IMPACT OF LENGTH AND COATING OF INTRODUCER SHEATH AND COMPRESSION HAEMOSTATIC DEVICES ON CLINICAL OUTCOMES AND VASCULAR INJURY IN RELATION TO TRANSRADIAL CORONARY PROCEDURES

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Medicine

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May 2012

ABSTRACT

Background

Radial artery spasm is the most common cause of patient discomfort and reduces the procedural success rates during transradial coronary artery procedures. The impact of transradial procedures on the vascular function of the radial artery is unknown.

Hypothesis

Hydrophilic coating of the introducer sheath will reduce radial artery spasm and the TR Band compression device will reduce patient discomfort and time taken to achieve haemostasis. Transradial procedures cause impairment of vascular function.

Methods

790 patients were randomly assigned in a factorial design to receive long (23 cm) hydrophilic, long uncoated, short (13 cm) hydrophilic and short uncoated introducer sheaths during transradial procedures. The primary end point was radial artery spasm and secondary end points were patient's discomfort and local vascular complications. Similarly, patients were randomly assigned to receive either TR band or Radistop and the outcome measures evaluated were patient tolerance of the device, local vascular complications and the time taken to achieve haemostasis. Radial artery endothelium-dependent and endothelium-independent functions were assessed in 35 patients.

Results

Procedural success was achieved in 96% of the cases and radial artery spasm accounted for 2.2% of failed cases. There was significantly less radial artery spasm observed and patient-reported discomfort in patients receiving a hydrophilic coated sheath. No difference was observed between long and short sheaths. Radial artery occlusion was observed in 9.5% of the patients and was not influenced by sheath length or coating. Younger age, female sex, diabetes, and lower body mass index were identified as independent predictors of clinical radial artery spasm. Patients in the Radistop group reported significantly more pain across all categories of severity and time taken to achieve haemostasis was significantly longer in the TR Band group. Endothelium dependent dilatation in the catheterized arm decreased significantly in the coated and uncoated groups, respectively. These values returned towards baseline levels 3 months later. GTN induced vasodilatation decreased significantly in both groups. Values returned to baseline at 3months.

Conclusions

Hydrophilic coating of the introducer sheath reduces the incidence of radial artery spasm. Sheath length did not influence this effect. Both TR Band and Radistop devices are safe and effective as haemostatic compression devices following transradial procedures. However, more patients felt discomfort with the Radistop device and the time taken to achieve haemostasis was longer with the TR band. Placement of a catheter sheath inside the radial artery disrupts endothelium-dependent and independent vasodilator function, which largely recovers after 3 months. No differences were evident between hydrophilic-coated and uncoated sheaths or long and short sheaths.

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Author's Declaration

This thesis is the result of my own work. The material contained in the thesis has not been presented, nor is currently being presented, either wholly or in part for any other qualification. The research and clinical work were both carried out exclusively at the Liverpool Heart and Chest Hospital NHS Trust, Liverpool. All studies described in this thesis were performed by me.

Acknowledgements

I extend my sincere gratitude to Dr John Morris, Dr Rodney Stables, Dr Joseph Mills, Dr Nick Palmer, Dr Raphael Perry, and Dr Mike Fisher for allowing me to recruit their patients and for supporting this research project. I would like to appreciate and thank Dr Ellen Dawson, Professor Danny Green and their team from Department of Sports Physiology, John Moore's University, Liverpool for their support and help in conducting physiological studies. I also would like to thank Dr Mahesh Pauriah and Dr Abdul Hakeem for helping in recruitment and day to day running of this trial. Lastly, I also wish to affirm my appreciation to my wife Vandana for her encouragement and understanding, my children Anu and Maanya for their inspiration during the study period.

Chapter 1 Introduction

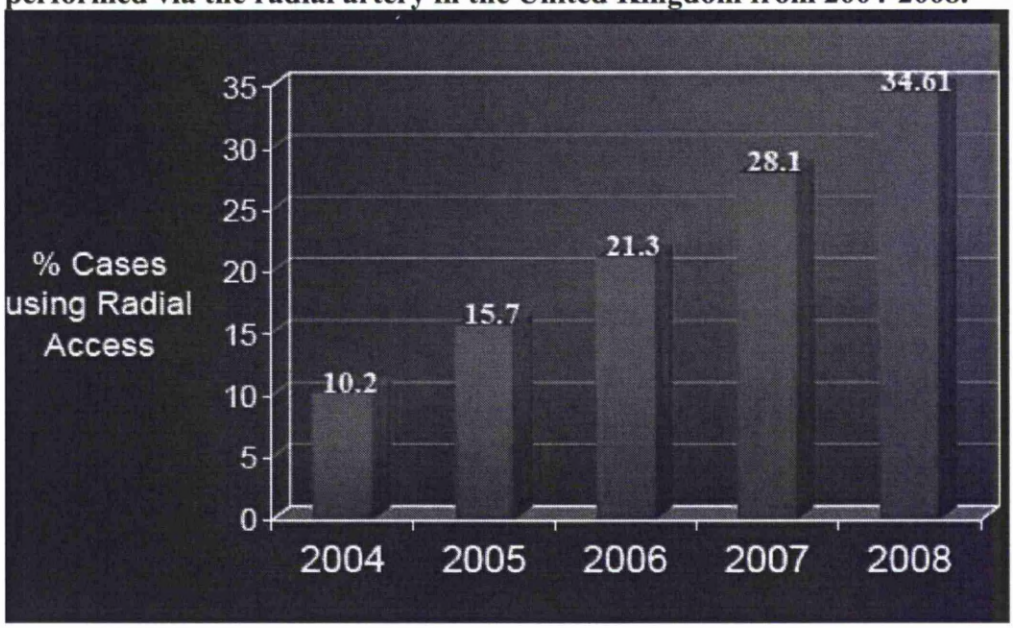
1.1 General Introduction

The transradial approach for coronary angiography was first described by Campeau in 1989(1) and the technique was extended to percutaneous transluminal coronary angioplasty and stenting by Kiemeneij and Laarman (2). Since then a widespread proliferation of coronary procedures via the radial artery has taken place (3-8).

The safety of the radial approach, compared to the conventional femoral approach for coronary procedures, is mainly due to favourable anatomic relations of the radial artery. No major veins or nerves are located near the radial artery at the wrist, minimising the chance of neurological or vascular injury. Haemostasis is easily achieved because of the superficial course of the radial artery. Thrombotic or traumatic radial arterial occlusion does not endanger the viability of the hand if an adequate collateral blood supply from the ulnar artery is present.

A meta-analysis by Hamon et al. (9) of twelve randomised trials, including 3,224 patients, comparing radial and femoral approaches for coronary procedures has shown similar major adverse cardiac events with radial and femoral approach (2.1% vs. 2.4%). However, radial access was associated with a significantly lower rate of entry site complications (0.3% vs. 2.8%). There was higher rate of procedural failure with radial approach in the earlier studies but there was the trend towards equalization of the rate of procedural success over the years.

Figure 1-1 Annual increase in coronary catheterisation procedures performed via the radial artery in the United Kingdom from 2004-2008.



The proportion of coronary procedures being performed via a radial approach in the United Kingdom have been steadily increasing and about one third of the total number of cases were performed via a radial approach in the United Kingdom in the year 2008 (British Cardiovascular Intervention Audit 2008) (Figure 1.1). This percentage ranges from 10% to 90% of the total procedures performed via radial approach at each centre (Figure 1.2). The radial approach is used at similar rates in various clinical syndromes (Figure 1.3).

Figure 1-2 Rates of cases performed via a transradial approach at individual centres across the United Kingdom from 2006-2008.

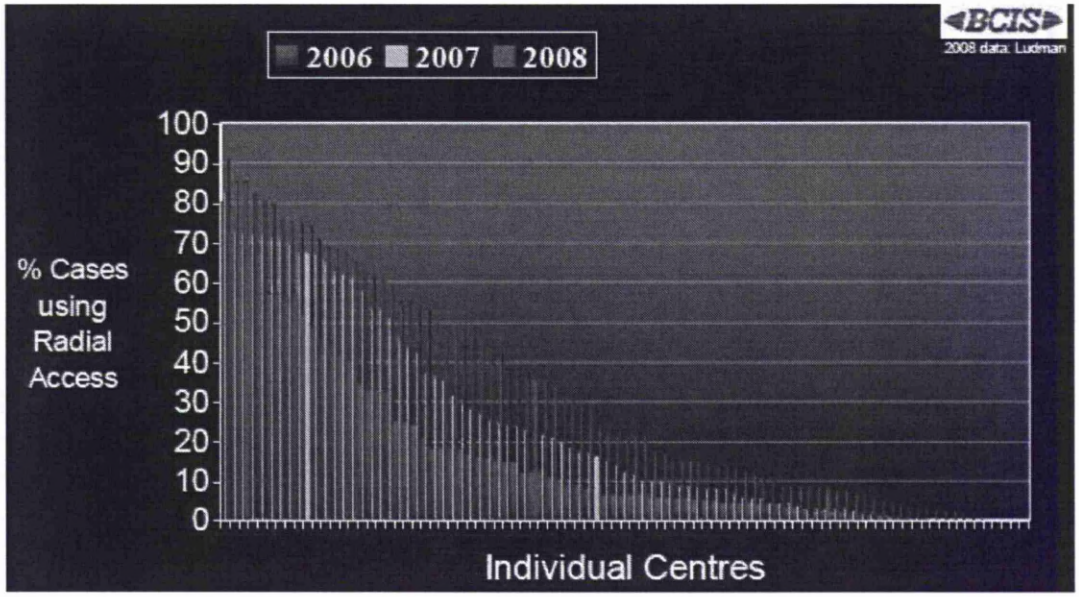
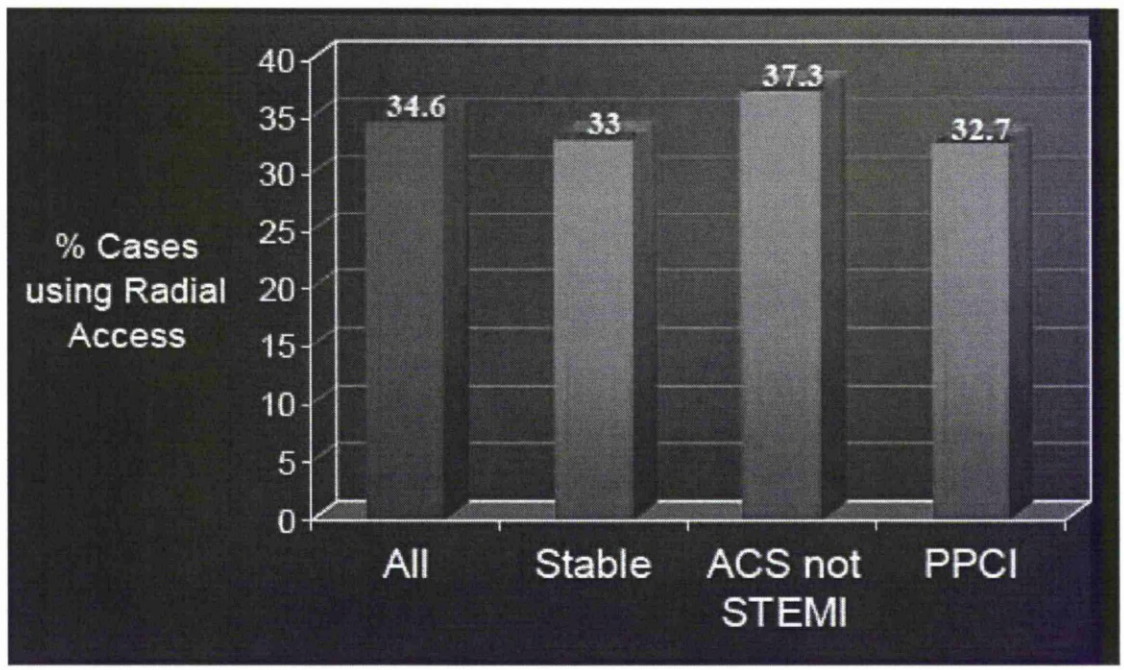


Figure 1-3 Rates of coronary catheterisation cases performed via transradial access by different clinical settings in United Kingdom during year 2008



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Failure to complete the procedure via the radial approach occurs for several reasons: firstly, there may be failure to successfully puncture and cannulate the radial artery because of the small size of the vessel, a tortuous course, or radial artery spasm. Secondly, it may be difficult to intubate the coronary ostia due to difficulty in manipulating the catheter due to radial artery spasm or excessive tortuousity of the vasculature. Thirdly, the procedure may fail because of inadequate catheter support.

In this introductory chapter I aim to:

1) Provide an overview of literature on the various problems encountered during transradial coronary procedures, and their impact on the procedural success and complications.

2) Outline our current understanding of the factors playing role in the pathogenesis of radial artery spasm, and local vascular complications.

3) Review the studies to date that have examined various mechanistic and pharmacological approaches to ameliorate the incidences of radial artery spasm, and local vascular complications

4) Outline the studies and methods evaluating the vascular function (endothelium-dependent and endothelium-independent) of the radial artery, and the impact of transradial catheterisation.

