis, fatty liver and sickle cell disease. Variations of this theory suggest that fat is mobilised from tissue stores by stress hormones (Xue and Zhang, 1992), and that emboli consist variously of aggregated chylomicrons, very low density lipoproteins, erythrocytes and/or platelets (Bergentz, 1961; Evarts, 1970; Hulman, 1988). Factors that have been implicated in inducing coalescence include: C-reactive protein, ether anaesthesia, increased secretion of adrenocortical hormone, products of protein degradation and the alpha toxin of *Clostridium welchii* (Hulman, 1988). The occasional occurrence of fat embolism syndrome in non-traumatic conditions is the most convincing evidence in support of this alternative to the mechanical hypothesis, and fat embolism has been induced in an animal model by immobilisation without direct trauma (Xue and Zhang, 1992). However, the role of biochemical factors in the genesis of fat emboli following traumatic injury remains speculative.

The Pathophysiology of the Pulmonary and Systemic Manifestations of the Fat Embolism Syndrome

Pulmonary fat embolism occurs in 80-100% of subjects with skeletal injury (Sevitt, 1962 and 1977).[1] Whilst this is generally accepted, the clinical significance of pulmonary fat embolism has been the subject of much controversy. Early authors promoted the concept of a pulmonary syndrome, and pointed to the acute respiratory distress that could occur following injury (Warthin, 1913; Gaus, 1924). Others argued that in most cases fat embolism was subclinical and produced little if any effect (Cohnheim, 1889). This debate continued (Robb-Smith, 1941; Wilson and Salisbury, 1944; Glas et al., 1953; Scully, 1956; Emson, 1958), and in 1962, Sevitt concluded that:

"The body of evidence, pathological, clinical and experimental, indicates that even histologically gross embolism is unlikely to be clinically important."

Where pulmonary dysfunction developed after injury, Sevitt suggested that it was neurogenic in origin, secondary to cerebral fat embolism. In support of this thesis, Sevitt pointed to the fact that respiratory distress typically occured several days after injury, yet fat emboli were at their most numerous at the time of injury. Furthermore, to produce symptoms in experimental animal models a much greater degree of embolism was required than ever occured in man. Nevertheless, he conceded that it was possible that pulmonary emboli might produce symptoms in subjects with limited cardiovascular or pulmonary reserve, and in later work acknowledged that pulmonary fat emboli were probably responsible for early subclinical hypoxaemia in patients with fractures (Sevitt, 1977).

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[1]This was appreciated by the early German writers, for example Scriba (1880), who concluded that pulmonary fat embolism occurred after every injury to bone. The presence of free fat in sputum and fat globules in alveolar macrophages have been discredited as diagnostic tests for the fat embolism syndrome for many years (Sevitt, 1962). In view of this it is perhaps surprising that new diagnostic tests for the fat embolism syndrome continue to be described that are based on the detection of fat within the lungs (Masson and Ruggieri, 1985; Chastre et al., 1990; Castella et al., 1992).

In contrast, Peltier (1965 and 1988) proposed that the fat embolism syndrome was primarily a pulmonary disease and emphasised the importance of increased pulmonary vascular resistance secondary to widespread microvascular occlusion by fat emboli. Massive fat embolism could obstruct the pulmonary circulation, and lead to hypoxaemia as a result of ventilation-perfusion inequality. Rapid deterioration could follow, with death from acute cor pulmonale. This hypothesis was supported by experimental studies, in which injection of neutral fat caused death by pulmonary vascular obstruction (Peltier, 1956b). Subsequently, Hagley (1983) described five subjects who developed massive pulmonary fat embolism shortly after injury, and more recently several case reports were published that also supported the concept of a fulminating fat embolism syndrome (Mayron et al., 1985; Marshall et al., 1991; van Miert et al., 1991; Reid and Hill, 1992; Green, 1992).

Whilst injection of neutral fat causes pulmonary vascular occlusion, injection of free fatty acids causes a chemical pneumonitis, and produces a similar clinical picture to that found in those patients developing pulmonary dysfunction several days after trauma (Peltier, 1956b; Fonte and Hausberger, 1971; Parker et al., 1974). This observation lead to the theory of a secondary phase of tissue damage in fat embolism syndrome, caused by free fatty acids released by the hydrolysis of fat emboli within the lungs, and accounted for the latent interval between the injury and the onset of symptoms in many patients.

More recent research has focused on the contribution of rheological changes to the pathogenesis of pulmonary and systemic tissue damage. Modig (1977) suggested that release of tissue thromboplastin following trauma generates platelet and fibrin microemboli that become trapped in the pulmonary microvasculature. Microvascular stasis results, leading to interstitial oedema, intra-alveolar haemorrhage and ultimately the adult respiratory distress syndrome. Fat emboli may be irrelevant to this process, and although present in lungs after trauma, simply an epiphenomenon. Evarts (1970) considered the contribution of aggregated erythrocytes to microvascular stasis following trauma, whilst van Besouw and Hinds (1989)

suggested that pulmonary fat emboli become coated with platelets which subsequently release a variety of mediators leading to vasospasm, bronchospasm, ventilation-perfusion mismatch and capillary congestion. In practice, there is remarkably little evidence to either support, or refute these theories.

The pathogenesis of the systemic manifestations of the fat embolism syndrome also remains incompletely understood. The presence of a petechial rash and/or cerebral dysfunction implies that fat emboli have entered the arterial circulation (Watson, 1970). It is generally accepted that systemic embolism occurs as fat emboli are fluid and deformable, and migrate directly across the pulmonary vascular bed, or through pulmonary precapillary shunts, to reach the pulmonary veins (Sevitt, 1962). Many believe that the pathological changes seen in the systemic fat embolism syndrome are entirely secondary to the mechanical effects of small vessel occlusion. Sevitt (1977) suggested that the absence of endothelial changes was evidence against a chemical or toxic action of emboli in systemic organs. The frequency of histological changes in the brain and myocardium reflected the inherent susceptibility of these tissues to hypoxia. However, the severity of the neurological deficit does not correlate with the amount of fat in the brain at postmortem (Dines et al., 1975), and some authorities have suggested that an encephalopathy may result from the release of free fatty acids, in a similar fashion to the processes thought to occur in the lungs (Jacobson et al., 1986). Another unexplained feature is the preferential localisation of petechiae to the cerebral white matter, whilst emboli are more common in the cerebral cortex (Kamenar and Burger, 1980).

Transoesophageal Echocardiography and the Fat Embolism Syndrome

The stimulus for these investigations came from a serendipitous observation during an intraoperative study. A transoesophageal echocardiogram had been requested to exclude myocardial or aortic injury in a subject with multiple injuries following a road traffic accident. No damage to the heart or great vessels was detected, but a large echogenic mass suddenly appeared within the right atrium whilst a femoral

fracture was being nailed. The mass appeared to be fixed at the orifice of the inferior vena cava and was thought to represent a fat embolus trapped within a fenestrated Eustachian valve. Numerous smaller echogenic masses were also observed passing through the right heart chambers during the operative procedure, and postoperatively the patient developed features consistent with the fat embolism syndrome.

Clinical evidence of the fat embolism syndrome occurs in 0.5-11% of patients with traumatic long bone or pelvic fractures and continues to be associated with high morbidity and mortality (Fabian et al., 1990). It is usually assumed that the major degree of fat embolism occurs at the moment of injury, however embolism can continue for several days and is probably dependent on various local factors including mobility of the fracture, manipulation, and operation (Sevitt, 1977). As operative treatment of long bone fractures is often performed within 24 hours of injury it may not be possible to determine the contribution of a surgical procedure to the pathogenesis of the fat embolism syndrome. However, it is clear that the fat embolism syndrome can complicate elective orthopaedic procedures without a preceding history of trauma, and it may also develop in patients undergoing delayed operative treatment of fractures (Peltier, 1952; Jones, 1975; Talucci et al., 1983; ten Duis et al., 1988).

It is well established that transoesophageal echocardiography is sensitive in the detection of intracardiac masses including thrombus (Ashemberg et al., 1986), tumour (Pozzoli et al., 1991), and also air embolism during cardiac and neurosurgical procedures (Cucchiara et al., 1984). This case, and a previous report (Ulrich et al., 1986) suggested that transoesophageal echocardiography might be a useful technique to detect fat embolism during orthopaedic procedures and prompted the following investigation. The study had two aims: to determine the incidence and spectrum of echocardiographically-detected fat embolism during orthopaedic surgery; to determine whether transoesophageal echocardiography might be used to predict the development of the fat embolism syndrome in patients with traumatic injuries.

Methods

Transoesophageal echocardiography was performed continuously during surgical treatment of patients with pelvic and long bone fractures. After anaesthesia had been induced, the probe was positioned to provide continuous imaging of the right atrium and right ventricle. The probe was left in this position throughout the operative period and was removed immediately before reversal of anaesthesia. All studies were recorded on VHS video tape for subsequent analysis. Monitored physiological parameters included heart rate, blood pressure, electrocardiogram, pulse oximetry, and end-tidal CO_2 levels.

Postoperatively, all subjects were examined by a clinician blinded to the echocardiographic data (Mr John Keating, Senior Orthopaedic Registrar) for evidence of the fat embolism syndrome. Where appropriate, relevant investigations were performed (arterial blood gases, chest radiography). Diagnosis of the fat embolism syndrome required the presence of at least two out of three criteria (ten Duis et al., 1988; Fabian et al., 1990):

1. Hypoxia ($pO_2 < 9$ kPa) whilst breathing air, in the absence of concurrent respiratory disease (eg bronchopneumonia, pulmonary contusion).
2. Radiological evidence of pulmonary infiltration.
3. Clinical evidence of systemic fat embolism (petechial rash, cerebral dysfunction).

Analysis of echocardiographic images was performed off-line by myself, without knowledge of the postoperative clinical details. Each study was graded according to the duration of embolism, and the size and quantity of embolic material.

Results

There were 24 patients (12 male, 12 female), mean age 38 years (range 17-85 years). Based on the appearance of embolic material within the right heart chambers

three categories of embolism were defined:

Group I. The echocardiographic recordings in this group of 14 patients showed little or no evidence of embolic phenomena.

The 14 patients had 12 tibial fractures and two femoral fractures, all closed injuries. Four fractures were caused by high-energy trauma, and all were nailed within 24 hours. The intraoperative physiological parameters remained within normal limits, and the subsequent clinical progress of all 14 patients was uneventful. No patient developed evidence of the fat embolism syndrome.

Group II. Echocardiography in this group of six patients revealed showers of moderate quantities of embolic material that consisted of small masses 1-10 mm diameter (Figure 3.1). The duration of embolism in this group was always greater than one minute.

Three patients had tibial fractures and three had femoral fractures. Three fractures were the result of high-energy injuries; one tibial fracture was a Gustilo type-I open injury, the others were closed. All fractures were internally fixed within 24 hours.

Little or no intracardiac embolism was observed during skin preparation, draping, or skin incision in any patient. Emboli usually appeared within 10 seconds of starting to reduce the fracture, when a shower of highly echogenic masses was seen within the right atrium. Broaching the intramedullary canal, passage of the reamers, and nail insertion were accompanied by additional showers of emboli. The duration and amount of embolism tended to be greatest during reaming and nail insertion. Despite these appearances, no intraoperative physiological abnormalities were recorded and no Group II patient developed evidence of the fat embolism syndrome.

Group III. Echocardiography in this group of four patients demonstrated large amounts of echogenic material that comprised multiple masses 1-10 mm diameter,

with larger, discrete emboli 1-8 cm in length (Figure 3.2). Embolism in these patients lasted for more than 2 minutes.

There were four patients, two with femoral and two with tibial fractures. Three of the fractures were caused by high-energy trauma and one tibial fracture was a Gustilo type-II open injury. Two patients were operated upon within 24 hours of injury; one within three days, and one within eleven days.

Embolic material appeared within the right atrium during reaming and nailing manoeuvres. Three of the four Group III patients developed fat embolism syndrome, two of whom required ventilation. One of these subjects developed profound hypotension, arterial destauration and a fall in end-tidal CO_2 levels during intramedullary reaming. The patient died of fat embolism syndrome 32 hours postoperatively, and histological examination demonstrated widespread microvascular fat deposition. This case is described in greater detail in the following section.

Conclusions

In this study, reaming and intramedullary nailing were frequently accompanied by the appearance of embolic material within the right heart chambers. These findings confirm those of Ulrich et al. (1986) who detected echogenic material in a majority of patients undergoing total hip replacement. The precise nature of the embolic material is uncertain as current echocardiographic techniques do not allow tissue characterisation. The possibility that these appearances were secondary to thrombus dislodged from leg veins cannot be excluded, however detailed histological studies performed in the subject with massive intraoperative embolism revealed widespread microvascular fat deposition (described in the following chapter).[2]

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[2]Preliminary results from subsequent studies undertaken by Mr James Christie, Consultant Orthopaedic Surgeon, have revealed that samples of right atrial blood, taken during periods of echocardiographically-detected embolism, contain a high lipid content compared to control specimens (Gurd, 1970) (Personal Communication).

Figure 3.1

Grade II Fat Embolism. Small echogenic masses appearing within the right heart chambers during reaming.

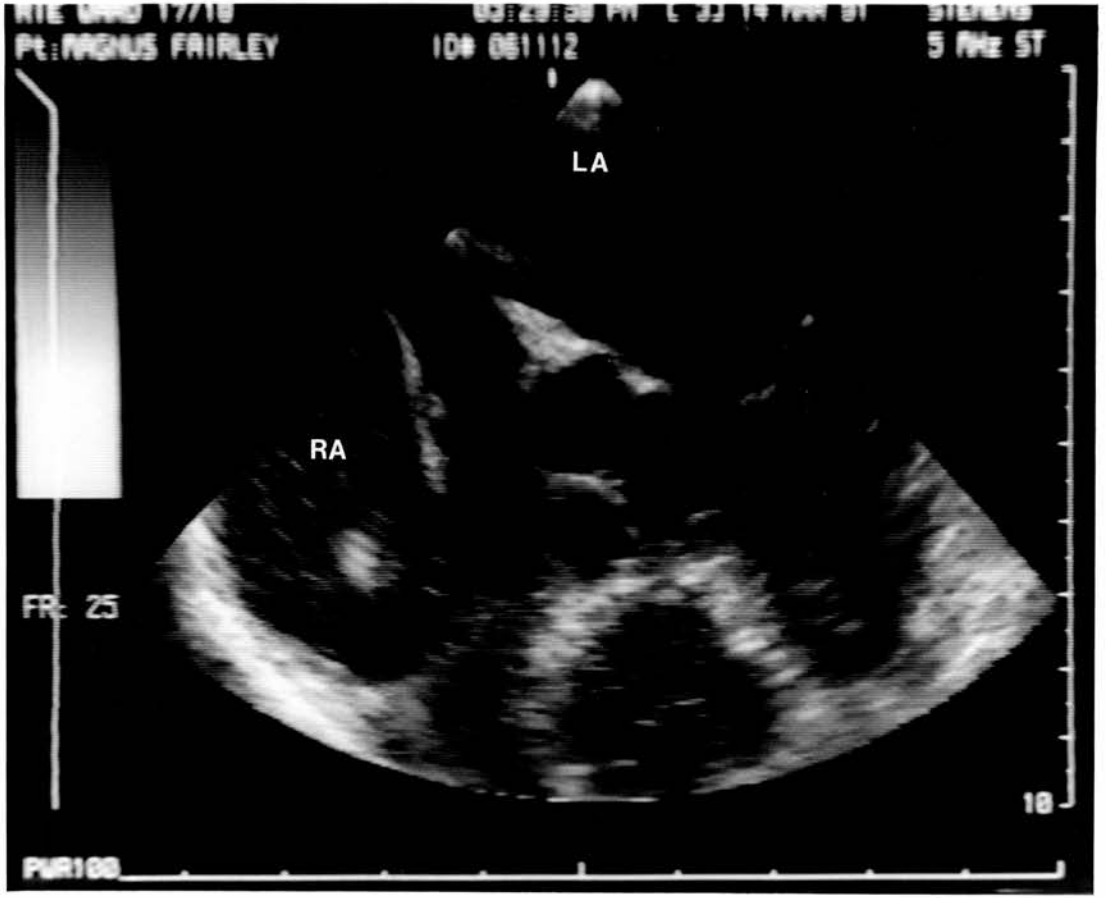
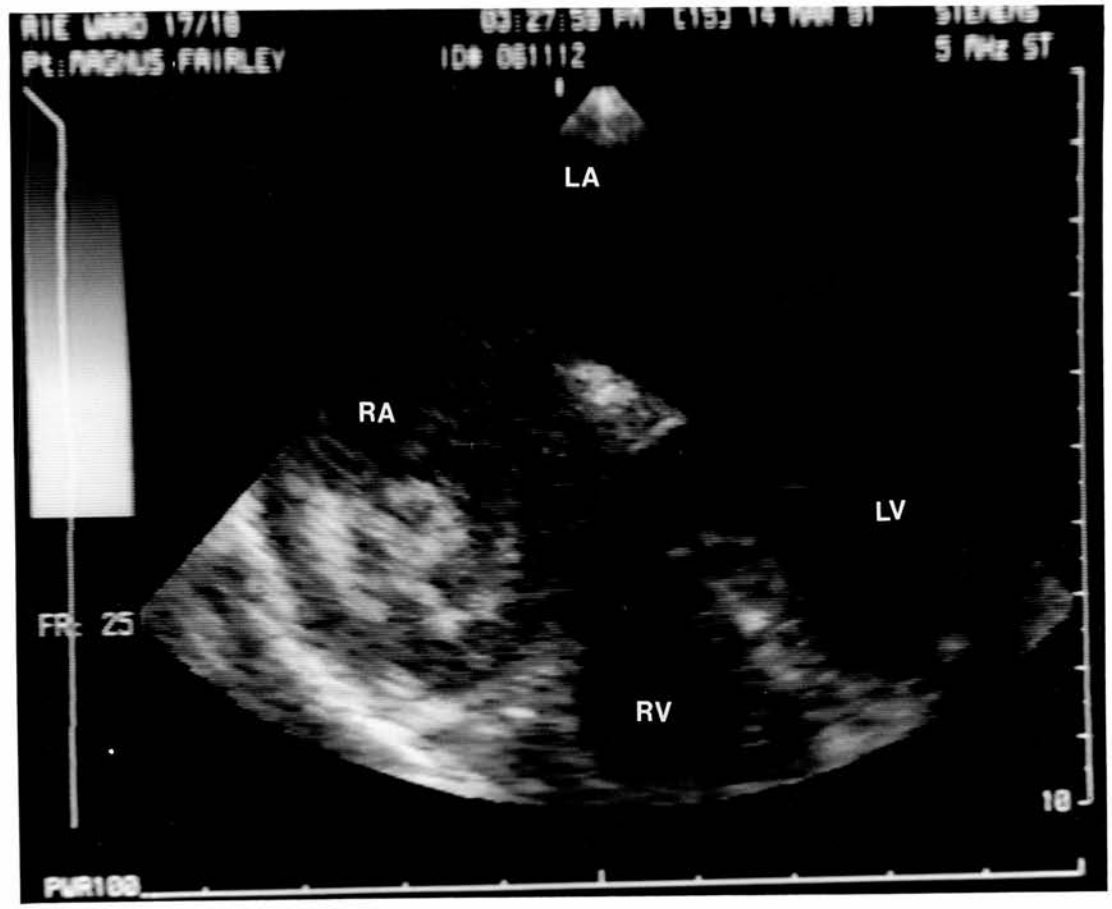


Figure 3.2

Grade III Fat Embolism. Large masses are seen within the right atrium.



The close temporal association between procedures involving the medullary canal and the appearance of echocardiographically-detected embolism is consistent with the mechanical theory of fat embolism. Intramedullary pressure is increased by reaming and nailing procedures (Manning et al., 1983), and this is thought to promote the entry of fat globules into the venous circulation via damaged medullary veins (Young and Griffith, 1950; Sevitt, 1962). Internal fixation of femoral fractures was first introduced during World War II and considerable controversy surrounded its use in the early years. It was feared that embolism might be precipitated, and cases of fat embolism syndrome were reported (Peltier, 1952). More recent studies have failed to find any increased risk with intramedullary fixation, and indeed the presence of a fracture may actually lessen the risk of fat embolism by decompressing the medullary contents during manipulation. Many surgeons now believe intramedullary fixation to be beneficial, reducing the risk of pulmonary complications by allowing early mobilisation (Talucci et al., 1983; ten Duis et al., 1988).

The frequency of echocardiographically-detected embolism aroused considerable surprise amongst experienced orthopaedic and anaesthetic colleagues. Nevertheless, these results are entirely consistent with much of the earlier literature. Intramedullary contents were detected in the femoral vein during reaming of a rabbit tibia (Olerud et al., 1969). Nearly twenty years before the present study, Jones (1975) used a non-imaging ultrasonic phonocardiogram to detect turbulence within the right atrium and claimed that fat embolism occurred during total hip replacement. Haemodynamic instability and falls in oxygen saturation are occasionally observed during reaming and prosthesis insertion. These results suggest that fat embolism might be responsible, although alternative mechanisms have been suggested including use of acrylic bone cement (Pelling and Butterworth, 1973), and neurally mediated phenomena (Reikeras, 1987).

The diagnosis of the fat embolism syndrome is entirely based on clinical features, but there are no uniformly accepted criteria. Gurd and Wilson (1974) considered one major and four minor criteria plus fat macroglobulinaemia to be diagnostic (Table

3.1), but these criteria may lead to underdiagnosis (Murray and Racz, 1974). A fat embolism index was suggested by Schonfeld et al. (1983), whilst a diagnosis based solely on the presence of respiratory insufficiency was used by Lindeque et al. (1987). Lindeque's criteria may lead to overdiagnosis, particularly following trauma where respiratory abnormalities may arise from pulmonary contusion or aspiration. Where these conditions can be excluded, diagnosis of the fat embolism syndrome based on the presence of pulmonary dysfunction has the merit of increased sensitivity, and has formed the basis of previous prospective studies (ten Duis et al., 1988; Fabian et al., 1990). Accordingly these methods were followed in our study.

These results raise the possibility that transoesophageal echocardiography might be a valuable technique to predict which patients are at greatest risk of developing the fat embolism syndrome following traumatic injuries. Embolic material was often observed during reaming and nailing, and although there were no clinical sequelae in the majority of subjects, three patients with pronounced intraoperative embolism subsequently developed features consistent with the fat embolism syndrome. The presence of large, discrete embolic masses appeared to be particularly predictive. These results are preliminary and require to be confirmed in a larger prospective series, nevertheless they do suggest for the first time the possibility of preclinical diagnosis of the fat embolism syndrome.

It is generally assumed that most cases of post-traumatic fat embolism syndrome are secondary to embolism that has occurred at the time of the original injury, rather than during subsequent surgical procedures. A notable finding in this series was that clinical evidence of the fat embolism syndrome occurred only in those subjects with particularly pronounced intraoperative embolism. No specific factors were identified to predict the degree of intraoperative embolism, but it is possible that transoesophageal echocardiography identifies a high risk group of subjects who have already had major fat embolism at the time of injury and are prone to develop further embolism in response to surgical procedures. These findings do not establish a direct causal role for these emboli in the subsequent development of the fat

embolism syndrome. It is possible that echocardiographically-detected embolism merely serves as a useful marker for the release of other potentially damaging agents released into circulation during bony manipulation, such as tissue thromboplastin, fibrin degradation products, thromboxane, or leukotrienes (Talucci et al., 1983).

Current therapy of the fat embolism syndrome is limited to supportive measures that are instituted following the development of the characteristic clinical features. Research into specific prophylactic measures has been limited by the absence of an accepted method to identify high risk subjects before the syndrome becomes established. These preliminary results suggest that intraoperative transoesophageal echocardiography might identify those subjects at greatest risk before clinical features become apparent, allowing trials of prophylactic therapy to be undertaken. Larger prospective studies are required to determine the precise relationship between intraoperative embolism and the development of the fat embolism syndrome in patients with traumatic long bone injuries.

Fulminating Fat Embolism Syndrome Caused by Paradoxical Embolism Through a Patent Formaen Ovale.

As discussed in the preceding section, most authorities have assumed that the systemic manifestations of the fat embolism syndrome arise when pulmonary fat emboli gain access to the arterial circulation. Sevitt (1962) suggested that emboli crossed the pulmonary vascular bed, either by direct passage through the capillaries, or through precapillary shunts. Few authors have considered the possibility that systemic embolism may arise by other routes, and although Emson (1958) raised the possibility of paradoxical embolism through a patent foramen ovale, he presented no evidence to support this.

A remarkable series of events was recorded by transoesophageal echocardiography during the investigation described in the preceding account. These events are recorded here in greater detail as they allow a unique insight into the nature of fulminating fat embolism, and are the first documented reports of paradoxical embolism of fat through a patent foramen ovale.

Case Report

A 79 year old man was admitted following a fall which resulted in a closed fracture of the right femoral shaft. Physical and radiological findings were otherwise normal. He had a history of myocardial infarction one year earlier, and had made an uncomplicated recovery from an avulsion fracture of the right lesser trochanter two years earlier. Laboratory investigations were normal and the electrocardiogram demonstrated a minor intraventricular conduction defect and no Q waves.

A decision was made to treat the fracture by closed reduction and fixation with an intramedullary nail. The patient received subcutaneous heparin preoperatively and remained well until elective surgery on the 11th day after injury. Anaesthesia was induced with propofol and pancuronium, and following endotracheal intubation the

patient received mechanical ventilation with oxygen, enflurane and nitrous oxide. The electrocardiogram, oxygen saturation (SaO_2) and end-tidal CO_2 levels were monitored continuously and the transoesophageal echocardiography probe was introduced as part of the study protocol.

Immediately prior to surgery the blood pressure was 152/80, the electrocardiogram showed sinus rhythm, the SaO_2 was 98%, and the end-tidal CO_2 was 28.5 mm Hg. Echocardiography revealed normal left ventricular function with no regional wall motion abnormality, trivial mitral incompetence, and an enlarged right atrium and coronary sinus. Moderately severe tricuspid regurgitation was present and pulmonary artery systolic pressure was estimated to be 45 mm Hg using continuous wave Doppler (Chapter 5). There was no evidence of an atrial septal defect, and the fossa ovalis was identified and appeared intact with no displacement during the respiratory cycle. No interatrial shunting was identified with colour flow Doppler. Prior to surgery no abnormal masses or echogenic material were seen within the heart chambers.

Echocardiographic monitoring was performed continuously and recorded on video tape. Several seconds after the insertion of a guide wire into the medullary cavity a shower of small (1-2 mm) echogenic masses appeared within the right atrium and right ventricle. No masses were seen within the left atrium or left ventricle, and there were no changes in monitored physiological parameters. Reaming of the medullary cavity resulted in a large increase in the quantity of echogenic material with complete opacification of the right atrium and the right ventricle (Figure 3.3). Amongst the mass of smaller echoes were numerous highly echogenic bodies, 1 cm in diameter and 1-7 cm long. These masses could be seen coiling within the right atrium, sometimes rebounding from the closed tricuspid valve, and often persisting for several cardiac cycles before passing into the right ventricle and the pulmonary artery (Figure 3.4).

Figure 3.3

Fat Embolism Within the Right Atrium and Right Ventricle During Intramedullary Reaming. Both right heart chambers are completely opacified with embolic material.

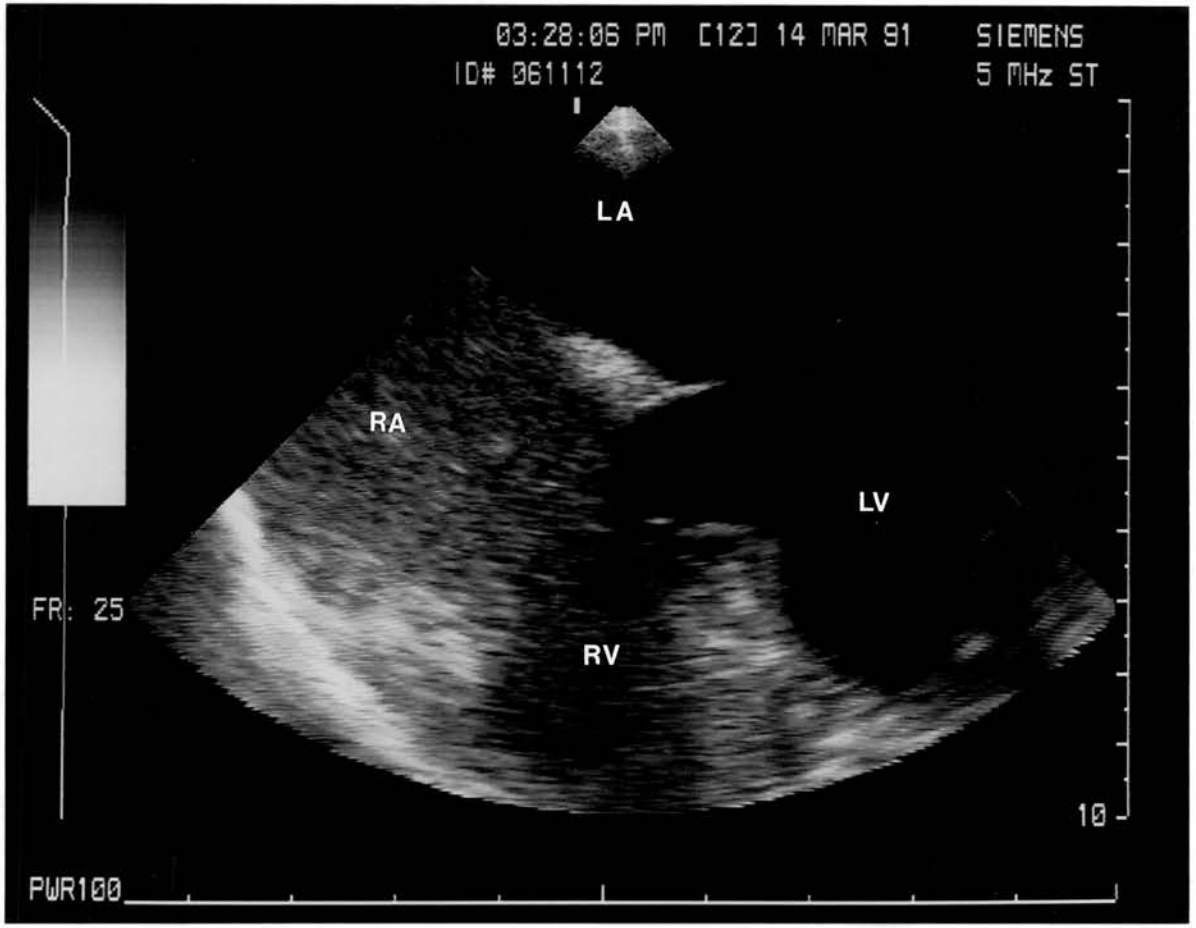
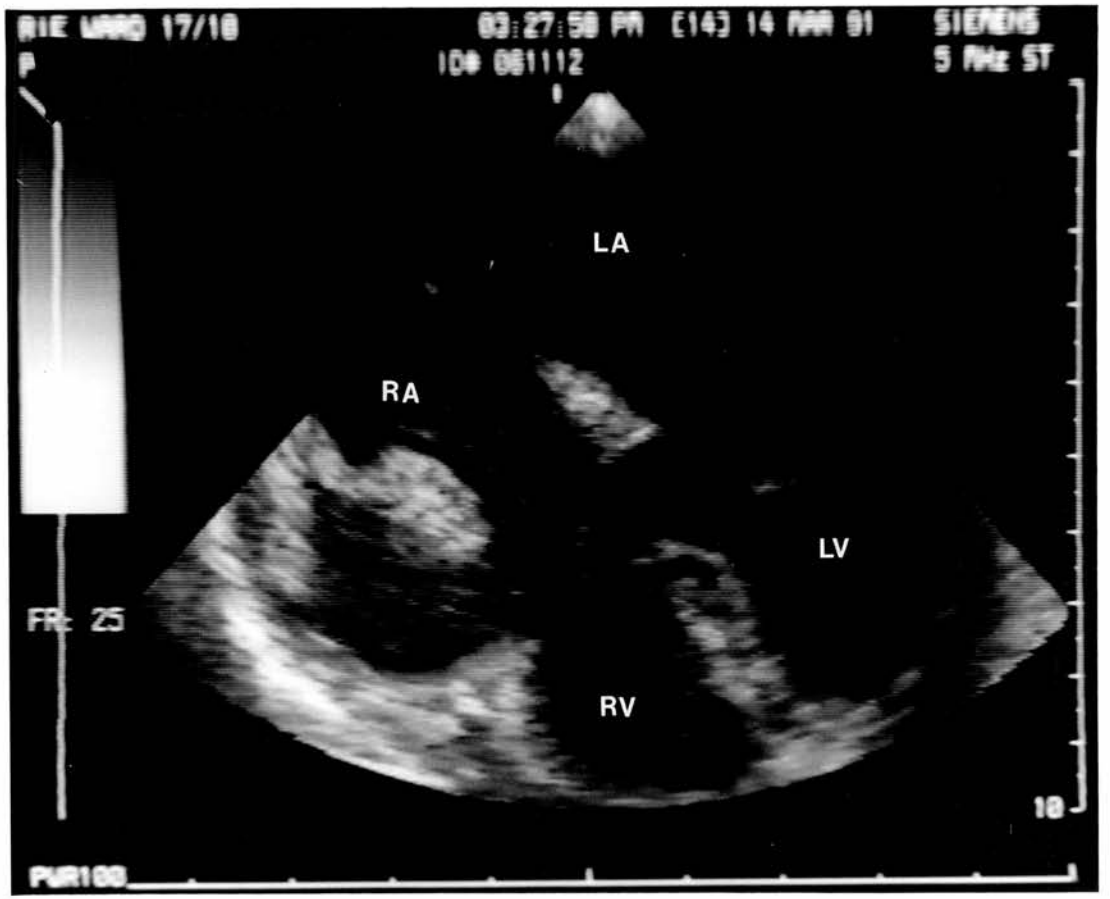


Figure 3.4

Large Fat Embolus Amongst Smaller Echogenic Masses Within the Right Atrium.



Complete opacification of the right heart chambers persisted, and after 60 seconds, the inter-atrial septum was observed to bulge into the left atrium and the flap valve of the fossa ovalis opened with passage of large quantities of embolic material into the left atrium (Figure 3.5). Initially, septal movements occurred in phase with the ventilatory cycle, however after a few minutes the septum became persistently displaced and colour flow mapping confirmed the presence of a right to left shunt across the fossa ovalis. Medullary reaming was halted, but paradoxical embolism continued for a further 20 minutes. Numerous embolic masses of up to 1 cm diameter could be seen passing through the left atrium and ventricle, and into the aorta (Figure 3.6).

During this period the SaO_2 decreased to 75%, the end-tidal CO_2 to 9 mm Hg and the arterial blood pressure to 72/40. Transoesophageal echocardiography demonstrated dyskinesia of the interventricular septum, right ventricular dilatation, severe tricuspid incompetence and the estimated pulmonary artery systolic pressure increased to 80 mm Hg. There was a self-limiting episode of ventricular tachycardia. The patient was resuscitated and the surgery was completed with the insertion of an intramedullary nail. Nailing was also accompanied by large quantities of embolic material appearing within all four cardiac chambers.

The patient was admitted to the Intensive Care Unit and a Swan Ganz catheter was inserted. The pulmonary and the systemic vascular resistances were elevated (785 and 3084 $dyn.s.cm^5$ respectively) and the cardiac index was reduced (1.6 $l.min^{-1}.m^{-2}$). Mechanical ventilation was continued and inotropic drug therapy was commenced for persistent hypotension and oliguria (dobutamine 5-20 $\mu g.kg^{-1}.min^{-1}$ and dopamine 4 $\mu g.kg^{-1}.min^{-1}$). The electrocardiogram revealed non-specific ST segment and T wave changes. Measurement of arterial blood gases during ventilation with 50% oxygen, revealed a pH of 7.39, partial pressure of oxygen of 75 mm Hg, and a partial pressure of carbon dioxide of 31.5 mm Hg. The patient remained comatose and neurological examination revealed lower limb hyperreflexia and bilateral extensor plantar responses. Three hours postoperatively several generalised

Figure 3.5

Transoesophageal Echocardiographic View of the Inter-Atrial Septum.

The fossa ovalis is displaced into the left atrium and the flap valve has opened allowing passage of fat emboli. Echogenic material is seen on both sides of the inter-atrial septum.

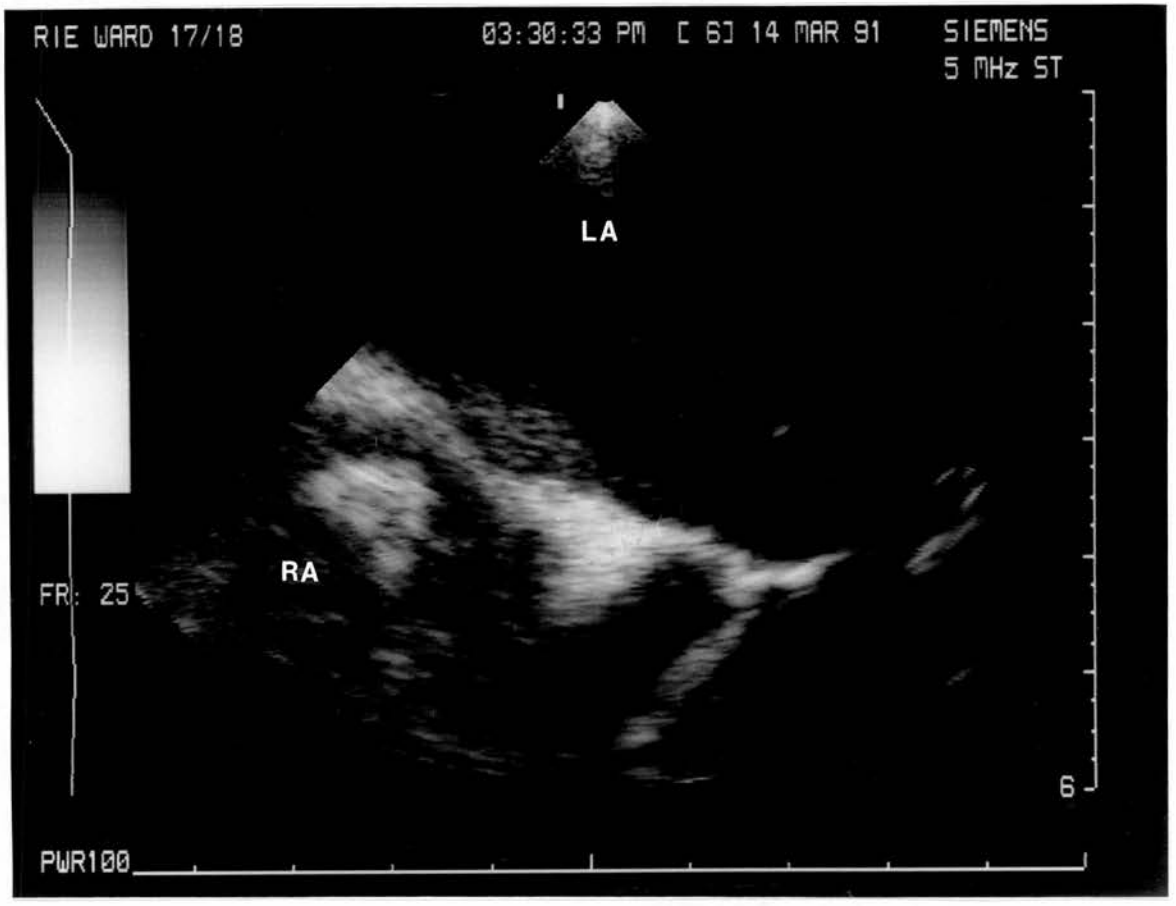
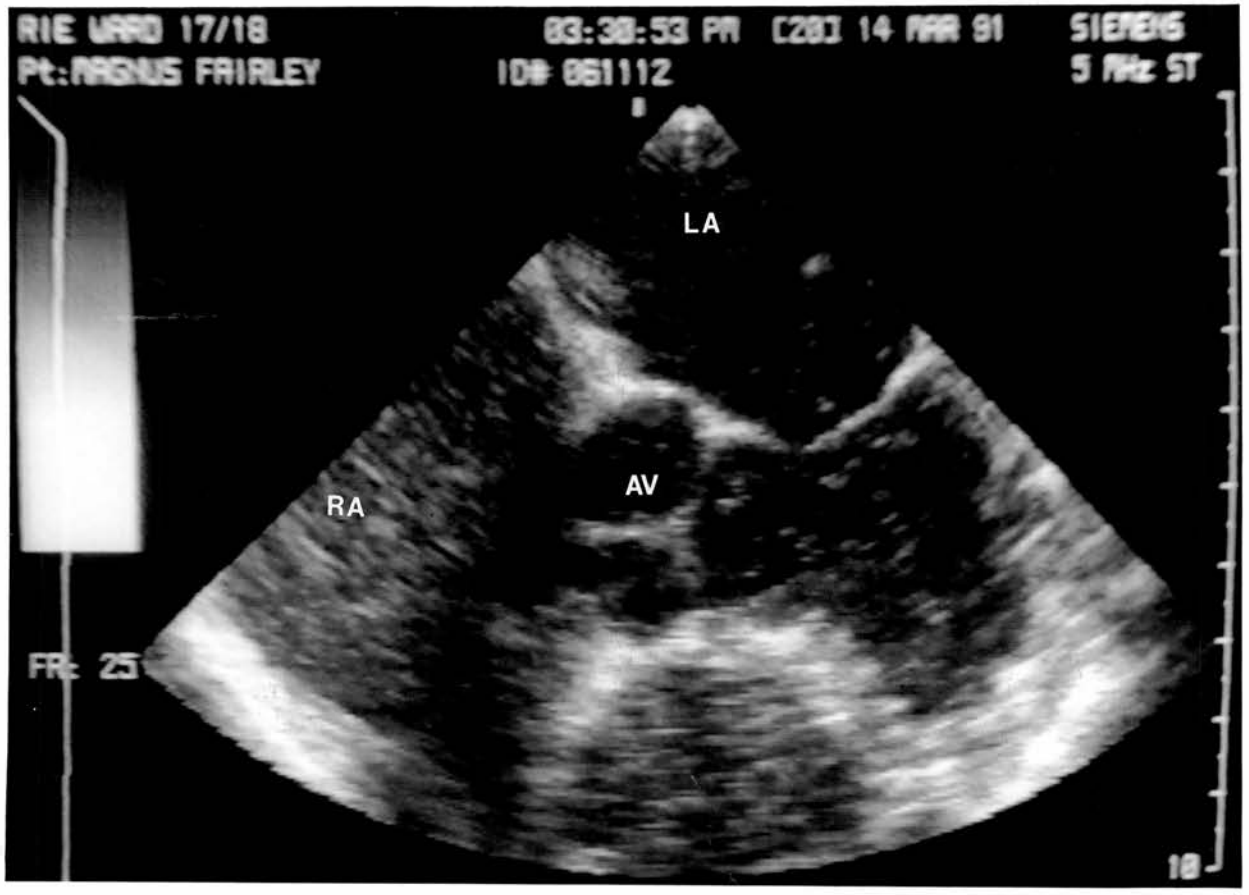


Figure 3.6

Paradoxical Embolism. Large amounts of embolic material can be seen within the left and right heart chambers.



convulsions were treated with phenytoin infusion (loading dose 10 $mg.kg^{-1}$). A right sided subconjunctival hemorrhage and scattered petechial hemorrhages appeared on the trunk and upper arms eighteen hours postoperatively. Progressive arterial hypoxaemia developed (partial pressure of oxygen of 59.5 mm Hg) despite an inspired oxygen concentration of 100% and the chest X-ray demonstrated bilateral pulmonary infiltrates. The cardiac index fell to 1.2 $l.min^{-1}.m^{-2}$ and did not increase in response to increased doses of dobutamine (20-70 $\mu g.kg^{-1}.min^{-1}$). The patient remained oliguric and died of cardiac and respiratory failure 32 hours postoperatively.

Postmortem examination confirmed the diagnosis of fat embolism syndrome. Scattered petechial haemorrhages were found affecting the pericardium, skin and interlobar fissures of both lungs. Histological examination revealed widespread microvascular occlusion by fat emboli, particularly within the lungs, kidney, myocardium and brain, with evidence of infarction in the cerebrum, cerebellum and brain stem (Figures 3.7-3.9). Examination of the heart revealed the presence of a patent foramen ovale, with a maximum aperture width of 0.5 cm. There was dilatation of the tricuspid valve ring consistent with right ventricular failure and there was subendocardial fibrosis compatible with previous myocardial infarction. Bone specimens taken during reaming, and from the fracture site, revealed widespread immature mesenchymal cells within the intertrabecular spaces, consistent with early fracture healing. There was no evidence of deep vein thrombosis or pulmonary thromboembolism.

Conclusions

The spectrum of the fat embolism syndrome includes subclinical, mild and fulminating presentations. This patient developed fulminating fat embolism syndrome fulfilling Gurd's three major diagnostic criteria (Gurd, 1970): a petechial rash, respiratory distress, and cerebral signs (Table 3.1). As in previous patients in this series, the close temporal association between medullary reaming and intracardiac

Figure 3.7

Autopsy Specimen of Lung. (Osmic acid, original magnification x 100).

Pulmonary microvascular occlusion by fat emboli (FE).

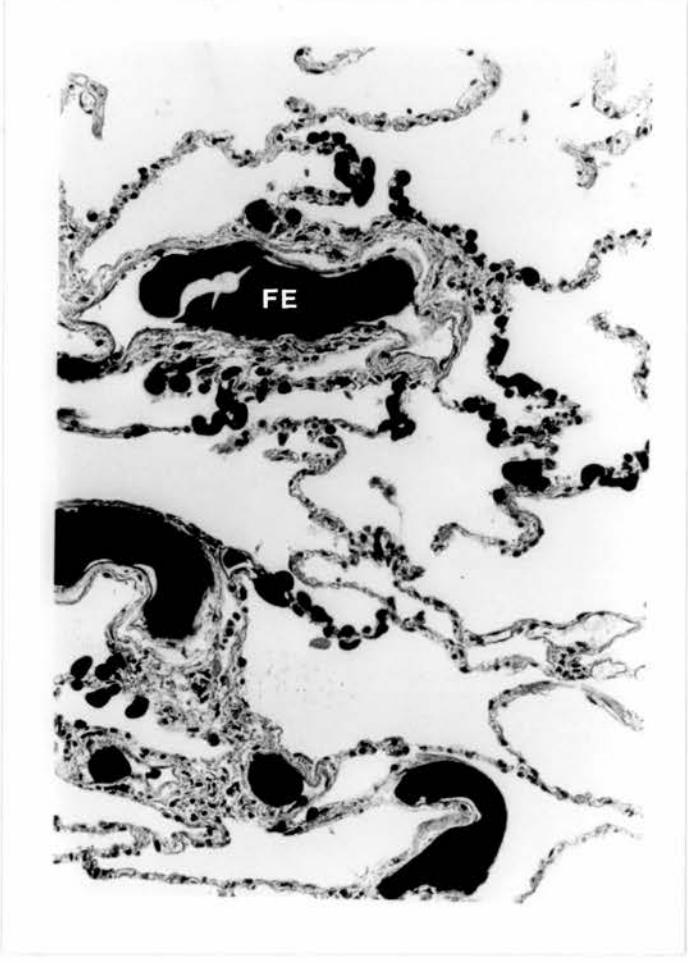


Figure 3.8

Autopsy Specimen of Myocardium. (Osmic acid, original magnification x 400).

Myocardial microvascular occlusion by fat emboli.

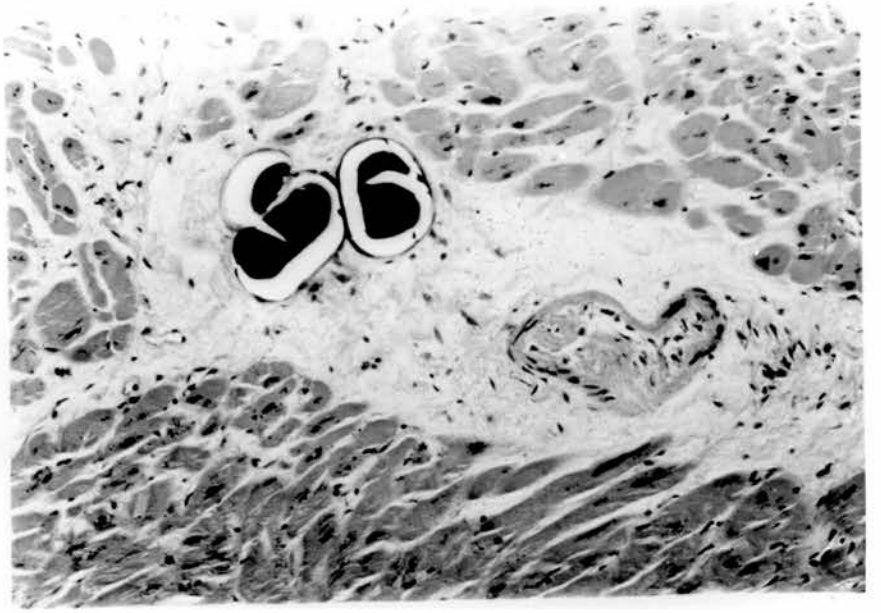
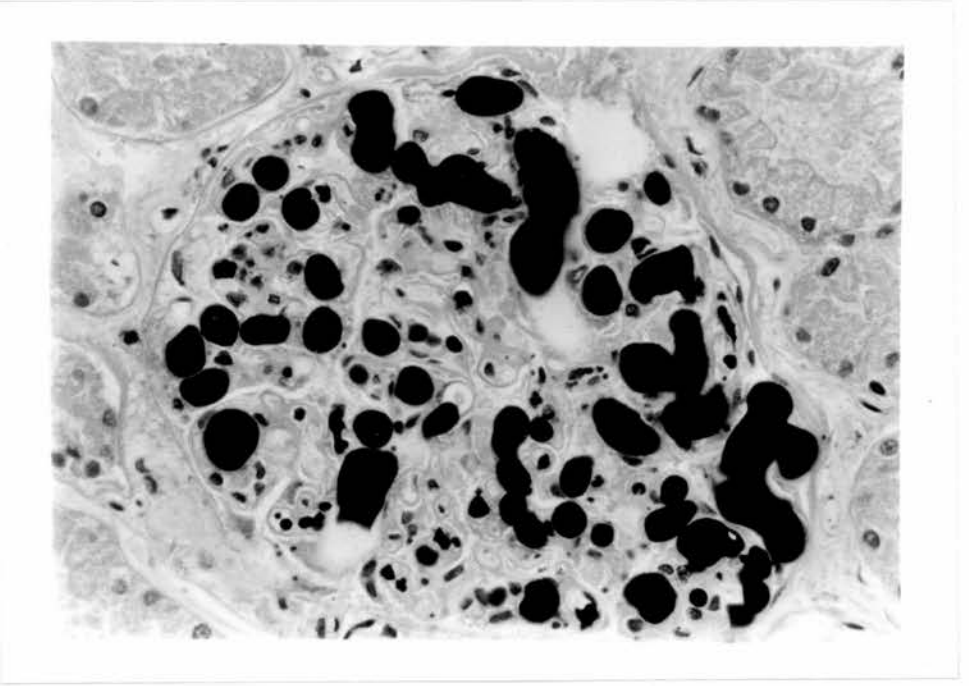


Figure 3.9

Autopsy Specimen of Kidney. (Osmic acid, original magnification x 400).

The renal glomerulus is occluded by fat emboli.



embolism is consistent with the mechanical theory of fat embolism. Although the echogenic masses seen within the heart were not sampled at the moment of embolism, subsequent histological studies demonstrated widespread pulmonary and systemic intravascular fat deposition consistent with fat embolism.

The sequence of events is entirely consistent with Peltier's hypothesis that the fat embolism syndrome is primarily a pulmonary disease caused by widespread microvascular occlusion that results in increased pulmonary vascular resistance (Peltier, 1988). Transoesophageal echocardiography demonstrated severe and prolonged fat embolism that resulted in increases in pulmonary artery pressure and pulmonary vascular resistance. Acute cor pulmonale developed with right ventricular dilatation and severe tricuspid incompetence. Although similar events have been assumed in patients developing fulminating fat embolism (Mayron et al., 1985; van Miert et al., 1991; Marshall et al., 1991; Reid and Hill, 1992; Green, 1992) this case is unique in that fat was visualised at the moment of embolism and the opportunity to witness the deterioration of cardiac function has never occurred previously.

The delayed appearance of a petechial rash, neurological dysfunction and the development of progressive pulmonary dysfunction are also characteristic of the fat embolism syndrome and are entirely consistent with the theory of a secondary phase of tissue damage, possibly due to the toxicity of free fatty acids liberated by the hydrolysis of fat emboli in the lungs (Peltier, 1956; Fonte and Hausberger, 1971).

Paradoxical embolism of air and thrombus across a PFO is well recognised. Passage of fat has not been reported previously and represents an alternative mechanism to transpulmonary shunting that might be responsible for the systemic manifestations of the fat embolism syndrome. Shunting across a PFO can occur during coughing, following the release phase of the Valsalva manoeuvre, and during mechanical ventilation, (Leonard et al., 1982; Lemaire et al., 1982; Langholz et al., 1991) and paradoxical embolism has occurred in pulmonary thromboembolism, chronic lung

disease, and right ventricular failure (Lang et al., 1988; Nagelhout et al., 1991). In this patient, passage of fat across the PFO may have been precipitated by increased right atrial pressure secondary to acute cor pulmonale. The fact that fat is readily deformable accounts for the passage of masses larger than the diameter of the PFO (Sevitt, 1962). The observation of phasic displacement of the fossa ovalis with the ventilatory cycle suggests that the use of mechanical ventilation may have contributed to this process by cyclic increases in right atrial pressure. The foramen ovale is patent in 20-34% of individuals, (Hagan et al., 1984) and the possibility that this route might be a significant factor in the pathogenesis of the systemic manifestations of the fat embolism syndrome was considered by Emson (1958) and Sevitt (1962). In Emson's study, none of 24 subjects with systemic fat embolism had evidence of an atrial septal defect at autopsy, however it is not clear whether probe patency of the foramen ovale was excluded. A more recent transoesophageal echocardiographic study revealed a minor right to left shunt through a PFO in only 1 of 6 subjects who had recovered from post-traumatic fat embolism syndrome (Nijsten et al., 1989). However, these authors did not perform contrast echocardiography, which is suggested to be obligatory to exclude the presence of a PFO (Konstadt et al., 1991).

Increasingly transoesophageal echocardiography is used to monitor perioperative cardiac function in high risk patients. In these studies echocardiographically-detectable fat embolism was observed in 40% of patients undergoing major orthopaedic procedures. At present routine echocardiographic monitoring cannot be recommended, however future research may provide guidelines for the use of transoesophageal echocardiography and for terminating procedures if evidence of marked embolisation is found. Further research is required to determine the significance of patency of the foramen ovale in patients developing the fat embolism syndrome following traumatic injury.

CHAPTER 4

INTRAOPERATIVE TRANSOESOPHAGEAL ECHOCARDIOGRAPHY II: DETECTION OF PERIOPERATIVE MYOCARDIAL ISCHAEMIA AND ASSESSMENT OF GLOBAL LEFT VENTRICULAR PERFORMANCE

Introduction

Despite advances in surgical techniques, ventricular dysfunction is occasionally observed in the early postoperative period following coronary artery bypass surgery (CABG). The various factors that result in this impairment of cardiac function have not been fully characterised. Perioperative myocardial infarction is a well recognised cause of irreversible ventricular dysfunction following cardiopulmonary bypass (CPB) (Force et al., 1990). However, recent authors have also promoted the concept of left ventricular "stunning", a global impairment of left ventricular function occurring in the early postoperative period that may have the potential to recover (Braunwald and Kloner, 1982).

It is not certain whether these processes are distinct pathophysiological entities, or simply represent different ends of the same spectrum. Various authors have discussed the difficulties involved in the diagnosis of perioperative myocardial infarction. The presence of a persistent new Q wave on the electrocardiogram is generally accepted to be a specific, but not a sensitive indicator of myocardial infarction (Force et al., 1985). Cardiac enzyme release invariably occurs after CPB, however high postoperative concentrations of CK-MB have been correlated with histological evidence of infarction (Van Lente et al., 1989), and cardiac enzyme release has been used to estimate the incidence of non-Q wave infarction (Force et al., 1985). Depending on the diagnostic criteria adopted, the incidence of perioperative infarction varies between 1.5 - 23% (Val et al., 1983; Hannan et al., 1990). It is generally accepted that perioperative infarction results in increased in-hospital

mortality and may also represent an adverse prognostic factor following discharge (Chaitman et al., 1983; Force et al., 1990).

The pathophysiology of perioperative myocardial infarction in patients undergoing CABG is complex. Inadequate myocardial protection during cardiac arrest whilst on CPB is an important factor. Histologically this is characterised by the presence of a contraction band, suggesting reperfusion of ischaemic myocardium (Bulkley and Hutchins, 1977). Use of cold potassium cardioplegia has diminished the incidence of this type of infarction (Force et al., 1985), however myocardial function may be compromised following a period of ischaemia despite successful restoration of coronary blood flow (Braunwald and Kloner, 1982). The mechanisms responsible for this myocardial stunning are uncertain, but may involve a continuation of destructive processes initiated during ischaemia, depletion of high energy phosphates, or reperfusion injury, possibly involving oxygen-free radicals and activated leukocytes. Myocardial stunning has been demonstrated in various animal models (Braunwald and Kloner, 1982) and although its significance is more difficult to demonstrate in the clinical setting, case reports have indicated that it may be an important clinical phenomenon (Ballantyne et al., 1987).

Various strategies have been examined in an attempt to minimise cardiac dysfunction following a period of myocardial ischaemia. These include novel approaches to myocardial protection during CPB, for example intermittent aortic cross-clamping, warm blood cardioplegia and retrograde coronary sinus perfusion (Reduto et al., 1981; Rosenkranz et al., 1983; Bhayana et al., 1989). A novel approach involves the use of AICA riboside (5-amino-4-imidazole carboxamide), a purine nucleoside analogue which has a protective action in a variety of animal models promoting improved recovery of post-ischaemic contractile function (Gruber et al., 1989).

In isolated Langendorf-perfused hearts subjected to 45 minutes of ischaemia followed by reperfusion, AICA riboside improves the recovery of left ventricular developed pressure (Bullough et al., 1990). In vivo, similar protective actions have been found

in various animal models including coronary occlusion with reperfusion (McAllister et al., 1987; Gruber et al., 1989; Hori et al., 1990), coronary embolisation (Takashima et al., 1990), pacing-induced myocardial ischaemia (Young and Mullane, 1991) and experimental cardiopulmonary bypass (Bolling et al., 1992). Possible beneficial actions of AICA riboside include suppression of neutrophil activation, augmentation of blood flow in ischaemic myocardium, suppression of arrhythmogenesis and reduction in infarct size (Gruber et al., 1989). The precise mechanism through which AICA riboside exerts its protective actions is uncertain. A direct action appears to be unlikely, and it is hypothesised that the benefits may be mediated through increased production of adenosine from ischaemic tissue (Gruber et al., 1989). Adenosine possesses both antioxidant and anti-ischaemic properties, and is thought to play a central role in ischaemic preconditioning (Liu et al., 1991).[1]

Acadesine is the generic formulation of AICA riboside, manufactured by Gensia Pharmaceuticals (Gensia Europe Ltd., Bracknell, United Kingdom). To date, trials with this agent have shown it to be well tolerated and free from major adverse effects. Preliminary experience in patients undergoing CABG has demonstrated that acadesine treatment is associated with a trend towards a lower incidence of perioperative myocardial infarction (Leung et al., 1992). In the following account I describe the use of transoesophageal echocardiography as one of the modalities used to assess the possible cardioprotective properties of acadesine in patients undergoing CABG.

Intraoperative Monitoring Using Transoesophageal Echocardiography

It is well recognised that myocardial ischaemia results in the development of characteristic abnormalities in myocardial wall motion. The realisation that these

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[1]Ischaemic preconditioning is the phenomenon in which a short period of ischaemia, followed by reperfusion, triggers adaptive changes that protect the myocardium from the effects of a subsequent, prolonged period of ischaemia (Murry et al., 1986).

regional wall motion abnormalities (RWMAs) could be identified using echocardiography was partly responsible for the development of transoesophageal echocardiography in the United States, where its potential role in intraoperative monitoring was recognised by the anaesthetic community (Kremer et al., 1982). Since this first report was published, numerous studies have appeared describing the use of intraoperative transoesophageal echocardiography to monitor cardiac function. Its precise role continues to evolve, but many authorities believe that transoesophageal echocardiography is the most sensitive method of monitoring for myocardial ischaemia in high risk patients undergoing major cardiac and non-cardiac surgical procedures (Smith et al., 1985; Leung et al., 1989; Van Daele et al., 1990). In contrast to its role in monitoring regional myocardial function, transoesophageal echocardiographic assessment of global left ventricular performance has not been investigated extensively. This is a difficult area to study in the intraoperative setting, nevertheless some authors have suggested that transoesophageal echocardiography might find a useful role (Matsumoto et al., 1980; Clements et al., 1990).

Assessment of Regional Left Ventricular Function

In 1935 Tennant and Wiggers described how interruption of the regional arterial supply resulted in the development of characteristic myocardial wall motion abnormalities (Tennant & Wiggers, 1935). In animals a RWMA develops within seconds of the onset of ischaemia, and is accompanied by a rise in regional lactate production (Waters et al., 1977). That identical processes occur in humans was established following the development of percutaneous transluminal coronary angioplasty. Regional wall motion abnormalities develop within 20 seconds of balloon inflation and precede electrocardiographic changes (Hauser et al., 1985; Wohlgerlernter et al., 1986). Increasing ischaemia results in a characteristic sequential decline in regional systolic function with the development of segmental hypokinesia, progressing through akinesia, and finally to dyskinesia. These changes are accompanied by a reduction in myocardial wall thickening, and systolic thinning may occur with severe myocardial ischaemia.

Recognition of the limitations of the electrocardiogram (ECG) in the detection of myocardial ischaemia intraoperatively led to exploration of alternative approaches to patient monitoring. Two-dimensional transthoracic echocardiography detected RWMAs reliably, but was impractical during most major surgical procedures. In contrast, transoesophageal echocardiography gave safe, reproducible images of the left ventricle in anaesthetised patients. The first report of the use of transoesophageal echocardiography for the diagnosis of perioperative myocardial infarction was published in 1984 when a new anteroseptal RWMA was detected in a patient following CPB (Beaupre et al., 1984). A variety of studies have appeared since in which transoesophageal echocardiography has been utilised to detect myocardial ischaemia and predict the development of perioperative infarction in patients undergoing both cardiac and non-cardiac surgery.

In the first major study, Smith et al. (1985) studied 50 subjects undergoing CABG or major vascular surgery. New RWMAs were detected in 24 subjects, whilst only six subjects exhibited ischaemic changes in the ECG. Where ECG changes developed, these were always associated with the development of a new RWMA, and persistent RWMAs developed in all three subjects who sustained a perioperative myocardial infarction. It was concluded that:

"...transesophageal echocardiography seems superior to the ECG for the detection of intraoperative myocardial ischaemia and should allow earlier identification of patients at higher risk of postoperative cardiovascular complications."

In a similar study, Leung et al. (1989) reported that 44% of patients undergoing CABG developed a new RWMA perioperatively. Only 18% of echocardiographic ischaemic episodes were accompanied by simultaneous ECG changes, whilst 67% of ECG ischaemic episodes were accompanied by a RWMA. These authors' conclusion that transoesophageal echocardiography was superior to the ECG for perioperative monitoring was also supported by van Daele et al. (1990). In this study, transoesophageal echocardiography was found to be more sensitive than either

the ECG, or measurement of changes in pulmonary capillary wedge pressure, for the detection of myocardial ischaemia in patients undergoing CABG.

The incidence and natural history of new RWMAs have been explored in a variety of cardiac and non-cardiac surgical settings. In Leung's study of patients undergoing CABG, although transient perioperative RWMAs occurred in 44% of patients, only those that occurred after CPB appeared to have prognostic importance (Leung et al., 1989). In this study, six out of 18 patients developing a RWMA post-CPB had an adverse cardiac outcome, compared to only one out of 10 patients who developed a RWMA before CPB. The absence of a new RWMA post-CPB was associated with a favourable prognosis. There has been less research into the implications of the development of RWMAs in patients undergoing non-cardiac surgery. However in one study, although new RWMAs were observed in 20% of high risk patients, these episodes were rarely associated with postoperative cardiac complications (London et al., 1990).

Transoesophageal echocardiography has been used as a research tool in several studies investigating perioperative changes in regional left ventricular function. The effects of different anaesthetic regimens on the incidence of perioperative myocardial ischaemia has been studied (Mitchell et al., 1989). It has also been used to detect improvement in the function of "hibernating" myocardium following revascularisation (Topol et al., 1984; Lazar et al., 1989). Considerable debate has concerned selection of the most appropriate methodology for analysis of echocardiographic images. Computer-assisted quantitative analysis has been utilised by several groups to calculate a variety of measurements including systolic wall thickening and regional fractional area change (Topol et al., 1984; Stanley et al., 1988). However the validity of these quantitative methods has been questioned and Leung et al. (1989) have suggested that these techniques are limited by inherent difficulties including asynchrony of regional wall motion during systole, poor epicardial definition and uncertainty regarding the frame of reference caused by rotation and translation of the heart during systole. Semi-quantitative analysis, in

which subjective assessment of regional wall motion is made at specified intervals by an experienced observer, has been favoured by other groups (Smith et al., 1985; Leung et al., 1990; van Daele et al., 1990). At present the controversy regarding the use of either quantitative or semi-quantitative techniques remains unresolved.

Assessment of Global Left Ventricular Performance

As was indicated above, although post-ischaemic global myocardial dysfunction has been demonstrated in a variety of experimental models, it is a difficult topic to investigate in the clinical setting. Conventionally, the "pumping" performance of the heart depends on the loading conditions (preload and afterload), the heart rate, and myocardial contractility (Braunwald, 1992). These are difficult to control in individual subjects, particularly following CPB when physiological conditions may change rapidly. Despite these difficulties, global myocardial function has been studied in patients undergoing CABG and various attempts have been made to compare the relative benefits of different methods of myocardial protection (Reduto et al., 1981; Bhayana et al., 1989).

A variety of haemodynamic measurements can be made that may allow investigators to make inferences about left ventricular function in patients following CPB. Perhaps the simplest measure of myocardial performance is the cardiac index. A fall in cardiac index, without a change in loading conditions, has been taken by some authors as evidence of depressed cardiac contractility (Gray et al., 1979; Roberts et al., 1980 & 1981). However this has not been a universal finding, and some investigators have reported no change in cardiac index after CPB (Reduto et al., 1981; Bhayana et al., 1989). The left ventricular stroke work index (LVSWI) reflects both volume production and pressure generation by the heart, and a fall has sometimes been cited as evidence of impaired contractility following CPB (Gray et al., 1979; Roberts et al., 1980 & 1981; Mangano, 1985; Bhayana et al., 1989). Cardiac output can be measured under different loading conditions and ventricular function curves (Starling curves) constructed for individual patients. These curves

have shown significant depression of cardiac function in the first 24 hours following CPB (Gray et al., 1979; Mangano, 1985).

Several groups have used radionuclide ventriculography to measure serial changes in left ventricular ejection fraction in patients undergoing CABG. No consistent pattern has emerged from these studies. A transient reduction in ejection fraction in the first 24 hours after surgery has been reported, and some authors suggest that this is secondary to impaired myocardial contractility (Gray et al., 1979; Roberts et al., 1980 & 1981; Philips et al., 1983). In contrast, other groups have found that the ejection fraction is increased over the same period (Ellis et al., 1979), whilst Lawrie et al. (1979) and Reduto et al. (1981) reported that the ejection fraction increased in some patients, and fell in others.

Fewer studies have utilised echocardiography to assess changes in global left ventricular performance following CPB. Ren et al. (1985) used epicardial echocardiography in subjects undergoing CABG, and calculated left ventricular volumes using the biplane Simpson's rule. The global ejection fraction was usually unchanged, but fell in subjects who sustained a perioperative myocardial infarction. The main limitation of epicardial echocardiography is that it can only be performed prior to sternal closure. In contrast, transoesophageal echocardiography can be performed continuously, and might allow left ventricular performance to be assessed into the immediate postoperative period.

To date, transoesophageal echocardiography has not been widely used to assess global left ventricular performance. Its main limitation is that a true long axis image of the left ventricle cannot usually be achieved from the oesophagus preventing calculation of end-diastolic and end-systolic volumes. Hence the global ejection fraction cannot be derived. However, Dubroff et al. (1983) utilised epicardial echocardiography to measure the fractional area change in the short-axis of the left ventricle in patients undergoing CABG. This measurement was used as an index of the global ejection fraction and would be feasible with transoesophageal

echocardiography. Support for this approach comes from experimental observations in which 87% of the stroke volume was found to result from shortening in the short-axis of the ventricle (Rankin et al., 1976). Furthermore, in an intraoperative study close correlation was shown between the short-axis fractional area change calculated by transoesophageal echocardiography and the global ejection fraction measured by radionuclide angiography (Clements et al., 1990).

The major limitation of using the global ejection fraction, or a surrogate measure such as the fractional area change, as an index of overall left ventricular performance is that these measurements are partly determined by cardiac loading conditions. Accordingly, unless myocardial loading conditions are held constant, it may not be possible to determine whether an observed change is secondary to an alteration in myocardial contractility. Gauss et al. (1991) used transoesophageal echocardiography to investigate the possible cardiodepressant properties of different anaesthetic agents. These authors suggested that the end-systolic quotient (systolic pressure/end-systolic diameter) was a relatively load-independent measure of inotropy. However, this measurement is not completely independent of loading conditions and the authors acknowledged that it will vary in response to changes in afterload. At present, no echocardiographic measurement that is totally independent of loading conditions has been identified that can be applied readily to intraoperative transoesophageal echocardiography. Nevertheless, previous studies have suggested that if cardiac loading conditions are considered, then the ejection fraction can be used to gain some insight into left ventricular contractility (Gray et al., 1979; Roberts et al., 1980 & 1981).

In the following account I describe the use of transoesophageal echocardiography as a research tool in a study investigating the possible cardioprotective properties of acadesine. The primary aim of this study was to determine whether acadesine treatment resulted in a lower incidence of perioperative myocardial ischaemia and/or infarction, as determined by a combination of echocardiography, ECG and enzymatic criteria. A secondary aim was to test the hypothesis that acadesine treatment would

diminish the extent of myocardial stunning following CPB. Global left ventricular performance was assessed perioperatively using both conventional haemodynamic indices, and transoesophageal echocardiography to measure the fractional area change at serial time points.

Study of the Cardioprotective Effects of Acadesine During Coronary Artery Bypass Surgery

Methods

This was a double-blind randomised controlled study that ran independently, but in parallel with a multicentre trial sponsored by Gensia Europe Ltd.: "Study of the effects of acadesine on cardiac clinical outcomes in patients undergoing coronary artery bypass grafting". This trial was conducted at 27 hospitals in Belgium, Canada, France, Germany, Norway, Sweden, the Netherlands and the United Kingdom. Patients recruited to this trial in the Royal Infirmary, Edinburgh were invited to undergo perioperative transoesophageal echocardiography. Transoesophageal echocardiography was not performed in the other centres, but in all other respects the protocol followed was identical to that followed in the other centres. The data generated from Edinburgh was included in the final multicentre analysis.

The inclusion and exclusion criteria are shown in Table 4.1. The following drugs could not be administered for up to 48 hours before, and 48 hours after infusion of acadesine: intravenous calcium channel antagonists, adenosine, methyl xanthines, dipyridamole, alcohol, and fluorinated inhalational anaesthetic agents. Tea, coffee and smoking were prohibited for 12 hours prior to surgery, and for 48 hours thereafter.

In each case the surgeon was Mr Ciro Campanella, Senior Lecturer and the anaesthetist was Dr Colin Sinclair, Consultant Anaesthetist. Surgical and anaesthetic techniques were standardised using standard techniques including multi-dose cold crystalloid potassium cardioplegia and moderate systemic hypothermia. Premedication consisted of lorazepam and morphine, and anaesthesia consisted of alfentanyl with muscle relaxation provided by pancuronium. All patients had pulmonary artery balloon floatation catheters and radial arterial lines inserted for haemodynamic monitoring.

Table 4.1 Study of the Cardioprotective Effects of Acadesine During Coronary Artery Bypass Surgery: Entry Criteria.

Inclusion Criteria
At least 50% stenosis of the left main coronary artery or 70% of two or more major coronary arteries.
Exclusion Criteria
Haemodynamically significant valve disease.
Acute myocardial infarction within one week of surgery.
History of uric acid nephropathy.
Renal insufficiency (creatinine >248 μmol/l).
Hepatic dysfunction (AST or ALT $>$ 120 μ/l).

AST: Aspartate transaminase; ALT: Alanine transaminase

Patients were randomised to receive treatment with either acadesine (Gensia Pharmaceuticals Ltd.) or placebo. Subjects randomised to active treatment received a perioperative infusion of acadesine (0.1 mg/kg/min made up in 0.9% saline) and acadesine was also added to the cardioplegia solution (5 μg/ml). The infusion was commenced 15 minutes prior to induction of anaesthesia, and continued over seven hours to a total volume of 770 ml. Control subjects received an infusion of 770 ml of 0.9% saline over the same period, and sterile water was added to the cardioplegia solution. Both acadesine and placebo solutions were supplied in unlabelled containers having been prepared by pharmacy department technicians.

The transoesophageal echocardiography probe was inserted immediately after induction of anaesthesia, and positioned in the gastric fundus so that the left ventricle was imaged in short-axis at mid-papillary muscle level. All studies were recorded on VHS video tape for subsequent analysis. A continuous recording was made until CPB was initiated. Recordings were resumed immediately on weaning from CPB and continued in the operating room until the patient was transferred to the intensive care area (ICU). In the ICU, a five minute recording of left ventricular function was made every 30 minutes until six hours had elapsed after weaning from CPB.

Haemodynamic measurements included mean arterial blood pressure (MAP), heart rate (HR), right atrial pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and cardiac output. The cardiac index (CI), systemic vascular resistance (SVR) and left ventricular stroke work index (LVSWI) were derived (Appendix). Cardiac output was determined by thermodilution as described in Chapter 5. Two sets of haemodynamic measurements were made prior to CPB: after induction of anaesthesia (baseline) and immediately prior to sternotomy. Additional haemodynamic measurements were made at the following times after CPB: 15 minutes, 30 minutes, 90 minutes, 120 minutes, 150 minutes, 240 minutes, 480 minutes, 720 minutes and 1440 minutes. Use of intra-aortic balloon counterpulsation, inotropic drugs and pacemakers was at the discretion of the surgeon or anaesthetist.

An ECG was recorded preoperatively, immediately on arrival in the ICU, and on successive days until discharge from hospital. Venous blood samples were taken for analysis of creatinine kinase isoenzyme (CK-MB) concentration preoperatively and at the following times after CPB: 1 hour, 4 hours, 8 hours, 12 hours, 16 hours, 20 hours, 24 hours, 28 hours, 32 hours, 36 hours, 42 hours, 48 hours, and 60 hours. Measurement of CK-MB concentration was performed using the Hybritech immunoassay technique by Dr David Holt, St George's Hospital, London.

Analysis.

All analysis was performed by myself without knowledge of the subjects' randomisation status. The randomisation code was broken only after all analysis had been completed.

Regional Myocardial Function: the echocardiographic recordings were analysed off-line using the methodology described by Leung et al. (1989). The left ventricle was divided into the following four segments: posterior, lateral, anterior, and septal using the papillary muscles as internal landmarks. Regional wall motion in each segment was graded as follows:

0 = normal (radial shortening $>30\%$ with obvious myocardial wall thickening)
1 = mild hypokinesis (radial shortening 10-30%)
2 = severe hypokinesis (radial shortening $<10\%$)
3 = akinesis
4 = dyskinesis

A RWMA was deemed to have developed when the wall motion of any segment worsened by two or more grades and lasted for more than 1 minute. During the intraoperative period regional wall motion was assessed every 5 minutes. Following transfer to the ICU, regional wall motion was assessed every 30 minutes until six hours had elapsed from the end of CPB. Recordings were accepted for analysis where they met the following conditions:

1. The short-axis view of the left ventricle at mid-papillary muscle was recorded at baseline and subsequent recordings accepted only if taken at the same level.
2. Only sinus beats that were preceded by a sinus beat were accepted. Ventricular paced rhythm was accepted provided that at least 80% of the endocardial and epicardial perimeters were visualised allowing analysis of myocardial wall thickening.

Global Myocardial Function: the fractional area change (area ejection fraction: AEF) of the left ventricular short-axis view at mid-papillary muscle level was calculated before sternotomy and at the following times after CPB: 15 minutes, 30 minutes, 120 minutes and 240 minutes (Appendix). Left ventricular endocardial outlines were traced using the tracker-ball and intrinsic software of the echocardiographic machine. Measurements were made at end-diastole and end-systole, defined as the peak of the corresponding R wave on the electrocardiogram, and the smallest left ventricular cavity area respectively. Leading edge to leading edge measurements were used throughout.

Perioperative myocardial infarction was diagnosed when one of the following criteria was met (Chapelle et al., 1986):
1. ECG: Presence of new Q waves on ECG and/or typical ST elevation persisting for more than one hour.
2. Elevation of CK-MB concentrations to $\geq$ 100ng/ml any time postoperatively, or to $\geq$ 70ng/ml more than 12 hours postoperatively, and with the preceding, or following CK-MB sample value $\geq$ 50% of this peak value.

Statistical analysis was performed by applying χ^2 test, t test, or Mann-Whitney test as appropriate (Kirkwood, 1988).

Results

A total of 41 patients was recruited. Nineteen were randomised to receive active treatment and 22 to placebo. The two groups were well matched with respect to age, sex, extent of coronary artery disease, previous myocardial infarction, preoperative left ventricular function, cardioactive medication, baseline haemodynamic measurements, aortic crossclamp time, total duration of cardiopulmonary bypass and number of vessels grafted (Tables 4.2 & 4.3). The transoesophageal echocardiography probe was successfully inserted in 40 of the 41 patients.

Morbidity and Mortality: there were no deaths in either group, nor were there any differences in the need for postoperative inotropic support or use of intra-aortic balloon counterpulsation (Table 4.4). There was a trend towards a lower rate of pacemaker use in the acadesine group but this was not statistically significant. Perioperative myocardial infarction was diagnosed in nine patients. There was a trend towards a lower incidence of myocardial infarction in the acadesine group, however the numbers are small and do not reach statistical significance.

Regional Myocardial Function: the baseline echocardiogram demonstrated normal systolic function in all four quadrants in 25 subjects prior to sternotomy. Fifteen subjects had at least one quadrant exhibiting a RWMA on the baseline recording: six with regions of akinesia and nine with regions of mild or severe hypokinesia. There was no difference between the acadesine and control groups in the prevalence of RWMAs at baseline. New RWMAs (Figure 4.1) developed perioperatively in 6 (29%) control subjects and 4 (21%) acadesine-treated subjects (Table 4.4). These differences did not reach statistical significance.

Global Myocardial Function: although the mean AEFs were increased immediately after CPB in both the acadesine and control groups, these increases did not reach statistical significance and no differences were observed at the other time points compared to baseline values (Figure 4.2). There were no differences between the

Table 4.2 Acadesine Study: Demographic Details.

Variable	**Control** (n=22)	**Acadesine**[1] (n=19)
Males	19 (86%)	17 (89%)
Females	3 (13.6%)	2 (10.5%)
Mean Age	62y (50-72y)	63y (47-73y)
Previous MI	13 (59%)	9 (47%)
Heart Failure	1 (4.5%)	3 (16%)
Unstable Angina	2 (9%)	0
Good LV Function	20 (91%)	16 (84%)
Impaired LV Function[2]	2 (9%)	3 (16%)
Previous CABG	0	1 (5%)
Two Vessel CAD	6 (27%)	5 (26%)
Three Vessel CAD[3]	16 (73%)	14 (74%)
Beta-blocker Treatment	20 (91%)	14 (74%)
Calcium Antagonist Treatment	19 (86%)	14 (74%)
Long Acting Nitrate Treatment	22 (100%)	19 (100%)
Mean Number of Vessels Grafted (S.E.)	2.5 (0.2)	2.7 (0.2)
Mean Cross-clamp Time (mins ± S.E)	44.3 (3.4)	48.2 (4.0)
Mean Bypass Time (mins ± S.E.)	82.5 (5.3)	94.2 (6.9)

MI: Myocardial infarction; CAD: Coronary artery disease; LV: Left ventricular

[1]No significant differences between control and acadesine groups for all variables.
[2]Ejection fraction <30%
[3]Includes left main stem disease.

Table 4.3 Baseline Echocardiographic and Haemodynamic Measurements.

Variable	**Control** (n=22)	**Acadesine**[1] (n-19)
Patients with Pre-existing RWMA	8 (38%)[2]	7 (37%)
Area Ejection Fraction (%)	48.6 (2.9)	47.2 (3.6)
Cardiac Index ($l.min^{-1}.min^{-2}$)	2.6 (0.1)	2.6 (0.2)
Heart Rate (bpm)	56.4 (1.8)	61.5 (2.7)
Mean Arterial Pressure (mmHg)	72.6 (2.0)	76.9 (3.3)
Right Atrial Pressure (mmHg)	6.7 (0.5)	6.3 (0.6)
Pulmonary Capillary Wedge Pressure (mmHg)	10.0 (0.7)	8.8 (0.6)
Left Ventricular Stroke Work Index ($gm.m^{-1}.m^{-2}$)	39.6 (1.9)	40.1 (2.7)
Systemic Vascular Resistance ($dynes.sec^{-1}.cm^{-5}$)	1096 (53)	1120 (75)

All values mean (S.E.) except where indicated.
[1]No significant differences between control and acadesine groups for all variables.
[2]The transoesophageal echocardiography probe could not be inserted in one control subject.

Table 4.4 Major Outcomes.

Outcome	**Control** (n=22)	**Acadesine**[1] (n=19)
Death	0	0
Myocardial Infarction	6 (27%)	3 (16%)
Intra-Aortic Balloon Pump	2 (9%)	1 (5%)
Prolonged Inotrope Use[2]	7 (32%)	6 (32%)
Pacemaker	9 (41%)	5 (26%)
Off-CPB Unsupported[3]	15 (68%)	12 (63%)
Transient RWMA[4]	2 (9%)[6]	2 (10%)
Permanent RWMA[5]	4 (19%)[6]	2 (10%)

[1]No significant differences between control and acadesine groups for all variables.
[2]Postoperative inotropic support required for >20 minutes.
[3]No requirement for inotropic or mechanical support following CPB.
[4]New RWMA occurring perioperatively and resolving before the final recording in the ICU.
[5]New RWMA occurring perioperatively and persisting until the final recording in the ICU.
[6]The transoesophageal echocardiography probe could not be inserted in one control subject.