1.2 Radial artery spasm

1.2.1 Mechanisms and incidence of radial artery spasm

Much of the discomfort and difficulty of transradial procedures is related to vasospasm induced by the introduction of a sheath or catheter into the radial

artery (11, 12, and 13). Circulating levels of catecholamine play a role in radial artery spasm (147); therefore local anaesthesia and adequate sedation to control anxiety should reduce circulating catecholamines during catheter insertion and may be important preventative measures. The incidence of radial artery spasm has been reported to be around 10-20%, and in about 2-5% of the patients this prevents the successful completion of the procedure by the radial route (11, 12, and 13). Radial artery spasm has been mainly defined in the literature as patient discomfort encountered during manipulation of the arterial sheath or catheter in the radial artery and can be associated with considerable difficulty in moving the sheath or catheter. This friction is mainly due to mismatch between the outer diameter of the radial sheath or catheter and the inner diameter of the radial artery.

This mismatch can occur because of a smaller radial artery diameter compared to the radial sheath size or due to radial artery spasm reducing the effective diameter. There are several other factors that can also play a role in this mismatch, such as fixed atherosclerotic lesions, vessel tortuousity and entry into the smaller aberrant arteries.

The occurrence of radial artery spasm during transradial coronary procedure could play a role in patient's and/or physician's preference when choosing between the transradial and the transfemoral approach.

1.2.2 Measurement of radial artery spasm

In clinical practice, radial artery spasm is mainly described as increased resistance during manipulation of the intra-arterial equipment and may or may not be associated with the patient complaining of pain in the forearm.

Researchers have used combination of operator's and patient's questionnaires to measure the extent of radial artery spasm. There have also been attempts to quantify the radial artery spasm objectively by the use of an automatic pull-back device for removal of the arterial sheath (14). This device consists of a motorized trolley that railroad over a fixed platform. The trolley houses a digital force gauge and a controller unit, which are connected to personal computer for system control and data collection. The controller unit guides the movement of the trolley according to the commands set by the operator and the digital force gauge makes multiple instantaneous recordings during the pull-back. With the use of this device researchers have shown in 50 consecutive patients a mean maximal pull-back force of 0.53±0.52 kgf (range 0.1 to 3.0 kgf). In 48 patients the maximal pull-back force was reached within the first five seconds of the pull-back. All patients with clinical radial artery spasm, as assessed by a combination of operator's and patient's questionnaires and defined as pain perceived by the patient and/or difficulty perceived by the operator during sheath insertion, removal or catheter manipulation, had a maximum pull-back force greater than 1.0 kgf, while the remaining patients had a maximum pull-back force less than 1.0 kgf. .

Thus there are quantitative and qualitative methods of assessing radial artery spasm during transradial procedures. However, the quantitative methods can only measure the spasm during sheath withdrawal, but this is not the clinical spasm that may prevent completion of the procedure. The clinical spasm during the procedure and the pull-back force needed to remove the sheath may be related. There is no recognised way of quantifying the spasm that grips the catheter and makes torsion difficult during the procedure. Therefore, there is a

need to use a qualitative definition of spasm for our study. A qualitative definition of spasm has been used widely by several researchers to assess the efficacy of different drugs and equipment used during transradial procedures, and their impact on radial artery spasm (12, 13, and 14).

1.2.3 The impact of vasodilator agents on radial artery spasm

It has been demonstrated, in isolated radial artery ring segments, that nitro-glycerine and verapamil are effective agents in preventing arterial spasm (15). A study using the automatic pull back device has shown that an intra-arterial cocktail of verapamil and nitro-glycerine reduces the incidence of pain from 14% to 34%. The mean pull-back force was also significantly lower (0.53±0.52 kgf vs. 0.76±0.45 kgf) compared to the patients not receiving any vasodilating drug (12). Clinically-important radial artery spasm in this study was seen in 8% of patients receiving a spasmolytic cocktail compared with 22% in the control group ($p=0.029$).

Salmeron et al have shown, in a randomised controlled trial, that verapamil is more effective in preventing radial artery spasm than phentolamine (13). Both vasodilator agents induced a significant increase in radial artery diameter (2.22±0.53 to 2.48±0.57mm for verapamil and 2.20±0.53 to 2.45±0.53mm for phentolamine). However, verapamil was more effective in preventing radial artery spasm (13.2% vs. 23.2% in phentolamine treated patients), assessed qualitatively.

The SPASM study (16) group randomised patients to placebo, molsidomine, verapamil or a combination of both verapamil and molsidomine, administered via the radial sheath. They concluded that the incidence of radial artery spasm was lowest in patients receiving verapamil and molsidomine (4.9%), compared

to verapamil 2.5mg or 5mg (8.3 and 7.9%), or molsidomine 1mg (13.3%) or placebo (22.2%, $p<0.0001$). Jose Ronaldo et al (17) have also shown, in a randomised double blind trial of 50 patients, that the use of diltiazem as an adjunctive drug to isosorbide mononitrate, administered through the transradial sheath decreased the rate of vascular complications. The complications (spasm, occlusion and partial obstruction) occurred in four patients (17.4%) in the control group and did not occur in diltiazem group. They also demonstrated an increased radial artery diameter after 30 minutes in the diltiazem group. Coppola et al (18) have shown that the addition of nitroprusside to nitroglycerine did not further reduce the incidence of spasm. However, after multivariate analysis, the following variables were found to be independent predictors of radial artery spasm: radial artery diameter (RD)/height index, RD/body surface area (BSA) index, and sheath outer diameter (OD)/RD index. The sex of the patient, presence of diabetes, body surface area and smoking history did not play any role in predicting the occurrence of radial artery spasm.

Similarly, Chen et al (19) have shown the effectiveness of a heparin and nitroglycerine combination in preventing radial artery spasm. In this study there was no difference seen in the incidence of radial artery spasm between patients treated with heparin, nitroglycerine and verapamil and those treated with heparin and nitroglycerine only.

Recently, Kim et al (20) have shown the effectiveness of nicorandil in preventing radial artery spasm. In a randomised study comparing 4mg of nicorandil and 200μg of nitroglycerine, the authors concluded that both agents induced significant radial artery vasodilatation. Nicorandil caused a significant increase in the mean radial artery diameter, compared to the cocktail, at the middle

segment of the radial artery (0.32 mm+/- 0.23 mm for nicorandil and 0.24+/- 0.15 mm for nitroglycerine, $p<0.05$). There was no significant difference in the rate of radial artery spasm, defined as discomfort during pull-back of the sheath (50.7% vs. 50.2%).

Fukuda et al (20) have examined the incidence of radial artery spasm by radial arteriography immediately after and five months after the procedure in 48 patients. They quantified radial artery spasm by the degree of stenosis in the radial artery compared between the first (performed just after the transradial procedure) and the second arteriography (performed five months after the procedure using a transbrachial approach). The radial artery diameter soon after the transradial procedure may be small because of radial artery spasm, and the investigators compared the radial artery diameter with baseline radial artery diameter on arteriography few months after the procedure. In this study the authors defined more than 75% stenosis in the radial artery, 25-75% stenosis, and less than 25% stenosis as severe spasm, moderate spasm, and mild spasm, respectively. They concluded that some degree of radial spasm was seen in all patients with severe spasm seen in 50% of patients, moderate spasm in 23%, and mild spasm in 27% of patients. They also found a correlation between severe spasm and the diameter of the artery. The diameters of both the proximal and distal radial arteries in patients with severe spasm were significantly smaller than those with mild or moderate spasm (proximal site: severe group 2.39±0.70mm versus mild group 2.98±0.46mm, $p<0.05$, and moderate group 2.96±0.77mm, $p<0.05$, distal site: severe group 2.26±0.60mm versus mild group 2.73±0.47mm, $p< 0.05$, and moderate group 2.86±0.71mm, $p<0.05$). .

1.2.4 The impact of the introducer sheath on radial artery spasm

There are several different types of transradial introducer sheaths available from various manufacturers. The introducer sheaths from each manufacturer differ in sheath design and physical properties of the sheath. The main variables are the length of the sheath, the material from which it is constructed and the presence or absence of a hydrophilic coating.

To remove an introducer sheath from the radial artery the operator must overcome the friction between the outer wall of the sheath and the inner radial artery wall and the friction between the outer wall of the sheath and the skin and the subcutaneous connective tissue. This latter effect is likely to be much smaller than the friction within the artery and can be ignored. The friction within the vessel depends on the ratio of the inner luminal diameter of the vessel and the outer diameter of the sheath and the tone of the arterial wall musculature (anxiety and repeated punctures increases the tone and spasm) at the time of the procedure. The force required to insert or remove the sheath also depends on the surface properties of the two surfaces (hydrophilic coating might reduce friction) and also the surface area of contact between the two surfaces (proportional to the length of sheath in contact with radial artery wall).

Therefore the potential advantage of a long sheath may be the free movement of the guide catheter and the guide wire in relation to the radial artery wall. This reduced mechanical stimulation of radial artery wall might be associated with less radial artery spasm and endothelial injury. However if spasm develops, it might be more difficult to retrieve a long sheath. The opposite may be true for the short length introducer sheath; they may be easier to retrieve in the event of spasm but could provide more substrate for the spasm because of mechanical

stimulation of the arterial wall by guide catheters and wires. Similarly introducer sheaths coated with lubricious material could be easier to retrieve in the event of spasm because of reduced friction.

Saito et al (21) have tested *in vitro* the static friction resistance between the introducer sheath with and without a hydrophilic coating and also tested the durability of the lubricant. For this experiment the sheath introducers were fixed to a strain gauge, and a glass tube filled with water and plugged by silicon rubber was slowly removed. The static friction resistance between the sheath introducer and the silicon rubber plug was defined as the maximum force between the glass tube moved away from the sheath introducer. They also assessed the incidence of clinical radial artery spasm two groups, with and without hydrophilic coating of a 6F (outer diameter 2.6 mm), 16cm long sheath from Terumo, Japan. The hydrophilic coating caused a 70% decrease in the friction force in the *in vitro* model (1060±105 to 312±40 gram force, p= <0.0001). Dynamic friction resistance, measured during 200 repeated forward and backward movements of the sheath introducers at a constant rate of 1,000 per minute, was highest in both groups at the beginning of the tests and was preserved during the tests. At all time points during the tests, dynamic friction resistance was significantly lower in sheaths with hydrophilic coating. The easiness of sheath insertion into the radial artery was not different in either group. The positional stability of the sheath introducer was worse in the hydrophilic group (sheath easily moved during procedures in 70% cases in hydrophilic group as compared to 20% in control group, p=0.0242). The easiness of sheath removal was better in hydrophilic group (sheath were removed easily in 60% cases in hydrophilic group as compared to 20% in control group, p=0.00003). Radial artery spasm

occurred in one patient in the hydrophilic group and in four patients in the uncoated group (2.7 vs. 11%, p=0.15). They concluded that hydrophilic coating of the introducer sheath is useful during transradial procedures.

Jean Dery et al (22) have assessed the impact of hydrophilic coating in a randomised study of 90 patients. They used 6F, 19cm long hydrophilic coated sheaths or 6F, 21cm uncoated sheaths, both from Cook, In. The researchers assessed the peak traction force by electronic traction gauge and quantification of pain at the time of removal of the introducer sheath. The mean±SD peak traction force at sheath removal was 265±167g and 865±318g in the coated and uncoated groups respectively (69% reduction, $p<0.001$). The mean maximal pain score was 0.6±1.2 and 4.8±2.9 in the coated and uncoated groups respectively (88% reduction, $p<0.0001$). They concluded that the use of a hydrophilic coated introducer sheath considerably reduces the traction force and pain experienced by the patient during sheath removal.

Keimeneij et al (23) also assessed the effects of hydrophilic coated sheaths on the incidence of the radial artery spasm. All patients received 6F 25cm long radial sheaths from Terumo and a vasodilator cocktail of heparin and nitroglycerine was used routinely. The automatic pullback device, as described previously (14), was used for sheath removal at the end of the procedure. Three patients in the coated group experienced discomfort during sheath removal compared to 12 patients in the uncoated group (7% vs. 27%, p=0.02). The maximal pull-back force was significantly lower in the coated group compared to the uncoated group (0.24±0.31 vs. 0.44±0.33 kgf, p=0.003). Similarly, the mean pullback force was significantly lower in the coated group (0.14±0.23 vs. 0.32±0.24 kgf; $p<0.001$). They concluded that removal of the coated Terumo

transradial sheath required less traction force than an identical uncoated sheath. The coated sheath was also associated with less discomfort for the patient.

Koga et al (24) assessed the impact of hydrophilic coated catheters on the incidence of radial artery spasm during transradial procedures. They concluded that there was a reduced incidence of radial artery spasm with the use of the hydrophilic coated catheters (1% vs. 11%, p=0.007).

Therefore, there are a small number of studies investigating the effect of hydrophilic coating on the introducer sheath in patients undergoing transradial coronary procedures. The available data suggests the usefulness of the hydrophilic coated sheaths. However, these studies are small; some of them are non-randomised and had routine use of vasodilator cocktail during the procedure. Therefore it is very difficult to assess the true impact of hydrophilic coating on the incidence of radial artery spasm as concomitant vasodilator use might mask or exaggerate the true effect of coating on the introducer sheath. There is a lack of data in the literature comparing the effect of different lengths of introducer sheath and the impact on the incidence of radial artery spasm during transradial coronary procedures.