Figure 4.1

Regional Wall Motion Abnormality. The left ventricular posterior wall is akinetic.

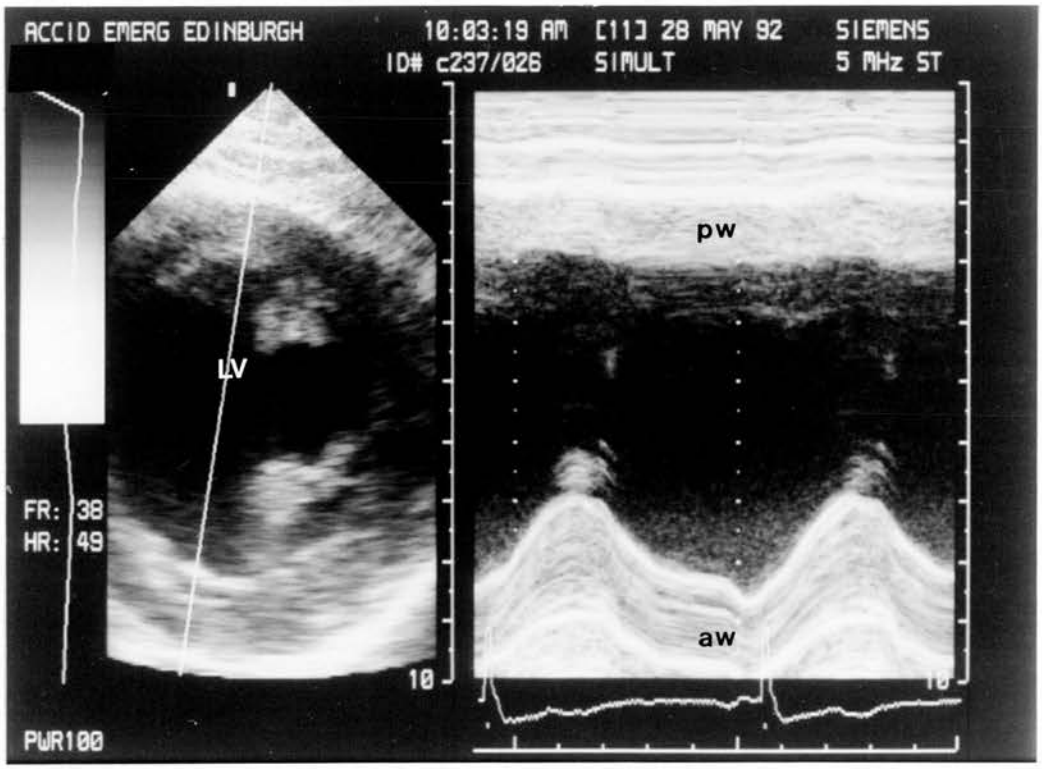
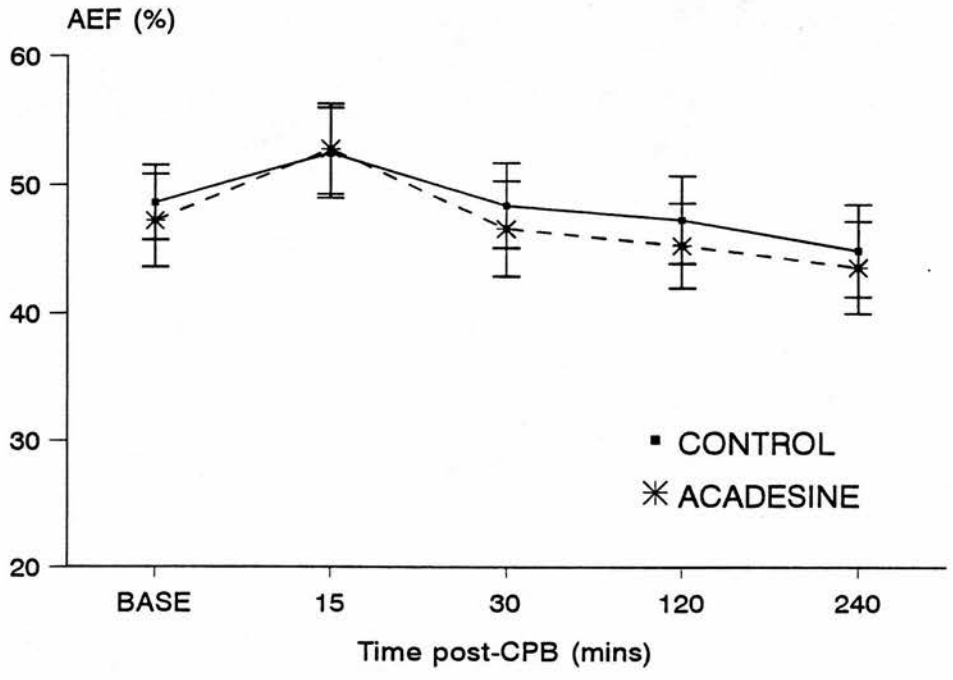


Figure 4.2

Perioperative Changes in Area Ejection Fraction. Data expressed as mean (S.E.).



p= non-significant for acadesine versus control at all time points

p= non-significant for acadesine and control versus baseline at all time points

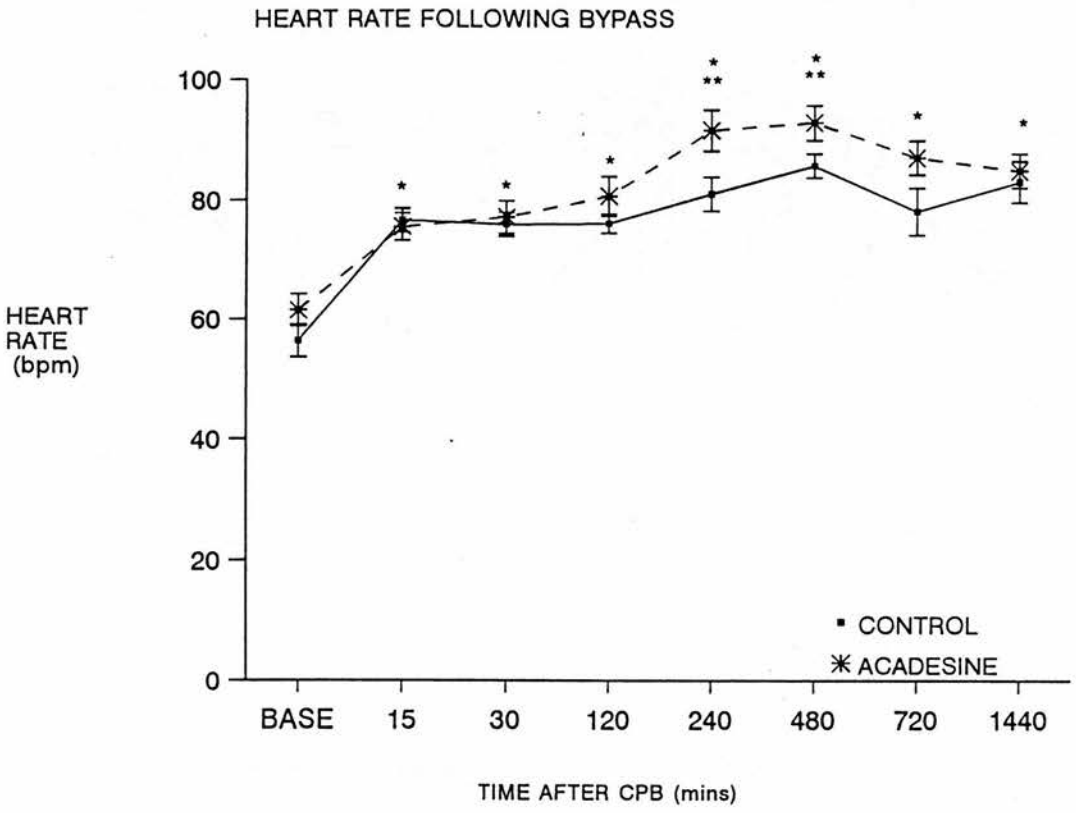
acadesine and control groups in the change in mean AEF at any time point.

Haemodynamic Measurements: postoperatively, HR and CI increased and SVR decreased significantly in both groups when compared to their respective baseline values (Figures 4.3-4.5). However there was no change in LVSWI (Figure 4.6). The CVP and PCWP did not change significantly at any time point, and only minor changes were observed in the MAP (Table 4.5). No major differences were observed between the acadesine and control groups in any of the postoperative haemodynamic variables.

Predictive Value of Echocardiography and Electrocardiography: of the nine subjects with perioperative myocardial infarction, persistent RWMAs developed in three subjects and a transient RWMA was seen in one subject. No new RWMAs were observed in four subjects and echocardiography was not possible in one case. The positive predictive value of a new RWMA for the diagnosis of myocardial infarction was 40%, and the negative predictive value 87%. Diagnostic changes in CK-MB concentrations were observed in all nine patients with perioperative myocardial infarction, but only three exhibited diagnostic ECG changes. For any adverse outcome (perioperative myocardial infarction, use of intraaortic balloon pump, prolonged inotrope usage) the development of any RWMA was predictive in 6/14, a persistent RWMA was predictive in 3/14, electrocardiography was predictive in 4/15, and CK-MB release $>$ 70 ng/ml was predictive in 9/15.

Figure 4.3

Heart Rate Following CPB.

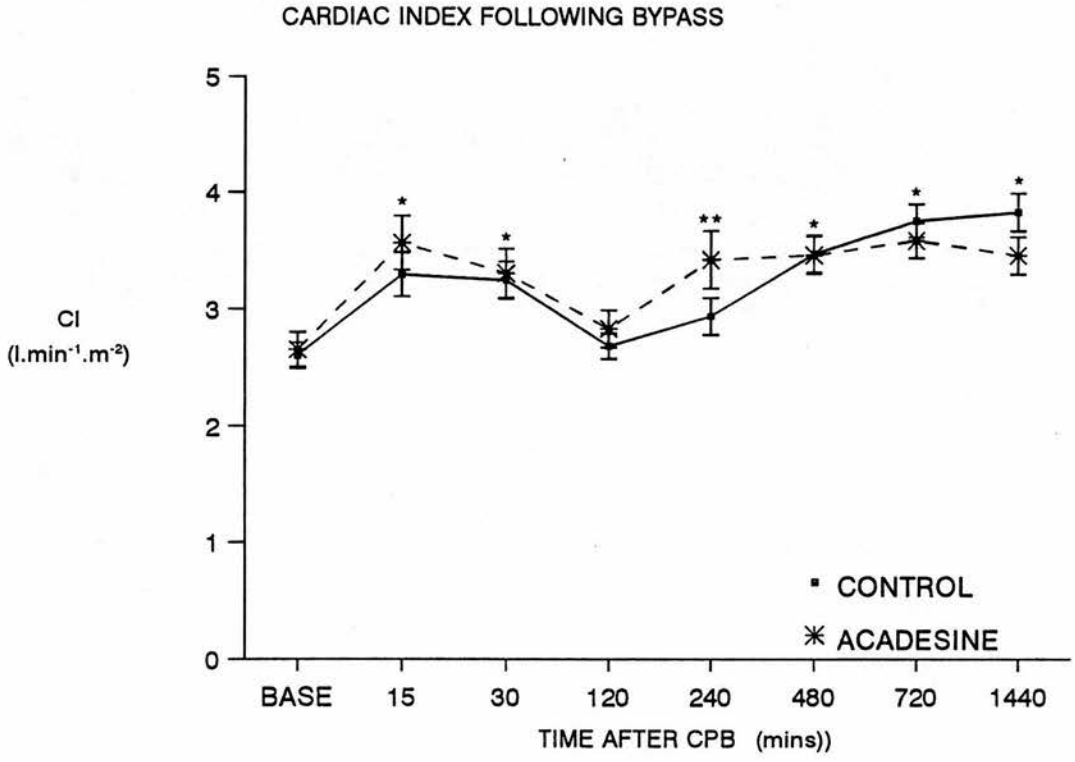


*p<0.05 for acadesine and control versus baseline

**p<0.05 for acadesine versus control

Figure 4.4

Cardiac Index Following CPB.



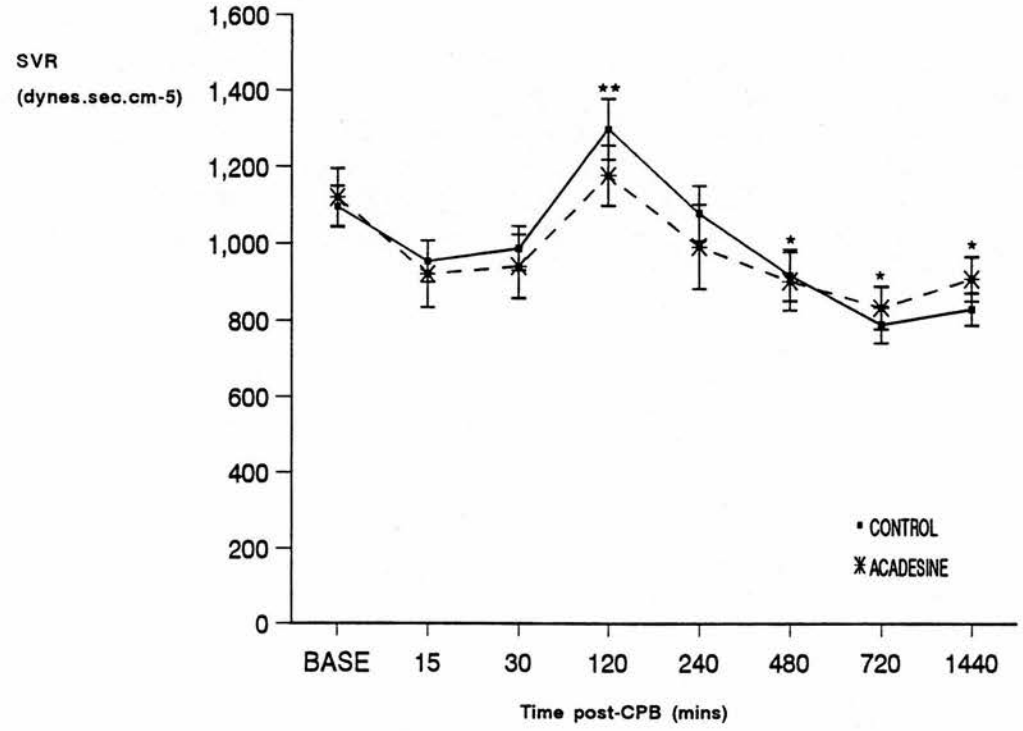
p= non-significant for acadesine versus control at all time points

*p= <0.05 for acadesine and control versus baseline

**p= <0.05 for acadesine versus baseline

Figure 4.5

Systemic Vascular Resistance Following CPB.



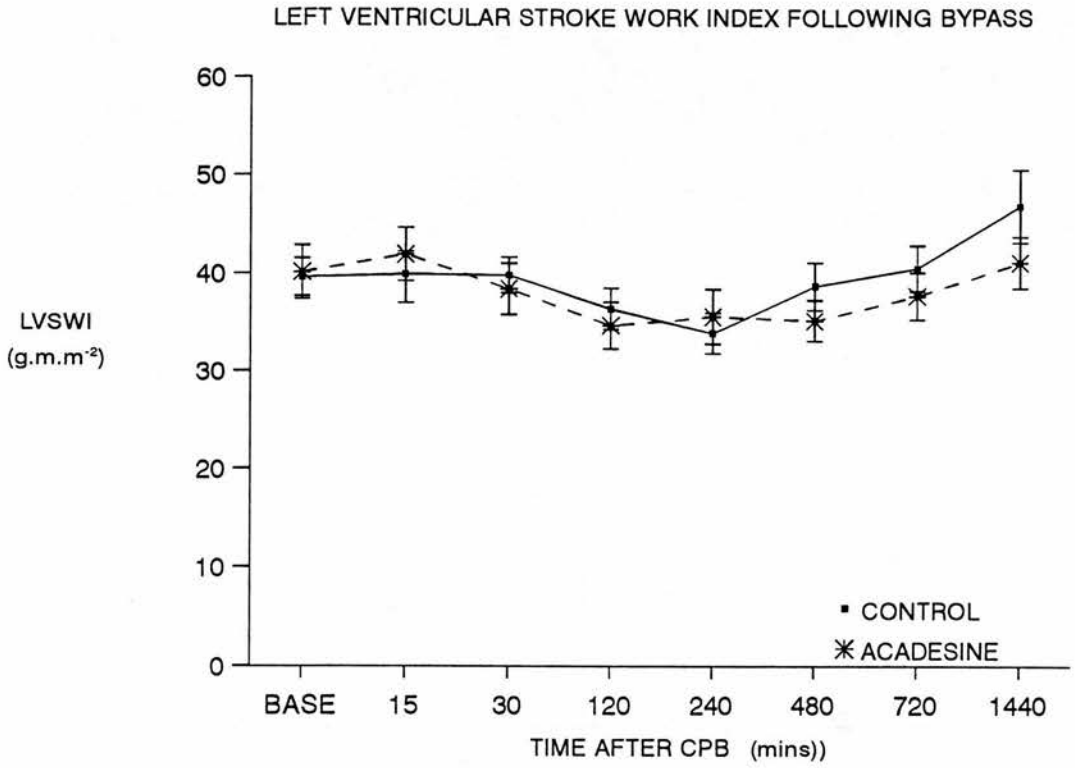
p= non-significant for acadesine versus control at all time points

*p<0.05 for acadesine and control versus baseline

**p<0.05 for control versus baseline

Figure 4.6

Left Ventricular Stroke Work Index Following CPB.



p=non-significant for acadesine versus control at all time points

p=non-significant for acadesine and control at all time points against baseline

Table 4.5 Haemodynamic Variables Following Cardiopulmonary Bypass

	Time Post Bypass (minutes)							
	Baseline	CPB+15	CPB+30	CPB+120	CPB+240	CPB+480	CPB+720	CPB+1440
Mean Arterial Blood Pressure (mmHg)[1]								
Control	72.6 (2.0)	78.6 (2.9)	79.8 (2.0)[2]	84.9 (3.1)[3]	77.5 (2.6)	79.9 (2.7)[2]	75.0 (2.8)	80.3 (2.5)[2]
Acadesine	76.0 (3.3)	76.9 (2.7)	75.8 (2.2)	81.2 (2.3)	80.9 (3.2)	78.3 (3.0)	75.0 (1.9)	79.6 (2.1)
Pulmonary Capillary Wedge Pressure (mmHg)[1]								
Control	10.0 (0.7)	11.2 (0.7)	10.7 (0.7)	8.9 (1.0)	9.3 (0.8)	9.9 (0.8)	10.0 (0.9)	9.0 (0.8)
Acadesine	8.8 (0.6)	10.3 (0.7)	9.5 (0.4)	7.7 (0.7)	9.1 (0.8)	9.6 (1.0)	9.0 (1.0)	7.8 (1.0)
Right Atrial Pressure (mmHg)[1]								
Control	6.7 (0.5)	7.4 (0.6)	7.3 (0.4)	6.2 (0.6)	7.3 (0.5)	8.3 (0.6)	7.6 (0.6)	6.6 (0.9)
Acadesine	6.3 (0.6)	6.5 (0.4)	6.9 (0.3)	6.3 (0.6)	7.3 (0.7)	6.9 (0.5)	6.7 (0.4)	5.0 (0.8)

All values mean (S.E.).

[1]No significant differences from baseline values for all time points in both control and acadesine groups, and between control and acadesine groups at all time points, except:
[2]$p < 0.05$ versus baseline
[3]$p < 0.005$ versus baseline

Conclusions

None of the parameters used in this study was able to detect a beneficial cardioprotective effect of acadesine treatment in patients undergoing CABG. Although fewer patients in the acadesine-treated group developed perioperative myocardial infarction or echocardiographic evidence of ischaemia (a transient or permanent RWMA), the absolute number of such events was small in both groups, and the differences observed failed to reach statistical significance. Similarly, no differences were observed between the acadesine-treated and the placebo-treated groups in any of the parameters used to assess global left ventricular function. The failure to demonstrate a significant improvement in outcome raises the following possibilities:

-Acadesine treatment has no clinically relevant action in reducing the incidence of perioperative ischaemia or infarction, or in protecting against myocardial stunning.
-Acadesine has cardioprotective properties but its effect on perioperative ischaemia and infarction failed to reach significance because the study lacked statistical power,
-The parameters chosen to assess myocardial function were not sufficiently sensitive to detect differences between the two groups.

Evidence Supporting a Cardioprotective Role for Acadesine in Humans: before the present study was initiated a single clinical trial had suggested that acadesine might possess useful cardioprotective properties (Leung et al., 1992). One hundred and sixteen patients undergoing CABG were randomised to receive acadesine or placebo infusion perioperatively. The incidence of perioperative myocardial infarction in the acadesine group was 5%, compared to 14% in the placebo group. Although this did not reach statistical significance, a significantly smaller rise in CK-MB levels was found in the acadesine group. Subsequently the results of the larger multicentre trial, to which this present study had contributed, were reported in abstract form (Europe/Canada Perioperative Ischaemia Research Group, 1993). This study randomised a total of 821 subjects undergoing CABG to receive treatment with

acadesine or placebo. No significant reduction in major cardiovascular outcomes was observed in acadesine-treated patients, however on subgroup analysis there was a 59% reduction in the incidence of myocardial infarction for acadesine-treated patients with unstable angina ($p = 0.002$). Whilst these results are consistent with a cardioprotective action for acadesine in selected patient groups, there is no conclusive evidence at present that acadesine possesses clinically useful properties in the majority of patients undergoing CABG. As the transoesophageal echocardiographic study included only two subjects with unstable angina, it is not possible to examine this data any further to determine whether acadesine treatment might have had a beneficial action in this subgroup.

Detection of Perioperative Ischaemia using Transoesophageal Echocardiography: Implications for Study Design: the incidence of new RWMAs in patients undergoing CABG has not been examined previously in a representative British setting, however rates of up to 44% have been reported from North America (Leung et al., 1989; Gordon et al., 1992). In the present study, the incidence of new RWMAs in the control group was 28.6%. Numerous factors might be responsible for this variation including differences in anaesthetic and surgical techniques, different patient populations, and different criteria used between studies to define new RWMAs (Vandenberg and Kerber, 1990). In the present study the rate of new RWMAs in the acadesine-treated group was 26% lower than in the control group. If a power calculation is performed using the control incidence rate of 28.6%, a future study would require at least 692 patients in each group to give a 90% chance of detecting a 26% reduction in the incidence of new RWMAs with acadesine treatment at a level of significance of 5%. This would clearly be a major undertaking, and would probably exceed the capabilities of any single centre.

There are additional methodological considerations. The sensitivity and specificity of transoesophageal echocardiography in the detection of myocardial ischaemia is not known. In the original studies transoesophageal echocardiography was found to be superior to existing techniques in the detection of perioperative myocardial ischaemia

(Smith et al., 1985; Leung et al., 1989; Van Daele et al., 1990). However discordance between transoesophageal echocardiography and electrocardiography has been reported more recently. London et al. (1990) found that although ischaemia was diagnosed more frequently by transoesophageal echocardiography, that there were frequent occasions in which ECG ischaemia was evident without accompanying RWMAs. Similar results were reported by Leung et al. (1990) when only 8 of 18 ECG episodes of ischaemia were associated with RWMAs. In the present study, although the ECG was not monitored for ST depression intraoperatively, discordance was also noted in some subjects between the electrocardiographic evidence of myocardial infarction and the echocardiographic results. Of three subjects who exhibited ECG and enzymatic evidence of perioperative myocardial infarction, echocardiography demonstrated a RWMA in only two. Conversely, the ECG was abnormal in only two out of four subjects with new RWMAs and elevated CK-MB concentrations. These differences may in part be explained by the inability of transverse plane transoesophageal echocardiography to image in more than one plane without altering the probe's position. As a consequence, RWMAs developing elsewhere may be unobserved (Chung et al., 1991). In theory, biplane or multiplane imaging might increase the sensitivity of the technique by allowing a greater proportion of the left ventricle to be imaged. To date there has been little intraoperative experience with these modalities.

It has also never been established that all new RWMAs necessarily reflect myocardial ischaemia. Other possible aetiologies include: stunned or hibernating myocardium, areas of scarring unmasked by changes in loading conditions, myocardial temperature heterogeneity after CPB, tethered non-ischaemic myocardium adjacent to ischaemic or infarcted myocardium and cardiac conduction abnormalities (Leung et al., 1990). Regional wall motion abnormalities affecting normal left ventricles have also been reported after prolonged exercise (Douglas et al., 1990). Nevertheless, Vandenberg and Kerber (1990) suggest that:

"..there is extensive experimental and clinical literature supporting the view that in the

setting of coronary artery disease a new RWMA is most likely to be secondary to acute ischemia or infarction."

However this is not necessarily applicable in the context of recent CPB. During this period, structural, metabolic and haemodynamic parameters change rapidly and could conceivably give rise to alterations in regional myocardial function unrelated to ischaemia. An illustration of this is provided by the frequent observation of dyskinetic motion of the interventricular septum early after cardiac surgery. The mechanism for this is not completely understood, however recent evidence suggests that it is not due to myocardial ischaemia, but may be secondary to cardiac translation induced by events occurring during CPB (Lehmann et al., 1990).

Despite these theoretical considerations reasonable evidence has accumulated that the development of a new RWMA following CPB is moderately predictive of an adverse clinical outcome. Leung et al. (1989) studied 50 patients undergoing CABG. A new RWMA was detected following CPB in 18 patients, of whom six had an adverse cardiac outcome (death, myocardial infarction or heart failure). No adverse events occurred in patients without a new RWMA. A 33% positive predictive value and a 100% negative predictive value were calculated. Almost identical results were reported by Gordon et al. (1992) who found that the development of a new RWMA post-CPB carried a 33% positive predictive value for the diagnosis of perioperative myocardial infarction. The results of the present study are similar, echocardiography achieving a positive predictive value of 40% and a negative predictive value of 87% for the diagnosis of perioperative myocardial infarction.

Assessment of Global Left Ventricular Performance: In the present study, it was hypothesised that if the cardioprotective actions of acadesine diminished the extent of myocardial stunning, this might be reflected as better global left ventricular function following cardiopulmonary bypass. However, no differences were observed in any of the measured haemodynamic parameters, or in the changes in the AEF between the acadesine-treated and placebo-treated groups. As was discussed earlier in this chapter, accurate assessment of global left ventricular performance is difficult

to achieve in the clinical environment. There is no ideal method to quantify cardiac contractility, and the most commonly used echocardiographic, haemodynamic and radionuclide techniques are affected by cardiac loading conditions (Quinones et al., 1975; Gaasch et al., 1978). Nevertheless if loading factors are unchanged postoperatively, reduced cardiac contractility has been inferred from changes in such parameters as the cardiac index, LVSWI and ejection fraction (Gray et al., 1979; Roberts et al., 1980 & 1981; Mangano, 1985; Bhayana et al., 1989).

In the present study it is difficult to draw definitive conclusions regarding left ventricular contractility in the acadesine and control groups following CPB, although some cautious interpretation is possible. The fact that the AEF was unaltered following CPB is not necessarily evidence against the presence of myocardial stunning, as the fall in SVR that was seen in both groups might have compensated for any reduction in myocardial contractility. However, the left ventricular loading conditions, PCWP and SVR, behaved identically in both the acadesine and control groups throughout the study period and no differences were observed between the two groups in the mean AEF. Accordingly it might be inferred that global left ventricular function behaved similarly in each group, and that no major benefit was observed from acadesine treatment. Ventricular function curves have previously demonstrated evidence of impaired left ventricular contractility following CPB. The design of the present study did not allow ventricular function curves to be constructed, however the cardiac index increased in both groups following CPB, and there was no significant difference in LVSWI. Whilst it is possible that the measures used to assess global left ventricular function in this study were insensitive to changes in contractility, the haemodynamic results are consistent with the echocardiographic findings and demonstrate no significant differences between the acadesine and the control groups.

An additional confounding factor that is difficult to control in the clinical setting is the use of inotrope and vasodilator drugs. However, more than 60% of subjects in both groups did not require inotropic or mechanical support postoperatively. Whilst

these observations do not exclude the possibility that impaired left ventricular contractility does occur following CPB, particularly as this may have been "masked" by the fall in SVR, they do suggest that clinically significant cardiac depression did not occur in the majority of patients following CPB.

Transoesophageal Echocardiography in Perioperative Monitoring: Conclusions

Transoesophageal echocardiography has significant strengths as an investigative tool in studies of perioperative cardiac function, however it also has important limitations. Nevertheless, significant methodological difficulties affect all the commonly used investigative techniques and the limitations of haemodynamic measurement, radionuclide ventriculography and electrocardiography have been discussed. If transoesophageal echocardiography is used to monitor regional myocardial function, it must be recognised that the incidence of new RWMAs in patients undergoing CABG is relatively low, that its sensitivity and specificity in the diagnosis of myocardial ischaemia is uncertain, and that it has only limited positive predictive value for the diagnosis of perioperative myocardial infarction. There is however, considerable evidence that transoesophageal echocardiography is superior to the ECG, and whilst acknowledging that the criteria used to define an ischaemic episode are not fully validated, there is reasonable evidence that the development of a new RWMA following CPB is predictive of an adverse cardiac outcome. Global left ventricular function remains difficult to assess in the perioperative environment and the ejection fraction is of limited value in view of its sensitivity to cardiac loading conditions. Alternative echocardiographic approaches to this problem are being explored. The relationship between meridional wall stress and left ventricular dimensions may be a load-independent index of myocardial contractility and attempts have been made to investigate this using transoesophageal echocardiography (O'Kelly et al., 1988). In theory this might facilitate more detailed investigation of global left ventricular function perioperatively, however left ventricular wall thickness must be measured accurately and poor epicardial definition is frequently encountered with transoesophageal echocardiography. Nevertheless, this topic remains under

investigation and might ultimately extend the role of transoesophageal echocardiography in intraoperative monitoring.

CHAPTER 5

INTRAOPERATIVE TRANSOESOPHAGEAL ECHOCARDIOGRAPHY III: ASSESSMENT OF CARDIAC HAEMODYNAMICS

Introduction

Transoesophageal echocardiography is used increasingly during cardiac operations to help assess the quality of a surgical procedure immediately after weaning from cardiopulmonary bypass (Reichert et al., 1990; Sheikh et al., 1990). Residual defects and technically unsatisfactory results may be identified, and where necessary, immediate revisionary surgery can be attempted before the patient leaves the operating theatre. The potential applications of transoesophageal echocardiography have been expanded by the relatively recent incorporation of spectral Doppler capabilities. To date however, transoesophageal echocardiography has found only a limited role in haemodynamic assessment in the intraoperative setting. This largely reflects its inability to perform quantitative Doppler studies of flow in structures that lie perpendicular to the oesophagus including the aortic valve (Figure 1.2), and both the left and the right ventricular outflow tracts (Stumper et al., 1990). Where haemodynamic measurements have been needed, either epicardial echocardiography or invasive pressure monitoring have usually been required (Sreeram et al., 1990; Stumper et al., 1990; Muhiudeen et al., 1990). This is a significant limitation of intraoperative transoesophageal echocardiography.

This chapter explores the role of transoesophageal echocardiography in the assessment of intraoperative haemodynamics, and describes the use of transgastric imaging, a novel imaging plane that extends the capabilities of intraoperative echocardiography.

Studies with Transgastric Imaging

One of the standard monographs on transoesophageal echocardiography describes how the left ventricle may be imaged in short axis by positioning the probe in the gastric fundus (Seward et al., 1988). However these authors do not appear to have recognised that by making a minor adjustment to this imaging position several additional views of the heart and great vessels can be obtained. This novel plane was first described by Hoffman et al. (1992) who explored the utility of transgastric imaging in the assessment of complex congenital heart disease. To date, there have been no reports of its use to facilitate intraoperative haemodynamic assessment.

The plane is obtained by advancing the transoesophageal echocardiographic transducer approximately 5 cm from the transgastric position that images the left ventricle in short axis at mid-papillary muscle level. Subsequently, additional anteflexion and lateral rotation of the transducer will bring the left ventricular outflow tract, aortic valve and ascending aorta into view. In this plane these structures run longitudinally away from the transducer, and so are optimally aligned for spectral Doppler studies (Figure 5.1). The left atrium, mitral valve and interventricular septum are also visible in this view. By slightly withdrawing the probe and making minor rotational adjustments, the right ventricular outflow tract, pulmonary trunk and left pulmonary artery are also demonstrated (Figure 5.2). These views can be obtained in most patients using a 5 MHz transverse plane transducer. There are several potential applications of the transgastric plane:

Assessment of Aortic Stenosis

Haemodynamic assessment of the severity of aortic stenosis is generally performed using a combination of transthoracic echocardiography and cardiac catheterisation. However, it is not always possible to determine the pressure gradient across the aortic valve owing to inability to pass a catheter across a heavily calcifed valve. Similarly, in some poorly echogenic subjects the transthoracic echocardiogram may

Figure 5.1

Transgastric Imaging. The left ventricular outflow tract, aortic valve and ascending aorta are optimally aligned for spectral Doppler interrogation.

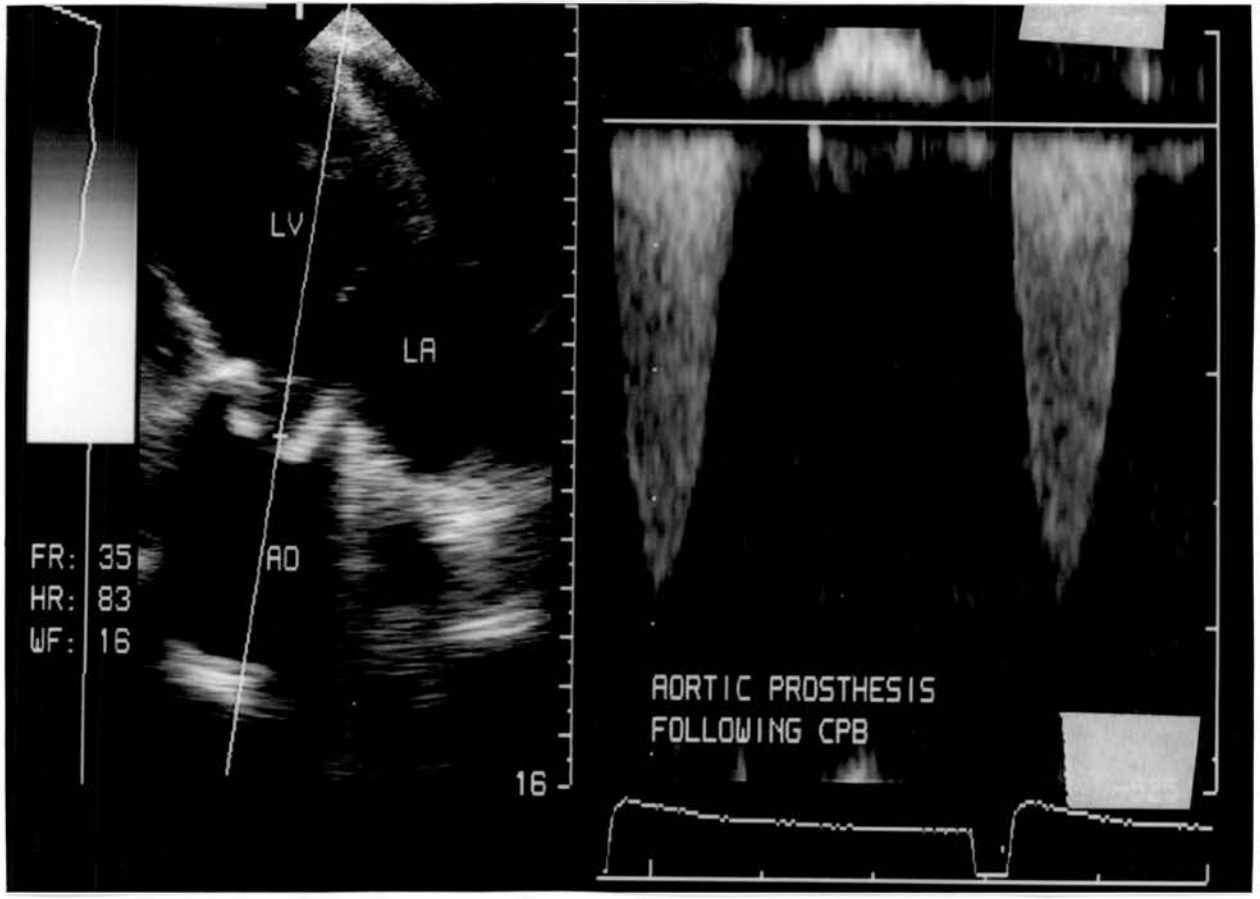
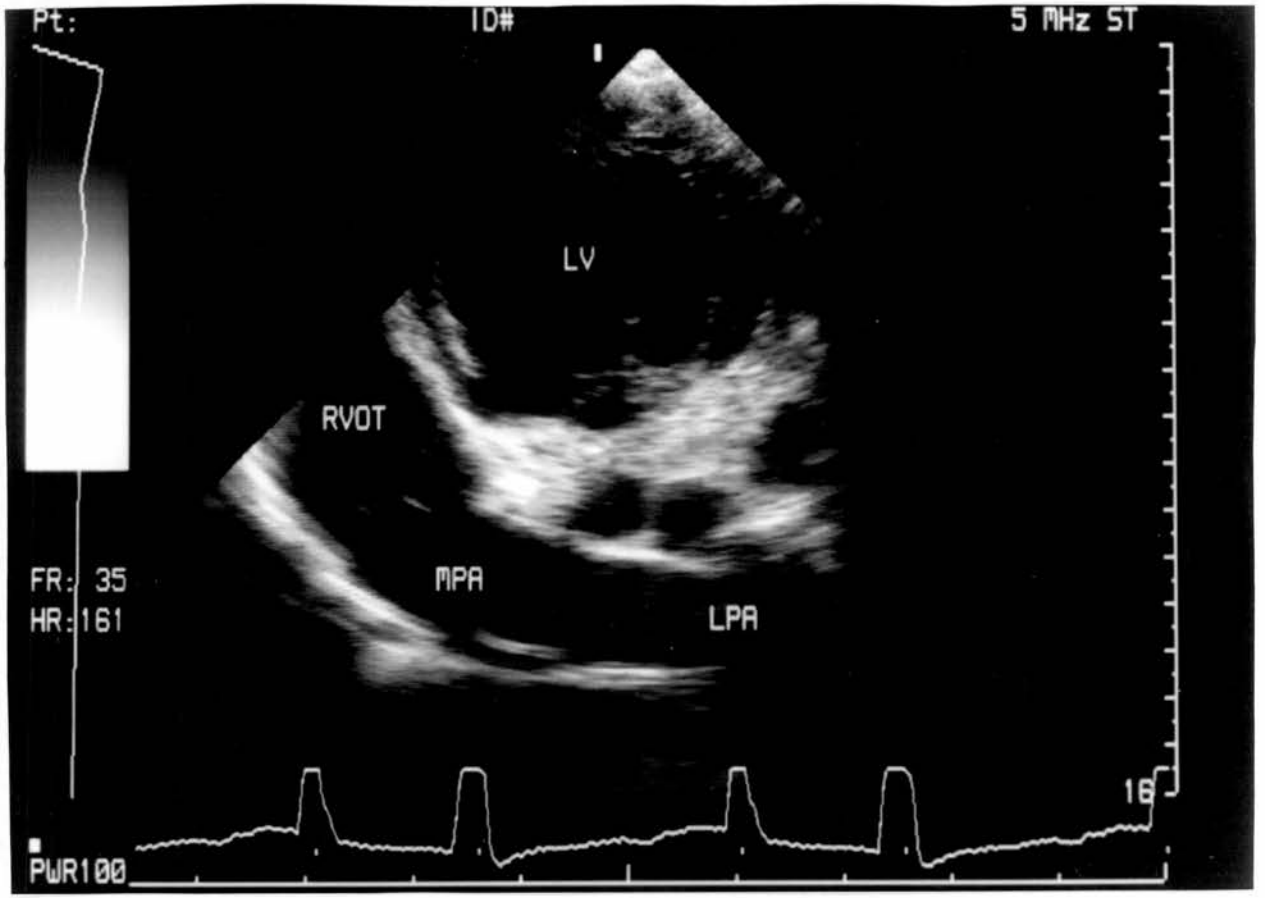


Figure 5.2

Transgastric Imaging. Minor adjustment to the transducer position shown in Figure 5.1 brings the right ventricular outflow tract, main pulmonary artery and left pulmonary artery into view.



be difficult and satisfactory Doppler recordings may not be obtained. There is a potential role for an alternative method of assessing the severity of valvular stenoses. As previously discussed, although transoesophageal echocardiography gives highly detailed views of the aortic valve, Doppler interrogation is not possible from the oesophagus as the ultrasound beam cannot be aligned to the direction of blood flow. Attempts have been made to estimate the aortic valve area using two-dimensional transoesophageal echocardiography (Hofmann et al., 1987; Stoddard et al., 1991), however scanning in the transverse plane may fail to detect aortic stenosis when the bodies of the leaflets remain mobile if there is commissural fusion or a tight stenosis at the orifice (Sutherland 1991). The present study examines whether transgastric imaging facilitates Doppler interrogation of the aortic valve using transoesophageal echocardiography.