1.2.5 The potential effects of radial artery spasm on other complications

The above studies have shown that radial artery spasm can cause discomfort to the patient and difficulty in retrieving the sheath at the end of the procedure. Spasm occurring during the procedure could cause increased friction between the sheath and the inner lining of the radial artery, resulting in damage to the endothelial lining of the radial artery. This interaction could result in the

sustained endothelial damage and be a precursor for thrombus formation. Potentially, this can increase the incidence of non-occlusive and occlusive radial artery injury. This is a hypothesis and, although there is no proof of this, there is some evidence to support a link between vasospasm and subsequent neointimal hyperplasia. In the coronary vasculature there is limited data supporting a relationship between vasospasm and neointimal hyperplasia (25, 26). Suzuki et al (25) have found high incidence (in 68% patients) of neointimal hyperplasia, thrombus formation and intimal haemorrhage at the site of spasm from coronary atherectomy samples. They concluded that coronary vasospasm may provoke vascular injury that leads to the formation of neointima in these patients similar to that seen with restenosis after transluminal intervention.

1.3 Radial artery occlusion

Although radial artery occlusion was a major concern of the early transradial operators, the consequences of the radial artery occlusion are usually benign. The dual arterial supply to the hand appears robust and the avoidance of ischaemic complications was promoted by the original recommendation by Kiemeneij that transradial procedures be performed only in patients with a documented patent ulnar artery and palmar arch. This has traditionally been evaluated using Allen's test, but ultrasound Doppler and plethysmography prior to the procedure are more accurate (27).

1.3.1 The incidence of radial artery occlusion

Several factors influence the incidence of radial artery occlusion following transradial catheterisation. Consistent factors which influence the frequency of radial artery occlusion include radial artery size at baseline, radial sheath to artery ratio, duration of the sheath placement, prior procedures, and the presence of diabetes mellitus (28, 29, 30, 13, 14, and 15).

Bedford and Wollman (31) found a 25% rate of radial artery occlusion after a relatively short period of radial artery cannulation (less than 20 hours), as opposed to a 50% rate of radial artery occlusion in cannulation lasting more than 24 hours. In another study Bedford (32) has reported an 11% incidence of radial artery occlusion in cannulation lasting 1-3 days, whereas that lasting 4-10 days resulted in a 29% incidence of radial artery occlusion. Mandel and Douched (33) described the occurrence of partial or complete thrombosis of the radial artery as 19.7% in the cannulation lasting from 0-12 hr, while the incidence of occlusion rose to 48.8% in cannulation lasting more than 48 hrs. All these reports were in the setting of long term hemodynamic monitoring of the arterial pressure in Intensive Care Units, using short cannulae of much smaller diameter than used in cardiac catheterisation procedures. Much lower rates of radial artery occlusions are seen following transradial coronary procedures, probably because radial sheaths are removed immediately following the procedure and the patients often receive periprocedural anti-thrombotic treatment.

Stella et al (28) have shown radial artery occlusion rates of 5.3% demonstrated by ultrasonography at discharge and, at 1 month, persistent occlusion was found in 2.8% of patients undergoing coronary angioplasty using 6F guide catheters. They studied 563 patients prospectively undergoing coronary procedures via the

transradial route. None of the patients with radial artery occlusion manifested signs of compromised perfusion of the hand. In this study the incidence of radial artery occlusion was numerically lower in females (2.9% vs. 6% in males, p=0.09). This finding does not support the hypothesis that a smaller vessel diameter, as found in females, is more prone to occlusion after cannulation than larger vessels found in males. Nagai et al (35) have shown early (2±2 days after catheterisation) radial artery occlusion rates of 9% with spontaneous recannalisation noted late after procedure (95±29 days after catheterisation) in 60% of the cases assessed for absent forward flow by Doppler ultrasound.

1.3.2 The effect of antithrombotic therapy

Transradial procedures can result in radial artery spasm, endothelial damage and arterial dissections. Severe radial artery spasm causing blood stagnation and endothelial injury could potentially cause thrombus formation and result in radial artery occlusion. Antithrombotic agents are often given during transradial procedures to reduce the thrombotic complications of transradial coronary procedures.

Adequate anticoagulation is shown to be of significance in the patients undergoing transradial procedures. Many operators have shown radial artery occlusion rates varying from 3-10% in anticoagulated patients undergoing transradial procedures (28, 29, 30). In contrast, the incidence of radial artery occlusion was as high as 30% in patients receiving 1,000 units of heparin during diagnostic catheterisation as compared to 5000 units of heparin (34).

1.3.3 The effects of catheter and radial artery size

Catheter size has also been shown to be a predictor of radial artery occlusion. One study has shown that the ratio between the diameter of the arterial sheath and the radial artery has an impact on the rate of radial artery occlusion (29). The incidence of occlusion was 4% in patients with a ratio of greater than one, as compared to 13% in those with a ratio of less than one.

1.4 Non-occlusive radial artery injury

Recent studies have demonstrated that permanent radial artery injury without occlusion may occur following transradial intervention in some patients. The mean radial artery internal diameter, as measured by ultrasound, was smaller in patients undergoing repeat transradial interventional procedures compared to those undergoing a first time procedure (30). These investigators found the mean radial arterial diameter was significantly decreased from 2.63±0.35 to 2.51±0.29mm during follow at one to four months ($p=0.01$). However there was no significant difference in the vascular access times of the initial and repeated procedures (2.9±3.1 vs. 3.3±3.6 minutes, $p=0.08$), and success rate of repeat procedures was similar to those of the initial procedure. The incidence of radial artery occlusion was higher for repeat procedures. The investigators used 5F sheaths in the majority of the patients undergoing diagnostic angiography. Nagai et al evaluated vascular complications following transradial coronary procedures by two-dimensional echo and colour Doppler ultrasound studies before, early (1 to 8 days, mean 2±2 days), and late (37-182 days, mean 95±29 days) after catheterisation (35). Early after the procedure, segmental stenosis was noted in 22% and no flow in 9% of the patients. Late after the procedure,

segmental stenosis was seen in 1%, diffuse stenosis in 22% and no flow in 5% of the patients. They also examined the risk factors for vascular complications using multivariate analysis and found that radial artery diameter before the procedure was one of the significant and independent determinants of no flow both early and late after the procedure. The difference in the radial artery diameter and the sheath size was related to the occurrence of diffuse stenosis late after the procedure, diabetes mellitus was related to no flow or diffuse stenosis. The rate of vascular complications late after the procedure was correlated with the difference in size between the radial artery and the sheath size. When the sheath diameter was larger than the radial artery diameter, vascular complications increased significantly from 14% to 38% ($p<0.01$). The authors have suggested that early stenotic events relate to haematoma or thrombosis at the puncture site and diffuse stenosis represents intimal thickening related to a catheter-induced intimal injury. As patients with ischaemic heart disease may require repeated coronary procedures, the role of the introducer sheath in causing local complications is important. It is advisable, wherever possible, to choose the sheath smaller than radial artery diameter or a sheath that causes fewer vascular complications.

Further studies have shown that this progressive narrowing is due to intimal hyperplasia. Wakeyama et al (36) assessed the extent and nature of radial artery injury following transradial intervention using intravascular ultrasound. In 100 consecutive patients undergoing transradial intervention (TRI) they found that in patients having a second transradial procedure the lumen area (LA) and minimal luminal diameter (MLD) were smaller than in those having a first transradial intervention (LA of $5.05\pm1.26mm^2$ in the repeat-TRI group vs. LA of

5.62±1.35mm² in the first-TRI group, p=0.032 and MLD of 2.37±0.31mm in the repeat-TRI group vs. MLD of 2.51±0.33mm in the first-TRI group, p=0.028), whereas the intima-media cross sectional area (IMcsa) and intima-media thickness (IMT) were significantly greater than those in first-TRI patients (IMcsa 2.24±0.65mm² in the first-TRI group vs. 2.89±0.68mm² in the repeat-TRI group, p<0.0001; IMT of 0.31±0.007mm in the first-TRI group vs. 0.46±0.10mm in the repeat-TRI group, p< 0.0001). In the proximal radial artery there was no significant difference in the vessel area, LA, IMcsa, or MLD between the two groups.

Edmundson and Mann (37) have also shown that non-occlusive radial artery injury is common after transradial interventional procedures. Intravascular ultrasound evaluation revealed a variable degree of intima-media hyperplasia in all patients who had had a previous transradial procedure. The luminal cross sectional diameter and area were significantly smaller in the repeat procedure group than in a control group (6.7±0.8mm^2 vs. 5.0±0.7mm^2, p<0.01). They found that vasoreactivity to nitroglycerine was maintained in both groups of patients. However, the sample size in this study was small and the results may have been affected by a preponderance of females in one group and diabetics in the other. The above-mentioned observational studies, involving small number of patients in cross-sectional fashion, have shown that injury to the radial artery is common after transradial procedures. They have identified several factors such as radial artery diameter, introducer sheath diameter, sex of the patient and diabetes as playing a significant role in predicting radial artery injury following transradial procedures. The ramifications of radial artery occlusion and injury are important not only in patients undergoing repeat interventional procedures, but also in

patients in whom the radial artery may be used as a conduit for coronary artery bypass surgery or for the creation of arteriovenous fistulae for haemodialysis.

1.5 Haemostasis after transradial procedures

The transradial approach has become an attractive alternative to the femoral and the brachial routes for coronary angiography and angioplasty. Because of the superficial course of the radial artery, haemostasis can be obtained easily by local compression. Mechanical compression devices are favoured over manual compression as this allows immediate removal of the intra-arterial devices when the concomitant use of aggressive antiplatelet and antithrombotic therapies require prolonged pressure to achieve secure haemostasis. There are several devices available for mechanical compression of radial artery following transradial procedures.

1.5.1 Currently-available devices

1.5.1.1 Tourniquets

Among mechanical compression devices, tourniquets are widely used with good results and low complication rates. However, a simple tourniquet has the main disadvantage of being uncomfortable for the patient because of non-selective delivery of pressure around the wrist. This can induce venous congestion of the hand, which can be extremely unpleasant and painful.

1.5.1.2 The Radistop radial compression system

The Radistop radial compression system is manufactured by RADI Medical Systems AB, Uppsala, Sweden. This device was developed with following objectives:

1) Application of immediate and sustained haemostasis after sheath removal in spite of anticoagulant and antiplatelet therapy.

2) Safety during and after arterial compression.

3) Delivery of haemostatic pressure locally on the puncture site with sustained arterial and venous residual flow.

4) Patient comfort allowing painless prolonged compression and immediate ambulation.

5) No increase in the incidence of chronic radial artery occlusion compared to other techniques.

Chatelain et al (38) tested the efficacy of this device in 159 patients (130 male, age 60±11 years). Haemostasis after sheath removal was considered difficult to achieve in four patients (2.5%), requiring repositioning of the compression pad with application of higher pressure. The device was considered uncomfortable and painful by 28 patients (18%), but in no patient was it necessary to interrupt compression for that reason. The mean compression time with the Radistop system was 151±82 minutes (114±64 minutes in the angiography group and 223±64 minutes in the angioplasty group, p=0.001). This difference was related to a smaller sheath size and no use of antithrombotic medication in patients undergoing angiography alone. There were 23 (15%) local complications reported: in seven patients (4.4%), the radial pulse was absent but no patient had clinical evidence of hand ischemia, one patient had chronic radial artery

occlusion and one patient had recurrent bleeding after two hours. In 15 patients (9%), a small haematoma was observed around the puncture site after compression. All patients in this study were given an intra-arterial bolus of heparin and the sheath was removed immediately after the procedure. There was no mention of the length or type of radial sheath used in these cases.

1.5.1.3 The TR Band

This compression device was launched by Terumo (Terumo Corporation, Tokyo, Japan) with the advantage of directed radial artery compression. This is performed with the help of two separate inflatable balloons. A large balloon compresses the entire puncture site and the small balloon gives it an angled direction point compression. The transparent band allows full visualisation of the puncture site during the post-procedure period and the balloon can be deflated slowly over a period of time. The presence of a valve allows precise control of the volume of air in the compression balloon.

This device was tested by Pancholy et al (118) in a randomised study comparing the TR Band with conventional pressure haemostasis in 436 patients. They reported a significantly lower incidence of early (at 24 hours) radial artery occlusion compared to conventional pressure compression (11.2% vs. 4.4%, $p<0.005$) and also late (at 30 days) radial artery occlusions (7.2% vs. 3.2%, $p<0.05$). They introduced the concept of "patent haemostasis"; prevention of bleeding while maintaining luminal flow, achieved by the TR band and speculated that this was responsible for better outcomes.

1.5.1.4 Hydrophilic wound dressings

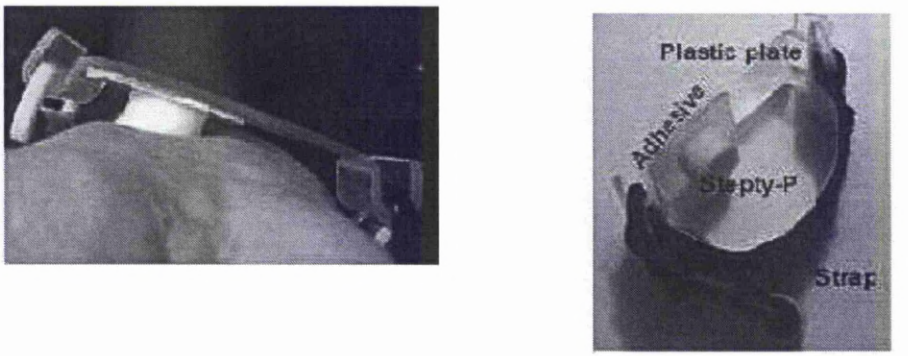
A non-compressive, soft, non-woven hydrophilic wound dressing device called Closure Pad (Scion Cardio-Vascular, Miami, Florida) is available. This haemostatic device is constructed from polypropyl acetate, a hydrophilic, naturally-occurring biopolymer. Once it comes in contact with blood it causes it to coagulate and achieves haemostasis. This device was developed because there are a few disadvantages of compression devices, such as restriction of wrist movement with the Radistop, the necessity of prolonged application of device, and the risk of late occlusion. This Closure Pad device is applied immediately after removal of the sheath, over the puncture site, allowing a small amount of blood to come in contact with the dressing. Pressure is maintained for 30 seconds and the site is covered with a sterile dressing. Choi et al (39) compared this device with a modified tourniquet in a randomised study of 80 patients. The mean haemostasis time for the hydrophilic wound dressing group was 58.7±32.6 minutes and for the compression device group was 131.3±59.1 minutes ($p<0.001$). Local haematomas were reported in one patient (2.5%) in the compression device group and two patients (5%) in HWD group. These data have shown that the Closure Pad can decrease haemostasis time without any increase in local complications. However, the sample size was small and only included patients undergoing diagnostic coronary catheterisation.

1.5.1.5 Adapty

The Adapty (Medikit, Tokyo, Japan) (Figure 1-4) device consists of a pad fixed to a transparent plastic plate, to which a self-adhesive strap can be applied. Ochiai et al (40) tested the safety and efficacy of this device in 200 patients and

found this device was effective in achieving haemostasis in 99.5% of patients. However they did not report compression times, vascular complications or discomfort level with this device.

Figure 1-4 The Adapty haemostatic compression device



1.5.2 The effect of compression on radial artery flow and complications

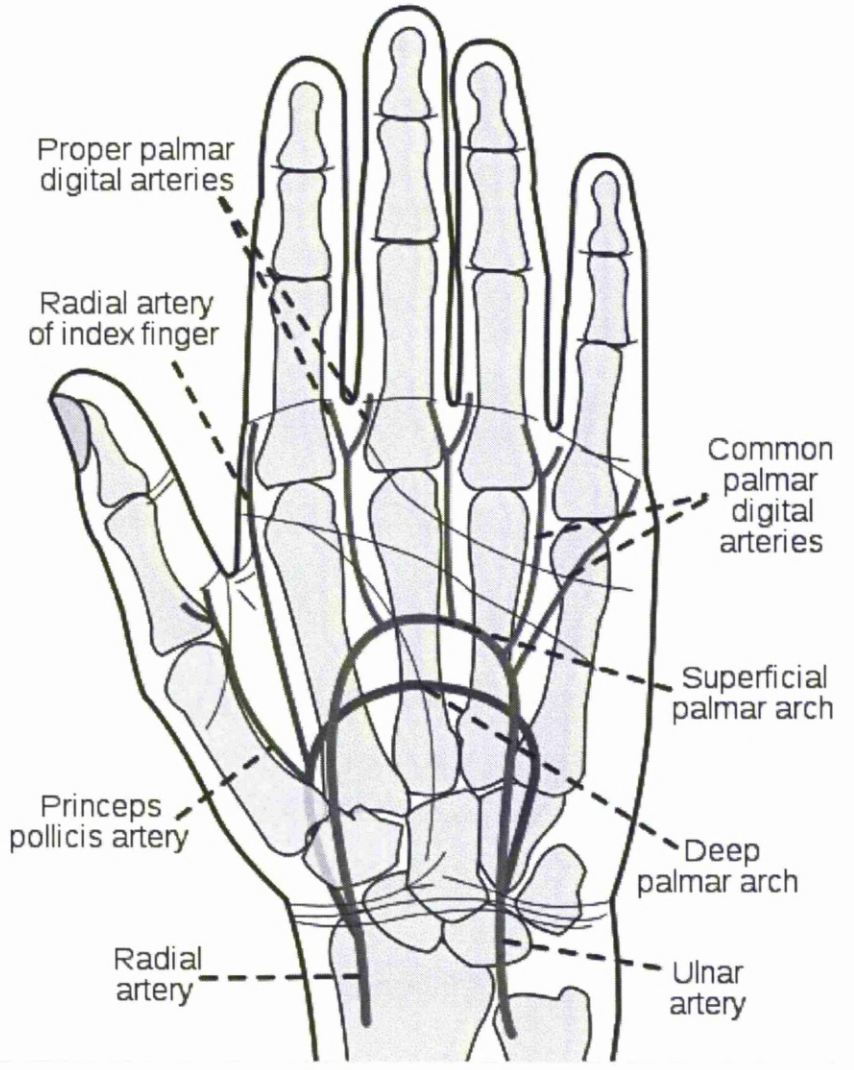
There is some data available to assess the effect of compression of the radial artery to achieve haemostasis following transradial procedures. This interruption of blood flow by compression devices might also influence the incidence of radial artery occlusion and other vascular complications. Recently, Samartin et al (41) have analysed the possible relationship between compression after transradial procedures and radial artery occlusion. In this study of 275 consecutive patients, arterial sheaths were removed immediately after the procedure and a conventional compression dressing using a tourniquet was applied for two hours. The pulse oximeter signal in the index finger during ipsilateral ulnar compression was used as the assessment of the radial artery flow. Radial artery flow was absent in 174 cases (62%) immediately after access site compression. After two hours of conventional haemostasis, radial artery flow was absent in 162 cases (58%) before bandage removal. At seven-day follow-up

12 patients (4.4%) had absent pulsations and radial artery flow was absent in 29 cases (10.5%). Logistic regression analysis showed that absent flow before compressive bandage removal was the only independent predictor of radial artery occlusion at follow up (OR=6.7, 95% CI 1.95-22.9; P=0.002). Flow-limiting compression was frequently seen in this study and the absent radial artery flow during compression was found to be a predictor of radial artery occlusion. Therefore there are several different compression and non-compression devices available to achieve haemostasis following transradial procedures. Transradial procedures are gaining popularity because of the ease of achieving haemostasis and thereby reducing the risk of major entry site complications, hospital staff workload and cost. There is limited data available in the literature comparing these different devices and also assessing the patient comfort level, haemostasis time, vascular complications and radial artery occlusion rates.

1.6 The importance of hand collateral arteries via the ulnopalmar arches

Traditionally the modified Allen's test has been used widely to evaluate the patency of ulnopalmar arches and collateral supply (Figure 1-5). This is a subjective test and assessed as the time taken for hand to blush after compression over both arteries then release of the ulnar artery compression. Up to 5-10 seconds are considered satisfactory for collateral supply. More objective tests like plethysmography and pulse oximetery, which are more sensitive in assessing the collateral circulation are described in the section below.

Figure 1-5 Superficial and deep palmar arch and collateral supply of the hand.



1.6.1 Methods of assessing ulno-palmar circulation

The modified Allen's test is performed as follows: after firm compression of both radial and ulnar arteries, the patient is asked to forcefully clinch their hand several times to expel blood from the hand. The hand is then opened, avoiding hyperextension of the wrist and fingers, before release of the ulnar artery compression. The amount of time taken to achieve a maximal palmar blush after

release of the ulnar artery while maintaining occlusive pressure of the radial artery is measured.

Plethysmography (PL) and oximetery (OX) tests are recorded with a pulse oximeter with a clamp sensor applied to the thumb. PL readings are recorded before and immediately after radial artery compression for as long as two minutes. PL readings were divided into four types: A, no damping of pulse tracing immediately after radial artery compression; B, damping of the pulse tracing; C, loss of the pulse tracing followed by recovery within two minutes; D, loss of pulse tracing without recovery within two minutes. OX results were either positive (oximetery signal present) or negative (oximetery signal absent) during radial artery compression.

Barbeau et al (42) have compared these two methods in 1010 consecutive patients undergoing a transradial approach. In men the mean time to maximal blushing was 4.7±2.7 seconds for both the left and right hands, compared with 4.1±2.3 seconds and 4.0±2.1 seconds for the left and right hands respectively in women. Overall, an Allen's test result of less than nine seconds was found in 86.5%, 87.8%, 80.8% and 93.6% of patients on the right side, left side, both sides, or any side, respectively. In multivariate analysis including age, height, weight, sex, and the presence of diabetes mellitus or previous bypass grafting, the only predictors of failure to achieve an Allen's test result of less than nine seconds were increased age and male sex. Plethysmography and oxymetery type A or B pattern was found in 90.8%, 89.5%, 83.9%, and 96.3% of patients on the right side, left side, both sides, or any side, respectively. Increasing age and male sex was found to be predictor of failure to achieve PL and OX type A, B, or C. On the basis of an Allen's test result of nine seconds or more, 6.3% of patients

were excluded from the transradial approach, whereas with PL and OX types A, B, and C, only 1.5% of patients were excluded.

Doppler ultrasonography can also be used to assess the hand collateral circulation. Ruengsakulrach et al (43) have evaluated the hand circulation of 71 patients by means of the Allen's test and ultrasound in patients scheduled for coronary artery bypass grafting. Among 71 hands, four (5.6%) had an abnormal Allen's test result (more than 10 seconds) and two (2.8%) of dorsal digital arteries in the thumb showed no flow during radial artery compression, as measured by ultrasonography. They concluded that the absence of flow in the dorsal digital thumb artery with radial artery compression should be considered an absolute contraindication to the radial artery harvesting.

1.6.2 The relation between tests of collateral circulation and ischaemic complications

There are no studies demonstrating a relationship between the time to maximal blushing using the Allen's test and ischaemic symptoms and complications to the hand. Some authors, however, because of an absence of complications after radial artery cannulation for monitoring even in patients with abnormal Allen's test results, have suggested that the Allen's test is not predictive of ischaemic complications and therefore probably not necessary (44, 45, and 46). Collateral recruitment may explain in part the paucity of ischaemic hand complications reported in the literature despite the widespread use of the radial artery for monitoring and coronary interventions.

Greenwood et al (47) assessed the accuracy of the modified Allen's test in predicting hand ischaemia in patients undergoing transradial coronary

angiography. These investigators, over a period of four months involving 55 patients, measured the Allen's test time, circulation in the radial artery (RA), ulnar artery (UA), principal artery of thumb (PAT), and thumb capillary lactate levels before and after 30 minutes of radial artery occlusion. Patients with an abnormal Allen's test were all men, had a larger radial artery (3.4 vs. 2.8mm, $p<0.001$), and a smaller ulnar artery (1.9 vs. 2.5mm, $p< 0.001$), compared to patients with a normal Allen's test. After 30 minutes of radial artery occlusion in patients with abnormal Allen's test, the blood flow velocity to the principal artery of thumb improved from 3.2 to 7.7cm/s ($p<0.001$) yet remained reduced relative to the patients with a normal Allen's test (7.7 vs. 21.4cm/s, $p<0.001$). The thumb capillary lactate levels were elevated in patients with an abnormal Allen's test (2.0 vs. 1.5mmol/l, $p=0.019$). They concluded that after 30 min of radial artery occlusion, patients with an abnormal Allen's test showed significantly reduced blood flow and increased thumb capillary lactate, suggestive of ischaemia.

Debate persists about the necessity of doing Allen's test prior to transradial procedures and denies the benefits of transradial procedures to patients with an abnormal Allen's test (5-10%). The radial artery approach has been widely used for last 15 years and there are no cases of hand ischaemia reported in literature. Therefore many high-volume operators and cardiac centres have stopped using the Allen's test prior to transradial procedures.

1.7 Physiological changes in the radial artery following transradial procedures

The radial artery is a muscular artery and therefore more prone to spasm. As the size of the radial artery is small, and similar to the dimensions of the catheter and sheath used for transradial procedures, this predisposes the injury to the vessel wall during transradial procedures. These procedures can result in disruption and damage to endothelium and potentially cause injury to internal elastic laminae and tunica media resulting in neointimal proliferation and arterial remodelling. A small study has examined by ultrasound both endothelium-mediated and non-endothelium-mediated vasodilatation of the radial artery before and after transradial catheterisation (117). The study group consisted of 18 patients and a short sheath (7-12cm) with no hydrophilic coating used. They found that, at baseline, the mean radial artery diameter was 2.56±0.45mm. The mean diameter significantly increased to 2.86±0.48mm at 24 hours (p=0.001). At one week it was 2.75±0.44mm (p=0.03 compared to baseline). At one month the radial artery diameter was similar to baseline (2.60±0.27mm, p=0.95). The maximum diameter achieved after 0.4mg sublingual nitroglycerine was similar throughout the study period. Overall, there was a small vasodilatory response to post-ischaemic hyperaemia (flow-mediated dilatation; change in radial artery diameter in response to hyperaemia, 2.7±4.7% from baseline), suggesting a high prevalence of endothelial dysfunction in this population. The response did not change significantly throughout the study period (3.4±3.7; 3.5±3.9; 4.8 ±4.7 % at one, seven and 30 days respectively). Nitroglycerine- induced vasodilatation decreased significantly at 24 hours with a return to baseline at seven days (14.1±7.9% at baseline and 6.6±8.4% at one day, 9.8±8.5% at seven days and 13.0±8.9% at 30 days). This study showed that hyperaemia-induced

vasodilatation did not change significantly whereas nitroglycerine-induced vasodilatation was significantly attenuated at 24 hours, but had improved at one week and one month. This is probably related to local trauma provoked by the sheath and catheters. The study was performed on a mixed group of patients using different diameter sheaths (ranging from 4F to 6F) and the majority of patients were males. The radial artery diameter was measured with ECG-gated ultrasound measurements and there is a potential for error and intra-observer variability. The exact extent of endothelial damage and its impact on radial artery physiology in the long term are not known.