Methods

11 patients undergoing aortic valve replacement for aortic stenosis were studied intraoperatively using transoesophageal echocardiography. Prior to cannulation for cardiopulmonary bypass, the aortic valve was interrogated with continuous wave Doppler ultrasound in the transgastric plane. The instantaneous gradient was derived using the Bernouilli equation (Hegrenæs and Hatle, 1985) and compared with the transvalvular pressure gradient measured at cardiac catheterisation, or where this had not been performed, the gradient estimated preoperatively using transthoracic echocardiography.

Results

The aortic valve was not visualised in 2 subjects using transgastric imaging. In the remainder, the transgastric plane was optimally aligned allowing the ultrasound beam to be directed parallel to the direction of blood flow across the valve. Close agreement was found between the aortic pressure gradient measured preoperatively and the estimated intraoperative gradient (Table 5.1).

Table 5.1 Assessment of Aortic Stenosis using Transgastric Imaging.

Patient	Preoperative Gradient (mm Hg)	Transgastric Gradient (mm Hg)
JM	120 E	88
MM	45 E	40
WC	72 C	72
JI	80 C	85
SW	80 C	90
NM	26 C	17
JB	71 C	60
AL	72 C	58
JR	Not measured	70
GR	80 C	Not possible
SP	100 E	Not possible

C: catheter gradient; E: echo gradient

Conclusions

These results indicate that the severity of aortic stenosis can usually be assessed using transoesophageal echocardiography with continuous wave Doppler imaging in the transgastric plane. Satisfactory imaging was obtained in the majority of subjects. Although these subjects were anaesthetised, the probe is also readily positioned in

the transgastric plane under conditions of light sedation during routine diagnostic studies.

Doppler techniques measure the instantaneous pressure difference between two chambers. Accordingly, the gradient estimated by ultrasound is usually greater than the peak to peak gradient measured by withdrawal during cardiac catheterisation. Furthermore, preoperative haemodynamic conditions are likely to have been different from those present intraoperatively. Given these two sources of variability, reasonably close agreement was found between preoperative and intraoperative estimates of the severity of aortic stenosis.

Intraoperative Evaluation of the Aortic Valve and Left Ventricular Outflow Tract Using Transgastric Imaging

Assessment of intraoperative haemodynamics may sometimes be required during procedures involving the aortic valve and left ventricular outflow tract. Examples of this include: assessment of systolic anterior motion of the anterior mitral leaflet following mitral valve repair, evaluation of septal myectomy in hypertrophic obstructive cardiomyopathy, and following resection of a subaortic membrane in subvalvar stenosis (Maron et al., 1985; van Herwerden et al., 1991). Haemodynamic studies may also be necessary before cardiopulmonary bypass to confirm the physiological significance of a lesion, and afterwards to determine an acceptable haemodynamic result.

Epicardial echocardiography has often been utilised previously when haemodynamic assessment was required (Ungerleider et al., 1990). However epicardial imaging is disruptive to the surgeon, requires considerable expertise, and carries the potential risk of contaminating the surgical field. Furthermore, some haemodynamic abnormalities arising after cardiopulmonary bypass are transient and often resolve over a short period. Accordingly, epicardial echocardiography may require to be repeated several times to assess fully the functional significance of an obstructive

lesion. In contrast, the transgastric plane facilitates continuous and repeated haemodynamic assessment as the transoesophageal echocardiographic probe can be left in position throughout a procedure.

The following study was performed to assess the value of routine transgastric imaging in patients undergoing cardiac surgery.

Methods

Intraoperative transoesophageal echocardiography was performed on 29 patients undergoing cardiac surgery. Conventional imaging planes were utilised (basal short axis, four chamber and left ventricular short axis), in addition to intermittent use of transgastric imaging. Haemodynamic and structural information gained by the use of transgastric imaging was compared with that obtained by the use of conventional imaging planes. The surgical procedures comprised: aortic valve replacement (AVR), n = 14; mitral valve replacement (MVR), n = 1; AVR and MVR, n = 2; AVR with aortic root replacement and coronary reimplantation, n = 1; mitral valve repair, n = 1; coronary artery bypass grafting, n = 10.

Results

Satisfactory visualisation of the aortic valve and the left ventricular outflow tract was achieved in 23 subjects using transgastric imaging. Conventional views were obtained in all 29 subjects.

Coronary Artery Bypass Surgery: regional and global myocardial function was most readily assessed in the left ventricular short axis plane. No additional benefit was seen with transgastric imaging in this group.

Mitral Valve Surgery: in one patient undergoing MVR, the severity of posterior mitral leaflet prolapse was underestimated preoperatively with transgastric imaging

in comparison to the four chamber view. Two patients had evidence of small jets of periprosthetic regurgitation following MVR. The site and extent of mitral incompetence was best assessed using the basal short axis and four chamber views. A regurgitant jet was not identified in one patient with transgastric imaging. Only transgastric imaging enabled Doppler interrogation of the left ventricular outflow tract following mitral valve repair, however Doppler assessment of mitral valve inflow was readily achieved from both the four chamber and transgastric views.

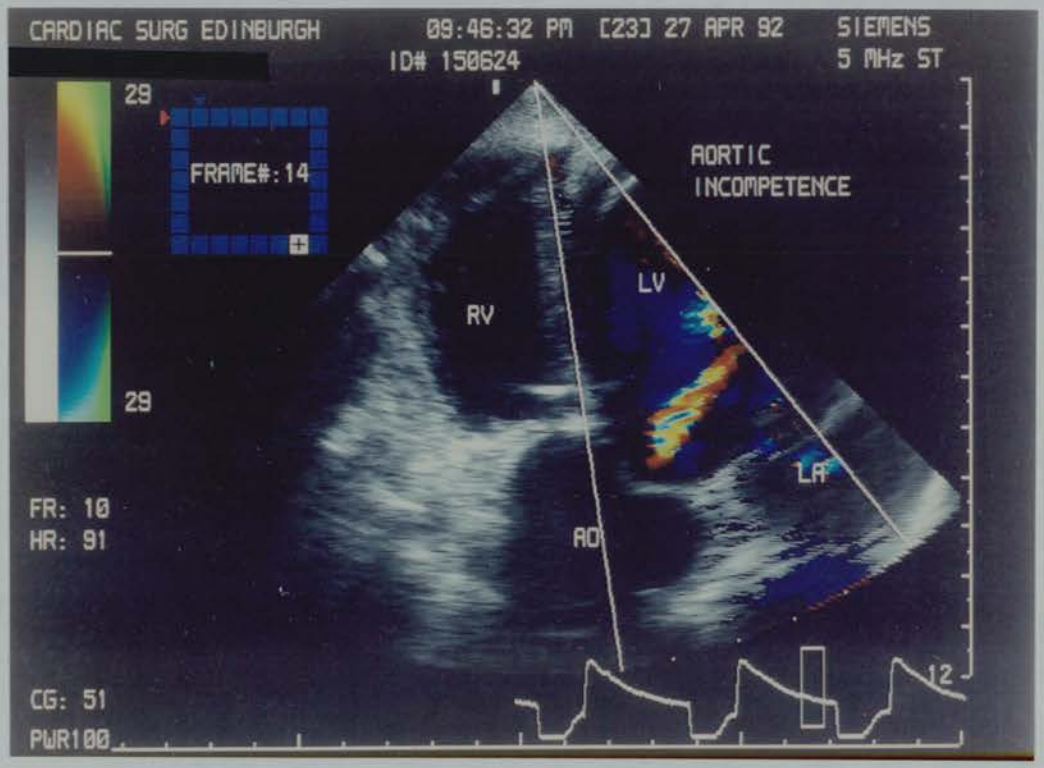
Aortic Valve Surgery: the basal short axis position proved optimal for detailed morphological assessment of the aortic root and aortic valve leaflets before cardiopulmonary bypass. In the presence of a native mitral valve assessment of aortic incompetence was best performed by interrogating the left ventricular outflow tract with colour flow Doppler from the basal short axis position. However, this was not possible in the presence of a prosthetic mitral valve as acoustic shadowing prevented adequate visualisation of the left ventricular outflow tract. In two such patients, only transgastric imaging was able to detect the presence of aortic regurgitation (Figure 5.3). Spectral Doppler assessment of prosthetic aortic valve function was possible only with transgastric imaging. Transient aortic bioprosthetic dysfunction was diagnosed in one subject immediately after cardiopulmonary bypass. This case is described in detail later.

Conclusions

Use of the transgastric plane extends the utility of transoesophageal echocardiography in the intraoperative setting. Its primary benefit appears to be in enabling haemodynamic assessment of the left ventricular outflow tract and aortic valve, regions poorly aligned for spectral Doppler studies from the oesophagus. The main limitation of this plane is that most of the target structures are imaged at a distance of 10 cm or more from the transducer. At this depth resolution is limited with a 5 MHz transducer and colour flow Doppler performs poorly. Accordingly, detailed morphological assessment is best performed from conventional oesophageal views.

Figure 5.3

Aortic Incompetence Detected Using Transgastric Imaging.



However, where a mitral prosthesis prevents visualisation of structures from the oesophagus, the transgastric plane provides an alternative window on the left ventricular outflow tract facilitating assessment of aortic incompetence. Thus, the transgastric plane can extend the potential of intraoperative transoesophageal echocardiography by complementing the conventional imaging planes.

Intraoperative Diagnosis of Prosthetic Valve Dysfunction Using Transgastric Imaging

To illustrate the value of transgastric imaging a case is described in which transoesophageal echocardiography allowed diagnosis of prosthetic valve dysfunction shortly after weaning from cardiopulmonary bypass.

Case Report

A 57 year old man was referred for aortic valve replacement having developed dysfunction of a 25 mm Carpentier-Edwards bioprosthesis. Preoperative cardiac catheterisation revealed severe mixed aortic valve disease, good left ventricular function and normal coronary arteries. Arterial and central venous monitoring lines, a pulmonary artery catheter and a 5 MHz transverse plane transoesophageal echocardiography probe were inserted following induction of anesthesia.

Using standard imaging planes, echocardiography revealed good left ventricular function, septal hypokinesia and severe aortic prosthetic incompetence. Poor alignment to the direction of blood flow prevented quantitative Doppler assessment of the aortic prosthesis from the oesophagus, but by positioning the probe in the transgastric position alignment was optimal for continuous wave Doppler interrogation of the left ventricular outflow tract and the aortic valve. Prior to CPB, the peak systolic velocity across the valve was 4.5 $m.s^{-1}$, and severe aortic regurgitation was demonstrated, confirming the preoperative diagnosis.

The patient was placed on CPB without difficulty. The aorta was cross-clamped, the aortic root was opened and the orifices of the coronary arteries were identified and cannulated, and cardioplegia was delivered arresting the heart in diastole. The left ventricle was vented through the right superior pulmonary vein. The leaflets of the dysfunctional valve were found to be perforated and stenosed, and the prosthesis was removed and a 23 mm Carpentier-Edwards valve was inserted in its place. Air was evacuated from the heart chambers and, following removal of the cross-clamp, the heart spontaneously reverted to sinus rhythm. The patient was gradually weaned from CPB without inotropic therapy.

Immediately after weaning from CPB continuous wave Doppler interrogation of the aortic prosthesis was performed from the transgastric position. This revealed a peak systolic velocity of 4.8 $m.s^{-1}$, corresponding to a peak instantaneous gradient of 92 mm Hg, suggesting severe valvular stenosis (Figure 5.4). The mean gradient was 54 mm Hg and the acceleration time was 107 ms. Pulsed Doppler interrogation of the left ventricular outflow tract localised the obstruction to the bioprosthesis revealing a peak velocity of 1.2 $m.s^{-1}$ immediately proximal to the aortic valve (Figure 5.5). The calculated aortic valve area was 0.89 cm^2 and the ratio of time velocity integral proximal to the valve to time velocity integral across the valve (V_{LVOT}:V_{AV}) was 0.28 (normal for an aortic bioprosthesis >0.35), suggesting true valvular stenosis (Rothbart et al., 1990).

Despite the abnormally elevated transvalvar gradient, the patient's clinical condition remained satisfactory and no attempt was made to revise the procedure. The arterial blood pressure was 110/60 mm Hg, the heart rate was 80 $beats.min^{-1}$, the right atrial pressure was 9 mm Hg and the cardiac output was 5.8 $l.min^{-1}$. Echocardiography revealed good left ventricular function, dyskinesia of the interventricular septum, and no evidence of prosthetic aortic incompetence. Continuous monitoring from the transgastric position demonstrated that the peak systolic velocity across the aortic prosthesis remained unchanged for twenty minutes. Subsequently, there was a gradual reduction and ninety minutes after weaning from CPB the peak velocity had

Figure 5.4

Transient Aortic Valve Dysfunction. Immediately after cardiopulmonary bypass the peak systolic velocity was elevated at 4.8 $m.s^{-1}$. After five minutes the peak velocity remained elevated at 4.5 $m.s^{-1}$. Ninety minutes after CPB the peak systolic velocities had fallen to 2.65 $m.s^{-1}$.

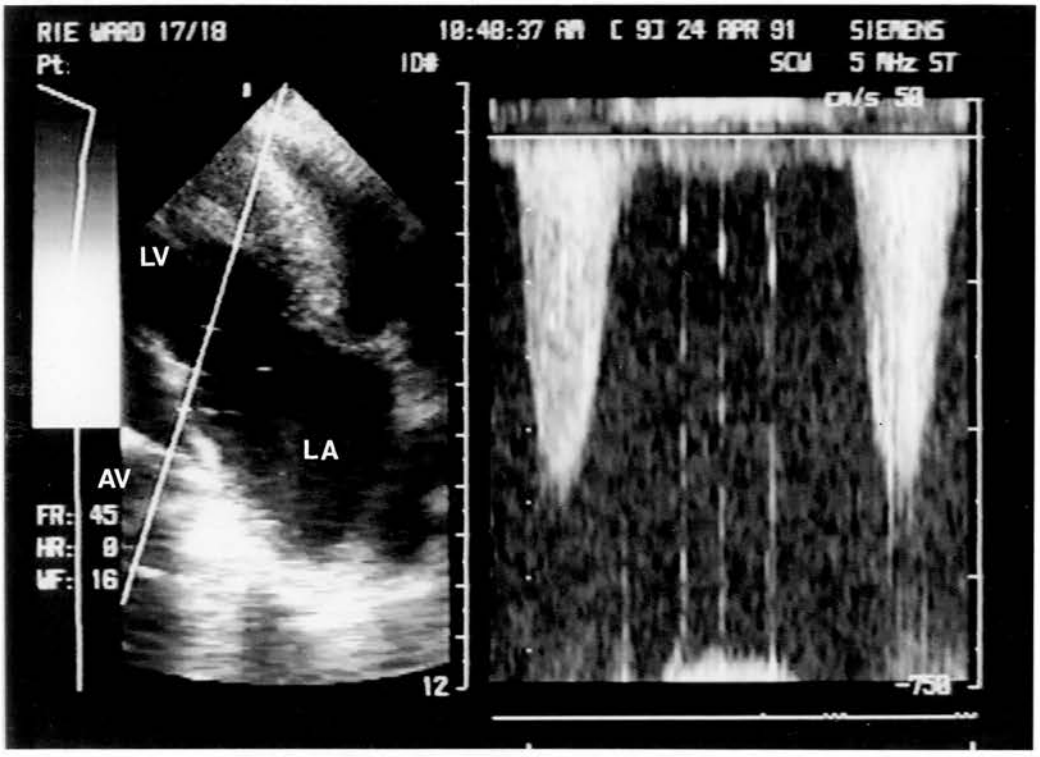
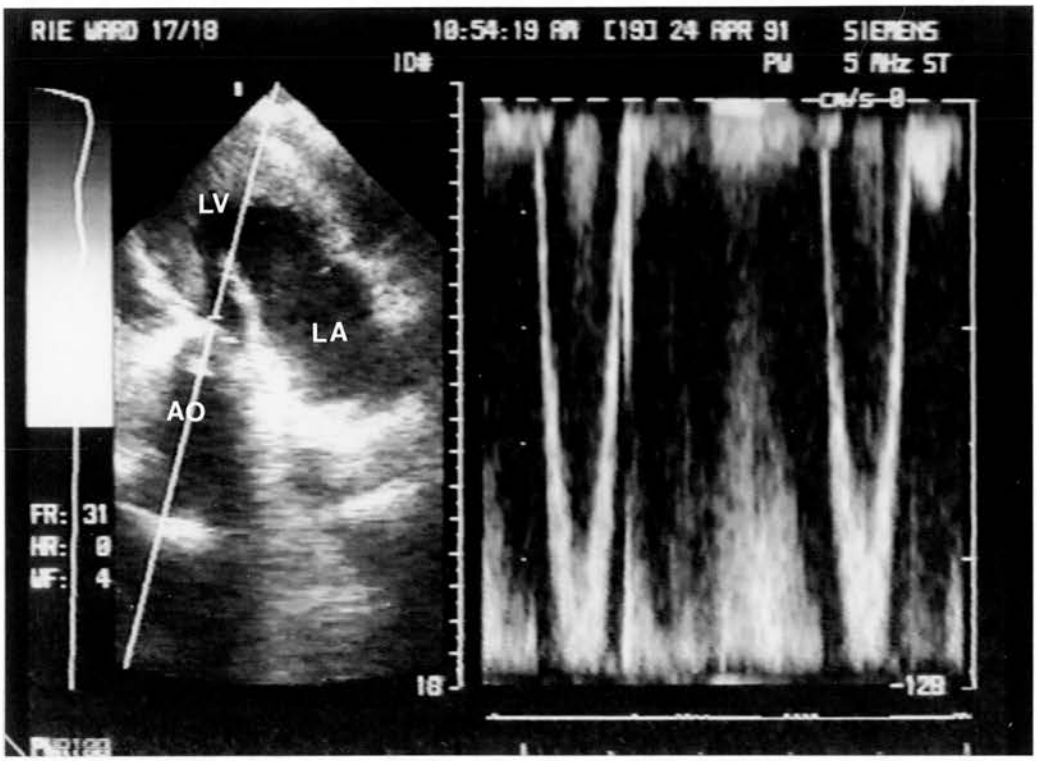


Figure 5.5

Transient Aortic Valve Dysfunction. Pulsed Doppler interrogation of the left ventricular outflow tract localised the obstruction to the aortic valve.



fallen to 2.65 $m.s^{-1}$ (peak instantaneous gradient 28 mm Hg). Over the same period, the arterial blood pressure increased to 115/70 mm Hg, the heart rate rose to 88 $beats.min^{-1}$, and the right atrial pressure increased to 12 mm Hg. The cardiac output fell to 4.4 $l.min^{-1}$.

The patient was returned to the ward and his subsequent recovery was uneventful. Precordial echocardiography was performed prior to discharge, and two months postoperatively. On both occasions there was normal prosthetic function and the instantaneous systolic gradient was unchanged at 30 mm Hg.

Conclusions

In this patient the peak systolic velocities measured across the aortic prosthesis following CPB were elevated to a degree that suggested significant valvular obstruction (Williams and Labovitz, 1985; Burstow et al., 1989; Rothbart et al., 1990). Although normally functioning prosthetic heart valves are inherently stenotic, transvalvar gradients measured intraoperatively are normally significantly lower than those measured in this instance (Levine et al., 1981; Khan et al., 1990). Such gradients are partly flow dependent and there was a progressive reduction in the peak systolic velocity in the 90 minutes following CPB, whilst cardiac output decreased by 24%. However, the ratio of V_{LVOT}:V_{AV}, which is a flow-independent measure of aortic bioprosthetic dysfunction (Rothbart et al., 1990; Baumgartner et al., 1992), was abnormal in our patient. This suggests that transient valvular stenosis may have contributed to the abnormally elevated transvalvular gradient.

As remedial surgery was not attempted the precise mechanism of valvular dysfunction is uncertain. Transient left ventricular outflow tract obstruction has been described following mitral valve repair, when epicardial echocardiography demonstrated a dynamic subaortic obstruction secondary to anterior motion of the mitral valve (van Herwerden et al., 1991). In our patient, pulsed Doppler echocardiography localised the site of the obstruction to the aortic valve, indicating

that a different mechanism was responsible for the elevated velocities. A study of Carpentier-Edwards bioprostheses, performed 6-15 months after insertion, has demonstrated that a small amount of leaflet inertia must be overcome before full opening of the valve can occur (Chaitman et al., 1979). The abnormal gradient seen in our patient might have been secondary to increased stiffness of the newly inserted valve, causing a transient outflow obstruction. Over the period of 90 minutes following CPB, leaflet compliance may have gradually increased, resulting in a reduction in the transvalvular gradient. Irrespective of the mechanism involved, obstruction to outflow may be a transient phenomenon following CPB, and may not require specific intervention.[1]

[1]It is not known whether transient elevations in transvalvar velocities are a common phenomenon immediately after CPB in patients undergoing aortic valve replacement. Since this case, I have performed transgastric imaging on an additional three subjects undergoing aortic valve replacement with Carpentier-Edwards bioprostheses. Peak systolic velocities measured in two subjects were not elevated following CPB, and were identical to those recorded from the precordium at discharge. In a third subject, the peak systolic velocity was 3.5 $m.s^{-1}$ immediately after CPB, but fell to 3.1 $m.s^{-1}$ after ten minutes and remained unchanged subsequently. I have never observed disproportionate elevation of transvalvar velocities following insertion of mechanical prostheses.

Perioperative Estimation of Cardiac Output Using Transgastric Imaging

Measurement of cardiac output is often of major importance in the critical care environment enabling pharmacological and mechanical support to be selected appropriately, and the response to therapy to be monitored (Barnard and Linter, 1993). Cardiac output is most commonly measured by thermodilution. However this technique is invasive and requires the insertion of a pulmonary artery catheter, and minor deviations in technique may introduce large errors (Schuster and Nanda, 1984). Cardiac output may also be measured using Doppler ultrasound, thus avoiding the risks and expense involved with more invasive techniques. In experienced hands, transthoracic Doppler measurements can give reasonably reproducible and accurate estimates of cardiac output (Schuster and Nanda, 1984; Coats, 1990). This is a relatively straightforward technique in which a specific site, usually within the heart or ascending aorta, is interrogated with spectral Doppler ultrasound. Pulsed Doppler is generally preferred as this allows the velocity-time integral of flow during one cardiac cycle to be calculated and multiplied by the cross-sectional area at the sampling site to derive the stroke volume. This value is then multiplied by the heart rate to give the cardiac output.

Pulsed Doppler capabilities have become standard on transoesophageal echocardiography probes, and have been used to estimate cardiac output by interrogating flow across the mitral valve and within the pulmonary artery (Ellis et al., 1987; Roewer et al., 1987; Muhiudeen et al., 1991). To date, experience has been disappointing and only modest correlation has been shown with the thermodilution technique. This may be explained by the fact that the various assumptions inherent to the Doppler method may not be valid when the mitral valve and pulmonary artery are interrogated from the oesophagus. These assumptions include parallel alignment of the ultrasound beam with blood flow, a uniform profile of flow velocities at the sampling site and stability of cross-sectional area throughout the cardiac cycle (Coats, 1990).

The transgastric imaging position offers an alternative site for measurement of cardiac output using pulsed Doppler echocardiography. Experience with transthoracic imaging suggests that the most reliable sampling sites for estimation of cardiac output are the aortic annulus and the ascending aorta (Coats, 1990). At these sites there is little change in cross-sectional area during exercise or at different cardiac outputs, the flow velocity profile is flat, and the signal to noise ratio is high (Coats, 1990). Furthermore, as these regions are circular the cross-sectional area is readily derived from measurement of the diameter. As discussed previously, although parallel insonnation cannot be achieved from the oesophagus, in the transgastric plane the left ventricular outflow tract, aortic valve and ascending aorta are optimally aligned for spectral Doppler interrogation. Accordingly, use of transgastric imaging might allow accurate measurement of cardiac output, avoiding the need for more invasive techniques. This possibility was explored in the perioperative setting.

Methods

Twelve subjects undergoing coronary artery bypass grafting were studied (mean age 62 years, range 56-73 years). After induction of anaesthesia, a 7.5 French balloon-tipped floatation catheter (Arrow TD catheter) was inserted via the right internal jugular vein and positioned in the pulmonary artery. The transoesophageal echocardiography probe was positioned to image the left ventricular outflow tract and aortic valve in the transgastric plane. At four discrete time points, the cardiac output was estimated simultaneously by two independent investigators using pulsed Doppler echocardiography or thermodilution. Pulsed Doppler assessment was performed by positioning the sample volume at the aortic annulus and recording three successive Doppler waveforms. The mean velocity-time integral (VTI) of the three successive waveforms was determined by manually tracing the velocity profile of each waveform using the intrinsic software of the echocardiographic machine. The diameter of the aortic valve annulus at the sampling site was measured and the cross-sectional area (CSA) calculated.

Doppler cardiac output (CO) was calculated from the following equations:

$$\text{Stroke volume (SV) (ml)} = \text{VTI (cm)} \times \text{CSA (cm}^2\text{)}$$

$$\text{CO (ml/min)} = \text{SV} \times \text{HR (beats/min)}$$

Thermodilution measurement of cardiac output was performed using a bedside cardiac output computer (Kontron). Three successive injections of ice cold 5% dextrose were made at end-expiration and values differing by $\pm 10\%$ of the mean were rejected. The four study periods were: immediately prior to sternotomy, and 10 minutes, 60 minutes and 120 minutes after closure of the sternum.

Statistical analysis was by linear regression analysis (Kirkwood, 1988), and by calculation of the standard deviation of the mean difference between two techniques (Bland and Altman, 1986).

Results

Satisfactory visualisation of the aortic annulus and good quality Doppler envelopes were achieved in ten subjects, so that 40 cardiac output measurements were available for analysis. There was reasonable correlation between Doppler and thermodilution estimated CO ($r = 0.82$, $p < 0.001$) (Figure 5.6). The linear regression fit is $x = 1.4 + 0.746y$. Figure 5.7 shows the difference in CO measured by thermodilution and Doppler plotted against the mean cardiac output for the two techniques. The mean bias of Doppler-estimated CO is -0.281 l/min (standard deviation 0.635 l/min). Accordingly, for any single measurement of cardiac output, the Doppler-estimated cardiac output may be 0.96 l/min above, or 1.5 l/min below thermodilution-measured cardiac output. The sensitivity of Doppler in detecting a 15% or more change in cardiac output measured by thermodilution was 67%, with a specificity of 65%.

Figure 5.6

Correlation Between Doppler and Thermodilution Estimation of Cardiac Output.

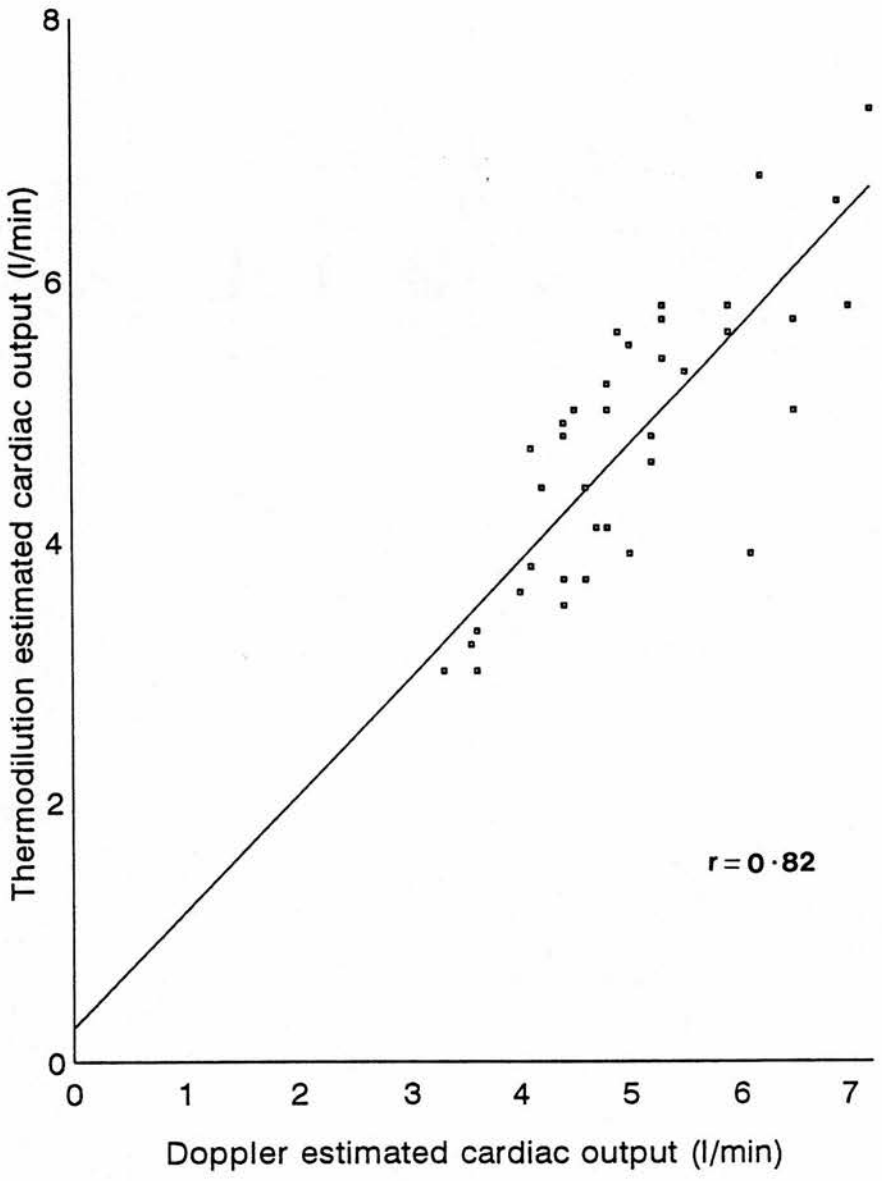
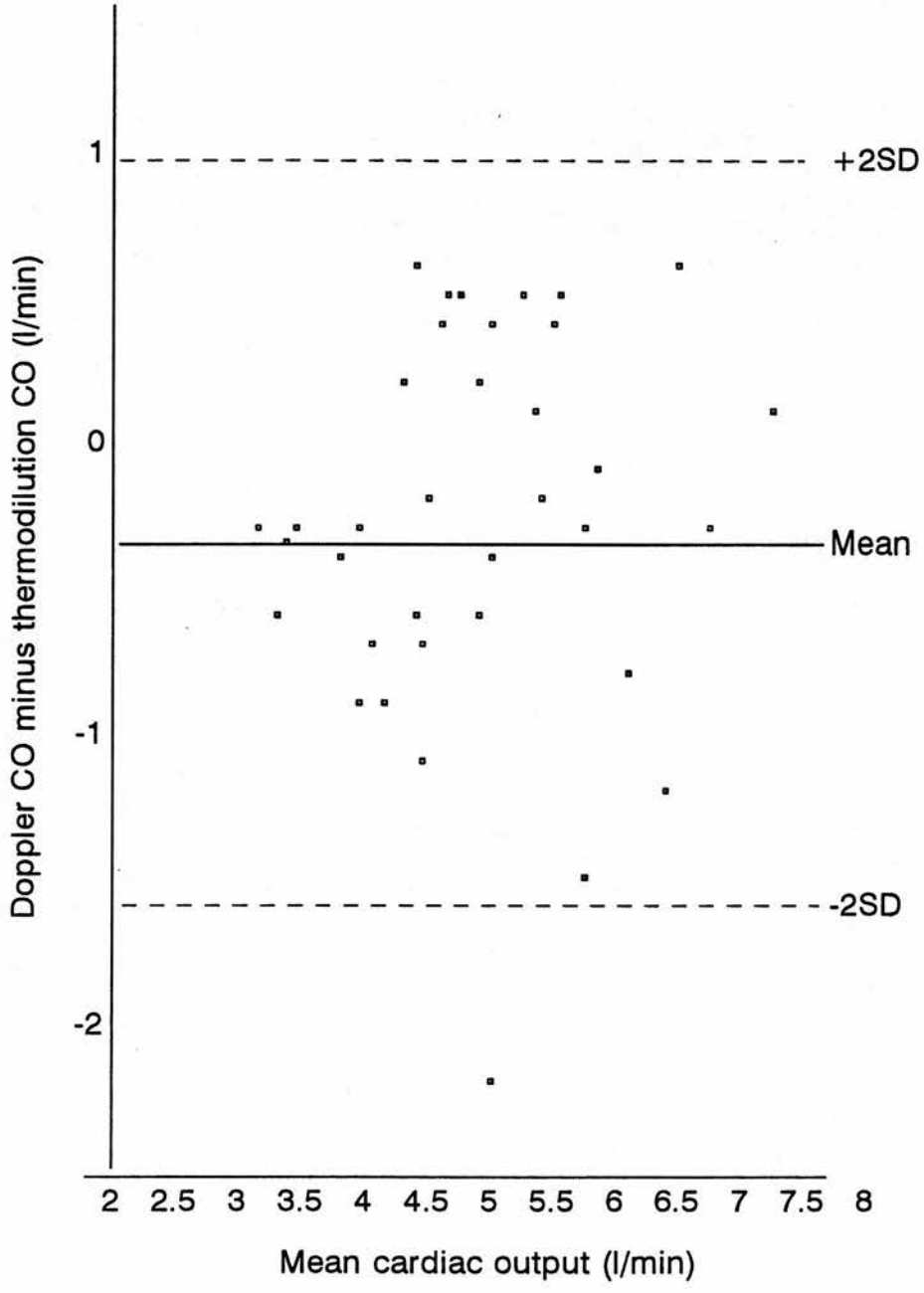


Figure 5.7

Comparison of Doppler and Thermodilution Estimation of Cardiac Output.



Conclusions

These results demonstrate that transoesophageal echocardiographic assessment of cardiac output using pulsed Doppler interrogation in the transgastric plane gives reasonable accuracy when compared with thermodilution. Although the range of agreement between the two techniques was relatively wide, the magnitude of these differences is similar to, or better than, that reported in previous studies in which different methods of cardiac output measurement were compared, for example between thermodilution and dye dilution (De Leeuw and Birkenhager, 1990), or thermodilution and radionuclide cardiography (Wenting et al., 1990).

In practice, there is no "gold standard" technique of cardiac output measurement in man. Indeed, in 1990 Hainsworth commented:

"A reliable (non-invasive) method of estimating cardiac output has long been a 'holy grail' in cardiovascular physiology and the multiplicity of methods, involving many physical and chemical approaches, attests to the difficulties."

Dye dilution and the Fick method are the standard reference techniques, favoured in some research protocols in view of their accuracy and good reproducibility (Fagard and Conway, 1990; De Leeuw and Birkenhager, 1990). However, thermodilution is probably the most widely used technique in clinical practice, being more convenient and allowing frequent serial measurement.

Although linear regression analysis often shows close correlation when thermodilution measurement of cardiac output is compared with other methods, this type of statistical analysis may conceal important differences. This may be overcome by calculating the mean difference and standard deviation of differences as described by Bland and Altman (1986). For example, measurement of cardiac output by thermodilution and dye dilution techniques usually results in close correlation between the two methods ($r = 0.91$-0.98) (Conway and Lund-Johansen, 1990).

Despite this, Russell et al. (1990) found that the mean difference between the two techniques was 1.85 l/min and the standard deviation of the difference was 1.24 l/min. Accordingly, for any single measurement of cardiac output, the value derived by dye dilution might lie between 4.3 l/min below, to 0.6 l/min above the value obtained by thermodilution. This discrepancy between the two techniques is not apparent from the correlation coefficent alone and several authorities have argued convincingly that the method described by Bland and Altman should always be employed when comparing two methods of clinical measurement (Gorback, 1990; Coats, 1990; De Leeuw and Birkenhager, 1990).

Thermodilution is extremely susceptible to error, for example minor alterations in injection technique may overestimate cardiac output by 59%, and errors are particularly likely at low cardiac output (Schuster and Nanda, 1984). Despite the potential for inaccuracy, thermodilution is the standard method used to measure cardiac output in patients undergoing cardiac surgery, justifying its use in this study. Given the inherent limitations of this study, Doppler echocardiography performed satisfactorily with respect to thermodilution. In previous studies, intraoperative transoesophageal echocardiography has been used to estimate cardiac output by pulsed Doppler interrogation of flow in the descending aorta (Freund, 1987; Haude et al., 1989), at the mitral annulus (Ellis et al., 1987; Roewer et al., 1987; Muhiudeen et al., 1991) and in the pulmonary artery (Roewer et al., 1987; Muhiudeen et al., 1991). In each study, the Doppler technique was compared with thermodilution. Unfortunately, the majority of these studies are of limited value, as the results were largely limited to expression of the correlation coefficient, without calculation of the mean difference between the two techniques. Even without this statistic, experience with transoesophageal echocardiography has been disappointing and only modest correlation has been shown with thermodilution. The largest study to use appropriate statistical analysis sampled flow at both the mitral annulus and within the pulmonary artery (Muhiudeen et al., 1991). Neither position allowed accurate estimation of cardiac output, and the results compare unfavourably with the findings of the present study using transgastric imaging. The only previous study to

report close agreement between transoesophageal echocardiography and thermodilution used a non-imaging system to sample flow in the descending aorta (Haude et al., 1989). However, this technique is of limited value as it requires preoperative calibration with precordial Doppler.[2]

These results suggest that transoesophageal echocardiography might find a useful role in perioperative estimation of cardiac output. Transoesophageal echocardiography is often used in the transgastric short-axis view to monitor myocardial function intraoperatively (Chapter 4). By making minor adjustments to this imaging position the transgastric view can be obtained, allowing measurements of cardiac output to be performed repeatedly throughout a procedure. A potential limitation that is common to all echocardiographic techniques, is the occasional inability to obtain satisfactory Doppler recordings. This occurred in a minority of subjects in this series. An additional possible source of error may arise from inaccurate estimation of the cross-sectional area at the sampling site. As this value is derived by squaring the radius, any error made will be exaggerated. In this study the VTI was obtained by manually tracing the Doppler envelope. At present this is a relatively cumbersome, time-consuming technique, however the introduction of automated techniques would aid this process considerably. Finally, the reproducibility of cardiac output measurement by this technique requires to be assessed. This was not specifically addressed in this study as it would require duplicate measurements under conditions of cardiovascular stability, conditions not readily achieved during, or after cardiac surgery.

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[2]Furthermore use of this technique assumes a constant distribution of flow between the arch vessels and the descending aorta. This seems unlikely in the context of cardiac surgery and cardiopulmonary bypass.

Prediction of Pulmonary Artery Pressure with Transoesophageal Echocardiography

It is ten years since transthoracic continuous wave Doppler interrogation of tricuspid regurgitation was first used to estimate pulmonary artery pressure. In the absence of right ventricular outflow tract obstruction, the calculated right atrial-right ventricular systolic pressure difference added to the known, or estimated right atrial pressure, correlates well with the pulmonary artery systolic pressure (Yock, 1984; Currie, et al. 1985; Chan, et al. 1987). This technique is now part of routine clinical practice but only recently became feasible with transoesophageal echocardiography when steerable spectral Doppler capabilities were incorporated into the transducer systems.

To date there have been no reports of the use of transoesophageal echocardiography in this capacity. The major theoretical drawback is that the tricuspid valve is imaged obliquely with transoesophageal echocardiography, with the result that tricuspid regurgitant jets may not be optimally aligned for spectral Doppler interrogation (Seward et al., 1988). Where the direction of the Doppler ultrasound beam differs by more than about 30° to the direction of the regurgitant jet, the peak velocity of the jet will be significantly underestimated. Nevertheless, if the angle is less than 30° then a reasonable estimate of the true peak velocity would be expected.[3] Correction for the angle between the ultrasound beam and the regurgitant jet might allow a closer estimate of the peak velocity to be obtained, but this has not been tested previously.

Accordingly, the aim of this study was to determine whether a reliable estimate of pulmonary artery systolic pressure could be achieved using transoesophageal echocardiography.

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[3]Where the angle between the Doppler ultrasound and the regurgitant jet is 10° the peak velocity will be underestimated by less than 2%. At 30° the error will be 13%. At 40° the error will be 23%.

Methods

40 subjects undergoing cardiac surgery were studied (26 coronary artery bypass grafting, 7 mitral valve replacement, 5 aortic valve replacement, 1 ventricular septal defect repair, 1 thoracotomy for thoracic and cardiac trauma). The transoesophageal echocardiography probe and a pulmonary artery catheter (Arrow TD catheter) were positioned after induction of anaesthesia. The probe was positioned in the oesophageal four chamber position to image the right atrium and tricuspid valve, and the severity of tricuspid regurgitation (TI) was assessed semi-quantitatively using colour flow Doppler. Severity of TI was based on the spatial extent of the regurgitant jet, where mild regurgitation was defined as backflow into the right atrium for less than 1/3 of its length, moderate regurgitation up to 2/3 of its length, and severe regurgitation where the jet extended for the entire right atrial length. Where TI was detected, the jet was interrogated with continuous wave Doppler and the peak systolic velocity (V) measured. The mean of five successive Doppler envelopes was taken if the subject was in sinus rhythm, and the mean of ten if in atrial fibrillation. The pulmonary artery systolic pressure was calculated using the Bernoulli equation ($4V^2$ + right atrial pressure) with, and without correction for the angle between the Doppler ultrasound and the TI jet (Figure 5.8). The angle corrected peak velocity was calculated as follows:

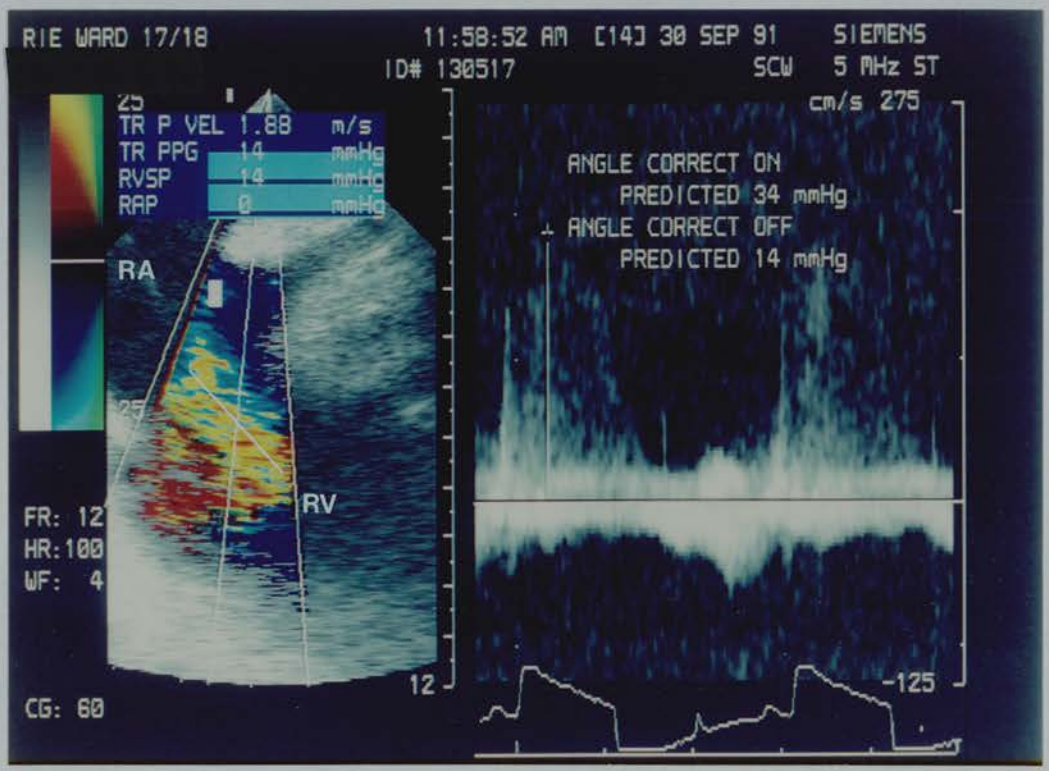
$$\text{Angle corrected peak velocity} = V / \cos(a)$$

where a = the angle between the Doppler ultrasound and the TI jet.

Measurements were made periodically during the intraoperative and immediate postoperative periods, whilst an independent observer simultaneously recorded the systolic pressure as measured by the pulmonary artery catheter. Statistical analysis was performed by calculation of the standard deviation of differences (SDD) (Bland and Altman, 1986), and by linear regression analysis (Kirkwood, 1988).

Figure 5.8

Calculation of Peak Velocity of Tricuspid Regurgitant Jet Using Angle Correction.



Results

No patient had clinical evidence of TI, but satisfactory Doppler envelopes were recorded in 29 subjects in whom TI was demonstrated by colour flow mapping. TI was assessed as mild in seven, moderate in twelve, and severe in ten. The Doppler ultrasound beam was well aligned to the TI jet in nine patients, but in the remainder the angle was $>30^{o}$.

There was only modest correlation between echocardiographically estimated and catheter measured pulmonary artery systolic pressure ($r=0.51$, $p<0.001$) in a range from 15 to 100 mm Hg. The Doppler technique underestimated the pulmonary artery systolic pressure in the majority of patients (mean difference -9.4 mm Hg, SDD 12.1 mm Hg). As 95% of the differences between the two techniques will lie within 1.96 standard deviations of the mean difference (Bland and Altman, 1986), a single Doppler estimate may fall within the range of 33 mm Hg below to 14 mm Hg above the true measurement. Better correlation was found between the two techniques when angle correction was employed ($r=0.80$, $p<0.001$) (Figure 5.9), although echocardiography tended to overestimate the systolic pressure (mean difference +2.9 mm Hg, SDD 6.8 mm Hg) (Figure 5.10). Accordingly, a single angle corrected Doppler estimate of systolic pressure will lie within the range of 10 mm Hg below to 16 mm Hg above the true measurement. Without angle correction, echocardiography was insensitive in detecting a 15% or greater change in systolic pressure (sensitivity 64%; specificity 57%), however with angle correction the sensitivity was increased (sensitivity 78%, specificity 67%).

Conclusions

Doppler envelopes were of sufficient quality to allow the peak velocity of the regurgitant jet to be measured in nearly 75% of these subjects undergoing cardiac surgery. However, despite adequate Doppler envelopes, there was poor correlation between pulmonary artery pressure estimated by echocardiography and that measured

Figure 5.9

Correlation between Doppler-estimated and actual PA pressure.

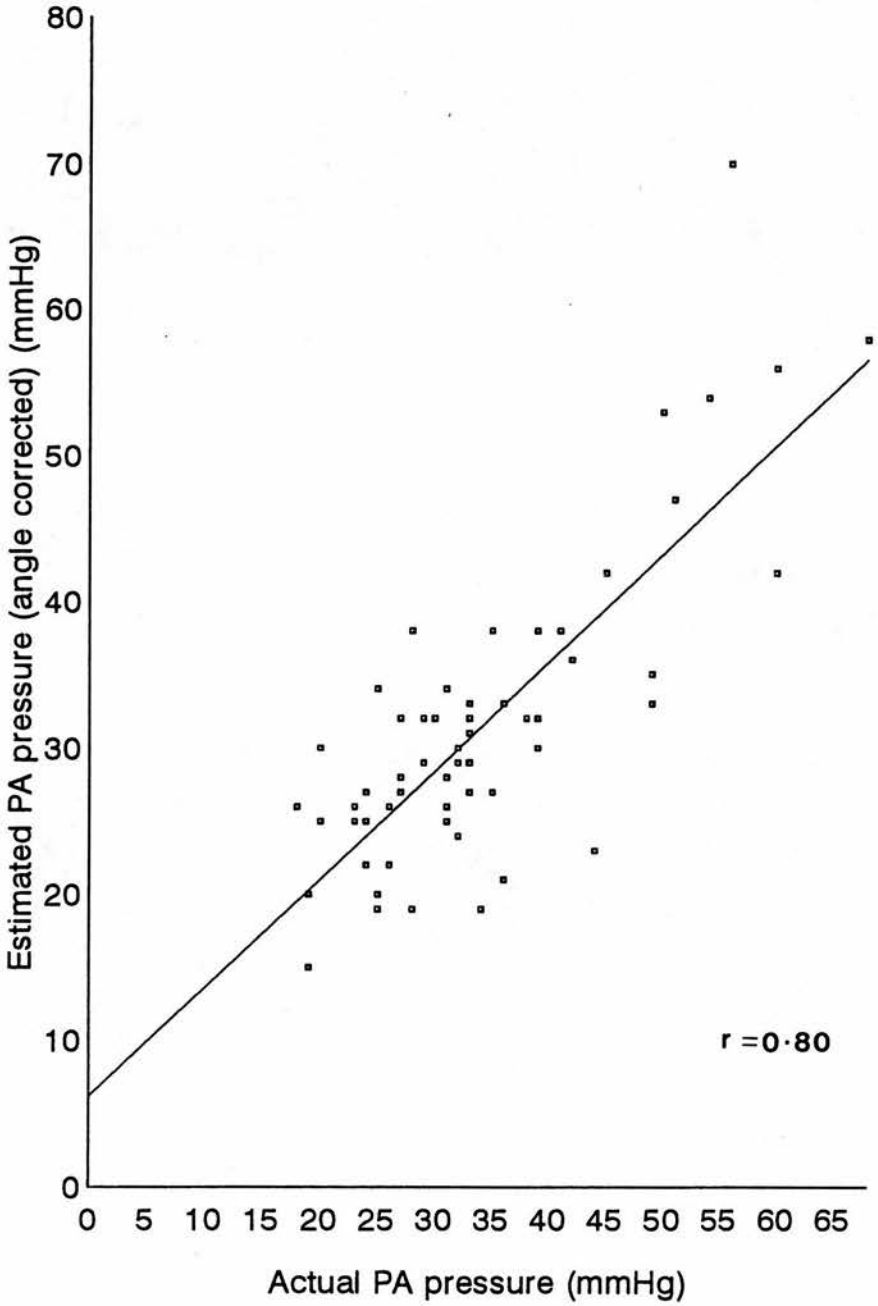
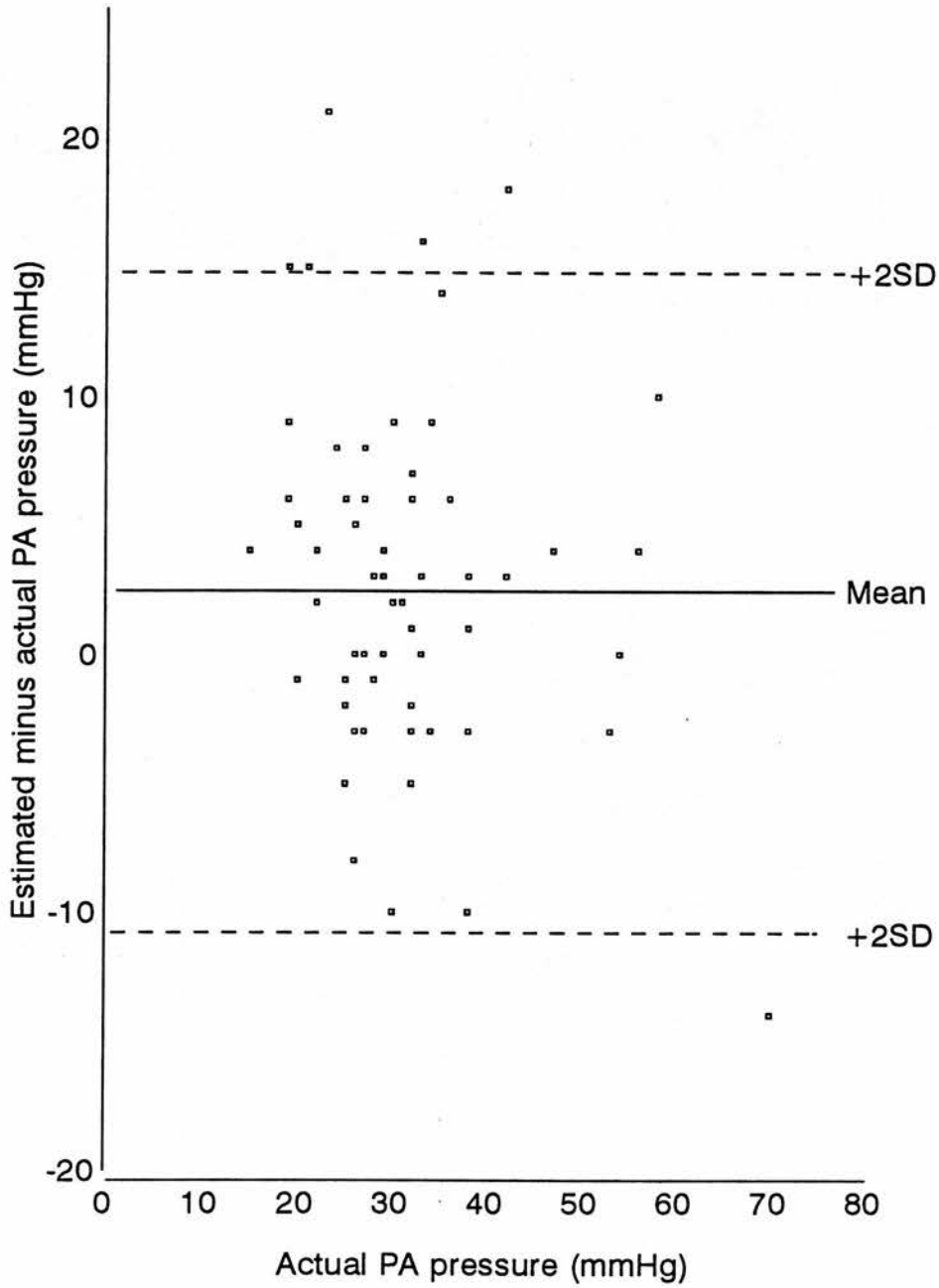


Figure 5.10

Comparison of Doppler-estimated and actual PA pressure.



directly by pulmonary artery catheter. Transoesophageal echocardiography underestimated the true systolic pressure by a mean of 9.4 mm Hg, with a large standard deviation, so that a single reading would have a 95% chance of lying between 33 mm Hg below, to 14 mm Hg above the true reading. This is clearly unacceptable for clinical purposes. Underestimation of the true peak systolic velocity probably accounts for much of the error. The orifice of the tricuspid valve is imaged obliquely from the oesophagus and the majority of regurgitant jets were poorly aligned to the interrogating ultrasound beam. The greater the angle between the jet and the ultrasound beam the greater the likely error, and this error will be compounded when deriving the systolic pressure, since the peak velocity is squared in the Bernoulli equation.

In theory, angle correction might compensate for poor alignment to a regurgitant jet. Colour flow mapping demonstrates the direction of the regurgitant jet in relation to the ultrasound beam and a correction can then be applied. The main drawback to this approach is that a regurgitant jet is spatially orientated in three dimensions, whilst transverse plane transoesophageal echocardiography only images in two dimensions. Accordingly, angle correction may only partially compensate for poor alignment, and additional error might be introduced. In this study, although angle correction improved the ability of transoesophageal echocardiography to estimate pulmonary artery systolic pressure, the margin of error for single measurements remained moderately large making this technique relatively unsatisfactory for absolute measurements. Within a single subject however, echocardiography had a reasonable chance of detecting a 15% or greater change in pulmonary artery pressure, suggesting that although this technique cannot provide reliable quantitative data, it may be sufficiently sensitive for semi-quantitative assessment.

Haemodynamic Assessment Using Transoesophageal Echocardiography: Conclusions

The studies described in this chapter indicate that transoesophageal echocardiography has the potential to fulfil a greater role in the assessment of cardiac haemodynamics intraoperatively. The transgastric plane is complementary to the conventional oesophageal imaging planes, and can be obtained in the majority of patients using transverse plane transoesophageal echocardiography. It should be emphasised that although long axis imaging allows more comprehensive imaging of both the left and right ventricular outflow tracts, it is not helpful in haemodynamic assessment as blood flow remains poorly aligned to Doppler ultrasound directed from the oesophagus (Stumper et al., 1990b). Accordingly, although biplane imaging may become more widely used in the future, the transgastric plane will continue to play an important role in the assessment of cardiac haemodynamics.

CHAPTER 6

CONTRIBUTION OF TRANSOESOPHAGEAL ECHOCARDIOGRAPHY TO DIAGNOSIS AND PATIENT MANAGEMENT IN INTENSIVE CARE

Introduction

Increasingly, transoesophageal echocardiography is used during cardiac surgery to monitor cardiac function and guide surgical procedures. Its role postoperatively in the intensive care unit is less well defined. Isolated case reports and small series have suggested that it can play a valuable role in emergency diagnosis and clinical decision making, particularly in mechanically ventilated patients, in whom adequate imaging can be difficult to achieve with transthoracic echocardiography (Topol et al., 1983; Chan, 1988; Kocher et al., 1990; Davila-Roman et al., 1990; Simpson et al., 1991).

One of the earliest reports indicated that transoesophageal echocardiography might assist in the emergency diagnosis of early postoperative complications following cardiac surgery (Chan, 1988). Seven patients developing hypotension within 48 hours of operation were studied. Three were found to have evidence of cardiac tamponade, one had rupture of the ventricular septum, and the remainder had impaired cardiac function. In every case transoesophageal echocardiography enabled a diagnosis to be made when transthoracic echocardiography had been unsuccessful. Several small series from various North American centres followed, although the patients were drawn from a variety of different critical care settings. The largest series of patients studied following cardiac surgery was reported in abstract form. Of 29 patients developing haemodynamic difficulties postoperatively, problems requiring surgical reintervention were found in 19 (Davila-Roman et al., 1990). A series of 51 critically ill patients in intensive care was reported from the Mayo Clinic (Oh et al., 1990). Twenty-five were in the coronary care unit, 11 in medical intensive care and

15 in the surgical intensive care unit. The commonest indication for transoesophageal echocardiography was unstable haemodynamics: in 10 patients following myocardial infarction, and in 7 patients postoperatively. Transoesophageal echocardiography was shown to be safe and highly successful in enabling a specific diagnosis to be reached. Pearson et al., (1990) also reported their experience in a variety of different intensive care settings. The commonest indication was suspected aortic dissection (29%) and perhaps surprisingly given the intensive care setting, suspected cardiac source of embolism was the second most common indication (26%). Transoesophageal echocardiography was felt to give critical information that was not obtained by transthoracic echocardiography in 44% of studies, and in the remainder was useful in excluding various pathological conditions with greater certainty.

In theory transoesophageal echocardiography might also be used to monitor cardiac function electively during the initial period of postoperative intensive care. This has received little attention, however continuous monitoring might facilitate early detection of such complications as myocardial ischaemia or infarction, hypovolaemia and pericardial effusion. In the following study I examined the clinical utility of elective and emergency transoesophageal echocardiography over a 12 month period in the cardiac surgical intensive care setting.

Methods

During the period 1 August 1991 to 31 July 1992, 33 patients who had undergone coronary artery bypass grafting were monitored electively with transoesophageal echocardiography for 4 hours following their return to the intensive care unit. All patients were sedated and mechanically ventilated, and had also undergone intraoperative monitoring with transoesophageal echocardiography. Continuous invasive haemodynamic monitoring was performed (central venous pressure, intra-arterial pressure and pulmonary artery pressure) and the pulmonary artery occlusion pressure was measured intermittently. The electrocardiogram (ECG) was monitored with a single lead (III).

The basic echocardiographic imaging plane was the short axis view of the left ventricle at mid-papillary muscle level. Images were assessed in real-time every 15 minutes, or more frequently as dictated by the patient's clinical condition. Regional function was assessed as previously described by scoring the wall motion of each myocardial quadrant (Chapter 4). Global myocardial function was monitored by subjective assessment of overall left ventricular contraction using a five point scale: 1: hyperdynamic, 2: normal, 3: mild impairment, 4: moderate impairment, 5: severely impaired. Left ventricular preload was assessed qualitatively from changes in end-diastolic and end-systolic areas in the short axis view. The echocardiographic findings were made available to the clinical staff responsible for the overall management of the patient.

Forty emergency transoesophageal echocardiography studies were performed over the same 12 month period on patients in the cardiac surgical intensive care unit. Transthoracic echocardiography was performed as a preliminary investigation in every case, and transoesophageal echocardiography performed only where diagnostic information had not been obtained. Most subjects were mechanically ventilated at the time of the study, the remainder (n=7) were given intravenous sedation in accordance with standard procedures. All studies were performed by myself.

Results

Elective monitoring: valuable clinical information was obtained in 12 out of 33 subjects. A new regional wall motion abnormality (RWMA) consistent with myocardial ischaemia or infarction was identified in a patient who unexpectedly developed severe postoperative hypotension. Persistence of RWMAs that had developed intraoperatively were shown in 3 patients. No ischaemic changes were observed in the ECG in any subject. Transoesophageal echocardiography suggested hypovolaemia as the cause of hypotension in 6 patients. In three of these subjects, echocardiography demonstrated hypovolaemia before a fall in central venous pressure or pulmonary artery wedge pressure had occurred. These haemodynamic parameters

changed subsequently and all 6 patients responded to fluid challenge. In two additional patients with hypotension, transoesophageal echocardiography supported the clinical diagnosis of impaired left ventricular function and helped exclude other factors.

Emergency studies: indications for emergency transoesophageal echocardiography are shown in Table 6.1.

Table 6.1 Indications for Emergency Transoesophageal Echocardiography

Indication	**Number**
Unexplained postoperative hypotension	9
Failure to wean from intra-aortic balloon pump	4
Suspected prosthetic valve dysfunction	11
Exclusion of intracardiac source of embolism	4
Suspected aortic pathology	3
Major thoracic trauma	8
Unexplained sepsis	1

Important diagnostic information was obtained by transoesophageal echocardiography in eleven of the thirteen patients with unexplained hypotension or failure to wean from intra-aortic balloon pump. This included: severe global impairment of left ventricular function in four patients and moderate impairment in three patients. Other diagnoses included: major regional wall motion abnormalities in two patients,

pericardial tamponade in one patient, and patch dehiscence following repair of a ventricular septal defect in one patient. No diagnostic information was obtained in two patients, although severe tricuspid incompetence of uncertain significance was demonstrated in one instance.

In suspected prosthetic valve dysfunction transoesophageal echocardiography revealed paraprosthetic leakage in four patients, a ruptured bioprosthetic leaflet in one, a thrombosed mitral prosthesis in one, and no abnormality in the remaining five subjects.

Intracardiac source of embolism was excluded in all four patients studied.

In suspected aortic pathology, transoesophageal echocardiography revealed a thoracic aneurysm in one subject and excluded dissection in two subjects.

In patients with thoracic trauma, transoesophageal echocardiography revealed a pericardial effusion in two subjects and myocardial wall motion abnormalities suggesting myocardial contusion in two. Aortic rupture was visualised in one subject (Figure 6.1) and aortic injury was excluded in all other patients.

No evidence of endocarditis was seen in one patient with unexplained septicaemia.

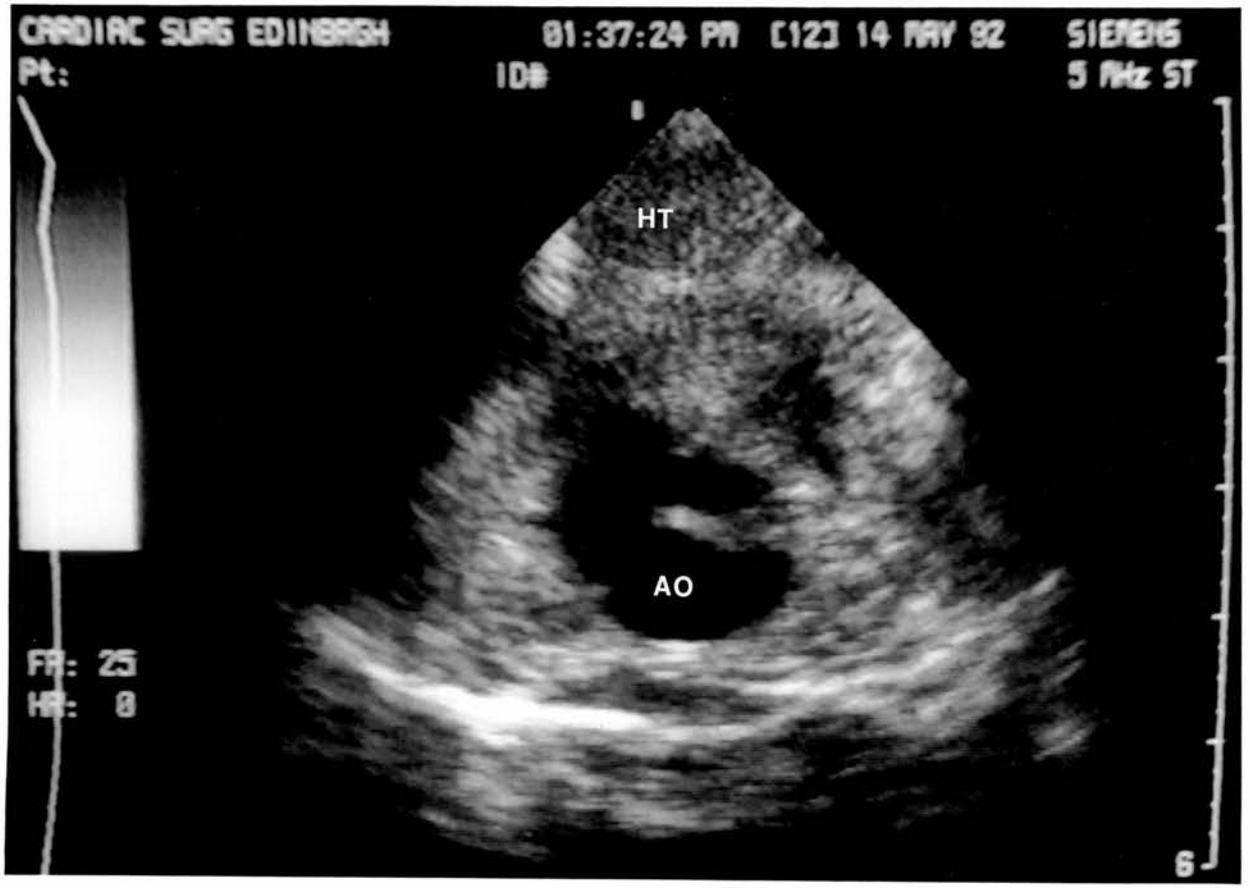
Complications: one patient developed ventricular tachycardia that degenerated into ventricular fibrillation during emergency transoesophageal echocardiography. Resuscitation was successful. No complications resulted from elective monitoring with transoesophageal echocardiography.

Conclusions

This is the largest series to date to examine the role of transoesophageal echocardiography in diagnostic imaging in the cardiac surgical intensive care unit.

Figure 6.1

Aortic Rupture Caused by High Speed Deceleration Injury. The posterior aortic wall has been disrupted and there is a large haematoma compressing the lumen.



The findings are consistent with earlier studies in which diagnostic information was frequently obtained when transthoracic imaging had been inadequate (Chan, 1988; Davila-Roman et al., 1990). The major advantage of transoesophageal echocardiography over transthoracic echocardiography in this environment, is that satisfactory imaging is not prevented by the presence of mechanical ventilation, dressings and drains.

The emergency studies were all performed on patients within a cardiac surgical intensive care unit. Given the prevalence of cardiac abnormalities in this setting, the high yield of diagnostic information in this series is readily explicable. It is uncertain whether transoesophageal echocardiography would be of similar benefit within a general intensive care unit where the predominant clinical problems usually comprise septicaemia, ventilatory failure and multi-organ dysfunction. During the latter period of the study, several requests for emergency transoesophageal echocardiography were received from the general intensive care unit. Six studies were performed and the yield of specific diagnostic information was low, although a diagnosis of infective endocarditis was made in one case of unexplained septicaemia. Nevertheless, previous authors have suggested that transoesophageal echocardiography does indeed have a useful diagnostic role in this setting (Oh et al., 1990; Porembka and Hoit, 1991).

When transoesophageal echocardiography was used electively to monitor cardiac function in patients following coronary artery bypass grafting, useful clinical information was obtained in 12 out of 33 subjects. Admittedly this information did not have a major impact on postoperative decision making, however transoesophageal echocardiography was useful in confirming clinical diagnoses, particularly of impaired left ventricular function and hypovolaemia. The pulmonary artery occlusion pressure is a poor measure of left ventricular preload in situations that result in a change in left ventricular compliance. This may occur with use of positive-end expiratory pressure, in myocardial ischaemia and following cardiopulmonary bypass (Raper et al., 1986). This may account for the observation

that hypovolaemia sufficient to cause hypotension occurred without a major change in pulmonary artery occlusion pressure or central venous pressure, but was recognised echocardiographically. These observations are consistent with similar reports that transoesophageal echocardiography may provide a more reliable guide to changes in left ventricular filling than does invasive pressure monitoring (Beaupre et al., 1983; Roizen et al., 1984). In the present study the diagnosis of left ventricular hypovolaemia was made subjectively on the basis of changes in end-diastolic and end-systolic areas in the short axis view. In the clinical environment subjective assessment of echocardiograms is common, justifying the approach adopted in this study, however these results must be interpreted with caution and viewed as preliminary. Before echocardiography can be advocated as a technique to monitor left ventricular filling postoperatively, more detailed studies are required to examine its sensitivity and specificity, to compare qualitative versus quantitative assessment, and to examine its reproducibility in the diagnosis of hypovolaemia.

There have been few reports of the use of transoesophageal echocardiography for elective monitoring of cardiac function postoperatively. Leung et al., (1989) using off-line analysis, reported that 25% of patients develop a RWMA in the intensive care unit following coronary artery bypass surgery. These authors suggested that RWMAs developing in this phase represent important adverse prognostic factors. In contrast to Leung's study, only one patient in the present series was observed to develop a new RWMA when monitored in real-time. Saada et al., (1989) demonstrated that real-time analysis is less sensitive than off-line analysis in the detection of RWMAs and this may account for the difference between the two studies. Nevertheless, as this study was designed to determine the clinical utility of elective monitoring with transoesophageal echocardiography, real-time analysis was selected. In theory, detection of a new RWMA might enable specific therapy to be initiated with the aim of improving the balance between myocardial oxygen supply and demand. However, the benefits of treating new RWMAs have not been examined, and in view of the low numbers detected when real-time monitoring was performed, at present there does not appear to be a conclusive case for elective

monitoring postoperatively using transoesophageal echocardiography.

The incidence of complications with transoesophageal echocardiography is low. In the European Cooperative Study one death ocurred in 10,419 studies (Daniel et al., 1991). Given the clinical condition of most patients in the intensive care setting it might be expected that transoesophageal echocardiography would be more hazardous than in a stable, outpatient population. Indeed, Oh et al., (1990) reported a complication rate of 4% in their series of critically ill patients, compared to less than 1% in stable patients. In the present series, one patient developed a life-threatening arrhythmia, but was successfully resuscitated.

Complications during prolonged monitoring with transoesophageal echocardiography are rare, although transient vocal cord paralysis has been reported in two patients undergoing neurosurgery in an upright position (Cucchiara et al., 1984). This was thought to be secondary to localised pressure from the transducer tip, and providing extreme neck flexion is avoided the risk of pressure effects appears to be remote. No complications were seen in the electively monitored patients in this series.

Based on this experience I suggest that transoesophageal echocardiography can play a valuable role in emergency diagnosis in patients in the cardiac surgical intensive care unit. Studies are readily performed and, unlike transthoracic echocardiography, are not impeded by the presence of surgical dressings, mechanical ventilation and subcutaneous emphysema. Further studies are required before the routine use of transoesophageal echocardiography can be recommended for elective monitoring. Although the information derived from echocardiography was of some clinical interest, it failed to make a major impact on decision making. Unless the high cost of the technology decreases and the case for early detection and treatment of RWMAs becomes established, then elective monitoring with transoesophageal echocardiography appears unlikely to become widely adopted.

CHAPTER 7

CONCLUDING COMMENTS

Since the prototype probes were developed in the early 1980s there has been rapid growth in interest in transoesophageal echocardiography. Today, just over a decade after its first development, use of this imaging modality is no longer restricted to a few interested cardiologists and anaesthestists. The studies presented in this thesis illustrate the varied applications of transoesophageal echocardiography particularly in the fields of cardiology, cardiac surgery, anaesthesia and intensive care, but also in orthopaedic surgery and accident and emergency medicine. It is a technique that crosses interspecialty boundaries and by providing unique images of the heart, can provide new insights into old conditions and perhaps stimulate novel directions for future research.

The studies in patients undergoing CPR helped resolve some of the controversies surrounding the mechanisms that produce forward blood flow during resuscitation. These results also raised the possibility that transoesophageal echocardiography might become a useful technique to assess the effectiveness of CPR. The echocardiographic criteria for ineffective CPR remain to be validated, nevertheless, a recent study has also supported the possibility that transoesophageal echocardiography might be used to guide resuscitation attempts by identifying "hopeless CPR" (Wright, 1993).

In Chapter 3, I described the use of transoesophageal echocardiography to investigate the pathophysiology of the fat embolism syndrome. The results provided strong evidence for the mechanical theory of fat embolism and raised the possibility that the systemic manifestations of the condition might sometimes arise secondary to paradoxical embolism through a patent foramen ovale. These results suggested that transoesophageal echocardiography might be a useful technique to help investigate the pathophysiology of this condition and could perhaps allow prophylactic measures

and new treatments to be developed. Indeed, following publication of some of this work, a complimentary editorial in the *New England Journal of Medicine* suggested that these observations could have a profound influence on the elucidation of the disease and might provide an important direction for future research (Fabian, 1993). In the Royal Infirmary, Mr James Christie has continued to use transoesophageal echocardiography to investigate the phenomenon of fat embolism and it is hoped that these studies will allow new techniques to be developed to help prevent this syndrome. At the time of writing, paradoxical embolism across a patent foramen ovale has been observed in a further patient, post-mortem examination in a subject with Grade 3 embolism revealed a large pulmonary embolus that comprised a bone marrow core surrounded by thrombus, and preliminary rheological studies have suggested that high grade embolism is often accompanied by vigorous activation of the clotting cascade.

At present, intraoperative transoesophageal echocardiography has still not become a widely used technique during cardiac surgery in the United Kingdom. There are several possible explanations. Intraoperative echocardiography is time-consuming and the echocardiographic machine may require to be kept in the operating theatre for considerable periods. In many centres echocardiography is performed solely by cardiologists, who may have insufficient equipment or trained personnel to support their anaesthetic and surgical colleagues. Outside of specific research protocols intraoperative echocardiography is most likely to benefit patients undergoing mitral valve repair or correction of complex congenital heart defects. Such procedures are infrequent in many adult cardiac surgical centres where the routine workload consists of coronary artery bypass surgery, and aortic and mitral valve replacement. The potential benefits of transoesophageal echocardiography may be less readily apparent in these types of procedures, although as was discussed in Chapter 5, it might be used to estimate cardiac output perioperatively and for the immediate haemodynamic evaluation of prosthetic aortic valves.

Transoesophageal echocardiography was developed primarily as a diagnostic imaging

system and it has received less attention as a research technique. Some of the potential limitations of transoesophageal echocardiography as a research tool were discussed in Chapter 4. The relatively low prevalence of new RWMAs in patients undergoing CABG may be evidence of balanced anaesthetic regimens and optimal surgical techniques. However, it also implies that large sample sizes will be required if transoesophageal echocardiography is to be used in trials of new agents designed to reduce the incidence of perioperative ischaemia. Assessment of global left ventricular function following CPB remains difficult, and although transoesophageal echocardiography is relatively simple to perform, the area ejection fraction is not solely an index of myocardial contractility but will also be influenced by loading conditions. Alternative measurements currently under investigation, such as meridonal wall stress, might ultimately allow this problem to be overcome.

When this work was commenced transoesophageal echocardiography had not been widely used as a diagnostic imaging modality in cardiac surgical intensive care. Three years later its role in emergency diagnosis has become generally accepted. As discussed in Chapter 6 its value in elective monitoring remains to be determined. However the development of smaller probes may stimulate further assessment of the place of transoesophageal echocardiography in postoperative monitoring. Future developments, that may also increase its popularity in the perioperative and critical care settings might include automatic contour detection, on-line quantitative analysis of global and regional myocardial function, and cineloop display of baseline recordings for comparison alongside later recordings. Biplane and multiplane imaging are also likely to make considerable contributions. There seems little doubt that transoesophageal echocardiography will continue to contribute to medical practice over the next decade and longer.

APPENDIX

Formulae

Area Ejection Fraction (AEF) = $(LVA_d - LVA_s)/LVA_d$
where LVA_d is end-diastolic left ventricular cross-sectional area and LVA_s is end-systolic left ventricular cross-sectional area. In Chapter 2, the areas at end-relaxation and end-compression were substituted for LVA_d and LVA_s respectively.

Stroke Volume Index (SVI) = Stroke Volume/BSA
where BSA is body surface area.
Normal range: 40-70 $ml.m^{-2}$

Left Ventricular Stroke Work Index (LVSWI) = SVI x 0.0136 x (MAP-PCWP)
where MAP is mean arterial pressure and PCWP is mean pulmonary capillary wedge pressure.
Normal range: 40-80 $g.m^{-1}.m^{-2}$

Systemic Vascular Resistance (SVR): 80 x (MAP-RA)/CO
where RA is mean right atrial pressure and CO is the cardiac output.
Normal range: 770-1500 $dynes.sec^{-1}.cm^{-5}$

Cardiac Index (CI) = CO/BSA.
Normal range: 2.5-4.0 $l.min^{-1}.m^{-2}$

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Original Papers

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2. Pell ACH, Christie J, Keating J & Sutherland GR (1993). The detection of fat embolism by transoesophageal echocardiography during reamed intramedullary nailing. *J Bone Jt Surg*,**75-B**: 921-925.

3. Pell ACH, Pringle S, Guly UG, Robertson CE & Steedman D (1994). Assessment of the active compression-decompression device (ACD) in cardiopulmonary resuscitation using transoesophageal echocardiography. *Resuscitation*,**27**: 137-140.

4. Christie J, Burnett R, Potts HR & Pell ACH (1994). Echocardiography of transatrial embolism during cemented and uncemented hemi-arthroplasty of the hip. *J Bone Jt Surg*,**76-B**: 409-412.

5. Pell ACH, Guly UM, Sutherland GR, Bloomfield P, Steedman DJ & Robertson CE (1994). Mechanism of closed chest cardiopulmonary resuscitation investigated by transoesophageal echocardiography. *J Accident and Emergency Med*,**11**: 139-143.

Published Abstracts

1. Pell ACH, Robertson C, Steedman D, Sutherland GR & Bloomfield P (1992). New insights into the mechanism of cardiopulmonary resuscitation using transoesophageal echocardiography. *Resuscitation*,**24**: 175.

2. Pell ACH, Campanella C, Prasad S, Cale ARJ, Duncan AJ & Sutherland GR (1992). The role of transoesophageal echocardiography in cardiac surgical intensive care. *Br Heart J*,**68**: 136.

3. Pell ACH, Campanella C, Sinclair CJ, Scott DHT & Sutherland GR (1992). Does transoesophageal echocardiography aid diagnosis and patient management in adult cardiac surgical intensive care? *Eur Heart J*,**13(suppl)**: 40.

4. Pell ACH, Bloomfield P, Robertson CE, Guly UM, Steedman DJ & Sutherland GR (1993). Direct cardiac compression generates systemic blood flow during cardiopulmonary resuscitation: evidence against the thoracic pump. *J Am Coll Cardiol*,**21**: 147A.

5. Pell ACH, Keating JF, Christie J, Sutherland GR (1993). Use of transesophageal echocardiography to predict patients at risk of the fat embolism syndrome following traumatic injuries. *J Am Coll Cardiol*,**21**: 264A.

6. Guly UM, Pell ACH, Bloomfield P *et al.* (1993) Investigation of the mechanisms of cardiopulmonary resuscitation in man by transoesophageal echocardiography. *Ann Emerg Med*,**22**: 938.

7. Pell ACH, Keating JF, Christie J & Sutherland GR (1993). Identification of patients at risk of the fat embolism syndrome using transoesophageal echocardiography. *Br Heart J*,**69(suppl)**: 79.

Reviews

1. Pell ACH & Sutherland GR (1993). Intraoperative echocardiography: the relative roles of transesophageal and epicardial imaging. In: Roelandt JRTC, Sutherland GR, Iliceto S, Linker DT, eds. *Cardiac Ultrasound*. Churchill Livingstone, Edinburgh.

2. Guly UM, Pell ACH & Robertson CE (1993). Blood flow mechanisms during cardiopulmonary resuscitation. In: *Year Book of Intensive Care and Emergency Medicine*. Springer Verlag, Berlin-Heidelberg.

3. Pell ACH & Sutherland GR (1994). Intraoperative echocardiography: transoesophageal and epicardial imaging. *Hospital Update*,**Cardiology Seminar (Supplement)**: 11-19.

BIBLIOGRAPHY

ALS Working Party of the ERC (1992). Guidelines for advanced life support. *Resuscitation*,**24**: 111-121.

Ashemberg W, Shulter M, Kremer P *et al.* (1986). Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol*,**7**: 163-166.

Babbs CF, Taker WA, Paris RL, Murphy RJ & Davis RW (1982). CPR with simultaneous compression and ventilation at high airway pressure in 4 animal models. *Crit Care Med*,**10**: 501-504.

Ballantyne CM, Verani MS, Short HD, Hyatt C & Noon GP (1987). Delayed recovery of severely "stunned" myocardium with the support of a left ventricular assist device after CABG. *J Am Coll Cardiol*,**10**: 710-712.

Barnard MJ & Linter SPK (1993). Acute circulatory support. *Br Med J*,**307**: 35-41.

Baumgartner H, Khan S, DeRobertis M, Czer L & Maurer G (1992). Effect of prosthetic aortic valve design on the Doppler-catheter gradient correlation: An in vitro study of normal St. Jude, Medtronic-Hall, Starr-Edwards and Hancock valves. *J Am Coll Cardiol*,**19**: 324-332.

Beaupre PN, Cahalan MK, Kremer PF *et al.* (1983). Does pulmonary artery occlusion pressure adequately reflect left ventricular filling during anesthesia and surgery? (abstr). *Anesthesiology*,**59**: 3a.

Beaupre PN (1984). Intraoperative detection of changes in left ventricular segmental wall motion by transesophageal two-dimensional echocardiography. *Am Heart J*,**107**: 1021-1023.

Bergentz S-E (1961). Studies on the genesis of posttraumatic fat embolism. *Acta Chirug Scand*,**282**: 1-72.

Bhayana JN, Kalmbach T, Booth FVMcL, Mentzer RM & Schimert G (1989). Combined antegrade/retrograde cardioplegia for myocardial protection: a clinical trial. *J Thorac Cardiovasc Surg*,**98**: 956-960.