More recently, Burstein et al (49) assessed the impact of radial artery cannulation for coronary angiography and angioplasty on radial artery function. They studied 22 patients using a 6F short length sheath with routine use of a vasodilator cocktail. Baseline radial artery diameters were 2.36±0.9 mm in the cannulated arm and 2.38±1.1 mm in the non-cannulated arm. There were no significant changes in the non-cannulated arm immediately after the procedure and at nine week follow up, whereas radial artery diameter in the cannulated arm increased after the procedure (2.89±0.9 mm, $p<0.01$) and returned to its original size nine weeks after the procedure (2.46±0.9 mm, $p = 0.51$). The average flow-mediated dilatation (FMD) of the cannulated arm before the procedure was 13.2%. The average FMD of the cannulated arm immediately after the procedure was significantly decreased at 3.6% ($p <0.01$). The average FMD of the cannulated arm at follow up remained blunted at 0.2% and was significantly decreased compared with that before the procedure ($p<0.01$). In comparison there was no difference in the non-cannulated arm across the study periods.

Nitrate-responsiveness (increase in diameter in response to nitrate) in the cannulated arm before the procedure was 18.9%. This was significantly decreased immediately after the procedure (3.7%, $p < 0.01$) and at follow-up (8.6%, $p < 0.05$). No changes were seen in nitrate-responsiveness in the non-cannulated arm. They concluded that there was impaired vascular function of the radial artery for up to nine weeks following transradial procedures.

These studies show conflicting effects on FMD and nitrate-responsiveness of the radial artery in the cannulated arm following transradial procedures. The impaired FMD is probably as a result of endothelial damage and disruption during introducer sheath and catheter exchanges. However, the endothelial function should improve over time with endothelial repair. The impaired nitrate-responsiveness could be explained by impairment of smooth muscle function of the radial artery.

This impairment of vascular function as a result of injury sustained to the radial artery could theoretically be different with different diameter and length introducer sheaths. These sheaths will cause different extents of injury to the radial artery and therefore could have different effects on the vascular function of the radial artery. Long sheaths will be in contact with a larger area of radial artery endothelium and therefore there is potential for more endothelial injury. Catheters that are smaller in size than radial artery may induce less damage because they are not in contact with the arterial wall. Similarly, shorter sheaths will be in contact with a smaller area of radial artery endothelium and will cause less injury. However, in smaller sized radial arteries, where the catheter is in contact with the artery proximal to the sheath there will be more radial artery

irritation at the time of catheter manipulation or exchange with the use of a shorter length introducer sheath.

These physiological changes in the radial artery might have important implications for the patients. The radial artery is an important bypass conduit and may also be needed for the formation of an arterio-venous fistula in patients requiring haemodialysis. Further research into reducing the extent of vascular impairment of the radial artery following transradial procedures will help this group of patients.

1.8 Vascular function and the use of the radial artery as a graft conduit

The use of the radial artery as a conduit for coronary artery bypass surgery was first introduced in 1972. However, the use of this conduit was almost completely abandoned after 1976 because of high failure rates. These high failure rates were mainly due to intimal hyperplasia and hyperspasticity seen in radial artery grafts. In the early 1990's interest in the use of radial artery was revived because of improved harvesting procedures and the use of aspirin and vasodilators. As there has been increasing interest in total arterial revascularisation in coronary surgery, there has been resurgence in the use of the radial artery as an alternative arterial conduit (51). With increasing use of the radial artery as the access site for percutaneous coronary intervention there have been concerns raised and reluctance by cardiac surgeons to use the radial artery after transradial procedures as a bypass conduit. There is little scientific data to support or examine this issue.

Kamiya et al reported that there was significant intimal hyperplasia (68% vs. 39%, p=0.046)) and reduced early graft patency (77% vs. 98%) in patients in whom the radial artery had previously been used as an access route (48). This was a retrospective cohort of 67 consecutive patients who underwent isolated coronary artery bypass grafting using the radial arteries. They performed a further analysis on 18 patients to investigate the relationship between the occurrence of graft stenosis or occlusion and preoperative transradial catheterisation. Among introducer size, number, and the interval since previous catheterisation, the number of previous transradial catheterisations was the most significant factor affecting graft patency (p=0.07). This study also demonstrated that distal sites of the radial artery suffered from greater intimal hyperplasia after preoperative transradial catheterisation compared with those without transradial catheterisation. They concluded that preoperative transradial catheterisation decreased early graft patency and caused intimal hyperplasia in the radial artery. However, this did not affect early clinical outcomes. The authors concluded that use of the radial artery as a bypass conduit after transradial catheterisation should be undertaken cautiously, particularly when multiple previous procedures have been performed. The impact of endothelial damage and long term outcome following the use of radial artery as a bypass conduit is not yet known in prospective studies.

There is some data from surgical literature which examines the anatomy, pathology and physiological changes in radial artery in the context of its use as a bypass conduit. It is well known that the radial artery is a thick-walled muscular artery and is more prone to suffering from intimal hyperplasia and arteriosclerotic change than the internal mammary artery, which is an elastic

artery (51). Oshima et al (52) examined the intravascular ultrasound images of the radial artery in patients undergoing coronary artery bypass surgery. In a study of 58 patients, the mean luminal diameter was 3.28±0.69mm and 3.00±0.70mm at the proximal and distal segments respectively, with a minimal diameter of 2.58 ±0.73mm. A plaque area greater than 50% was seen in five radial arteries (8.6%), whose average plaque length was 26.4 ±30.8mm. Five of these radial arteries showed calcification and were considered unsuitable for grafting. This study shows that the radial arteries in patients with coronary artery disease are not normal and could influence the results of transradial procedures.

1.9 Sterile inflammation associated with transradial catheterisation and hydrophilic sheaths

There are a few reports in the literature of sterile inflammation at the site of radial artery access following transradial coronary procedures. These are mainly reported after the use of hydrophilic coated sheaths. Kozak et al (62) reported 33 cases out of total 2038 cases over a 3 year period. They also reported that radial abscesses occurred in 30 patients out of the 1063 cases (2.8%) in whom they could confirm the use of a hydrophilic coated sheath, but in no patient in whom they could document that an uncoated sheath was used. Typically the inflammatory lesion was noted 20 weeks after the procedure (range three days to three months). The lesion usually presented as violaceous tender nodule at the exact site of radial cannulation. Punch biopsy was performed in some of these lesions and all showed varying degrees of acute and chronic inflammation. None showed evidence of infectious organisms including bacteria, mycobacteria or fungi. Many patients received empirical antibiotic therapy without any benefit.

Several biopsy specimens showing a suppurative and granulomatous reaction also demonstrated an extracellular blue grey substance after staining. Macrophages were seen engulfing the substance, suspected of being the gel-hydrophilic coating of the catheter and the cause of this reaction.

The vascular sheath associated with these reactions was a hydrophilic polymer coated catheter. The hydrophilic polymer coating is composed of polyacrylamide and polyvinylpyrrolidone. Investigators mentioned that standard para-marketing animal studies were performed by the manufacturer and did not show any adverse reaction.

This complication is likely to be a sterile abscess (foreign body-type reaction) at the site of the sheath insertion caused by the shedding of the coating during the insertion or removal of hydrophilic coated sheath. None of these reactions have been shown to have any long term sequelae.

1.10 Historical Introduction

1.10.1 Anatomical aspects of the radial artery

The radial artery arises from the brachial artery bifurcation, below the elbow, at the radial tuberosity, and is the straighter continuation of the brachial artery. The other branch of the brachial artery, the ulnar artery, is usually of greater size and takes off at almost a right angle from the parent vessel (Figure 1.4).

The proximal radial artery course underneath the belly of the brachioradialis muscle and then progressively leaves the lower surface of the muscle, running beneath the antebrachial fascia, between the brachioradialis muscle and the flexor carpi radialis muscle. The medial portion of radial artery lies close to the superficial branch of the radial nerve. Near the wrist, the radial artery becomes

superficial, lying anterior to the radius and the pronator quadratus muscle, between the tendons of the brachioradialis and the flexor carpi radialis muscles (Figure 1.5).

From its more distal portion, the radial artery has many branches which anastomose with ulnar artery, providing the vascularisation of the hand. In about 15% of cases, the radial artery may show a high origin, between the axilla and the elbow (54).

The internal diameter of radial artery varies between 2-3 mm (55, 56, and 57).

Figure 1-6 The course of the radial and brachial artery

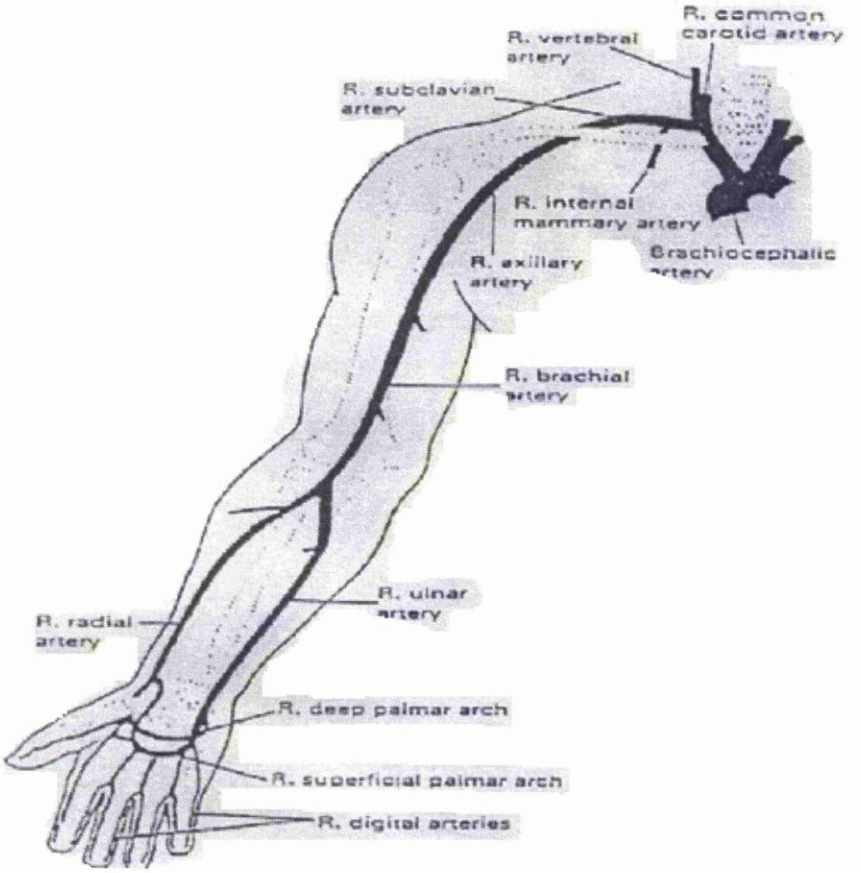
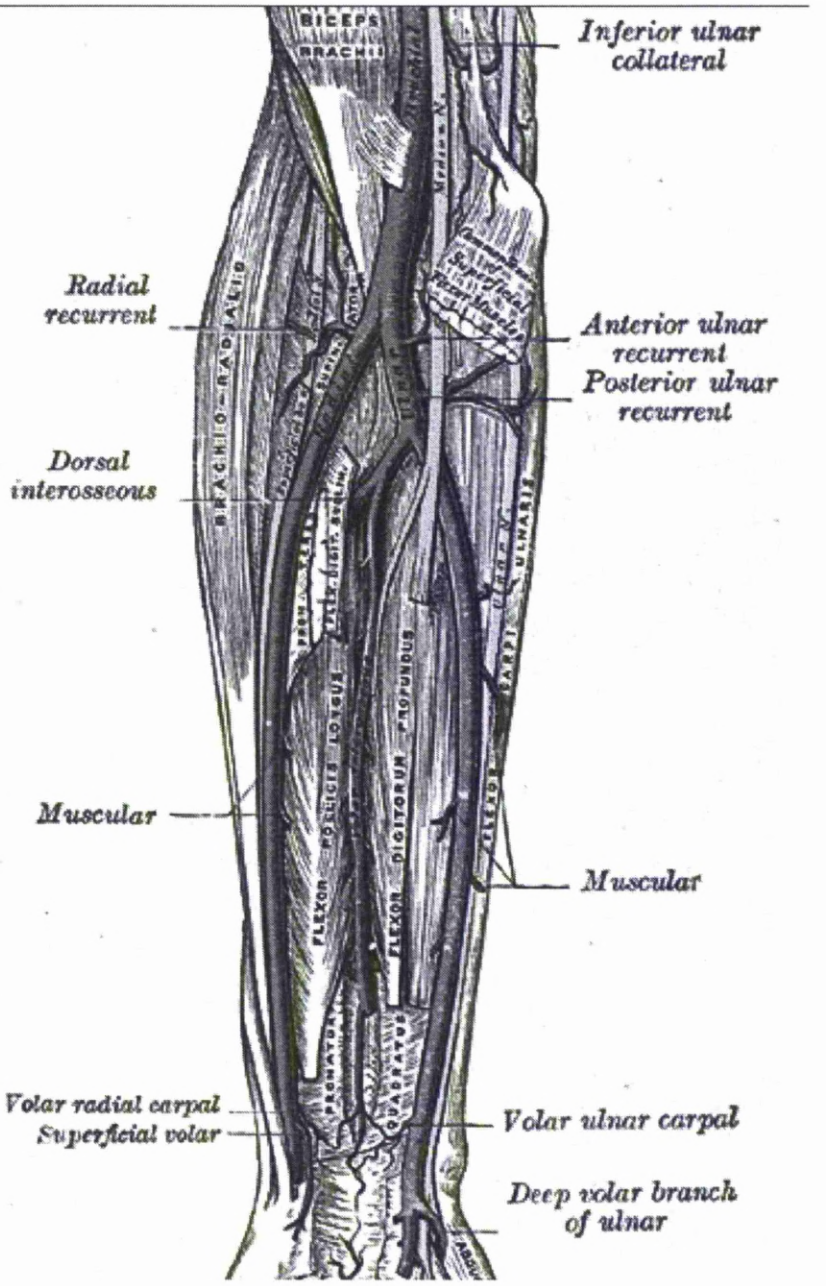