Bland JM & Altman DG (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*,**i**: 307-310.

Bolling SF, Groh MA, Mattson AM, Grinage RA & Gallagher KP (1992). AICA riboside improves post-ischemic cardiac recovery in dogs on cardiopulmonary bypass. *Ann Thorac Surg*,**54**: 93-98.

Braunwald E & Kloner RA (1982). The stunned myocardium: Prolonged, post-ischemic ventricular dysfunction. *Circulation*,**66**: 1146-1149.

Braunwald E (1992). Assessment of cardiac function. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine*: 419-443. 4th ed. WB Saunders, Philadelphia.

Bulkley BH & Hutchins GM (1977). Myocardial consequences of coronary artery bypass graft surgery: The paradox of necrosis in areas of revascularisation. *Circulation*,**56**: 906-913.

Bullough D, Fox M, Young M, Gruber H & Mullane K (1990). Acadesine regulates adenosine during early reperfusion to improve functional recovery in the post-ischemic guinea pig heart (abstr). *Japn J Pharmacol*,**52**: 85P.

Burstow DJ, Nishimura RA, Bailey KR *et al.* (1989). Continuous-wave Doppler echocardiographic measurements of prosthetic valve gradients- a simultaneous Doppler-catheter correlative study. *Circulation*,**80**: 504-514.

Castella X, Valles J, Cabezuelo MA, Fernandez R & Artigas A (1992). Fat embolism syndrome and pulmonary microvascular cytology. *Chest*,**101**: 1710-1711.

Chaitman BR, Bonan R, Lepage G *et al.* (1979). Hemodynamic evaluation of the Carpentier-Edwards porcine xenograft. *Circulation*,**60**: 1170-1182.

Chaitman BR, Alderman EL, Sheffield LT *et al.* (1983). Use of survival analysis to determine the clinical significance of new Q waves after coronary bypass. *Circulation*,**67**: 302-309.

Chan K, Currie PJ, Seward JB *et al.* (1987). Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery pressure. *J Am Coll Cardiol*,**9**: 549-554.

Chan K-L (1988). Transesophageal echocardiography for assessing cause of hypotension after cardiac surgery. *Am J Cardiol*,**62**: 1142-1143.

Chandra N, Rudikoff M & Weisfeldt ML (1980). Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. *Lancet*,**i**: 175-178.

Chapelle J-P, Allaf ME, Larbuisson R, Limet R, Lamy M & Heusghem C (1986). The value of serum CK-MB and myoglobin measurements for assessing perioperative myocardial infarction after cardiac surgery. *Scand J Clin Lab Invest*,**46**: 519-526.

Chastre J, Fagon J & Soler P *et al.* (1990). Bronchoalveolar lavage for rapid diagnosis of the fat embolism syndrome in trauma patients. *Ann Intern Med*,**113**: 583-588.

Chung F, Seyone C & Rakowski H (1991). Transoesphageal echocardiogram may fail to diagnose perioperative myocardial infarction. *Can J Anaesth*,**38**: 98-101.

Churchwell AL (1991). Evaluation of pulmonary venous flow by transesophageal echocardiography. *J Am Coll Cardiol*,**18**: 72-74.

Clements FM, de Bruijn NP & Kisslo JA (1986). Transesophageal echocardiographic observations in a patient undergoing closed-chest massage. *Anesthesiology*,**64**: 826-88.

Clements FM & de Bruijn NP (1987). Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. *Anesth Analg*,**66**: 249-261.

Clements FM, Harpole DH, Quill T, Jones RH & McCann RL (1990). Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography. *Br J Anaesthesia*,**64**: 331-336.

Coats AJS (1990). Doppler ultrasonic measurement of cardiac output: reproducibility and validation. *Eur Heart J*,**11(Suppl I)**: 49-61.

Cohen TJ, Tucker KJ, Redberg RF *et al.* (1991). Active compression-decompression resuscitation: a new method of cardiopulmonary resuscitation (abstr). *Circulation*,**84**: II-9.

Cohen TJ, Tucker KJ, Lurie KG *et al.* (1992a). Active compression-decompression. A new method of cardiopulmonary resuscitation. *JAMA*,**267**: 2916- 2923.

Cohen TJ, Tucker KJ, Redberg RF *et al.* (1992b). Active compression decompression. A novel method of cardiopulmonary resuscitation. *Am Heart J*,**124**: 1145-1150.

Cohen TJ, Goldner B, Maccaro P *et al.* (1993). Impoved resuscitation, 24-hour survival, and neurologic outcome with active compression-decompression cardiopulmonary resuscitation: the North Shore University Hospital ACD CPR survival trial (abstr). *Circulation*,**88**: I-10.

Cohnheim J (1889). *Lectures in General Pathology*, vol 1. New Sydenham Series, London.

Conway J & Lund-Johansen PL (1990). Thermodilution method for measuring cardiac output. *Eur Heart J*,**11(Suppl I)**: 17-20.

Criley JM, Blaufuss AH & Kissel GL (1976). Cough-induced cardiac compression. Self-administered form of cardiopulmonary resuscitation. *JAMA*,**236**: 1246-1250.

Cucchiara RF, Nugent M, Seward JB & Messick JM (1984). Air embolism in upright neurosurgical patients: detection and localization by two-dimensional transesophageal echocardiography. *Anesthesiology*,**60**: 353-355.

Cummins RO, Eisenberg MS, Hallston AP & Litwin PE (1985). Survival of out of hospital cardiac arrest with early initiation of cardiopulmonary resuscitation. *Am J Emerg Med*,**3**: 114-119.

Currie PJ, Seward JB, Chan K *et al.* (1985). Continuous wave Doppler determination of right ventricular pressure: A simultaneous Doppler-catheterisation study in 127 patients. *J Am Coll Cardiol*,**6**: 750-756.

Currie PJ, Schiavan WA, Stewart WJ, Lombardo HP, Burgess LA & Salcedo EE (1987). Evaluation of mitral prosthetic dysfunction with transesophageal echocardiography color flow doppler in ambulatory patients (abstr). *Circulation*,**76**: 39.

Currie PJ, Stewart WJ, Salcedo EE *et al.* (1988). Comparison of intraoperative transesophageal and epicardial color flow Doppler in mitral valve repair (abstr). *J Am Coll Cardiol*,**11**: 20A.

Dan M, Bonato R, Mazzucco A *et al.* (1990). Value of transesophageal echocardiography during repair of congenital heart defects. *Ann Thorac Surg*,**50**: 637-643.

Daniel WG, Nellesen U, Shroeder E *et al.* (1988). Left atrial spontaneous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. *J Am Coll Cardiol*,**11**: 1204-1211.

Daniel WG, Erbel R, Kasper W *et al.* (1991). Safety of transeophageal echocardiography. A multicenter survey of 10,419 examinations. *Circulation*,**83**: 817-821.

Davila-Roman VG, Barzilai B, Eaton M, Wareing TA & Kouchoukos NT (1990). Early postoperative complications detected by transesophageal echocardiography in cardiothoracic surgery patients (abstr). *J Am Coll Cardiol*,**15**: 130A.

De Leeuw PW & Birkenhager WH (1990). Some comments on the usefulness of measuring cardiac output by dye dilution. *Eur Heart J*,**11(Suppl I)**: 13-16.

Deshmukh HG, Weil MH, Rackow EC, Trevino R & Bisera J (1985). Echocardiographic observations during cardiopulmonary resuscitation: a preliminary report. *Crit Care Med*,**13**: 904-906.

Deshmukh HG, Weil MH, Gudipati CV, Trevino RP, Bisera J & Rackow EC (1989). Mechanism of blood flow generated by precordial compression during CPR. 1. Studies on closed chest precordial compression. *Chest*,**95**: 1092-1099.

Dines DE, Burgher IW & Okazaki H (1975). The clinical and pathologic correlation of fat embolism. *Mayo Clin Proc*,**50**: 407-411.

Douglas PS, O'Toole ML & Woolard J (1990). Regional wall motion abnormalities after prolonged exercise in the normal left ventricle. *Circulation*,**82**: 2108-2114.

Dubroff JM, Clark MB, Wong CYH, Spotnitz AJ, Collins RH & Spotnitz HM (1983). Left ventricular ejection fraction during cardiac surgery: a two-dimensional echocardiographic study. *Circulation*,**68**: 95-103.

Ellis JE, Runyon-Hass A, Lichtor JL, Keamy MF & Roizen MF (1987). Can Doppler ultrasound, targeted by two dimensional transesophageal echocardiography, be used to measure cardiac output? (abstr). *Anesthesiology*,**67**: A638.

Ellis RJ, Mangano DT & VanDyke DC (1979). Relationship of wedge pressure to end-diastolic volume in patients undergoing myocardial revascularization. *J Thorac Cardiovasc Surg*,**78**: 605-613.

Emson H (1958). Fat embolism studied in 100 patients dying after injury. *J Clin Pathol*,**11**: 28-35.

Erbel R, Borner N, Steller D *et al.* (1987). Detection of aortic dissection by transoesophageal echocardiography. *Br Heart J*,**58**: 45-51.

Erbel R, Rohmann S, Drexler M *et al.* (1988). Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach. A prospective study. *Eur Heart J*,**9**: 43-53.

Erbel R, Rennollet H, Engberding R, Visser C, Daniel W & Roelandt J (European Cooperative Study Group for Echocardiography) (1989). Echocardiography in diagnosis of aortic dissection. *Lancet*,**i**: 457-461.

Europe/Canada Perioperative Ischaemia Research Group (1993). Multinational study of the effect of acadesine on major cardiovascular outcomes associated with CABG surgery (abstr). *J Am Coll Cardiol*,**21**: 150A.

Evarts CM (1970). The fat embolism syndrome: a review. *Surg Clin N Am*,**50**: 493-507.

Fabian TC, Hoots AV, Stanford DS, Patterson CR & Mangiante EC (1990). Fat embolism syndrome: prospective evaluation in 92 fracture patients. *Crit Care Med*,**18**: 42-46.

Fabian TC (1993). Unraveling the fat embolism syndrome. *N Engl J Med*,**329**: 961-963.

Fagard R & Conway J (1990). Measurement of cardiac output: Fick principle using catheterization. *Eur Heart J*,**11(Suppl I)**: 1-5.

Feneley MP, Maier GW, Gaynor JW *et al.* (1987). Sequence of mitral valve motion and transmitral blood flow during manual cardiopulmonary resuscitation in dogs. *Circulation*,**76**: 363-375.

Fisher J, Vaghaiwalla F, Tsitlik J *et al.* (1982). Determinants and clinical significance of jugular venous valve competence. *Circulation*,**65**: 188-196.

Fonte DA & Hausberger FX (1971). Pulmonary free fatty acids in experimental fat embolism. *J Trauma*,**11**: 668-672.

Force T, Kemper AJ, Bloomfield P *et al* (1985). Non-Q wave perioperative myocardial infarction: assessment of the incidence and severity of regional dysfunction with quantitative two-dimensional echocardiography. *Circulation*,**72**: 781-789.

Force T, Hibberd P, Weeks G *et al.* (1990). Perioperative myocardial infarction after coronary artery bypass surgery. Clinical significance and approach to risk stratification. *Circulation*,**82**: 903-912.

Forney J & Ornato JP (1980). Blood flow with ventilation alone in a child with cardiac arrest. *Ann Emerg Med*,**9**: 624-626.

Frazin L, Talano JV, Stephanides L, Loeb HS & Gunnar RM. Esophageal echocardiography (1976). *Circulation*,**54**: 102-108.

Freund PR (1987). Transesophageal Doppler scanning versus thermodilution during general anesthesia: An initial comparison of cardiac output techniques. *Am J Surg*,**153**: 490-494.

Gaasch WH, Andrias CW & Levine HJ (1978). Chronic aortic regurgitation: the effect of aortic valve replacement on left ventricular volume, mass and function. *Circulation*,**58**: 825-836.

Gaus H (1924). The pathogenesis of fat embolism. *Arch Surg*,**9**: 593-605.

Gauss A, Heinrich H & Wilder-Smith HG (1991). Echocardiographic assessment of the haemodynamic effects of propofol: a comparison with etomidate and thiopentone. *Anaesthesia*,**46**: 99-105.

Glas WW, Grekin TD & Musselman MM (1953). *Fat embolism*. Am J Surg; **85**: 363-368.

Gorback MS (1990). Linear regression is a poor descriptor of accuracy. *Anesthesiology*,**73**: 793-794.

Gordon MA, Urban MK, Harris SN, O'Connor T & Barash PG (1992). Evaluation of post cardiopulmonary bypass electrocardiography vs. transesophageal echocardiography for the prediction of perioperative myocardial infarction (abstr). *Anesth Analg*,**74**: S114.

Gray R, Maddahi J, Berman D *et al.* (1979). Scintigraphic and hemodynamic demonstration of transient left ventricular dysfunction immediately after uncomplicated coronary artery bypass grafting. *J Thorac Cardiovasc Surg*,**77**: 504-509.

Gray WA, Capone RJ & Most AS (1991). Unsuccessful emergency medical resuscitation- are continued efforts in the emergency department justified? *N Engl J Med*,**325**: 1393-1398.

Green CP (1992). Fatal intra-operative fat embolism. *Anaesthesia*,**47**: 168.

Gruber HE, Hoffer ME, McAllister DR *et al.* (1989). Increased adenosine concentration in blood from ischemic myocardium by AICA riboside: effects on flow, granulocytes and injury. *Circulation*,**80**: 1400-1411.

Gurd AR (1970). Fat embolism: an aid to diagnosis. *J Bone Jt Surg*,**52B**: 732-737.

Gurd AR & Wilson RI (1974). The fat embolism syndrome. *J Bone Jt Surg*,**56**B: 408-416.

Hagan PT, Scholz DG & Edwards WD (1984). Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc*,**59**: 17-20.

Hagley SR (1983). The fulminant fat embolism syndrome. *Anaesth Intens Care*,**11**: 162-166.

Hainsworth R (1990). Non-invasive investigations of cardiovascular reflexes in humans. *Clin Sci*,**78**: 437-443.

Hallgren B, Kerstall J, Rudenstein CM & Swanborg A (1966). A method for the isolation and chemical analysis of pulmonary fat embolism. *Acta Chirug Scand*,**132**: 613-617.

Halperin HR, Tsitlik JE & Guerci AD (1986). Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. *Circulation*,**73**: 539-550.

Hannan EL, Kilburn H *et al* (1990). Adult open heart surgery in New York State-An analysis of risk factors and hospital mortality rates. *JAMA*,**264**: 2768-2774.

Hatle L & Angelsen B (1984). *Doppler ultrasound in cardiology: physical principles and clinical applications*. 2nd ed. Lea and Febiger, Philadelphia.

Haude M, Gerber Th, Brennecke R, Erbel R & Meyer J (1989). Continuous and noninvasive monitoring of cardiac output by transesophageal Doppler ultrasound. In: Erbel R, Khandheria BK, Brennecke R, Meyer J, Seward JB, Takik AJ, eds. *Transesophageal echocardiography. A new window to the heart*: 260-266. Springer-Verlag, Berlin.

Hauser AM, Gangadharan V, Ramos RG, Gordon S, Timmis GC & Dudlets P (1985). Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: Echocardiographic observations. *J Am Coll Cardiol*,**5**: 193-197

Hegrenæs L & Hatle L (1985). Aortic stenosis in adults. Non-invasive estimation of pressure differences by continuous wave Doppler echocardiography. *Br Heart J*,**54**: 396-404.

Higano ST, Oh JK, Ewy GA & Seward JB (1990). The mechanism of blood flow during closed chest cardiac massage in humans: transesophageal echocardiographic observations. *Mayo Clin Proc*,**65**: 1432-1440.

Hoffman P, Stumper O, Rydelwska-Sadowska W & Sutherland GR (1993). Transgastric imaging: A valuable addition to the assessment of congenital heart disease by transverse plane transesophageal echocardiography. *J Am Soc Echocardiogr*,**6**: 35-44.

Hofmann T, Kasper W, Meinhertz T, Spillner G, Schlosser V & Just H (1987). Determination of aortic valve area in aortic stenosis by two-dimensional transesophageal echocardiography. *Am J Cardiol*,**59**: 330-335.

Hori M, Kitakaze M & Takashima S (1990). AICA-riboside (5-amino-4-imidazole carboxamide riboside 100), a novel adenosine potentiator, attenuates myocardial stunning (abstr). *Circulation*,**82**: III-466.

Hulman G (1988). Pathogenesis of non-traumatic fat embolism. *Lancet*,**i**: 1366-1367.

Hutchins GM & Anaya OA (1973). Measurements of cardiac size, chamber volumes and valve orifices at autopsy. *John Hopkins Med J*,**133**: 96-106.

Iliceto S, Marangelli V, Memmola C & Rizzon P (1991). Transesophageal Doppler echocardiography evaluation of coronary blood flow velocity in baseline conditions and during dipyridamole-induced coronary vasodilatation. *Circulation*,**83**: 61-69.

Jacobson DM, Terrence CF & Reinmuth OM (1986). The neurologic manifestations of fat embolism. *Neurology*,**36**: 847-851.

Johnson SR & Svanborg H (1956). Investigation with regard to the pathogenesis of so-called fat embolism. Serum lipids, tissue esterase activity and the frequency of so-called fat embolism in soft-tissue trauma and fractures. *Ann Surg*,**144**: 145-151.

Jones RH (1975). Physiologic emboli changes observed during total hip replacement arthoplasty. A clinical prospective study. *Clin Orth Rel Res*,**112**: 192-200.

Jude JR, Kouwenhoven WB & Knickerbocker GG (1961). Cardiac arrest. Report of application of external cardiac massage on 118 patients. *JAMA*,**178**: 1063-1070.

Kamenar E & Burger PC (1980). Cerebral fat embolism: a neuropathological study of a microembolic state. *Stroke*,**11**: 477-484.

Khan SS, Mitchell RS, Derby GC, Oyer PE & Miller DC (1990). Differences in Hancock and Carpentier-Edwards porcine xenograft aortic valve hemodynamics. Effect of valve size. *Circulation*,**82(suppl IV)**: IV-117-IV-124.

Kirkwood BR (1988). *Essentials of medical statistics*. Blackwell Scientific Publications, Oxford.

Kocher GS, Jacobs LE & Kotler MN (1990). Right atrial compression in postoperative cardiac patients: detection by transesophageal echocardiography. *J Am Coll Cardiol*,**16**: 511-516.

Koehler RC, Chandra N, Guerci AD *et al.* (1983). Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. *Circulation*,**67**: 266-275.

Konstadt SN, Louie EK, Black S, Rao TLK & Scanlon P (1991). Intraoperative detection of patent foramen ovale by transesophageal echocardiography. *Anesthesiology*,**74**: 212-6.

Kouwenhoven WB, Jude JR & Knickerbocker GG (1960). Closed-chest cardiac massage. *JAMA*,**173**: 1064-1067.

Kremer P. Schwartz L, Cahalan MK *et al.* (1982). Intraoperative monitoring of left ventricular performance by transesophageal M-mode and 2-D echocardiography (abstr). *Am J Cardiol*,**49**: 956.

Kuhn C, Juchems R & Frese W (1991). Evidence for the "cardiac pump theory" in cardiopulmonary resuscitation in man by transesophageal echocardiography. *Resuscitation*,**22**: 275-282.

Lang I, Steurer G, Weissel M & Burghuber OC (1988). Recurrent paradoxical embolism complicating severe thromboembolic pulmonary hypertension. *Eur Heart J*,**9**: 678-681.

Langholz D, Louie EK, Konstadt SN, Rao TLK & Scanlon PJ (1991). Transesophageal echocardiographic demonstration of distinct mechanisms for right to left shunting across a patent foramen ovale in the absence of pulmonary artery hypertension. *J Am Coll Cardiol*,**18**: 1112-1117.

Lawrie GM, Reid JW, Young JB, Reduto LA, Burdine JA & Miller RR (1979). Sequential assessment of left ventricular performance following coronary artery bypass surgery with gated cardiac blood pool imaging (abstr). *Circulation*,**59,60:Suppl 2**: 238.

Lazar HL, Plehn JF, Schick EM, Dobnick D & Shemin RJ (1989). Effects of coronary revascularization on regional wall motion. *J Thorac Cardiovasc Surg*,**98**: 498-505.

Lehman EP & Moore RM (1927). Fat embolism including experimental production without trauma. *Arch Surg*,**14**: 621-662.

Lehmann KG, Lee FA, McKenzie WB *et al.* (1990). Onset of altered interventricular septal motion during cardiac surgery. Assessment by continuous intraoperative transesophageal echocardiography. *Circulation*,**82**: 1325-1334.

Lemaire F, Richalet JP, Carlet J, Brun-Buisson C & MacLean C (1982). Postoperative hypoxemia due to opening of a patent foramen ovale confirmed by a right atrium-left atrium pressure gradient during mechanical ventilation. *Anesthesiology*,**57**: 233-236.

Leonard RCF, Neville E & Hall RJC (1982). Paradoxical embolism: a review of cases diagnosed during life. *Eur Heart J*,**3**: 362-370.

Leung J, Stanley T, Mathew J *et al.* (1992). Effects of acadesine on perioperative cardiac morbidity in a placebo controlled, double blind study (abstr). *J Am Coll Cardiol*,**19**: 112A.

Leung JM, O'Kelly B, Browner WS, Tubau J, Hollenberg M, Mangano DT & the SPI Research Group (1989). Prognostic importance of postbypass regional wall-motion abnormalities in patients undergoing coronary artery bypass graft surgery. *Anesthesiology*,**71**: 16-25.

Levine FH, Carter JE, Buckley MJ, Daggett WM, Akins CW & Austen WG (1981). Hemodynamic evaluation of Hancock and Carpentier-Edwards bioprostheses. *Circulation*,**64(suppl II)**: II-192-II-195.

Lindeque BG, Schoeman HS, Domisse GF, Boeyens MC & Vlok AL (1987). Fat embolism and the fat embolism syndrome: a double blind therapeutic study. *J Bone Jt Surg*,**69B**: 128-131.

Little K, Auchincloss JM & Reaves CS (1974). A mechanical cardio-pulmonary life support system. *Resuscitation*,**3**: 63-68.

Liu GS, Thornton J, Van Winkle DM, Stanley AWH, Olsson RA & Downey JM (1991). Protection against infarction provided by preconditioning is mediated by A_1 adenosine receptors in rabbit heart. *Circulation*,**84**: 350-356.

London MJ, Tubau JF, Wong MG *et al.* (1990). The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. *Anesthesiology*,**73**: 644-655.

MacKenzie GJ, Taylor SH, McDonald AH & Donald KW (1964). Haemodynamic effects of external cardiac compression. *Lancet*,**i**: 1342-1345.

McAllister D, Engler R, Laikind P, Finley K & Gruber H (1987). Experimental infarct size reduction by a new mechanism: Augmented adenosine release (abstr). *Clin Res*,**35**: 303A.

Maier GW, Tyson GS, Olsen CO *et al.* (1984). The physiology of external cardiac massage: high-impulse cardiopulmonary resuscitation. *Circulation*,**70**: 86-101.

Mangano DT (1985). Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 hours. *Anesthesiology*,**62**: 571-577.

Manning JB, Bach AW, Herman CM & Carrico CJ (1983). Fat release after femur nailing in the dog. *J Trauma*,**23**: 322-326.

Maron BJ, McIntosh CL, Wesley YE & Arce J (1984). Application of intraoperative two-dimensional echocardiography to patients with obstructive hypertrophic cardiomyopathy undergoing ventricular septal myotomy-myectomy (abstr). *J Am Coll Cardiol*,**3**: 565.

Marshall PD, Douglas DL & Henry L (1991). Fatal pulmonary fat embolism during total hip replacement due to high-pressure cementing techniques in an osteoporotic femur. *Br J Clin Pract*,**45**: 148-149.

Mashiro I, Cohn JN, Heckel R, Nelson RR & Franciosa JA (1978). Left and right ventricular dimensions during ventricular fibrillation in the dog. *Am J Physiol*,**235**: H231-H236.

Mason JK (1959). Pulmonary bone marrow embolism in accident reconstruction. *J Clin Pathol*,**12**: 384.

Masson R & Ruggieri J (1985). Pulmonary microvascular cytology: a new diagnostic application of the pulmonary artery catheter. *Chest*,**88**: 908-914.

Matsumoto M, Oka Y, Strom J *et al.* (1980). Application of transesophageal echocardiography to continuous intraoperative monitoring of left ventricular performance. *Am J Cardiol*,**46**: 95-105.

Mayron R, Ruiz E, Mestitz ST & Omlie WR (1985). Tissue-fat embolism occurring in a patient with a severe pelvic fracture. *J Emerg Med*,**2**: 251-256.

Meloni L, Abbruzzese PA, Cardu G *et al.* (1990). Detection of microbubbles released by oxygenators during cardiopulmonary bypass by intraoperative transesophageal echocardiography. *Am J Cardiol*,**66**: 511-514.

Mitchell MM, Prakash O, Rulf ENR, van Daele MERM & Cahalan MK (1989). Does addition of nitrous oxide induce myocardial ischemia in patients with poor ventricular function? *Anesthesiology*,**71**: 526-534.

Modig J (1977). Posttraumatic pulmonary microembolism. Pathophysiology and treatment. *Ann Clin Res*,**9**: 164-172.

Muhiudeen IA, Roberson DA, Silverman NH, Haas G, Turley K & Cahalan MK (1990). Intraoperative echocardiography in infants and children with congenital cardiac shunt lesions: transesophageal versus epicardial echocardiography. *J Am Coll Cardiol*,**16**: 1687-1695.

Muhiudeen IA, Kuecherer HF, Lee E, Cahalan MK & Schiller NB (1991). Intraoperative estimation of cardiac output by transesophageal pulsed Doppler echocardiography. *Anesthesiology*,**74**: 9-14.

Murray DG & Racz GB (1974). Fat embolism syndrome (respiratory insufficiency syndrome). A rationale for treatment. *J Bone Jt Surg*,**56A**: 1338-1349.

Murry CE, Jennings RB & Reimer KA (1984). Preconditioning with ischaemia: a delay of lethal cell injury in ischaemic myocardium. *Circulation*,**74**: 1124-1136.

Nagelhout DA, Pearson AC & Labovitz AJ (1991). Diagnosis of paradoxical embolism by transesophageal echocardiography. *Am Heart J*,**121**: 1552-1554.

Niemann JT, Rosborough JP, Hausknecht M, Garner D & Criley JM (1981). Pressure-synchronized cineangiography during experimental cardiopulmonary resuscitation. *Circulation*,**64**: 985-991.

Nijsten MWN, Hamer JPM, ten Duis HJ & Posma JL (1989). Fat embolism and patent foramen ovale. *Lancet*,**i**: 1271.

Oh JK, Seward JB, Khandheria BK *et al.* (1990). Transesophageal echocardiography in critically ill patients. *Am J Cardiol*,**66**: 1492-1495.

O'Kelly BF, Knight AA, Tubau JF, Verrier ED & Mangano DT (1988). Intraoperative measurement of left ventricular contractility (abstr). *Circulation*,**74(suppl II)**: II-479.

Olerud S, Danckwardt-Lillestrom G & Lorenzi G (1969). Do medullary components appear in the femoral vein during reaming of the tibia? (abstr). *Emerg Surg Res*,**1**: 243.

Overbeck W (1969). Historical views concerning cardiac arrest and resuscitation. In: Stephenson HE, ed. *Cardiac arrest and resuscitation*: 26-40. The CV Mosby Co., St. Louis.

Paradis NA, Martin GB, Rivers EP *et al.* (1990). Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA*,**263**: 1106-1113.

Parker FB, Wax SD, Kusajima K & Webb WR (1974). Hemodynamic and pathological findings in experimental fat embolism. *Arch Surg*,**108**: 70-74.

Pearson AC, Castello R & Labovitz AJ (1990). Safety and utility of transoesophageal echocardiography in the critically ill patient. *Am Heart J*,**119**: 1083-1089.

Pearson JW & Redding JS (1965). Influence of peripheral vascular tone on cardiac resuscitation. *Anesth Analg*,**44**: 746-752.

Pelling D & Butterworth KR (1973). Cardiovascular effects of acrylic bone cement in rabbits and cats. *Br Med J*,**ii**: 638-641.

Peltier LF (1952). Fat embolism following intramedullary nailing. *Surgery*,**32**: 719-722.

Peltier LF (1956a). Fat embolism. The prophylactic value of a tourniquet. *J Bone Jt Surg*,**38A**: 835-840.

Peltier LF (1956b). Fat embolism III. The toxic properties of neutral fat and free fatty acids. *Surgery*,**40**: 665-670.

Peltier LF (1965). The diagnosis of fat embolism. *Surg Gynecol Obstet*,**121**: 371-379.

Peltier LF (1988). Fat embolism: a perspective. *Clin Orthop Rel Res*,**232**: 263-270.

Philips HR, Carter JE, Okada RD *et al.* (1983). Serial changes in left ventricular ejection frcation in the early hours after aortocoronary bypass grafting. *Chest*,**83**: 28-34.

Porembka DT & Hoit BD (1991). Transesophageal echocardiography in the intensive care patient. *Crit Care Med*,**19**: 826-835.

Pozzoli M, Smyllie JH & Roelandt JRTC (1991). Atrial lesions. In: Sutherland GR, Roelandt JRTC, Fraser AG, Anderson RH, eds. *Transesophageal Echocardiography in Clinical Practice*. Gower Medical Publishing, London.

Quinones MA, Gaasch WH, Cole JS & Alexander JK (1975). Echocardiographic determination of left ventricular stress-velocity relations in man. *Circulation*,**51**: 689-700.

Rankin JS, McHale PA, Arentzen CE, Ling D, Greenfield JC & Anderson RW (1976). The three-dimensional dynamic geometry of the left ventricle in the conscious dog. *Circ Res*,**39**: 304-313.

Raper R & Sibbald WJ (1986). Misled by the wedge? The Swan-Ganz catheter and left ventricular preload- a review. *Chest*,**89**: 427-434.

Redberg RF, Tucker KJ, Cohen TJ, Dutton JP, Callaham ML & Schiller NB (1993). Physiology of blood flow during cardiopulmonary resuscitation. A transesophageal echocardiographic study. *Circulation*,**88**: 534-542.

Reduto LA, Lawrie GM, Reid JW *et al.* (1981). Sequential postoperative assessment of left ventricular performance with gated cardiac blood pool imaging following aortocoronary bypass surgery. *Am Heart J*,**101**: 59-66.

Reichert SLA, Visser CA, Moulijn AC *et al.* (1990). Intraoperative transesophageal color-coded Doppler echocardiography for evaluation of residual regurgitation after mitral valve repair. *J Thorac Cardiovasc Surg*,**100**: 756-761.

Reid CBA & Hill DA (1992). Acute cor pulmonale and death due to massive fat embolism. *Aust N Z J Surg*,**62**: 320-322.

Reikeras O (1987). Cardiovascular reactions to intramedullary reaming of long bones in dogs. *Acta Anaesthes Scand*,**31**: 48-51.

Ren J-F, Panidis IP, Kotler MN, Mintz GS, Goel I & Ross J (1985). Effect of coronary bypass surgery and valve replacement on left ventricular function: assessment by intraoperative two-dimensional echocardiography. *Am Heart J*,**109**: 281-289.

Rich S, Wix HL & Shapiro EP (1981). Clinical assessment of heart chamber size and valve motion during cardiopulmonary resuscitation by two-dimensional echocardiography. *Am Heart J*,**102**: 368-373.

Robb-Smith AHT (1941). Pulmonary fat-embolism. *Lancet*,**i**: 135-141.

Roberts AJ, Spies SM, Meyers SN *et al.* (1980). Early and long-term improvement in left ventricular performance following coronary artery bypass surgery. *Surgery*,**88**: 467-475.

Roberts AJ, Spies SM, Sanders JH *et al.* (1981). Serial assessment of left ventricular performance following coronary artery bypass grafting. *J Thorac Cardiovasc Surg*,**81**: 69-84.

Robertson C & Holmberg S (1992). Compression techniques and blood flow during cardiopulmonary resuscitation. *Resuscitation*,**24**: 123-132.

Roewer N, Bednarz F, Dziadzka A & Schulte am Esch J (1987). Intraoperative cardiac output determination from transmitral and pulmonary blood flow measurements using transesophageal pulsed Doppler echocardiography (abstr). *Anesthesiology*,**67**: A639.

Roizen MF, Beaupre PN, Alpert RA *et al.* (1984). Monitoring with two-dimensional transesophageal echocardiography: comparison of myocardial function in patients undergoing supraceliac, suprarenal-infraceliac or infrarenal aortic occlusion. *J Vasc Surg*,**1**: 300-305.

Rothbart RM, Castriz JL, Harding LV, Russo CD & Teague SM (1990). Determination of aortic valve area by two-dimensional and Doppler echocardiography in patients with normal and stenotic bioprosthetic valves. *J Am Coll Cardiol*,**15**: 817-824.

Rudikoff MT, Maughan WL, Effron M, Freund P & Weisfeldt ML (1980). Mechanisms of blood flow during cardiopulmonary resuscitation. *Circulation*,**61**: 345-352.

Russell AE, Smith SA, West MJ *et al.* (1990). Automated non-invasive measurement of cardiac output by the carbon dioxide rebreathing method: comparisons with dye dilution and thermodilution. *Br Heart J*,**63**: 195-199.

Saada M, Cahalan MK, Lee E, Ionescu P & Schiller NB (1989). Real-time evaluation of echocardiograms (abstr). *Anesthesiology*,**71**: 344A.

Schiller NB, Shah PM, Crawford M *et al.* (1989). Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr*, **1**:3A.

Schleien CL, Berkowitz ID, Traystman R & Rogers MC (1989). Controversial issues in cardiopulmonary resuscitation. *Anesthesiology*,**71**: 133-149.

Schonfeld SA, Ploysongsang Y, DiLisio R *et al.* (1983). Fat embolism prophylaxis with corticosteroids. *Ann Intern Med*,**99**: 438-443.

Schuster AH & Nanda NC (1984). Doppler echocardiographic measurement of cardiac output: comparison with a non-golden standard. *Am J Cardiol*,**53**: 257-259.

Scuderi CS (1938). Fat embolism. Resume of the literature plus some newer thoughts on diagnosis. *Arch Surg*,**36**: 614-625.

Scully RE (1956). Fat embolism in Korean battle casualties. Its incidence, clinical significance, and pathologic aspects. *Am J Path*,**32**: 379-403.

Sevitt S (1962). *Fat Embolism*. Butterworths, London.

Sevitt S (1977). The significance and pathology of fat embolism. *Ann Clin Res*,**9**: 173-180.

Seward JB, Khandheria BK, Oh JK *et al.* (1988). Transesophageal echocardiography: technique, anatomic correlations, implementation, and clinical applications. *Mayo Clinic Proc*,**63**: 649-680.

Sheikh KH, DeBruijn NP, Rankin JS *et al.* (1990). The utility of transesophageal echocardiography and Doppler color flow imaging in patients undergoing cardiac valve surgery. *J Am Coll Cardiol*,**15**: 363-372.

Simpson IA, Munsch C, Smith EEJ & Parker DJ (1991). Pericardial haemorrhage causing right atrial compression after cardiac surgery. *Br Heart J*,**65**: 355-356.

Slogoff S & Keats AS (1986). Further observations on perioperative myocardial ischemia. *Anesthesiology*,**65**: 539-542.

Smith JS, Cahalan MK, Benefiel DJ *et al.* (1985). Intraoperative detection of myocardial ischemia in high-risk patients: electrocardiography versus two-dimensional transesophageal echocardiography. *Circulation*,**72**: 1015-1021.

Souquet J, Hanrath P, Zitelli L, Kemper P, Langenstein BA & Schluter M (1982). Transesophageal phased array probe for imaging the heart. *IEEE Trans Biomed Engineer*,**29**: 707-712.

Sreeram N, Kaulitz R, Stumper OFW, Hess J, Quaegebeur JM & Sutherland GR (1990). Comparative roles of intraoperative epicardial and early postoperative transthoracic echocardiography in the assessment of surgical repair of congenital heart defects. *J Am Coll Cardiol*,**16**: 913-920.

Stanley TE, Clements FM, Smith LR, Skelton TN, Jacobs JR & de Bruijn NP (1988). Effects of anesthetics on the regional myocardial function of the ischemic heart as assessed by quantitated transesophageal echocardiography. *Anesthesiology*,**69**: A8.

Stoddard MF, Arce J, Liddell NE, Peters G, Dillon S & Kupersmith J (1991). Two-dimensional transesophageal echocardiographic determination of aortic valve area in adults with aortic stenosis. *Am Heart J*,**122**: 1415-1422.

Stumper OFW, Elzenga NJ, Hess J & Sutherland GR (1990). Transesophageal echocardiography in children with congenital heart disease: An initial experience. *J Am Coll Cardiol*,**16**: 433-441.

Stumper OFW, Fraser AG, Ho SY *et al.* (1990b). Transoesophageal echocardiography in the longitudinal axis: correlation between anatomy and images and its clinical implications. *Br Heart J*,**64**: 282-288.

Stumper O, Sutherland GR, Sreeram N *et al.* (1991). Role of intraoperative ultrasound examination in patients undergoing a Fontan-type procedure. *Br Heart J*,**65**: 204-210.

Sutherland GR (1991). Lesions of the aortic valve and the left ventricular outflow tract. In: Sutherland GR, Roelandt JRTC, Fraser AG, Anderson RH, eds. *Transoesophageal echocardiography in clinical practice*: 7.1-7.11. Gower Medical Publishing, London.

Swenson RD, Weaver WD, Niskanen RA, Martin J & Dahlberg S (1988). Hemodynamics in humans during conventional and experimental methods of cardiopulmonary resuscitation. *Circulation*,**78**: 630-639.

Taams MA, Gussenhoven WJ, Bos E & Roelandt J (1988). Saccular aneurysm of the transverse thoracic aorta detected by transesophageal echocardiography. *Chest*,**93**: 436-437.

Takamoto S, Kyo S Adachi H, Matsumura M, Yokote Y & Omoto R (1985). Intraoperative color flow mapping by real-time two-dimensional Doppler echocardiography for evaluation of valvular and congenital heart disease and vascular disease. *J Thorac Cardiovasc Surg*,**90**: 802-812.

Takashima S, Hori M, Kitakaze M *et al.* (1990). AICA-riboside (5-amino-4-imidazole carboxamide riboside 100), a novel adenosine potentiator, attenuates myocardial ischemia in coronary microembolization (abstr). *Heart Vessels*,**4(Suppl)**: 41.

Talucci RC, Manning J, Lampard S, Bach A & Carrico CJ (1983). Early intramedullary nailing of femoral shaft fractures: a cause of fat embolism syndrome. *Am J Surg*,**146**: 107-110.

Taylor GJ, Tucker WM, Greene HL, Rudikoff MT & Weisfeldt ML (1977). Importance of prolonged compression during cardiopulmonary resuscitation in man. *N Engl J Med*,**296**: 1515-1517.

ten Duis HJ, Nijsten MWN, Klasen HJ & Binnendijk B (1988). Fat embolism in patients with an isolated fracture of the femoral shaft. *J Trauma*,**28**: 383-390.

Tennant R & Wiggers CJ (1935). The effect of coronary occlusion on myocardial contraction. *Am J Physiol*,**112**: 351-361.

Thomsen JE, Stenlund RR & Rowe GG (1968). Intracardiac pressures during closed-chest cardiac massage. *JAMA*,**205**: 46-48.

Topol EJ, Humphrey LS, Blanck TJJ *et al.* (1983). Characterization of post-cardiopulmonary bypass hypotension with intraoperative transesophageal echocardiography (abstr). *Anesthesiology*,**59**: 2a.

Topol EJ, Weiss JL, Guzman PA *et al.* (1984). Immediate improvement of dysfunctional myocardial segments after coronary revascularisation: detection by intraoperative transesophageal echocardiography. *J Am Coll Cardiol*,**4**: 1123-1134.

Tucker KJ, Galli F, Savitt, Kahsai D, Bresnahan L & Redberg RF (1993). Active compression-decompression resuscitation: effects on resuscitation success after in-hospital arrest (abstr). *Circulation*,**88**: I-I.

Uenishi M, Sugimoto H, Sawada Y, Terai C, Yoshioka T & Sugimoto T (1984). Transesophageal echocardiography during external chest compression in humans. *Anesthesiology*,**60**: 618.

UK Resuscitation Council (1984). *Cardiopulmonary resuscitation*. Laerdal Medical Limited, London.

Ulrich C, Burri C, Worsdorfer O & Heinrich H (1986). Intraoperative transesophageal two-dimensional echocardiography in total hip replacement. *Arch Orthop Trauma Surg*,**105**: 274-278.

Ungerleider RM, Greeley WJ, Sheikh KH *et al.* (1990). Routine use of intraoperative epicardial and Doppler color flow imaging to guide and evaluate repair of congenital heart lesions. *J Thorac Cardiovasc Surg*,**100**: 297-309.

Val PG, Pelletier LC, Hernandez ME *et al.* (1983). Diagnostic criteria and prognosis of perioperative myocardial infarction following coronary bypass. *J Thorac Cardiovasc Surg*,**86**: 878-886.

van Besouw J-P & Hinds CJ (1989). Fat embolism syndrome. *Br J Hosp Med*,**42**: 304-311.

van Daele MERM, Sutherland GR, Mitchell MM *et al.* (1990). Do changes in pulmonary capillary wedge pressure adequately reflect myocardial ischemia during anesthesia? *Circulation*,**81**: 865-871.