Figure 1-7 Anatomy of the radial artery.
(Taken from Anatomy of the Human Body by Henry Gray, [197])



1.10.2 Pathological aspects of the radial artery

The radial artery is a thick-walled muscular artery. The intima has one layer of endothelial cells beneath which multiple layers of subendothelial cells and a small number of myocytes are present. The internal elastic lamina has multiple fenestrations, and the media is constituted by many leiomyocytes, elastic and

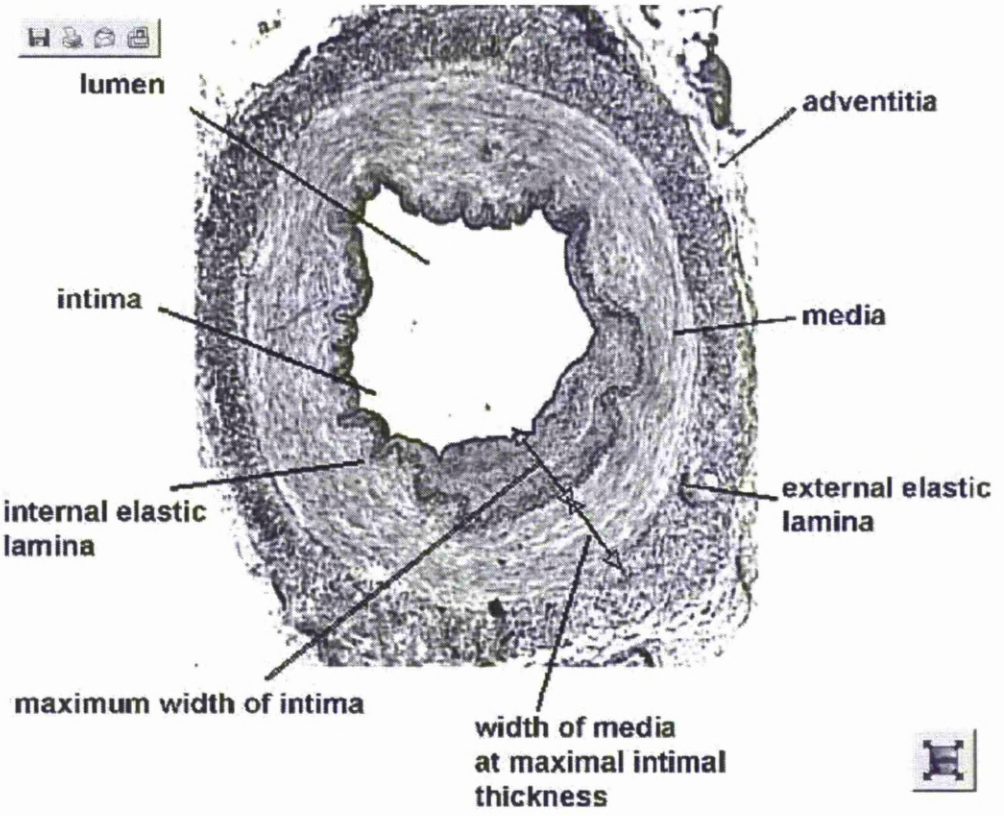
collagen fibres, fibroblasts, and rare macrophages. The external elastic laminae is less individualised than the internal lamina. There is some evidence that the vaso vasorum, nerves, and lymphatic vessels are confined to the adventitia, and do not join the medial layer within the structure of the adventitia (58).

The radial artery has a thick wall compared to other arteries and has higher density of muscle cells with the same amount of elastic tissue in its media (56) (Figure 1.8). Moreover, in the radial artery the myocytes are organised into multiple tight layers and this, together with the wider thickness of the media, may at least in part explain the propensity of the radial artery to spasm (58). Kaufer and colleagues (58) investigated the pathology of radial artery in 102 patients prospectively in the patients undergoing coronary artery bypass grafting using radial artery grafts. In their study an intima to media ratio of more than 0.25 was noted in 54% of the patients as compared to 23 % of left internal mammary artery (LIMA) specimens. They analysed the correlation between the degree of atherosclerosis and the various demographic factors. They found weak but statistically significant correlation between degree of atherosclerosis and diabetes ($r=0.2061$; $p= 0.038$), male sex ($r=0.3224$; $p=0.001$), and advanced age ($r=0.3262$; $p= 0.001$). Atherosclerotic involvement of the radial artery reduces the lumen of the artery and could be one factor predisposing to spasm and endothelial dysfunction.

A similar study from Vonson et al (57) has also shown that the radial artery is a muscular artery and the intima plus media thickness is around 529+/-52 μm, which may predispose radial artery to spasm causing occlusion and ischemia in patients undergoing bypass surgery. The radial artery is prone to accelerated

intimal hyperplasia following endothelial injury or focal damage to the intima (35, 36, 37, 48, 50, and 51).

Figure 1-8 Cross-section of the radial artery



1.10.3 Physiological function of the radial artery

According to the functional classification of the arterial grafts (60), the radial artery belongs to type 3, a type of graft that is more spastic than type 1 arteries. To further investigate the tendency to spasm of radial arteries, He et al (61) investigated the sub-type of adrenal-receptors found in the human radial artery in an ex-vivo study. They, for the first time, were able to demonstrate that the radial artery is an alpha-adrenoceptor dominant artery with little beta-adrenoceptor function and the alpha-1-adrenoceptor is dominant although alpha2 functions

also exist. Therefore, circulating catecholamines will primarily contract the radial arteries through the alpha-1 mechanism and the use of beta-blockers will be unlikely to evoke radial artery contraction or spasm during or after coronary artery bypass surgery. Radial artery spasm can result in the occlusion of radial artery in some cases. This understanding of radial artery physiology is important in the pathophysiology of radial artery spasm and occlusion, and their avoidance and treatment.

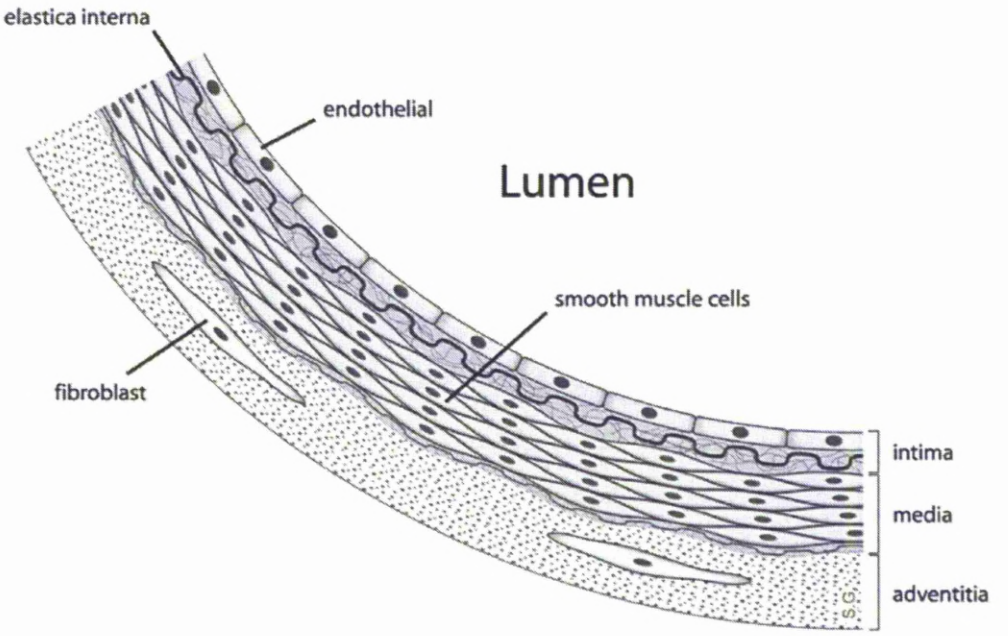
1.11 The physiological basis of radial artery vascular function and endothelial function

The endothelium is a single layer of cell lining covering the internal surface of blood vessels, cardiac valves, and numerous body cavities (Figure 1-9). The location of the endothelium exposes it to changes in the haemodynamic forces and blood-borne signals and allows it to respond by releasing vasoactive substances. A critical balance between endothelium-derived relaxation and contracting factors maintains vascular haemostasis. When this balance is disrupted it predisposes the vasculature to vasoconstriction, leucocyte adherence, platelet activation, mitogenesis, pro-oxidation, thrombosis, impaired coagulation, vascular inflammation, and atherosclerosis.

A transradial procedure has the potential to cause endothelial injury to the radial artery and result in endothelial dysfunction. Radial sheaths cause a mechanical insult to the lining and the muscular wall of the radial artery, cascading the above mentioned effects as seen by other stimuli like haemodynamic forces and blood-borne signals. Moreover, different lengths and coatings of the sheath might cause

different degrees of endothelial injury and there are several patient-related factors playing a significant role in causing radial artery injury.

Figure 1-9 Layers of the radial artery



1.11.1 Discovery of endothelium-derived relaxing factor and the L-arginine nitric oxide pathway

The era of endothelial biology was brought to the forefront by work from Dr Furchgott (63). He and his colleagues observed that in a ring preparation from a rabbit thoracic aorta, acetylcholine produced marked relaxation at a concentration lower than that required to produce contraction (64, 65, and 66). In investigating this apparent discrepancy they discovered that the loss of the relaxation response to acetylcholine could occur as a result of the unintentional rubbing of its intimal surface against foreign surfaces during its preparation. If care was taken to avoid rubbing of the intimal surface during preparation, the

tissue always exhibited relaxation to acetylcholine, and the possibility was considered that rubbing of the intimal surface had removed endothelial cells. They went on to demonstrate that relaxation of blood vessels by acetylcoline requires the presence of endothelial cells, and that acetylcholine, acting on muscarinic receptors of these cells, stimulates release of a substance that causes relaxation of vascular smooth muscle.

Following this discovery of endothelium-dependent vasodilatation by Furchgott and Zawadzki, vascular endothelium has been recognised as an important functional unit involved in the regulation of vascular smooth muscle tone. It was then hypothesised, when stimulated by vasoactive agents such as acetylcholine and bradykinin, endothelial cells secrete short-lived endothelium-derived relaxing factor(s) (EDRF), causing relaxation of the underlying smooth muscle cells. One EDRF was identified as nitric oxide or a closely related substance (67). Vasoconstriction dependent on or enhanced by intact endothelium was also observed in response to the various chemical and physical stimuli, such as noradrenaline (68), thrombin (68), hypoxia (69, 70), increased transmural pressure (71) and mechanical stretch (72).

The discovery that mammalian cells generate nitric oxide, a gas previously considered to be merely an atmospheric pollutant, has provided important information about many biologic processes. The quest to identify so-called EDRF led to the discovery in the vasculature of an enzyme called nitric oxide synthase that generates nitric oxide from the amino acid L-arginine (67, 74, 75, 76, 77, 78, 79, 80, and 81). This enzyme is constitutive, is calcium- and calmodulin-dependent, and releases picomoles of nitric oxide in response to receptor stimulation (82). The identification of a competitive inhibitor of this

enzyme, the methylated L-arginine analogue NG-monomethyl-L-arginine, has provided an important tool to investigate the relevance of nitric oxide in the biological process.

NG-monomethyl-L-arginine (L-NMMA) is a potent vasoconstrictor *in vitro*. It constricts vascular beds, produces a hypertensive response in animals and causes vasoconstriction of the forearm arterial circulation in humans (82). This action is completely endothelial-dependent, and its vasoconstrictor properties result from the inhibition of an endogenous vasodilator mechanism. These discoveries led to the conclusion for the first time that there is a physiological, nitric oxide-dependent vasodilator tone that is essential for the regulation of blood flow and pressure and indicated that the traditional concept of the cardiovascular system as a resistance network should be reassessed. The nitric oxide-dependent vasodilator tone seems to be maintained through the physical activation of endothelial cells by stimuli such as pulsatile flow and shear stress (82). Nitric oxide released from noradrenergic, non-cholinergic terminals may also contribute to the regulation of blood flow and pressure (83).

Several invasive and non-invasive techniques have been developed during the last few years to evaluate endothelial function. There are invasive studies which require the administration of intracoronary or intrabrachial infusions of vasoactive agents. These are still considered the gold standard for early detection of endothelial dysfunction. In addition, several non-invasive techniques have been developed, with comparable results and good reproducibility.

1.11.2 Flow-mediated dilatation

Peripheral arteries respond to physical and chemical stimuli by adjusting vascular tone and regulating blood flow (83). Increased blood flow in peripheral arteries leads to increased shear stress, increased nitric oxide production and vasodilatation (83). The vasodilatory response of the brachial artery to increased shear stress is called flow-mediated dilatation (FMD) and reflects the ability of vascular endothelium to produce nitric oxide (83).