Vandenberg BF & Kerber RE (1990). Transesophageal echocardiography and intraoperative monitoring of left ventricular function. *Anesthesiology*,**73**: 799-801.

van Herwerden LA, Fraser AG & Bos E (1991). Left ventricular outflow tract obstruction after mitral valve repair assessed with intraoperative echocardiography: noninterventional treatment. *J Thorac Cardiovasc Surg*,**102**: 461-463.

van Lente F, Martin A, Ratliff NB, Kazmierczak SC & Loop FD (1989). The predictive value of serum enzymes for perioperative myocardial infarction after cardiac operations. *J Thorac Cardiovasc Surg*,**98**: 704-710.

van Miert M, Thornington RE & van Velzen D (1991). Cardiac arrest after massive acute fat embolism. *Br Med J*,**303**: 396-397.

Warthin AS (1913). Traumatic lipemia and fatty embolism. *Int Clin*,**4**: 171-227.

Waters DD, Luz PD, Wyatt HL, Swann HJC & Forrster JS (1977). Early changes in regional and global left ventricular function induced by graded reductions in regional coronary perfusion. *Am J Cardiol*,**39**: 537-547.

Watson AJ (1970). Genesis of fat emboli. *J Clin Path*,**23,suppl.**(*Roy Coll Path*)**4**: 132-142.

Weale FE & Rothwell-Jackson RL (1962). The efficiency of cardiac massage. *Lancet*,**i**: 990-992.

Wenting GJ, Brouwer RML, Man in't Veld AJ & Schalekamp MADH (1990). First passage radionuclide cardiography for determination of cardiac output: A critical analysis. *Eur Heart J*,**11(Suppl I)**: 41-48.

Werner JA, Greene HL, Janko CL & Cobb LA (1981). Visualization of cardiac valve motion in man during external chest compression using two-dimensional echocardiography. Implications regarding the mechanism of blood flow. *Circulation*,**63**: 1417-1421.

Whitson RO (1951). A critique of fat embolism. *J Bone Jt Surg*,**33A**: 447-450.

Williams GA & Labovitz AJ (1985). Doppler hemodynamic evaluation of prosthetic (Starr-Edwards and Bjork-Shiley) and bioprosthetic (Hancock and Carpentier-Edwards) cardiac valves. *Am J Cardiol*,**56**: 325-332.

Wilson JV & Salisbury CV (1943-44). Fat embolism in war surgery. *Br J Surg*,**31**: 384-392.

Wohlgerlernter D, Cleman M, Highman HA *et al.* (1986). Regional myocardial dysfunction during coronary angioplasty: evaluation by two-dimensional echocardiography and 12 lead electrocardiography. *J Am Coll Cardiol*,**7**: 1245-1254.

Wright RF (1993). Clinical utility of transesophageal echocardiography during cardiopulmonary resuscitation (abstr). *Circulation*,**88**: I-192.

Xue H & Zhang Y-F (1992). Pulmonary fat embolism in rabbits induced by forced immobilization. *J Trauma*,**32**: 415-419.

Yock PG & Popp RL (1984). Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation*,**70**: 657-662.

Young JS & Griffith HD (1950). Dynamics of parenchymatous embolism in relationship to the dissemination of malignant tumours. *J Path Bact*,**62**: 293-311.

Young MA & Mullane KM (1991). Progressive cardiac dysfunction with repeated episodes of pacing-induced ischemia: protection by AICA riboside. *Am J Physiol*,**261**: H1570-H1577.

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RESUSCITATION

Assessment of the active compression-decompression device (ACD) in cardiopulmonary resuscitation using transoesophageal echocardiography

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Abstract

Transoesophageal echocardiography was used to investigate the haemodynamic profile achieved during active compression-decompression cardiopulmonary resuscitation in humans. The mechanism of antegrade blood flow achieved by ACD-CPR is consistent with the cardiac pump theory. Improved right heart compression, antegrade blood flow patterns and left ventricular filling were observed in some patients during ACD-CPR.

Key words: Cardiopulmonary resuscitation; Active compression-decompression device; Transoesophageal echocardiography

1. Introduction

Closed chest compression has been an integral component of cardiopulmonary resuscitation (CPR) since first described by Kouwenhoven in 1960 [1]. Despite the widespread use of this technique there is increasing appreciation that conventional resuscitation methods often result in poor cardiac output, and survival after a prolonged periods of CPR is uncommon [2,3]. Recent evidence suggests that use of the active compression-decompression device (ACD) (Fig. 1) may improve cardiac output and antegrade blood flow during resuscitation [4,5]. If confirmed, this might result in increased survival rates following CPR for cardiac arrest. Transoesophageal echocardiography (TEE) has led to new insights into the physiology of conventional CPR and can be used to monitor the effectiveness of resuscitation attempts [6–8]. Using TEE we have studied seven patients undergoing CPR to compare the effectiveness of resuscitation with the ACD with conventional chest massage.

2. Patients and methods

Adults with non-traumatic, normothermic cardiac arrest, admitted to the Accident and Emergency Department of the Royal Infirmary of Edinburgh were studied. All patients had sustained cardiorespiratory arrest in the pre-hospital setting and had received CPR and defibrillation by

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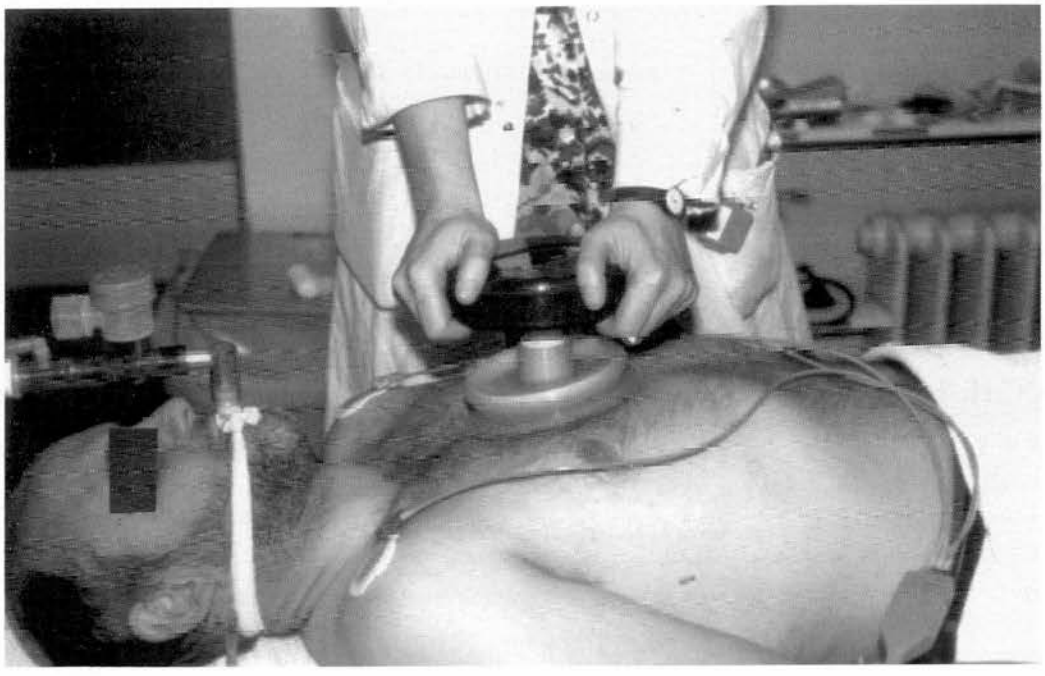

Fig. 1. The Active Compression-Decompression device.

ambulance staff where appropriate prior to arrival. On admission, patients were treated according to the guidelines of the Resuscitation Council (UK) [9,10]. All patients were intubated and ventilated with 100% oxygen with peak inspiratory pressures set at 30 cm of H_2O. Chest compression was performed using three different techniques according to a predetermined sequence: mechanical thumper (Michigan Instruments Thumper, Model 1004), ACD device, manual compression. Each technique was performed for five minutes. For all these methods, chest compression was performed at a rate of 80/min, with a ratio of five chest compressions to one ventilation. Compression was performed with sufficient force to compress the chest 6–7 cm (36–45 kg). The resuscitation attempts were led and controlled by a senior clinician who remained independent of the study. Ethical approval was received from the Lothian Health Board Ethics of Medical Research Committee.

TEE was performed using a 5-MHz transverse plane transducer that was positioned in the oesophagus following tracheal intubation and ventilation. Chamber compression and patterns of valve motion were determined from two-dimensional and M-mode echocardiography. Colour flow and spectral Doppler studies were performed for analysis of blood flow patterns within the heart and great vessels. All studies were recorded on VHS video tape to permit detailed subsequent analysis. Echocardiography continued until the resuscitation attempt was terminated or until spontaneous circulation was restored.

3. Results

Seven patients were studied (four male, three female; age range, 58–83 years; mean, 70.1 ± 9.9 years). The mean interval between the onset of cardiac arrest and initiation of TEE was 49 ± 8 min. The rhythm on presentation to the Accident

and Emergency Department was asystole in two patients, ventricular fibrillation in three patients and electromechanical dissociation in two patients. No subject survived to discharge from the Accident and Emergency Department.

The mechanisms responsible for generating forward blood flow were identical for all three techniques of cardiac compression and were consistent with the cardiac pump theory of CPR. In the compression phase direct compression of the right and left ventricles was seen. This resulted in ejection of blood into the pulmonary artery and aorta, respectively. Ventricular filling, from the right and left atria, occurred only in the relaxation phase.

The extent of ventricular compression varied according to the compression technique used. All three methods of chest compression produced relatively greater compression of the right heart chambers than the left. ACD produced a longer compression phase than manual or Thumper CPR. In three patients the use of the ACD was also associated with a greater degree of right heart chamber compression than when mechanical or manual compression was used. The extent of left heart chamber compression achieved was similar irrespective of the compression technique.

Colour flow Doppler imaging was of sufficient quality in four patients to allow analysis of blood flow patterns. Higher velocity blood flow was observed in two patients with the ACD, in comparison to manual or mechanical compression in the same subjects. This was assessed by an increase in colour intensity on colour flow doppler as cardiac displacement during CPR prevented accurate quantitative measurement of the velocity of blood flow. Persistence of spontaneous contrast within the left ventricle suggestive of ineffective CPR was observed during manual and mechanical chest compression in three subjects (Fig. 2). In one of these patients use of the ACD resulted in disappearance of the contrast from the left ventricle.

Underfilling of the left ventricle was pronounced at the outset of CPR in three subjects. These appearances were similar to those seen in patients with hypovolaemic shock and persisted despite mechanical chest compression. As a consequence, minimal compression of the left heart chambers resulted and little effective forward flow was evident with colour flow Doppler. Following the use of the ACD, increased left ventricular filling occured in two of these subjects, and improved forward flow patterns were demonstrated with colour flow Doppler.

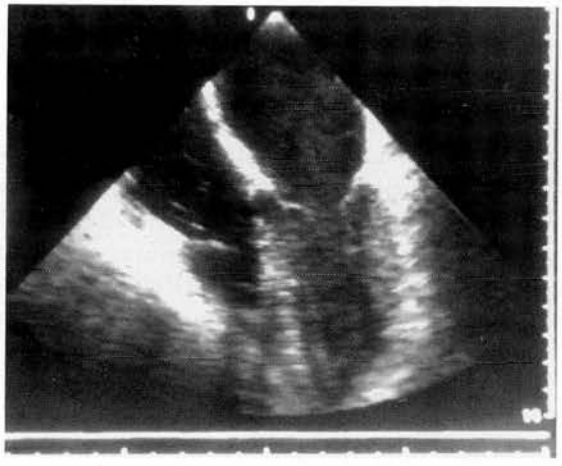

Fig. 2. TEE image of the start of the compression phase showing spontaneous contrast in the left ventricle.

Although spontaneous circulation was not regained in any of the subjects, TEE clearly demonstrated the return of spontaneous ventricular contractions in three subjects undergoing ACD CPR. In these patients asystole had persisted during manual and mechanical chest compression. However, these contractions were of low amplitude and did not result in effective blood flow as determined by colour flow Doppler or a palpable pulse.

4. Discussion

We used TEE to examine the physiology of CPR in subjects undergoing closed chest compression. The mechanism by which forward blood flow was achieved appeared identical for manual, mechanical and ACD CPR, and consistent with the cardiac pump theory [1,8].

TEE is a very promising method of assessing the effectiveness of CPR. The persistance of spontaneous contrast, left atrial and ventricular underfilling

and absent or poor chamber compression are associated with low velocity or no forward flow, using colour flow doppler.

Our preliminary observations suggest that the ACD device is at least as effective as manual or mechanical chest compression. The degree of left chamber compression was similar with all forms of CPR. Right heart compression however appeared greater with the ACD in three patients. The velocity of blood flow was observed to increase on changing from mechanical to ACD CPR in some cases and in one subject spontaneous contrast that had persisted throughout mechanical compression cleared with the ACD device.

The mechanisms responsible for these differences between mechanical CPR and the ACD are unclear. The active 'decompression' and increased negative intrathoracic pressure produced by the ACD may contribute to improved venous return and hence right ventricular filling and cardiac output. In two subjects right and left ventricular filling appeared to be improved by the ACD and this might have resulted in a greater cardiac output in response to chamber compression.

It is known that the right atrial-aortic pressure gradient is positively correlated with the likelihood of spontaneous restoration of cardiac output [11]. This may be increased by actively reducing right atrial pressure during the decompression phase of CPR. In a study examining the ACD device in dogs coronary perfusion pressure was increased by changing from standard to ACD CPR [5]. It is possible that our observation of the development of spontaneous ventricular contractions following a period of asystole may reflect improved coronary perfusion with the ACD.

To date experience with the ACD is limited and it is not yet possible to determine whether these echocardiographic observations will be reflected in clinical practice by improved survival from cardiac arrest. However our preliminary experience with this technique is promising and further studies are warranted to determine the role and clinical efficacy of ACD in CPR.

5. Acknowledgement

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6. References

1 Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed chest cardiac massage. J Am Med Assoc 1960; 173: 1064–1067.

2 Gray WA, Capone RJ, Most AS. Unsuccessful emergency medical resuscitation — are continued efforts in the emergency department justified? N Eng J Med 1991; 325: 1393–1398.

3 Cummins RO, Eisenberg MS, Hallston AP, Litwin PE. Survival of out of hospital cardiac arrest with early initiation of cardiopulmonary resuscitation. Am J Emerg Med 1985; 3: 114–119.

4 Cohen TJ, Tucker KJ, Lune KG et al. Active compression-decompression a new method of cardiopulmonary resuscitation. J Am Med Assoc 1992; 267: 2916–1923.

5 Cohen TJ, Tucker KJ, Redberg RF et al. Active compression decompression: A novel method of cardiopulmonary resuscitation. Am Heart J 1992; 124: 1145–1150.

6 Higano ST, Oh JK, Ewy GA, Seward JB. The mechanism of blood flow during closed chest cardiac massage in humans: Transesophageal echocardiographic observations. Mayo Clin Proc 1990; 65: 1432–1440

7 Kelvin C, Juchems R, Frese W. Evidence for the 'cardiac pump theory' in cardiopulmonary resuscitation in man by transoesophageal echocardiography. Resuscitation 1991; 22: 275–282.

8 Guly UM, Pell ACH, Bloomfield P et al. Investigation of the mechanisms of cardiopulmonary resuscitation using transoesophageal echocardiography. Ann Emerg Med 1993; 22: 938.

9 UK Resuscitation Council. Cardiopulmonary resuscitation. London: Laerdal Medical Ltd, 1984.

10 Advanced Life Support Working Party of the European Resuscitation Council. Guidelines for advanced life support. Resuscitation 1992; 24: 111–121.

11 Niemann JT, Criley JM, Rosborough JP, Niskanen RA, Alferness C. Predictive indices of successful cardiac resuscitation after prolonged arrest and experimental cardiopulmonary resuscitation. Ann Emerg Med 1985; 14: 521–528.

THE DETECTION OF FAT EMBOLISM BY TRANSOESOPHAGEAL ECHOCARDIOGRAPHY DURING REAMED INTRAMEDULLARY NAILING

A STUDY OF 24 PATIENTS WITH FEMORAL AND TIBIAL FRACTURES

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We performed transoesophageal echocardiography on 24 patients during reamed intramedullary nailing of 17 tibial and seven femoral fractures. In 14 patients there was only minimal evidence of emboli passing through the heart, but in six copious showers of small emboli (< 10 mm maximum dimension) were observed. In four other patients, there were also multiple large emboli (>10 mm maximum dimension). Three of these patients developed fat embolism syndrome postoperatively and one died. Earlier nailing was associated with smaller quantities of emboli.

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The fat embolism syndrome (FES) develops in 0.5% to 2% of all patients with fractures of the long bones (Gossling and Pellegrini 1982) and has been associated with high morbidity and mortality (Fuchsig et al 1967). Since the early 1980s the use of intramedullary nailing for tibial and femoral fractures has become popular, and excellent results have been reported (Christie et al 1988; Court-Brown, Christie and McQueen 1990). The trend towards intramedullary nailing is even greater for patients with multiple injuries, partly because early fixation is thought to minimise the associated respiratory complications (Riska and Myllynen 1982; Johnson, Cadambi and Seibert 1985; Bone et al 1989). A number of reports, however, have linked intramedullary nailing and reaming with the development of fat embolism (Manning et al 1983; Talucci et al 1983), and it has been suggested that intramedullary reaming may precipitate or exacerbate the release of embolic material from the fracture site into the systemic circulation.

The use of transoesophageal echocardiography to detect such embolic material as it passes through the heart was suggested in a case report by Wenda et al (1989). We have used the technique to monitor a series of patients during reamed intramedullary nailing. Our aim was to record any evidence of embolism and to relate the findings to the subsequent clinical course of the patient.

PATIENTS AND METHODS

We studied 17 tibial fractures and 7 femoral fractures in 24 patients. There were 12 men and 12 women with a mean age of 38 years (17 to 85). The index fracture was the only injury in 19 patients, but the other 5 had multiple injuries, with Injury Severity Scores (Baker et al 1974; Baker and O'Neill 1976) of over 16. In three patients the tibial fractures were compound: two had Gustilo grade-I wounds and one had a grade-II wound. All the fractures were treated with a locking intramedullary GK nail. Nailing was performed within 24 hours of injury in 22 patients; one tibial fracture was nailed after three days and one femoral fracture referred from another centre was nailed at ten days.

Transoesophageal echocardiography was performed throughout the operation. After anaesthesia had been induced, a 5 MHz transverse-plane echocardiography probe (Siemans, Sonoline SI1200) was positioned in the patient's oesophagus to provide continuous imaging of the right atrium and right ventricle. The probe was left in position throughout the procedure and was removed immediately before reversal of anaesthesia. VHS video tape recordings were made for subsequent analysis. Other intraoperative monitoring included heart rate, blood pressure, ECG, pulse oximetry, and end-tidal CO_2 levels. When a central venous catheter had been inserted for clinical purposes, 10 ml samples of right atrial blood were taken before surgery and when embolic material was

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Table I. Major and minor criteria for the diagnosis of fat embolism syndrome (FES). A positive diagnosis requires at least one major and four minor signs (after Gurd 1970)

Major criteria	Minor criteria
Petechial rash	Tachycardia > 110/min
Hypoxaemia (PaO_2 < 60 mmHg)	Pyrexia > 38.5°C
CNS depression	Retinal emboli on fundoscopy
Pulmonary oedema	Lipuria Thrombocytopenia Decreased haematocrit Fat globules in sputum

demonstrated within the heart chambers. These samples were analysed for fat content using the method described by Gurd (1970).

Before operation, no patient had clinical evidence of FES. The diagnosis of FES postoperatively was based on the major and minor criteria of Gurd (1970) (Table I). The analysis of the echocardiographic images was performed by an experienced observer (ACHP) with no knowledge of the postoperative course of the patient.

RESULTS

Echocardiography. The patients were divided into three groups based on the appearance of embolic material within the right heart chambers:

Group I. The echocardiographic recordings in this group showed little or no evidence of embolic phenomena (Fig. 1). The 14 patients had 12 tibial fractures and two femoral fractures, all closed injuries. Four fractures were caused by high-energy trauma, and all were nailed within 24 hours. In all 14 cases, intraoperative physiological parameters remained within normal limits, and the postoperative recovery and subsequent clinical progress were uneventful. No patient developed evidence of fat embolism.

Group II. This group of six patients showed showers of moderate quantities of echogenic material 1 to 10 mm in diameter. They had three tibial and three femoral fractures. Three fractures were the result of high-energy injuries; one tibial fracture was a Gustilo type-I open injury, the others were closed. All fractures were internally fixed within 24 hours.

Little or no intracardiac embolism was observed during skin preparation, draping, or skin incision in any patient, but emboli usually appeared within 10 seconds of starting the closed reduction of the fracture. A shower of highly echogenic masses was seen within the right atrium (Fig. 2). Successive showers of emboli were also associated with the broaching of the intramedullary canal, the passage of the reamers and the insertion of the nail. The volume and duration of the appearance of embolic material varied, but tended to be greatest with reaming and nail insertion.

Despite these appearances, no intraoperative physiological abnormalities were recorded and no patient developed postoperative respiratory problems or other evidence of fat embolism.

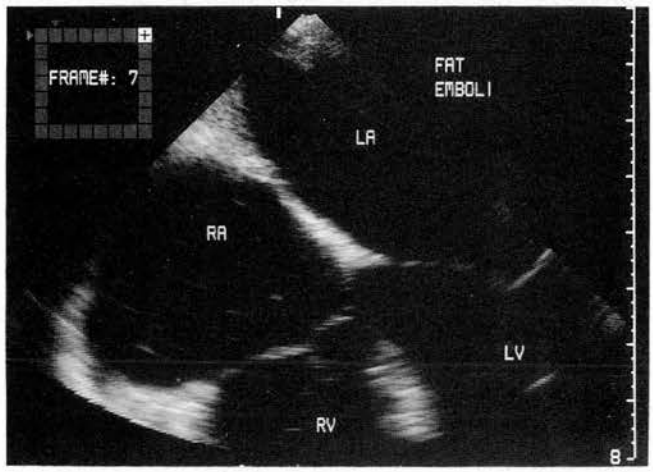

Fig. 1

Transoesophageal echocardiographic four-chamber view. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. A few small echogenic dots are seen in the right side of the heart during the reaming of a tibial fracture in a patient of group I. This echocardiogram was classified as being minimally positive.

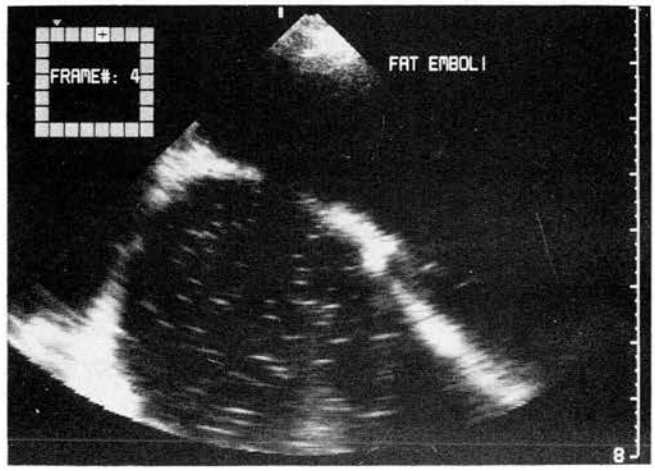

Fig. 2

The transoesophageal echocardiogram shows that the right atrium is filled with a shower of echogenic material of small diameter passing towards the right ventricle. This is from a patient in group II with moderately positive results.

Group III. Echocardiography in this group showed large quantities of echogenic material with multiple small masses of 1 to 10 mm diameter and also large discrete emboli 1 to 8 cm in maximum dimension (Fig. 3). There were four patients, with two femoral and two tibial fractures. Three of the fractures were caused by high-energy trauma and one tibial fracture was a Gustilo type-II open injury. Two of the nailings were performed within 24 hours, one after three days, and one after ten days following transfer from another hospital.

The passage of the reamers and of the nail was associated with the appearance of embolic material

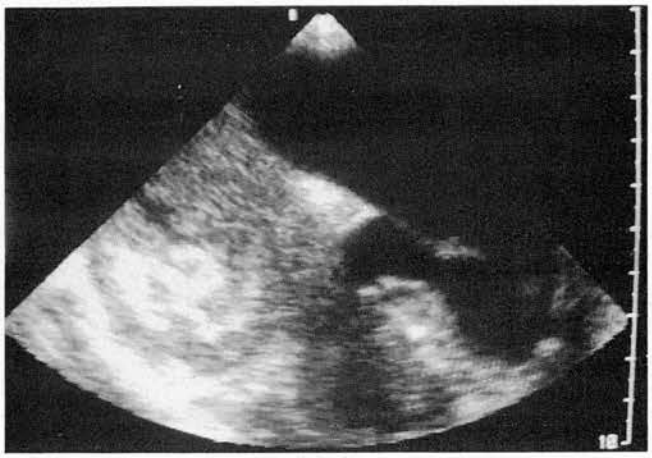

Fig. 3a

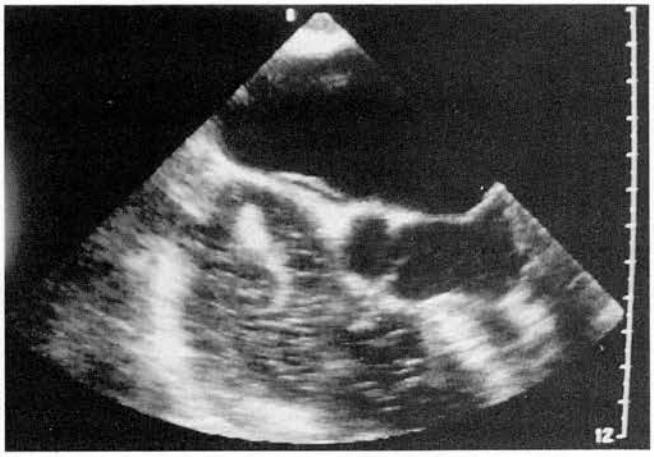

Fig. 3b

Transoesophageal echocardiograms of patients from group III. Figure 3a – A large embolus is seen in the right atrium which also contains smaller microemboli. Figure 3b – A similar view of the right atrium in another patient. A large serpentine embolus appeared and remained in the right atrium for several cardiac cycles before traversing the tricuspid valve to pass through the right ventricle and into the pulmonary circulation. Both of these patients developed severe FES.

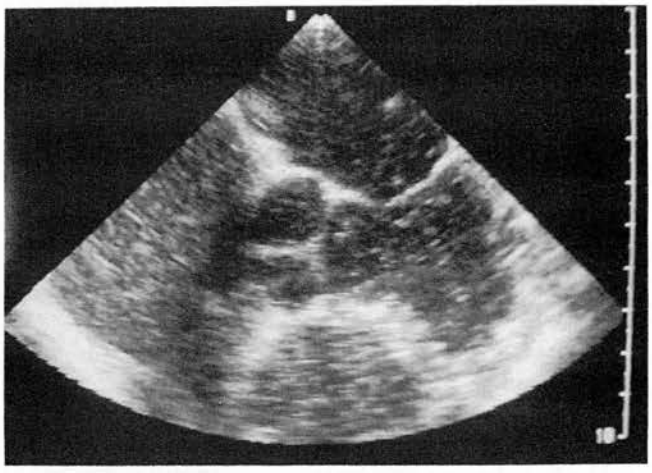

Fig. 4

Echocardiogram showing paradoxical embolism during reamed intramedullary nailing of a femoral fracture. The aortic valve is seen in the centre of the view with the four chambers of the heart around it; the left atrium is at the apex of the view. The fossa ovalis is displaced into the left atrium and a flap valve has opened, allowing passage of fat emboli. Echogenic material is seen on both sides of the interatrial septum.

within the right atrium; all the large masses were seen at these stages of the operation. Three of the four patients developed FES, and this was severe enough in two to require ventilation.

One of these two patients had developed profound hypotension during reaming (BP from 152/80 to 72/40), with arterial desaturation (SaO_2 98% to 75%) and a fall in end-tidal CO_2 (28.5 mmHg to 9 mmHg). Echocardiography had shown massive quantities of embolic material within the right heart chambers immediately after reaming had started. Although reaming was stopped, large quantities of embolic material continued to appear for 20 minutes. During this period there was right ventricular dilatation with the development of severe tricuspid incompetence. This precipitated paradoxical embolism through a patent foramen ovale, and large amounts of embolic material were seen to cross the interatrial septum into the left atrium, with subsequent passage through the left ventricle into the aorta (Fig. 4). This patient died of fat embolism 72 hours later.

Histology. We have performed a number of preliminary investigations into the composition of the observed emboli. Post-mortem examination of the patient who died of fat embolism showed the deposition of fat globules in the microvasculature of both pulmonary and systemic circulations, including renal and cardiac vessels (Fig. 5), but we were unable to locate any macroemboli corresponding to those observed during echocardiography. The right atrial blood samples obtained from five patients in groups II or III with moderate or severe emboli all showed a high lipid content on blood films examined by Gurd's method (1970).

DISCUSSION

Despite more than a century of research, the pathophysiology of FES remains contentious. Two theories have been proposed. The mechanical hypothesis considers that disruption of intramedullary veins allows marrow fat to gain direct access to the venous circulation and

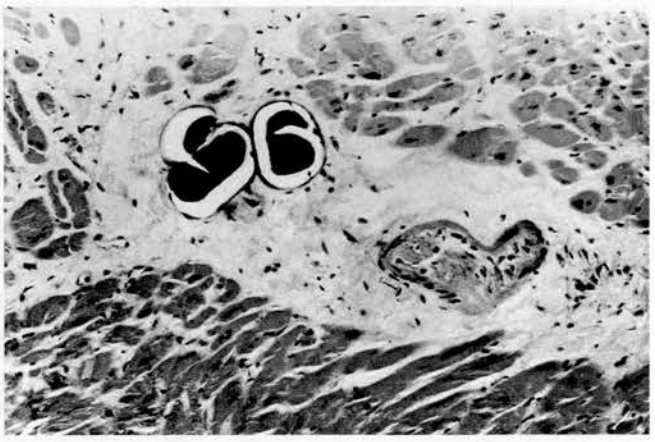

Fig. 5a

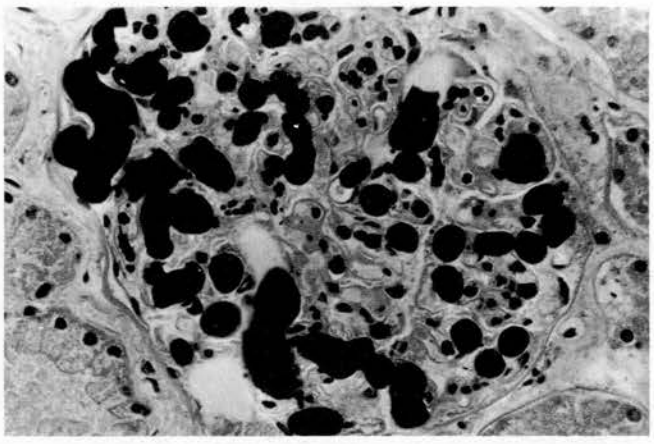

Fig. 5b

Histological specimens from the patient who died of fulminating FES. The osmic acid stain shows fat in black. Figure 5a – Fat in the lumen of a cardiac arteriole. Figure 5b – A renal glomerulus with heavy fat deposition in its vessels.

then to the lungs (Peltier 1988). Systemic embolisation may occur when fat migrates through pulmonary precapillary shunts into the pulmonary veins. This theory is supported by the finding of bone-marrow material in lung sections of patients with fractures of the long bones (Meek, Woodruff and Allardyce 1972; Weinberg and Finsterbush 1972). The second, biochemical, hypothesis suggests that chemical mediators released from the fracture change lipid solubility in blood, causing coalescence and subsequent embolisation. It has also been suggested that fatty acids released at the time of injury are directly toxic to the pneumocyte (Levy 1990).

Two of our findings are inconsistent with either hypothesis and suggest that the pathogenesis of FES needs re-evaluation. The first unexpected observation was the demonstration of very large emboli in four of our patients. Small fat emboli have been shown in other studies of reamed nailing, but the appearance of large emboli has not previously been recognised. The composition of the large emboli remains uncertain, but the echocardiographic appearances are not typical of thrombus. None of the observed large emboli was retrieved at post-mortem, but the widespread microscopic fat emboli that were found suggest that the large masses were at least partly of lipid material.

The first appearance of emboli in the heart was directly related to the manipulation and reaming of the fracture. It is therefore reasonable to assume that the material originated from the fracture site or the adjacent soft tissues. The large masses probably arise from the coalescence of fat and possibly other material such as thrombus, which subsequently disintegrate in the lung microvasculature. Preliminary haematological study of the venous blood in the heart also suggested a high lipid content. Both hypotheses for the pathogenesis of FES are based on the assumption that the embolic material, whatever its content, is in small aggregations. The potential effect of large volumes of embolic lipid has not previously been considered.

Our second finding of particular interest was the demonstration of paradoxical embolism in one case. The systemic manifestations of FES have been assumed to result from the passage of fat emboli through pulmonary precapillary shunts, or directly across the pulmonary capillary bed. The demonstration of paradoxical embolism across a patent foramen ovale followed by the development of systemic FES, suggests that this route may be more significant than previously appreciated. Patent foramen ovale has a prevalence of 20% to 34%, and although we can find no description of paradoxical embolism of fat, it is well recognised that paradoxical embolism of air and thrombus can occur. Pulmonary fat embolism will increase right atrial pressure, and this may open the flap valve of the fossa ovalis, allowing embolic material to cross to the left side of the heart without passage through the lungs. We saw clinical FES only in our group-III patients, in all of whom large volumes of embolic material had passed through the heart. The most severe clinical symptoms were in the two patients who had nailing delayed beyond 48 hours.

The implication of our findings for intramedullary nailing and its relationship to fat embolus is not yet clear. Our preliminary results suggest that transoesophageal echocardiography may have a useful role in the prediction of patients at risk of FES after nailing. Further study is required of the relationship between echocardiographic findings, the severity of fracture, the timing of surgery and the development of FES.

The post-mortem examination was performed on behalf of the Procurator Fiscal, whom we wish to thank for permission to report the details of this case.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES

Baker SP, O'Neill B, Haddon W, Long WB. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974; 14:187-96.

Baker SP, O'Neill B. The Injury Severity Score: an update. *J Trauma* 1976; 16:882-5.

Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilisation of femoral fractures: a prospective randomised study. *J Bone Joint Surg [Am]* 1989; 71-A:336-40.

Christie J, Court-Brown C, Kinninmonth AWG, Howie CR. Intramedullary locking nails in the management of femoral shaft fractures. *J Bone Joint Surg [Br]* 1988; 70-B:206-10.

Court-Brown CM, Christie J, McQueen MM. Closed intramedullary tibial nailing: its use in closed and type I open fractures. *J Bone Joint Surg [Br]* 1990; 72-B:605-11.

Fuchsig P, Brucke P, Blumel G, Gottlob R. A new clinical and experimental concept on fat metabolism. *N Engl J Med* 1967; 276:1192-3.

Gossling HR, Pellegrini VD. Fat embolism syndrome: a review of the pathophysiology and physiological basis of treatment. *Clin Orthop* 1982; 165:68-82.

Gurd AR. Fat embolism: an aid to diagnosis. *J Bone Joint Surg [Br]* 1970; 52-B:732-7.

Johnson KD, Cadambi A, Seibert GB. Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: effect of early operative stabilization of fractures. *J Trauma* 1985; 25:375-84.

Levy D. The fat embolism syndrome: a review. *Clin Orthop* 1990; 261:281-6.

Manning JB, Bach AW, Herman CM, Carrico CJ. Fat release after femur nailing in the dog. *J Trauma* 1983; 23:322-6.

Meek RN, Woodruff B, Allardyce DB. Source of fat macroglobules in fractures of the lower extremity. *J Trauma* 1972; 12:432-4.

Peltier LF. Fat embolism: a perspective. *Clin Orthop* 1988; 232:263-70.

Riska BE, Myllynen P. Fat embolus in patients with multiple injuries. *J Trauma* 1982; 22:891-4.

Talucci RC, Manning J, Lampard S, Bach A, Carrico CJ. Early intramedullary nailing of femoral shaft fractures: a cause of fat embolism syndrome. *Am J Surg* 1983; 146:107-11.

Weinberg H, Finsterbush A. Fat embolism: vascular damage to bone due to blunt trauma: intraosseous phlebography study. *Clin Orthop* 1972; 83:273-8.

Wenda K, Henrichs KJ, Biegler M, Erbel R. Nachweis von markembolien während oberschenkelmarknagelungen mittels transösophagealer echokardiographie. *Unfallchirurgie* 1989; 15:73-6.

CENTRAL GRAFTING FOR PERSISTENT NONUNION OF THE TIBIA

A LATERAL APPROACH TO THE TIBIA, CREATING A CENTRAL COMPARTMENT

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We report the operative technique and results of a new method of central grafting for persistent nonunion of the tibial shaft. The operation is performed through a lateral approach, anterior to the fibula. Fresh autogenous bone from the iliac crest is used to form a central bridge between the tibia and fibula above, below and at the level of the nonunion. In 48 tibiae, most with long-standing nonunion and some with infection or bone defects, sound healing was obtained in 45 after one operation. Only one failure needed amputation.

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Nonunion of the tibial shaft is difficult to treat, especially in the presence of infection and bone loss. We report the use in 47 patients of a new operative technique called central grafting (CG). The method involves the placement of fresh autogenous corticocancellous bone from the posterior iliac crest through a lateral approach, anterior to the fibula, to create a tibiofibular synostosis above, at and below the level of the nonunion. Bony continuity does not depend upon consolidation of the nonunion itself; the central bone mass and the fibula consolidate into a tubular bone which is strong enough to bear the weight of the body.

PATIENTS AND METHODS

From 1971 to 1988 we treated by CG a total of 47 patients with 48 traumatic nonunions of the tibial shaft. There were 14 women and 33 men; all but four were referred from other hospitals. Their average age at the time of grafting was 36 years (6 to 75), and the mean interval from the original injury was 2.4 years (0.4 to 13). The sites of the fractures are shown in Figure 1; 73% were caused by high-energy trauma.

When first seen in our department, 12 (25%) tibiae had active osteomyelitis with a purulent discharge, and 34 (71%) had a history of deep infection. Seventeen tibiae (35%) had loss of bone averaging 5.3 cm (1 to 20), and 14 of these defects were or had been infected. The average number of operations before CG was 4.7 (0 to 14). The primary treatment had been plating in 20 tibiae. Seventeen patients (36%) had been advised to have amputation.

Operative treatment was performed in two stages. After the removal of all implants, any infected screw holes were drilled to a larger diameter and all necrotic bone and soft tissues were excised widely, even if this created a large defect. The wound was left open and the leg immobilised in a long plaster cast, which was not changed unnecessarily to avoid damage to granulation tissue (Trueta and Barnes 1940). In three cases the large soft-tissue defects required free vascularised musculocutaneous grafts.

In another three cases, tibiae with gaps larger than 10 cm, the defect was bridged with an autogenous cortical graft as well as cancellous grafts.

The second stage was postponed until signs of

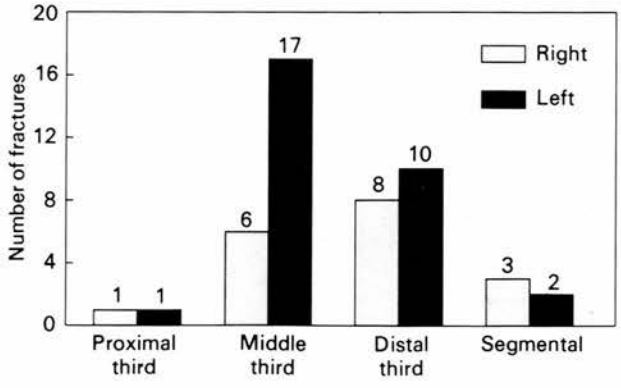

Fig. 1

The sites of 48 tibial fractures treated by central grafting.

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Mechanism of closed chest cardiopulmonary resuscitation investigated by transoesophageal echocardiography

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SUMMARY

Transoesophageal echocardiography (TOE) was performed during closed chest cardiopulmonary resuscitation (CPR) in 18 subjects in cardiac arrest. Compression of all four cardiac chambers resulted in forward flow in the pulmonary and systemic circulations, retrograde pulmonary vein flow and incomplete mitral valve closure. Antegrade pulmonary vein flow and left ventricular filling occurred exclusively during the relaxation phase. These findings support the cardiac pump theory of CPR and are incompatible with the thoracic pump mechanism. TOE merits further investigation as a device to monitor and guide resuscitation efforts during CPR.

Key words: blood flow, CPR, echocardiography mechanism

INTRODUCTION

More than 30 years after Kouwenhoven popularized closed chest CPR,[1] the mechanisms responsible for generating forward blood flow by this technique remain uncertain. The cardiac pump theory proposes that compression of the heart between the sternum and the vertebral column results in atrioventricular valve closure and ejection of blood into the systemic and pulmonary circulations.[1–3] In contrast, the thoracic pump theory suggests that the atrioventricular valves remain open during CPR, and that the left ventricle acts as a passive conduit for the passage of blood. In this model the heart is not compressed and flow is generated by pressure gradients between intrathoracic and extrathoracic vessels.[4,5] An understanding of the mechanisms that generate blood flow during CPR has become of practical importance in light of the realization that CPR is an imperfect method of sustaining the circulation. Cardiac output may be reduced by 80% or more, myocardial perfusion may be less than 5% of normal, and successful resuscitation beyond 15 min of CPR is uncommon.[6,7] A better understanding of the physiology of CPR might allow new resuscitation techniques to be developed. To elucidate these mechanisms, patients undergoing closed chest CPR were studied using TOE.