That there has been an abundance of FMD studies in the cardiovascular literature in the past decade is attributable to the idea that it provides a functional bioassay for *in vivo* endothelium-derived nitric oxide (NO) bioactivity in humans. In 1992 Celermaejer and colleagues (84) introduced the idea of using cuff occlusion to examine endothelial function by inducing arterial shear stress. It was known at that time that human conduit arteries dilated in response to increased blood flow (85, 86, 87) and that, in animals, this response was dependent on intact endothelium (88, 89).

Joannides and colleagues (90) published the first study involving L-NMMA infusion to block NO production after cuff occlusion in humans. They imaged the radial artery for diameter and flow at rest and after three minutes of ischaemia induced by a wrist cuff placed distal to the ultrasound probe. L-NMMA, infused into the brachial artery up stream, converted the radial artery FMD response (3.6%) to a constriction (-2.8%). This abolition of FMD by NO blockade in the absence of the changes in peak radial artery flow, although, L-NMMA decreased the duration of hyperaemia, raising the possibility of a confounding non-specific vasoconstrictor-mediated decrease in radial artery shear stress. This study provides strong evidence that FMD is an endothelium-

dependent process, mediated by nitric oxide. Doshi et al (90) have shown that the FMD response was abolished by an infusion of L-NMMA and was more effective if the occlusion cuff was placed distal to the ultrasound probe. Mullen et al (92) showed that a brachial artery infusion of L-NMMA decreased the radial artery diameter response to five minutes of distal wrist cuff occlusion from 5.3% to 0.7%. The L-NMMA infusion had no effect on either the peak or prolonged flow response after cuff deflation. Conversely, after 15 minutes of wrist cuff inflation, FMD was 9.6% but L-NMMA had no impact on radial artery dilatation. This physiologic study provided further evidence that the widely-used FMD approach in humans, involving a response to five minutes of occlusion is almost entirely abolished by L-NMMA. These studies reinforce the methodology of FMD used and this is essentially abolished by NO blockade.

The above-mentioned studies prove that FMD reflects the NO-mediated mechanism if the described protocol is followed. However, other internal molecules, such as endothelium derived prostanoids or endothelium derived hyperpolarising factor, may also contribute to the degree of flow-mediated vasodilatation (93).

The procedure of testing FMD is mainly as initially described by Celermajer et al (84) and then described by Corretti et al (97) in the report of the International Brachial Artery Reactivity Task Force. Vasoactive drugs must be discontinued at least 12 hours before the study, and the patient must refrain from cigarette smoking for at least six hours. The subject is positioned in a supine position, in a quiet room under constant room temperature. The brachial artery is imaged in the longitudinal plane using a linear array transducer (frequency 7-12Hz). The baseline diameter of the brachial artery is measured at rest and blood flow is

estimated. The diameter of the brachial artery is determined manually with electronic callipers or automatically using edge-detection software.

After baseline brachial artery diameter determination, ischaemia is produced by inflating a cuff placed at the distal forearm, at a pressure 50mmHg greater than systolic blood pressure. The release of the ischaemia cuff after five minutes leads to an increase in forearm blood flow, resulting in a vasodilatory effect on the brachial artery. The maximum blood flow velocity is detected by analysing mid-artery pulsed Doppler signals immediately or up to 15 seconds after cuff release, while the maximum diameter of the brachial artery is determined approximately 60 seconds after release or 45-60 seconds after the peak hyperaemia flow.

This method of FMD is reproducible, with a coefficient of variation for repeated measurements of brachial artery diameter in a good laboratory of about 3-4% in short term (two hour interval) and long term (three week interval) repeated measurements (98).This method is safer and faster than invasive methods, while its results are closely correlated with endothelial function in coronary arteries. However, it seems to be highly operator dependent, requires excellent patient co-operation, and has relatively poor resolution relative to arterial size.

1.11.3 Strain gauge plethysmography

This is another currently-used method for non-invasive evaluation of endothelial function in the brachial artery. This involves evaluation of the changes in forearm blood flow during reactive hyperaemia, by the use of strain gauge plethysmography (95, 96). This technique is non-invasive, simple and reproducible since its results are less observer-dependent than ultrasound. The technique evaluates the change of flow from baseline to the maximum flow

during reactive hyperaemia following five minutes of ischaemia in the distal forearm. Several studies have suggested that endogenous nitric oxide plays only a minor role in vasodilation during reactive hyperaemia, and that reactive hyperaemia is largely caused by endothelium-related mechanisms other than nitric oxide, such as adenosine, prostaglandins, and endothelium-derived hyperpolarising factor (96). Although this technique leads to less specific results than FMD, it is preferred by many centres because it is easily applied, does not require highly trained personnel, and its results are less observer-dependent. Forearm blood flow is measured using a mercury-filled silastic strain gauge plethysmograph. The strain gauge is attached to the upper forearm, at the position of maximum diameter. It is supported above the level of the right atrium and it is connected to a plethysmograph device. The upper arm congesting cuff is inflated to 40 mmHg for seven seconds in each 15 second cycle to occlude venous outflow from the arm, using a rapid cuff inflator. The FBF is estimated by the gradient of the tangent to the curve during the first cardiac cycles, and is expressed in ml/100ml of forearm tissue volume/minute. The final FBF is calculated as the mean of ten consecutive measurements, and always by two independent observers.

1.11.4 Intrabrachial infusion of vasoactive agents

After brachial artery cannulation and baseline infusion of saline for 30 minutes, acetylcholine is infused in the brachial artery with a gradually increasing infusion rate (e.g. 3, 12, 24, and 48μg per minute). Each infusion rate remains constant for five minutes. Forearm blood flow is measured for each infusion period. The same protocol is usually repeated with sodium nitroprusside infusion

for evaluation of endothelium-independent dilatation. The FBF during acetylcholine and nitroprusside infusions represents indices of endothelium-dependent and endothelium-independent dilatation respectively. To evaluate nitric oxide availability, acetylcholine infusion is repeated during simultaneous constant intra-arterial infusion of L-NMMA, a nitric oxide synthase inhibitor. This method is highly reproducible, since previous studies have shown a variation of 5-8% in the short term evaluation (two hour interval) as well as in the longer term (three week interval) (98). The method of intrabrachial vasodilator infusion, although reliable, reproducible, and easily applied, remains an invasive method with potential side effects such as injuries to the median nerve or the brachial artery (100).

1.12 Anatomical variations of the radial artery

The anatomy of the radial artery branching, anomalies and the diameter of the radial artery could play a significant role during a transradial approach for coronary intervention. Anomalies resulting in excessive tortuosity or sheath-artery diameter mismatch could lead to radial artery spasm and a failed procedure. There are some studies evaluating the anatomic features of the radial artery in patients undergoing transradial procedures. Valsecchi et al (119) have shown that in a prospective series of 2,211 patients undergoing transradial cardiac catheterisation, anatomic variations were noted in 22.8% patients on angiography. This included tortuous configurations (3.8%), stenosis (1.7%), hypoplasias (7.7%), radio-ulnar loop (0.8%), abnormal origin of the radial artery (8.3%) and lusoria subclavian artery (0.45%).Patients with anatomical variations had a significantly lower puncture (96.2% vs. 99.7%, p=0.001) and procedural

success (93.1% vs. 98.8%, p<0.0001). Recently, Lo et al (165) have reported an incidence of radial artery anomaly of 13.8% patients in a series of 1540 patients on angiography. This included high-bifurcating radial artery (7.0%), radial loop (2.3%), radial artery tortuousity (2.0%) and other miscellaneous anomalies including accessory branches (2.5%). Procedural failure was significantly higher in this group with radial artery anomalies than those wth normal anatomy (14.2% vs. 0.9%, p<0.001)

Yoo and colleagues (193) evaluated the anatomy and diameter of the radial artery using two-dimensional ultrasound in 1191 cases undergoing transradial cardiac catheterisation. They reported a mean radial artery diameter of 2.60±0.41 mm (2.69±0.40mm in men and 2.43±0.38mm in women, p<0.001). They found anomalous branching of the upper extremity artery (3.2%), high origin of the radial artery (2.4%), and tortuousity of the radial or the brachial artery (4.2%). The most common site of radial artery tortuousity was the proximal third of ante-cubital fossa.

1.13 Aims and scope of this study

It is clear from the literature to date that there is an increasing use of the transradial approach for coronary procedures and this is being applied in all clinical situations and patient subsets. However, there are complications specifically related to transradial approach, such as radial artery spasm, vascular injury to the radial artery, and radial artery occlusion. These complications could result in procedural failure, patient discomfort, or sustained vascular injury to the radial artery. Several technical advancements of the equipment and adjuvant pharmacotherapy have been shown to reduce these complications. There is

growing evidence that hydrophilic coating of the introducer sheath could reduce the incidence of radial artery spasm and thereby reduce the patient's discomfort. However, the impact of introducer sheath length on clinical outcomes is unknown. Similarly, there are not many data comparing various haemostatic compression devices.

In this study, I have investigated the impact of length and coating of the introducer sheath and compression devices on the incidences of procedural success, radial artery spasm, and local vascular complications. I have also studied the impact of introducer sheath coating on vascular function.

1.13.1 Hypotheses

This randomised trial will test the following three hypotheses:

1. We hypothesized that the use of a hydrophilic coating on the introducer sheath would reduce friction resistance between the sheath and the arterial wall. This would reduce traction force during sheath insertion or removal and the discomfort experienced by patients compared to similar uncoated introducer sheaths.

2. That long length introducer sheaths (23cm) could cause more friction resistance and thereby cause more radial artery spasm and patient discomfort compared to short length (13cm) introducer sheaths.

3. Both TR Band and Radistop haemostatic devices are safe and effective to achieve haemostasis after transradial coronary procedures. We hypothesised that the TR Band would cause less discomfort to the patient and reduce the time needed to achieve haemostasis when compared to the Radistop.

4. In a subgroup study, we would also test the hypothesis that hydrophilic coating of the introducer sheath would play a role in reducing endothelial damage and subsequent disturbance of endothelial function of the radial artery.

Randomised controlled trials provide the best quality evidence in medical research, (148) but they require a large commitment of time and effort, certainly from the investigators and often from participants. As a result, testing several hypotheses in parallel trials can be expensive and time consuming. For these reasons, we have tested these hypotheses in a factorial design, where participants are allocated to receive combinations of different treatments. A factorial design provides a cost-effective way of conducting trial of two or more interventions, each with its own primary outcome in one group of participants.

Factorial designs are relatively common in clinical trials. McAlister et al (149) examined the quality of the analysis and reporting of factorial trials published between January 2000 and July 2002 and identified 29 trials, including some of major importance (194, 195, 196). A factorial clinical trial has two or more treatments or interventions. For each intervention, the experiment may be whether the intervention is used, different intensities of the intervention or comparisons between mutually exclusive types of intervention. In a complete factorial design a participant can be randomised to any possible combination of the levels of the factors being considered (150).

In our study, we will be testing the coating and length of the introducer sheath and the type of haemostatic device used in study participants in different combinations. In order to realise the above-mentioned advantages, however, factorial trials require some special considerations, particularly at the design and

analysis stages (151). These considerations will be discussed in the next chapter in the sample size and statistical analysis sections.

1.13.2 The scope of this study

To examine the hypotheses posed, we investigated the impact of different length and coating of introducer sheaths from the same manufacturer on various clinical outcomes. We also studied comparative effects of two commonly used haemostatic compression devices.

In a sub-study we have investigated the impact of introducer sheath coating on endothelium-dependent and endothelium-independent vascular function.

Chapter 2 Methods: Clinical study

2.1 Aims and objectives of the study

- To assess the impact of length and hydrophilic coating of the transradial introducer sheath on the incidence of radial artery spasm, radial artery occlusion, local inflammatory reaction and other vascular complications.

- To compare the impact of the TR band and Radistop compression haemostatic devices on the time taken to achieve haemostasis, radial artery occlusion rates, local vascular complications and patient tolerance of the device.

2.2 Study design

This was a prospective, randomised, single-blind, single-centre study. All patients attending The Cardiothoracic Centre, Liverpool (now Liverpool Heart and Chest Hospital) for coronary angiography or coronary intervention by the transradial approach were screened and invited to participate in the study. Those giving consent to participate were randomised by computer-generated random numbers. The randomisation was performed in blocks of eight and the patients were randomised into eight groups. Each treatment group consisted of one type of the radial introducer sheath and one type of haemostatic compression device to be used during the transradial procedure. The eight randomised group are as following:

1. Long hydrophilic sheath (23 cm) + TR band
2. Long hydrophilic sheath + Radistop
3. Long uncoated sheath + TR band
4. Long uncoated sheath + Radistop
5. Short hydrophilic sheath (13 cm) + TR band
6. Short hydrophilic sheath + Radistop
7. Short uncoated sheath + TR band
8. Short uncoated sheath + Radistop

2.3 Study outline

Patients were screened in the pre-assessment clinic (elective procedures) or ward (urgent procedures). All eligible patients were approached and informed about the nature and purpose of the study. Those agreeing to participate were entered into the study after giving informed consent (Figure 2-1).

2.4 Inclusion and Exclusion Criteria

2.4.1 Inclusion criteria

1. Intended procedure via the radial route.
2. Patient more than 18 years of age and able to give informed consent.

2.4.2 Exclusion criteria

1. Unable or unwilling to give informed consent.
2. Haemodynamically unstable patient.
3. Patients with forearm A-V fistula or patients with chronic renal failure.
4. Previous ipsilateral transradial procedure.