METHODS

Adults with non-traumatic, normothermic cardiac arrest, admitted to the Accident and Emergency (A&E) Department of the Edinburgh Royal Infirmary were studied. All patients had sustained cardiorespiratory arrest in the pre-hospital setting and had received CPR and defibrillation where appropriate prior to arrival. On admission, patients were treated according to the guidelines of the UK Resuscitation Council.[8] Electrical DC counter shock and antiarrhythmic agents were used as indicated. All patients were intubated and ventilated with 100% oxygen. Chest compression was administered at a rate of 80 compressions min^{-1}, either manually or mechanically, using a Michigan Instruments Thumper Model 1004 functioning at a ratio of five chest compressions to one ventilation.[9] CPR was performed with sufficient force to compress the chest 6–7 cm (36–45 kg) and peak inspiratory pressure was set at 30 cms of H_2O. The resuscitation attempt was supervised by a senior clinician who remained independent of the echocardiographic study. The study received ethical approval from the Lothian Health Board Ethics of Medical Research Committee.

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TOE was performed using a 5 MHz transverse plane transducer (Siemens Sonoline SI1200), which was positioned in the oesophagus following tracheal intubation. Colour flow and spectral Doppler studies were performed for analysis of blood flow patterns within the heart, pulmonary veins, aorta and pulmonary artery. All studies were recorded on VHS video tape for subsequent analysis. Imaging continued until a spontaneous circulation was restored, or until the resuscitation attempt was terminated.

Echocardiographic images were studied to determine the extent of compression of the heart chambers, the timing and direction of blood flow and the patterns of valve motion. Quantitative assessment was performed using a video overlay programme (Datavue, Novamicrosonics Inc., Indianapolis, IN, USA). Frames showing the left ventricle at end-relaxation and at end-compression were selected and endocardial areas were measured with calculation of the area ejection fraction (AEF):

$$AEF = \frac{LVA_R - LVA_C}{LVA_R} \quad (1)$$

where LVA_R is end-relaxation left ventricular cross-sectional area and LVA_C is end-compression left ventricular cross-sectional area.

RESULTS

Study population

Eighteen patients were studied (12 male, six female, age range 26–87 years, median age 66 years). The median interval between the onset of cardiac arrest and initiation of TOE was 31 mins (19–71 min). The initial rhythm was asystole in 10 patients, ventricular fibrillation in four patients and electromechanical dissociation in four patients. Spontaneous circulation was restored in two patients. Mechanical compression was administered to nine patients, manual compression to one patient, and both mechanical and manual compression to eight patients. Post mortem findings were available in six patients, and revealed acute coronary thrombosis ($n = 5$), and drug overdose ($n = 1$). In the remainder a clinical diagnosis of sudden cardiac death was made. The TOE probe was inserted in all patients without difficulty and did not compromise the conduct of the resuscitation attempt. There were no complications associated with TOE and none of the subjects had evidence of oesophageal trauma at post mortem examination.

General observations

Image quality was good in all patients, and colour flow Doppler analysis of blood flow patterns within the heart and great vessels was possible in every case. Spontaneous echocardiographic contrast developed within the heart when CPR was stopped and disappeared when CPR was resumed. No differences were observed between manual and mechanical CPR.

Compression phase

The right atrial and right ventricular free walls were displaced towards the interatrial septum and interventricular septum respectively (Fig. 1), resulting in a marked reduction in cavity size (Table 1). This was accompanied by both tricuspid regurgitation and antegrade pulmonary artery flow. The lumen of the proximal right pulmonary artery was markedly compressed in four patients and aliasing of the colour flow Doppler signal suggested increased velocities consistent with outflow obstruction.

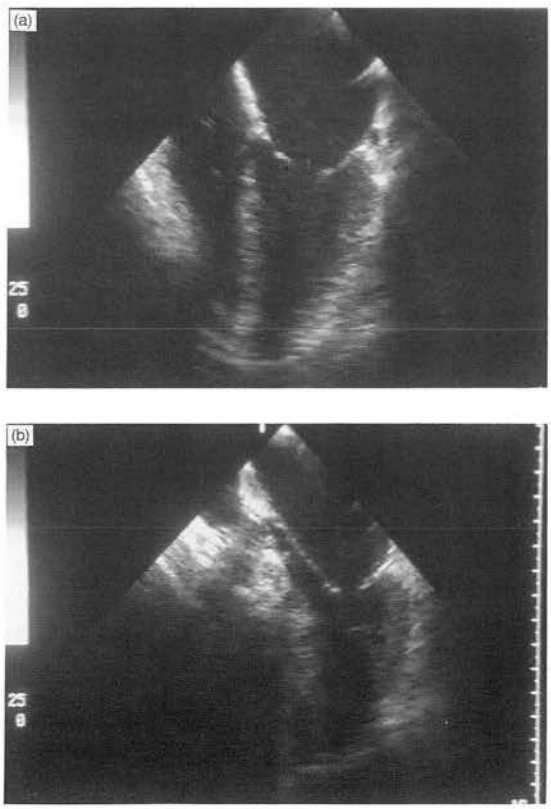

Fig. 1. Tranoesophageal echocardiographic four chamber view during relaxation (a) and compression (b) phases of CPR. There is incomplete coaptation of the mitral valve leaflets at peak compression.

Table 1. Extent of cardiac chamber compression during CPR

	Median area ejection fraction (%)	Range (%)
RA	62	49–85
RV	74	39–94
LA	23	10–43
LV	33	19–67

Chest compression resulted in a moderate reduction in left atrial and left ventricular chamber sizes (Table 1), retrograde pulmonary vein flow (Fig. 2), antegrade flow in the left ventricular outflow tract (LVOT) and ejection of blood into the aorta. The LVOT was compressed between the interventricular septum and the anterior leaflet of the mitral valve in five patients and was associated with aliasing of the colour flow Doppler signal. Similarly, at peak compression the proximal ascending aorta and superior vena cava were also markedly compressed and distorted. Regional differences in the extent of left ventricular compression were apparent, being greater at the base of the heart than at the mid-papillary muscle level.

Mitral valve motion was biphasic. Early in the compression phase there was partial leaflet separation, but with continued compression the two leaflets approximated, although full coaptation was not usually achieved. No antegrade flow occurred across the mitral valve during chest compression, and despite incomplete valve closure, mitral regurgitation was observed in only two subjects.

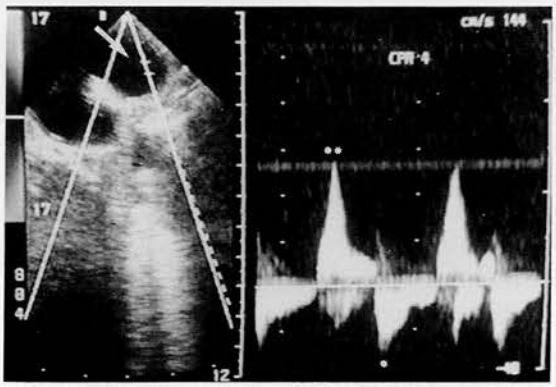

Fig. 2. Pulsed Doppler interrogation of left upper pulmonary vein (arrowed). Retrograde flow occurs during the compression phase (*) and antegrade flow during the relaxation phase (**).

Relaxation phase

Immediately on release of chest compression all four heart chambers re-expanded. Flow into the right atrium from the vena cavae and coronary sinus appeared to be turbulent, and the right ventricle filled through the open tricuspid valve. There was antegrade pulmonary vein flow into the left atrium and transmitral filling of the left ventricle. Mitral valve motion was also biphasic during the relaxation phase. The valve opened initially, but partial leaflet coaptation occurred later in the phase. The aortic valve closed and there was re-expansion of the ascending aorta and superior vena cava. Mild aortic incompetence was seen in two patients. Retrograde pulmonary artery flow was apparent, but the pulmonary valve and right ventricular outflow tract were visualized poorly with TOE.

Influence of underlying rhythm

Weak contractions of both ventricles and low amplitude movements of the atrioventricular valves were observed when the underlying rhythm was electromechanical dissociation. Systolic wall thickening and change in endocardial area associated with these contractions were minimal, and colour flow Doppler revealed no effective forward flow. No spontaneous contractions occurred in ventricular fibrillation or asystole.

Ineffective CPR

In five patients the left ventricle appeared markedly hypovolaemic and chest compression caused little change in left atrial and left ventricular areas. No flow was evident with colour flow Doppler and persistence of spontaneous echocardiographic contrast suggested ineffective CPR. Post mortem results in two of these subjects revealed no underlying explanation for the hypovolaemia.

DISCUSSION

Preliminary case reports have suggested that TOE might be used to investigate the events occurring during CPR,[10,11] as unlike precordial echocardiography, it can be performed continuously without compromising the resuscitation attempt. TOE is optimally positioned for visualization of both atria, the atrioventricular valves, the left ventricular outflow tract and the aortic valve, and blood flow patterns are readily demonstrated with colour flow Doppler.

These results support the cardiac pump model as the mechanism responsible for generating forward blood flow during CPR and are consistent with a recently published echocardiographic series.[12] Sternal depression caused direct compression of all four cardiac chambers and resulted in ejection of blood into the aorta and main pulmonary artery. Chamber compression was most marked on the right side of the heart, but the left atrium and ventricle were also compressed to a variable extent. In subjects with little left ventricular compression, no effective forward flow occurred.

A limitation of this study was the median delay of 30 min between the onset of the cardiac arrest and initiation of TOE. It has been suggested that the amplitude of mitral valve movements may diminish in prolonged resuscitation,[13] and the possibility that alternative mechanisms may operate during the initial stages of CPR cannot be excluded. Nevertheless, the effectiveness of CPR was demonstrated by the restoration of sinus rhythm after prolonged resuscitation in two subjects in whom the cardiac pump mechanism was clearly responsible for the production of systemic blood flow.

Whilst the thoracic pump mechanism can operate under certain conditions,[14] there was no evidence that it was responsible for the generation of forward flow in these subjects. This theory stipulates that the heart is not compressed, but that increased intrathoracic pressure is transmitted equally to all intrathoracic structures. As a result there is antegrade flow in the pulmonary veins and across the mitral valve throughout the compression phase. The evidence from TOE does not support this model. In particular, the presence of retrograde pulmonary vein flow and the absence of flow into the left ventricle during compression are incompatible with the thoracic pump mechanism.

The cardiac pump theory postulates that retrograde flow during chest compression is prevented by mitral valve closure. In this study, incomplete valve closure was observed in most subjects, yet mitral incompetence occurred in only two patients. This suggests that the pressures within the left atrium and the left ventricle may rise equally during the compression phase. During CPR, do both left heart chambers behave as a single chamber, compression of which results in ejection of blood into the aorta and retrograde pulmonary vein flow? There is limited published data on left atrial pressure changes during CPR to elucidate this issue. Similar pressures were recorded from the left atrium and femoral artery during CPR in subjects with mitral valve disease.[15] In contrast, a pressure gradient was demonstrated between the left ventricle and left atrium during CPR in dogs.[3]

Marked distortion of the left ventricular outflow tract, the aortic root and the right pulmonary artery commonly occurred during the compression phase and was associated with aliasing of the colour flow Doppler signal. Poor alignment from the oseophagus prevented spectral Doppler interrogation of flow at these sites, and it was not possible to ascertain whether significant outflow tract obstruction resulted. Experimentally, arterial collapse occurs when intrathoracic pressures and compressive forces are high, and this results in a reduction in carotid flow, a decreased stroke volume and the generation of a gradient between the left ventricle and the aorta.[2,4,5] Whether the effectiveness of CPR in humans is limited by similar mechanisms is unclear. Indeed, compression of the ascending aorta might even contribute to forward flow if it occurred at a time when left ventricular emptying had been completed. Distortion and compression of the superior vena cava was also frequently observed during CPR. The presence of venous valves in the internal jugular veins is well recognized,[4] however, compression of the superior vena cava might represent an additional mechanism by which pressure gradients are generated between the intrathoracic and extrathoracic venous systems during CPR.

TOE identified five subjects with left ventricular hypovolaemia in whom CPR was ineffective and resuscitation was unsuccessful. Left ventricular size decreases in ventricular fibrillation[16] and the volume of the left ventricle may be profoundly reduced at post mortem examination.[17] The pathophysiology of profound hypovolaemia is unexplained, and although it has been attributed to the position in the cardiac cycle at which the left ventricle arrests,[17] extreme vasodilation is an alternative explanation. Identification of subjects in whom conventional CPR is ineffective might allow new therapeutic techniques to be developed to optimize cerebral and myocardial perfusion during resuscitation. TOE merits further investigation as a technique to monitor and guide resuscitation efforts.

REFERENCES

1. Kouwenhoven W.B., Jude J.R. & Knickerbocker G.G. (1960) Closed-chest cardiac massage. *Journal of the American Medical Association* **173**, 1064–1067.
2. Maier G.W., Tyson G.S., Olsen C.O. *et al.* (1984) The physiology of external cardiac massage: high-

impulse cardiopulmonary resuscitation. *Circulation* **70**, 86–101.

3. Feneley M.P., Maier G.W., Gaynor J.W. *et al.* (1987) Sequence of mitral valve motion and transmitral blood flow during manual cardiopulmonary resuscitation in dogs. *Circulation* **76**, 363–375.
4. Rudikoff M.T., Maughan W.L., Effron M., Freund P. & Weisfeldt M.L. (1980) Mechanisms of blood flow during cardiopulmonary resuscitation. *Circulation* **61**, 345–352.
5. Niemann J.T., Rosborough J.P., Hausknecht M., Carner D. & Criley J.M. (1981) Pressure-synchronized cineangiography during experimental cardiopulmonary resuscitation. *Circulation* **64**, 985–991.
6. Del Guercio L.M.R., Coomaraswany R. & State D. Cardiac output and other hemodynamic variables during external massage in man. *New England Journal of Medicine* **269**, 1398–1401.
7. Robertson C. & Holmberg S. (1992) Compression techniques and blood flow during cardiopulmonary resuscitation. *Resuscitation* **24**, 123–132.
8. UK Resuscitation Council (1984) *Cardio-pulmonary Resuscitation*. Laerdal Medical Limited, London.
9. Steedman D.J. & Robertson C.E. (1990) Measurement of end-tidal carbon dioxide concentration during cardiopulmonary resuscitation. *Archives of Emergency Medicine* **7**, 129–134.
10. Higano S.T., Oh J.K., Ewy G.A. & Seward J.B. (1990) The mechanism of blood flow during closed chest cardiac massage in humans: transesophageal echocardiographic observations. *Mayo Clinic Proceedings* **65**, 1432–1440.
11. Kuhn C., Juchems R. & Frese W. (1991) Evidence for the 'cardiac pump theory' in cardiopulmonary resuscitation in man by transesophageal echocardiography. *Resuscitation* **22**, 275–282.
12. Redberg R.F., Tucker K.J., Cohen T.J., Dutton J.P., Callaham M.L. & Schiller N.B. (1993) Physiology of blood flow during cardiopulmonary resuscitation. A transesophageal echocardiographic study. *Circulation* **88**, 534–542.
13. Deshmukh H.G., Weil M.H., Rackow E.C., Trevino R. & Bisera J. (1985) Echocardiographic observations during cardiopulmonary resuscitation: a preliminary report. *Critical Care Medicine* **13**, 904–906.
14. Criley I.M., Blaufuss A.H. & Kissel G.L. (1976) Cough-induced cardiac compression. Self-administered form of cardiopulmonary resuscitation. *Journal of the American Medical Association* **236**, 1246–1250.
15. Thomsen J.E., Stenlund R.R. & Rowe G.G. (1968) Intracardiac pressures during closed-chest cardiac massage. *Journal of the American Medical Association* **205**, 46–48.
16. Mashiro I., Cohn J.N., Heckel R., Nelson R.R. & Franciosa J.A. (1978) Left and right ventricular dimensions during ventricular fibrillation in the dog. *American Journal of Physiology* **235**, H231–H236.
17. Hutchins G.M. & Anaya O.A. Measurements of cardiac size, chamber volumes and valve orifices at autopsy. *John Hopkins Medical Journal* **133**, 96–106.

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Management of minor head injuries in the accident and emergency department: the effect of an observation ward

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SUMMARY

The management of 483 patients presenting with minor head injury to the accident and emergency (A&E) departments of two Scottish hospitals was studied prospectively. Such patients comprised 5.7 and 3.9% of the total attendances to each department. Of the 277 patients assessed in the former department, 83 (30%) fulfilled at least one of the currently accepted criteria for recommending admission to hospital and 49 (17.7%) patients were actually admitted. Patients in whom head injury was not the principal reason for admission were excluded from the study. In the same time period the second department dealt with 206 patients with minor head injury, 49 (24%) of whom had criteria for admission. However, significantly fewer, 10 (4.9%) patients, were actually admitted. The major relevant factor when comparing the two departments was the existence in the former of an observation ward. These results support the view that easy access to hospital beds is a major determinant of management in patients presenting with minor head injury to the A&E department and may be more influential than clinical findings.

Key word: guidelines, head injury, management, observation ward

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INTRODUCTION

Patients with head injury comprise approximately 10% of total attendances at A&E departments in the UK.[1] It is estimated that about 1 000 000 recently head injured patients attend hospital each year in the UK — 1 per 50 of the population.[2] The great majority of these patients will have sustained minor injury only, however one of the greatest worries for medical staff in A&E departments is that they might discharge a head injured patient who later develops a complication such as intracranial haematoma or meningitis.

To help identify the group of at-risk attenders, guidelines have been prepared by several groups and are widely used by A&E doctors working in this country.[3,4] These include recommendations on those patients who require radiological and other investigations and general aspects of patient management and specialist referral. The primary purpose of these guidelines is to identify those patients at risk of developing complications as a consequence of their injury. Ideally their implementation would also restrict the number of patients with minor head injuries who are admitted to hospital without demonstrable risk[5] and since their introduction an associated fall in total numbers of head injury admissions has been recorded.[6]

Once the decision has been made by the examining doctor that a head injury attender requires admission, then the patient will most frequently be referred to a primary acute receiving ward. Only a small proportion of these patients, about 3–5% are referred directly to a neurosurgical unit.[2] Some A&E departments have direct access to a 'Short-stay' or 'Observation' ward and when this facility is available it is frequently used to observe the minor head injured patient. The aim of this study was to determine whether access to a short-stay ward significantly affected the threshold for admission of patients with minor head injuries and the implementation of head injury admission guidelines.

METHODS

A cohort of patients attending two large Scottish teaching hospital A&E departments was studied, these were Glasgow Royal Infirmary (GRI), and the

BRIEF REPORT: FULMINATING FAT EMBOLISM SYNDROME CAUSED BY PARADOXICAL EMBOLISM THROUGH A PATENT FORAMEN OVALE

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THE post-traumatic fat embolism syndrome is a multisystem disorder characterized by pulmonary and neurologic dysfunction, pyrexia, and a petechial rash.[1-4] More than a century after the first descriptions of the fat embolism syndrome, the cause of fat emboli and the pathogenesis of the systemic manifestations of this disorder remain incompletely understood. We describe a patient undergoing treatment of a femoral fracture in whom massive fat embolism was demonstrated by transesophageal echocardiography. Acute cor pulmonale developed, precipitating paradoxical fat embolism across a patent foramen ovale, with the subsequent development of the fat embolism syndrome. Embolism of fat across a patent foramen ovale is a possible mechanism responsible for the systemic features of fat embolism syndrome.

CASE REPORT

A 79-year-old man was admitted after a fall resulting in a closed fracture of the right femoral shaft. He had had a myocardial infarction one year earlier and had made an uncomplicated recovery from an avulsion fracture of the right lesser trochanter two years earlier. The results of laboratory investigations were normal, and the electrocardiogram demonstrated a minor intraventricular conduction defect and no Q waves.

A decision was made to treat the fracture by closed reduction and fixation with an intramedullary nail. The patient received subcutaneous heparin preoperatively and remained well until elective surgery on the 11th day after the injury. Anesthesia was induced with propofol and pancuronium, and after endotracheal intubation the patient was given mechanical ventilation with oxygen, enflurane, and nitrous oxide. The electrocardiogram, oxygen saturation, and end-tidal partial pressure of carbon dioxide were monitored continuously, and a transesophageal echocardiographic probe was introduced to monitor cardiac function. Immediately before surgery the blood pressure was 152/80 mm Hg, the electrocardiogram showed sinus rhythm, the oxygen saturation was 98 percent, and the end-tidal partial pressure of carbon dioxide was 28.5 mm Hg. Transesophageal echocardiography revealed normal left ventricular function with no regional wall-motion abnormality, trivial mitral incompetence, and an enlarged right atrium and coronary sinus. Moderately severe tricuspid regurgitation was present, and the pulmonary-artery systolic pressure was estimated to be 45 mm Hg when the continuous-wave Doppler capabilities of the transesophageal echocardiographic probe were used.[5] There was no evidence of an atrial septal defect, and the fossa ovalis was identified and appeared intact, with no displacement during the respiratory cycle. No interatrial shunting was identified with color-flow Doppler techniques. Before surgery, no abnormal masses or echogenic material was seen within the heart chambers.

Transesophageal echocardiographic monitoring was performed continuously and recorded on videotape. Several seconds after the insertion of a guide wire into the medullary cavity, a shower of small (1 to 2 mm) echogenic masses appeared within the right atrium and right ventricle. No masses were seen within the left atrium or left ventricle, and there were no changes in physiologic measurements. Manipulation of the medullary cavity resulted in a large increase in the quantity of echogenic material, with complete opacification of the right atrium and the right ventricle (Fig. 1). Among the mass of smaller echoes were numerous highly echogenic bodies, 1 cm in diameter and 1 to 7 cm long. These masses could be seen coiling within the right atrium, sometimes rebounding from the closed tricuspid valve, and often persisting for several cardiac cycles before passing into the right ventricle and the pulmonary artery (Fig. 2). Complete opacification of the right heart chambers persisted, and after 60 seconds the interatrial septum was observed to bulge into the left atrium and the flap valve of the fossa ovalis opened, with large quantities of embolic material passing into the left atrium (Fig. 3). Initially, the septal movements occurred in synchrony with the ventilatory cycle, but after a few minutes the septum became persistently displaced, and color-flow mapping confirmed the presence of a right-to-left shunt across the fossa ovalis. Medullary manipulation was halted, but paradoxical embolism continued for a further 20 minutes, and numerous embolic masses as large as 1 cm in diameter could be seen within the heart and aorta. During this period the oxygen saturation decreased to 75 percent, the end-tidal partial pressure of carbon dioxide to 9 mm Hg, and the arterial blood pressure to 72/40 mm Hg. Transesophageal echocardiography demonstrated dyskinesia of the interventricular septum, right ventricular dilatation, and severe tricuspid incompetence, and the estimated pulmonary-artery systolic pressure increased to 80 mm Hg. There was a self-limiting episode of ventricular tachycardia. The patient was resuscitated, and the procedure was completed with the insertion of an intramedullary nail. The nailing was accompanied by the appearance of large quantities of embolic material within all four cardiac chambers.

The patient was admitted to the intensive care unit, and a Swan–Ganz catheter was inserted. The pulmonary and systemic vascular resistances were elevated (to 1350 and 5301 dyn · sec · cm^{-5} per square meter of body-surface area, respectively), and the cardiac index was reduced (to 1.6 liters per minute per square meter). Mechanical ventilation was continued, and inotropic drug therapy was begun for persistent hypotension and oliguria (5 to 20 μg of dobutamine per kilogram of body weight per minute and 4 μg of dopamine per kilogram per minute). The electrocardiogram revealed nonspecific ST-segment and T-wave changes. Measurement of arterial-blood gases during ventilation with 50 percent oxygen revealed a pH of 7.39, a partial pressure of oxygen of 75 mm Hg, and a partial pressure of carbon dioxide of 31.5 mm Hg. The patient remained comatose, and neurologic examination revealed lower-limb hyperreflexia and bilateral extensor plantar responses. Three hours postoperatively, several generalized convulsions were treated with an infusion of phenytoin (loading dose, 10 mg per kilogram). A right-sided subconjunctival hemorrhage and scattered petechial hemorrhages appeared on the trunk and upper arms 18 hours postoperatively. Progressive arterial hypoxemia developed (partial pressure of oxygen, 59.5 mm Hg) despite an inspired oxygen concentration of 100 percent, and the chest film demonstrated bilateral pulmonary infiltrates. The cardiac index fell to 1.2 liters per minute per square meter and did not increase in response to increased doses of dobutamine (20 to 70 μg per kilogram per minute). The patient's oliguria continued, and he died of cardiac and respiratory failure 32 hours postoperatively.

Postmortem examination confirmed the diagnosis of fat embolism syndrome. Scattered petechial hemorrhages were found affecting the pericardium, the skin, and the interlobar fissures of both lungs. Microscopical examination revealed widespread microvascular occlusion by fat emboli, particularly within the lungs (Fig. 4), kidney, myocardium, and brain, with evidence of infarction in the

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Transesophageal echocardiographic monitoring was performed continuously and recorded on videotape. Several seconds after the insertion of a guide wire into the medullary cavity, a shower of small (1 to 2 mm) echogenic masses appeared within the right atrium and right ventricle. No masses were seen within the left atrium or left ventricle, and there were no changes in physiologic measurements. Manipulation of the medullary cavity resulted in a large increase in the quantity of echogenic material, with complete opacification of the right atrium and the right ventricle (Fig. 1). Among the mass of smaller echoes were numerous highly echogenic bodies, 1 cm in diameter and 1 to 7 cm long. These masses could be seen coiling within the right atrium, sometimes rebounding from the closed tricuspid valve, and often persisting for several cardiac cycles before passing into the right ventricle and the pulmonary artery (Fig. 2). Complete opacification of the right heart chambers persisted, and after 60 seconds the interatrial septum was observed to bulge into the left atrium and the flap valve of the fossa ovalis opened, with large quantities of embolic material passing into the left atrium (Fig. 3). Initially, the septal movements occurred in synchrony with the ventilatory cycle, but after a few minutes the septum became persistently displaced, and color-flow mapping confirmed the presence of a right-to-left shunt across the fossa ovalis. Medullary manipulation was halted, but paradoxical embolism continued for a further 20 minutes, and numerous embolic masses as large as 1 cm in diameter could be seen within the heart and aorta. During this period the oxygen saturation decreased to 75 percent, the end-tidal partial pressure of carbon dioxide to 9 mm Hg, and the arterial blood pressure to 72/40 mm Hg. Transesophageal echocardiography demonstrated dyskinesia of the interventricular septum, right ventricular dilatation, and severe tricuspid incompetence, and the estimated pulmonary-artery systolic pressure increased to 80 mm Hg. There was a self-limiting episode of ventricular tachycardia. The patient was resuscitated, and the procedure was completed with the insertion of an intramedullary nail. The nailing was accompanied by the appearance of large quantities of embolic material within all four cardiac chambers.

The patient was admitted to the intensive care unit, and a Swan–Ganz catheter was inserted. The pulmonary and systemic vascular resistances were elevated (to 1350 and 5301 dyn · sec · cm^{-5} per square meter of body-surface area, respectively), and the cardiac index was reduced (to 1.6 liters per minute per square meter). Mechanical ventilation was continued, and inotropic drug therapy was begun for persistent hypotension and oliguria (5 to 20 μg of dobutamine per kilogram of body weight per minute and 4 μg of dopamine per kilogram per minute). The electrocardiogram revealed nonspecific ST-segment and T-wave changes. Measurement of arterial-blood gases during ventilation with 50 percent oxygen revealed a pH of 7.39, a partial pressure of oxygen of 75 mm Hg, and a partial pressure of carbon dioxide of 31.5 mm Hg. The patient remained comatose, and neurologic examination revealed lower-limb hyperreflexia and bilateral extensor plantar responses. Three hours postoperatively, several generalized convulsions were treated with an infusion of phenytoin (loading dose, 10 mg per kilogram). A right-sided subconjunctival hemorrhage and scattered petechial hemorrhages appeared on the trunk and upper arms 18 hours postoperatively. Progressive arterial hypoxemia developed (partial pressure of oxygen, 59.5 mm Hg) despite an inspired oxygen concentration of 100 percent, and the chest film demonstrated bilateral pulmonary infiltrates. The cardiac index fell to 1.2 liters per minute per square meter and did not increase in response to increased doses of dobutamine (20 to 70 μg per kilogram per minute). The patient's oliguria continued, and he died of cardiac and respiratory failure 32 hours postoperatively.

Postmortem examination confirmed the diagnosis of fat embolism syndrome. Scattered petechial hemorrhages were found affecting the pericardium, the skin, and the interlobar fissures of both lungs. Microscopical examination revealed widespread microvascular occlusion by fat emboli, particularly within the lungs (Fig. 4), kidney, myocardium, and brain, with evidence of infarction in the

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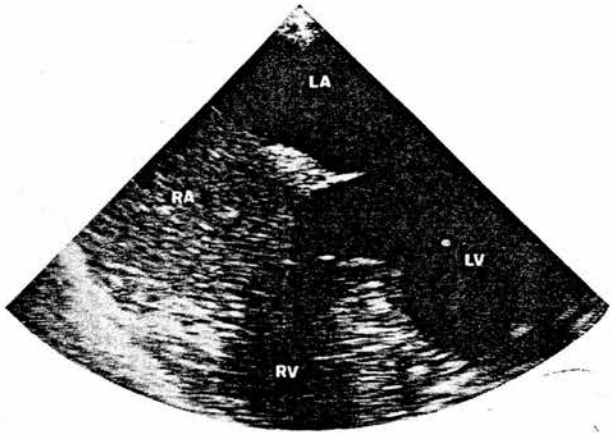

Figure 1. Transesophageal Echocardiographic Four-Chamber View, Showing Multiple Fat Emboli in the Right Atrium (RA) and Right Ventricle (RV) during Intramedullary Manipulation.
Both right heart chambers are completely opacified with embolic material. LA denotes left atrium, and LV left ventricle.

cerebrum, cerebellum, and brain stem. Examination of the heart revealed a patent foramen ovale, with a maximal aperture of 0.5 cm. There was dilatation of the tricuspid-valve ring that was consistent with right ventricular failure, and there was subendocardial fibrosis compatible with previous myocardial infarction. Bone specimens taken during manipulation and from the fracture site revealed widespread immature mesenchymal cells within the intertrabecular spaces that were consistent with early healing of the fracture. There was no evidence of deep-vein thrombosis or pulmonary thromboembolism.

Discussion

The fat embolism syndrome is an uncommon but well-described complication of skeletal trauma characterized by both pulmonary and systemic fat embolism.[1-4] Incomplete forms are common, and the spectrum of the fat embolism syndrome includes subclinical, mild, and fulminating presentations.[6,7] Our patient had a fulminating fat embolism syndrome that met Gurd's three major diagnostic criteria: a petechial rash, respiratory distress, and cerebral signs.[8] The origin of fat emboli has been debated since the original accounts of the syndrome in the late 19th century. The mechanical theory proposes that intramedullary veins are damaged by trauma, allowing marrow fat to intravasate and embolize to the lungs.[2] In contrast, the biochemical hypothesis suggests that fat emboli are composed of aggregated chylomicrons and very-low-density lipoproteins that coalesce within the vasculature after trauma, with the formation of fat macroglobules.[9-11] In our patient, the close temporal association between medullary manipulation and intracardiac embolism is consistent with the mechanical theory of fat embolism. Intramedullary pressure is increased by manipulation and nailing procedures, and these may have promoted the entry of marrow fat into medullary veins. Although the echogenic masses seen inside the heart were not sampled at the moment of embolism, subsequent histologic studies showed widespread pulmonary and systemic intravascular fat deposition consistent with fat embolism. These echocardiographic observations are also consistent with those of an experimental study that demonstrated the presence of marrow fat in the femoral vein within seconds of intramedullary manipulation.[12]

Peltier has proposed that the fat embolism syndrome is primarily a pulmonary disease and has emphasized the importance of increased pulmonary vascular resistance due to widespread microvascular occlusion.[2] Massive fat embolism obstructs the pulmonary circulation and leads to hypoxemia as a result of ventilation–perfusion inequality. Rapid deterioration may occur, with death from acute right ventricular failure. Our findings are consistent with this hypothesis. Transesophageal echocardiography demonstrated severe and prolonged embolization that resulted in increased pulmonary-artery pressure and pulmonary vascular resistance, right ventricular dilatation, and worsening tricuspid incompetence. The delayed appearance of a petechial rash, neurologic dysfunction, and the development of progressive pulmonary dysfunction are characteristic of the fat embolism syndrome and are consistent with the theory of a secondary phase of tissue damage, possibly due to the toxic effects of free fatty acids liberated by the hydrolysis of fat emboli in the lungs.[13,14] Histologic examination of patients with systemic fat embolism syndrome typically reveals widespread microvascular occlusion by fat emboli.[15] Such emboli are believed to reach the systemic circulation either through pulmonary-precapillary shunts or directly across the pulmonary-capillary bed.[1,16,17] Paradoxical embolism of air and thrombus across a patent foramen ovale is well recognized, but the passage of fat is an alternative mechanism responsible for the systemic manifestations of the fat embolism syndrome. Shunting across a patent foramen ovale can occur during coughing, after the release phase of the Valsalva maneuver, and during mechani-

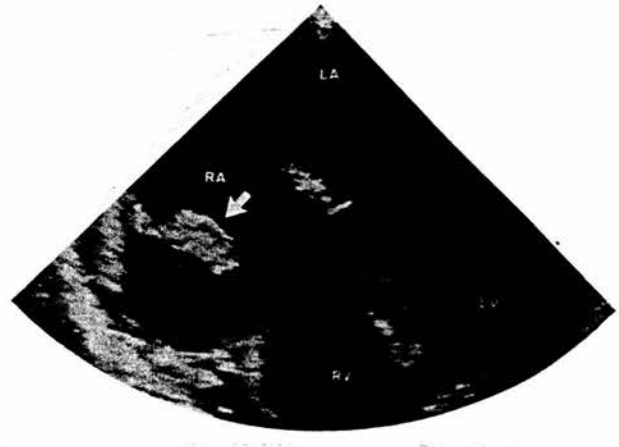

Figure 2. Transesophageal Echocardiographic Four-Chamber View, Showing a Large Fat Embolus (Arrow) among Smaller Echogenic Masses in the Right Atrium.
RA denotes right atrium, RV right ventricle, LA left atrium, and LV left ventricle.

cal ventilation,[18-20] and paradoxical thromboembolism has occurred in pulmonary embolism, chronic lung disease, and right ventricular failure.[21,22] In this case paradoxical embolism was precipitated by increased right atrial pressure due to acute cor pulmonale. The observation of phasic displacement of the fossa ovalis with the ventilatory cycle suggests that the use of mechanical ventilation may have contributed to this process by cyclic increases in right atrial pressure. The fact that fat is readily deformable accounts for the passage of masses larger than the diameter of the patent foramen ovale.[17] The foramen ovale is patent in 20 to 34 percent of people,[23] and the possibility that this route might be involved in the pathogenesis of the systemic manifestations of the fat embolism syndrome was considered by Sevitt.[17] In an early study of 24 subjects with systemic fat embolism, none had evidence of an atrial septal defect at autopsy,[24] but it is not clear whether patency of the foramen ovale was examined in this series. A right-to-left shunt through a patent foramen ovale was detected with color-flow Doppler techniques in only one of six subjects who had recovered from post-traumatic fat embolism syndrome.[25] However, the importance of these findings is uncertain, because more recent work indicates that both color-flow Doppler and contrast echocardiography are required to exclude the possibility of patency of the foramen ovale.[26]

Increasingly, transesophageal echocardiography is used to monitor perioperative cardiac function in patients at high risk. In our experience, echocardiographically detectable fat embolism may be observed in approximately 40 percent of patients undergoing major orthopedic procedures.[27] At present, routine echocardiographic monitoring cannot be recommended, but future research may provide guidelines for using transesophageal echocardiography and for terminating procedures if evidence of marked embolization is found.

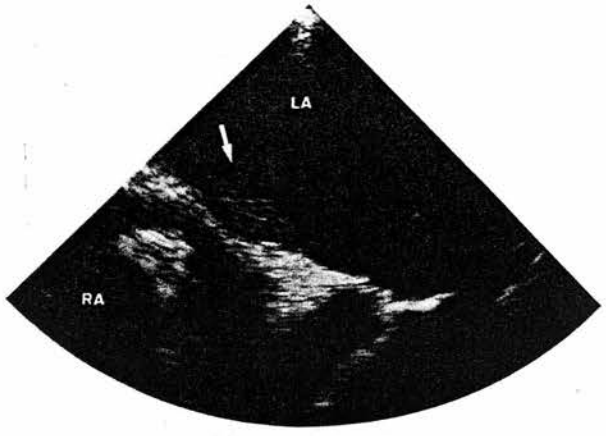

Figure 3. Transesophageal Echocardiographic View of the Interatrial Septum.
The fossa ovalis is displaced into the left atrium (LA) (arrow), and the flap valve has opened, allowing the passage of fat emboli. Echogenic material is seen on both sides of the interatrial septum. RA denotes right atrium.

Figure 4. Autopsy Specimen of the Lung.
Pulmonary microvascular occlusion by fat emboli is visible (osmic acid stain, ×110).

We are indebted to the coroner (Procurator Fiscal), on behalf of whom the postmortem examination was performed, for permission to report the details of this case.

References

1. Sevitt S. The significance and pathology of fat embolism. Ann Clin Res 1977;9:173-80.
2. Peltier LF. Fat embolism: a perspective. Clin Orthop 1988;232:263-70.
3. Levy D. The fat embolism syndrome: a review. Clin Orthop 1990;261:281-6.
4. Riska EB, Myllynen P. Fat embolism in patients with multiple injuries. J Trauma 1982;22:891-4.
5. Currie PJ, Seward JB, Chan K-L, et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol 1985;6:750-6.
6. Fabian TC, Hoots AV, Stanford DS, Patterson CR, Mangiante EC. Fat embolism syndrome: prospective evaluation in 92 fracture patients. Crit Care Med 1990;18:42-6.
7. Hagley SR. The fulminant fat embolism syndrome. Anaesth Intensive Care 1983;11:167-70.
8. Gurd AR. Fat embolism: an aid to diagnosis. J Bone Joint Surg [Br] 1970; 52:732-7.
9. Evarts CM. The fat embolism syndrome: a review. Surg Clin North Am 1970;50:493-507.
10. Lehman EP, Moore RM. Fat embolism including experimental production without trauma. Arch Surg 1927;14:621-62.
11. Hulman G. Pathogenesis of non-traumatic fat embolism. Lancet 1988;1: 1366-7.
12. Manning JB, Bach AW, Herman CM, Carrico CJ. Fat release after femur nailing in the dog. J Trauma 1983;23:322-6.

13. Peltier LF. Fat embolism. III. The toxic properties of neutral fat and free fatty acids. Surgery 1956;40:665-70.
14. Fonte DA, Hausberger FX. Pulmonary free fatty acids in experimental fat embolism. J Trauma 1971;11:668-72.
15. Kamenar E, Burger PC. Cerebral fat embolism: a neuropathological study of a microembolic state. Stroke 1980;11:477-84.
16. Watson AJ. Genesis of fat emboli. J Clin Pathol [Suppl] (R Coll Pathol) 1970;4:132-42.
17. Sevitt S. Fat embolism. London: Butterworth, 1962.
18. Langholz D, Louie EK, Konstadt SN, Rao TL, Scanlon PJ. Transesophageal echocardiographic demonstration of distinct mechanisms for right to left shunting across a patent foramen ovale in the absence of pulmonary hypertension. J Am Coll Cardiol 1991;18:1112-7.
19. Leonard RC, Neville E, Hall RJ. Paradoxical embolism: a review of cases diagnosed during life. Eur Heart J 1982;3:362-70.
20. Lemaire F, Richalet JP, Carlet J, Brun-Buisson C, MacLean C. Postoperative hypoxemia due to opening of a patent foramen ovale confirmed by a right atrium–left atrium pressure gradient during mechanical ventilation. Anesthesiology 1982;57:233-6.
21. Nagelhout DA, Pearson AC, Labovitz AJ. Diagnosis of paradoxic embolism by transesophageal echocardiography. Am Heart J 1991;121:1552-4.
22. Lang I, Steurer G, Weissel M, Burghuber OC. Recurrent paradoxical embolism complicating severe thromboembolic pulmonary hypertension. Eur Heart J 1988;9:678-81.
23. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17-20.
24. Emson HE. Fat embolism studied in 100 patients dying after injury. J Clin Pathol 1958;11:28-35.
25. Nijsten MW, Hamer JP, ten Duis HJ, Posma JL. Fat embolism and patent foramen ovale. Lancet 1989;1:1271.
26. Konstadt SN, Louie EK, Black S, Rao TL, Scanlon P. Intraoperative detection of patent foramen ovale by transesophageal echocardiography. Anesthesiology 1991;74:212-6.
27. Pell ACH, Keating JF, Christie J, Sutherland GR. Use of transesophageal echocardiography to predict patients at risk of the fat embolism syndrome following traumatic injuries. J Am Coll Cardiol 1993;21:Suppl A:264A. abstract.

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