Figure 2-1 Study procedures

Information sheet and consent form given

↓

Consent obtained on the day of procedure

↓

Randomisation

↓

Clinical procedure

↓

Questionnaire completed by operator (to comment on clinical radial artery spasm) immediately after the procedure, and other procedural details collected

↓

Questionnaire completed by patient (to comment on the level of discomfort during procedure)

↓

Patient assessed before discharge for radial artery patency [hand held Doppler and modified Allen's test] and local vascular complications by the investigator (SR)

↓

Long term radial artery patency and late vascular complications assessed at 4-6 month follow up visit

2.5 Study Outcomes

2.5.1 Primary end-point

1. The incidence of clinical radial artery spasm, as assessed by the operator.

2.5.2 Secondary end-points

1. The incidence of radial artery occlusion.

2. The incidence of local vascular complications.

3. Procedural success rates via the radial route.

4. Time taken to achieve haemostasis.

5. Patient tolerance of the haemostatic device.

6. The incidence of radial artery occlusion at follow-up.

7. The incidence of late vascular complications.

2.6 Sample size

We have tested three interventions, in a factorial design, in our patient population. Special emphasis is needed at the design stage to calculate the sample size of a factorial trial. The most commonly suggested procedure is to perform separate calculations based on the target effect sizes for each of the interventions. The trial sample size is then simply the largest of these, and the trial is said to be powered to detect the main effects of each intervention (152, 153). However, this sample size is based on the crucial assumption that there is no interaction between the interventions. If the trial is to have adequate power to detect an interaction, then the sample size generally needs to be increased. It has been suggested that if the interaction is of primary interest then it is essential that the

trial is powered to detect a reasonable target interaction effect. We have calculated the sample size with this pretext.

The incidence of clinical radial artery spasm is between 20 and 30% in studies in the literature, using several qualitative and quantitative definitions. We assumed that a 50% reduction in the incidence of radial artery spasm would be clinically significant. A factorial design was used to compare hydrophilic-coated and uncoated sheaths and short and long sheaths. This design allowed us to evaluate two factors (coating and length of introducer sheath) simultaneously and their impact on radial artery spasm without compromising the power of the study. The sample size was calculated for both hydrophilic-coated and long introducer sheaths and considering the primary end-point of clinical radial artery spasm.

The sample size for both coating and length of sheath independently was calculated as following:

p 1 = incidence of radial artery spasm from literature (20%)

p 2= incidence of radial artery spasm with the intervention (10%)

50% relative reduction in the incidence of radial artery spasm

$\alpha = 0.02$

$\beta = 0.05$

$$n = \frac{p1 \times (100-p1) + p2 \times (100- p2)}{(p2- p1)^2} \times f(\alpha, \beta)$$

$$F(\alpha, \beta) = 15$$

We calculated that we would need 375 patients in each arm of different introducer sheath types to detect a difference of this magnitude with statistical

confidence in the result. We decided to recruit 400 patients in each arm to compensate for missing data. This is with significance level of 0.02 (alpha error), and power of 95% (beta error 0.05). We have calculated this sample size to keep the chance of type II error low and also to adjust for a potential interaction effect. Therefore, our aim was to recruit 800 patients in total thus comparing 400 patients with long sheaths against 400 patients with short sheaths, 400 patients with coated sheaths against 400 patients with uncoated sheaths and 400 patients with each of the two different haemostatic compression devices.

2.7 Randomisation

Randomisation was performed by computer-generated random numbers from a proprietary database. The randomisation was performed in the blocks of eight to keep similar numbers of patients in each group throughout the study period. The person responsible for patient's registration and randomisation (SR) was not in any way concerned or involved in the treatment of the patient. The treating doctor was informed of the treatment allocation prior to the procedure by the investigator (SR).

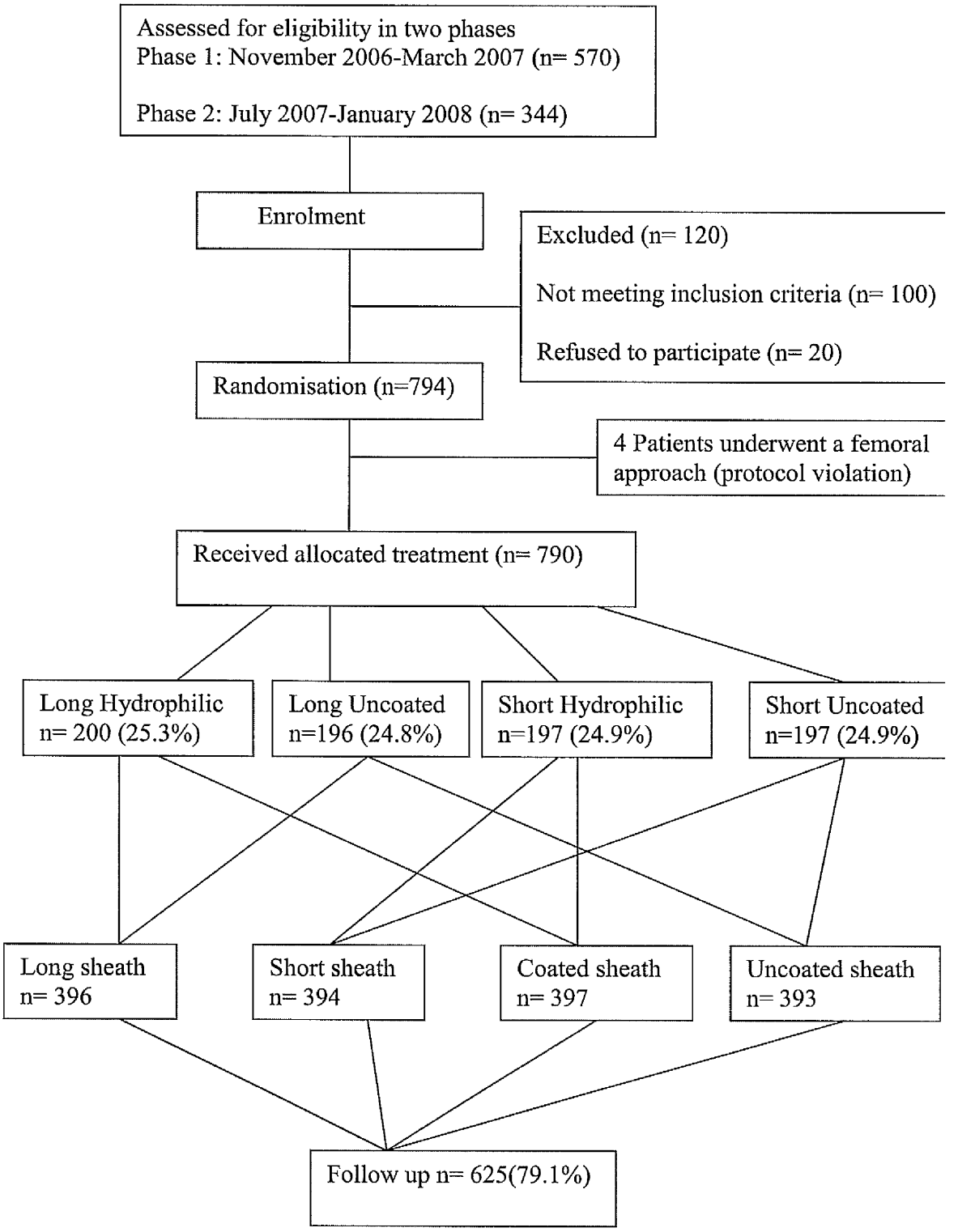
2.8 Recruitment

All patients scheduled to undergo transradial procedure at our centre (Liverpool Heart and Chest Hospital, formerly The Cardiothoracic Centre, Liverpool, UK) were contacted either at the pre-assessment clinic or inpatient cardiology wards. Five of the consultant cardiologists (JLM, RAP, RHS, NDP and JDM), who routinely use the radial artery for coronary procedures, agreed for their patients

to be entered into the study. During the study period all patients were screened to see which met the inclusion and exclusion criteria. Those suitable were asked to participate in the study. Willing patients were provided with the patient information sheet (Appendix 1) and informed consent (Appendix 2) obtained. The patient information sheet and consent form were approved by local research ethics committee and hospital academic committee (06/Q1502/94)

After consent was obtained, patients were randomised to treatment strategies as previously described. Following randomisation the operator of the case was informed of the type of sheath and compression device to be used.

Figure 2-2 Study outline diagram



2.9 Data Collection

2.9.1 Demographics

Baseline characteristics were measured including age, sex, height, weight, and wrist circumference. The indication and urgency for the transradial procedure was identified. The indications were grouped as stable angina, acute coronary syndrome and acute myocardial infarction. The procedure was classified as routine, urgent or emergent depending on the clinical situation.

2.9.2 Ulno-palmar circulation

Each patient had ulno-palmar collateral circulation assessed before the procedure and documented, although patients were not excluded from the study on the basis of these tests. Each patient had a modified Allen's test and a 'plethysmography and oximetry' test performed, as described below.

The modified Allen's test:

The modified Allen's test was performed according to the following protocol. The examiner faces the patient, whose hand is supinated and the test is performed in well lit room. The radial artery and ulnar artery are located by their pulses. The examiner's thumbs are placed over the radial artery and ulnar artery simultaneously, with the four fingers of each hand placed behind the patient's wrist and pressure is applied, sufficient to block the flow in the arteries. The patient is then asked to close his fist tightly several times to expel blood from the hand. The patient is then asked to relax the hand and extend the fingers into a slightly flexed position with the examiner maintaining the pressure on the radial

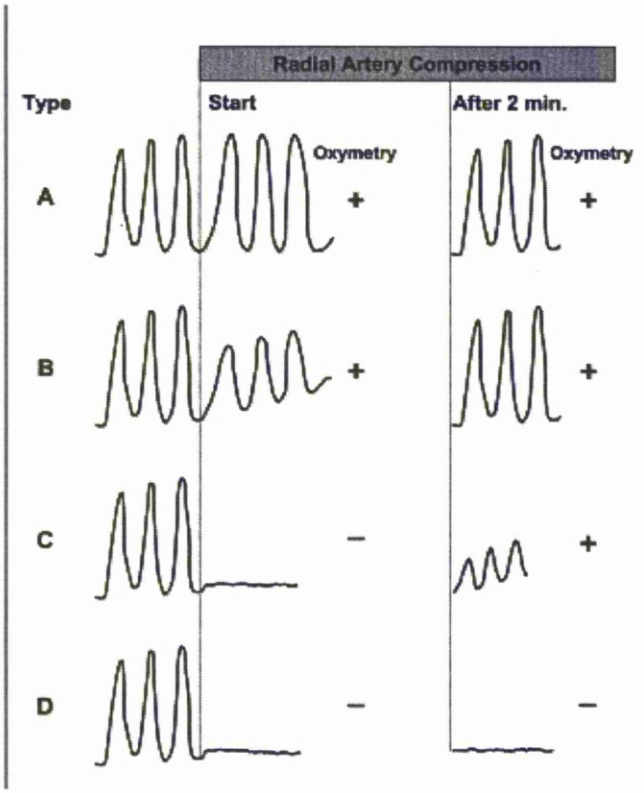
and ulnar arteries. The hand at this point should appear blanched. The examiner then releases the pressure on the ulnar artery and continues applying pressure to the radial artery. The return of colour to the hand and fingers to its normal colour is noted and recovery time in seconds is noted to document patent ulnar collateral circulation. One experienced observer [SR] performed these tests in the majority of the patients. In the remaining patients these tests were performed by experienced operators as per protocol. The time taken to achieve normal colour of the hand is categorised in following five groups: less than 5 seconds, 5-10 seconds, 10-15 seconds, 15-20 seconds, more than 20 seconds, and not at all.

The 'plethysmography and oximetry test:

The spectrophotometric principles of the plethysmography and oximetry (PL & OX) tests are well known (26). The PL & OX tests were carried out as described by Barbeau et al (27). These were undertaken with a pulse oximeter with a clamp sensor applied to thumb. After the pulse oximeter is applied to the thumb, the wave form on plethysmography and oxygen saturations are observed before compression is applied to the radial artery. Following this, the radial artery is occluded to block any forward flow for two minutes and the above measurements are repeated while pressure on the radial artery is maintained. Plethysmography readings are divided into four types: A; no damping of pulse tracing immediately after radial artery compression and after two minutes, B; damping or reduced amplitude of pulse tracing immediately after radial artery compression but recovering to normal at two minutes, C; loss of pulse tracing followed by recovery of pulse tracing within two minutes, D; loss of pulse tracing without recovery within two minutes. Oximetry results (SpO_2) were either positive

(reading present and constant) or negative during radial artery compression (Figure 2-3).

Figure 2-3 Plethysmography (PL) traces and oximetery (OX) recordings assessing ulno-palmar collateral circulation



2.10 Procedural Details

2.10.1 Radial artery cannulation

In the standard fashion, with the arm supported with the wrist in mild hyperextension, local anaesthesia was achieved with 2% lignocaine, after disinfection. The radial artery was punctured using a 21-gauge arterial needle through which a 0.018 inch platinum-tipped nitinol guidewire was introduced. Following this the needle was withdrawn and a 6F introducer sheath with dilator taper length of 2.5 cm was introduced. All introducer sheaths and other kit used

were from the same manufacturer (Cook, Incorporated) (Figure 2-4, Figure 2-5). Long sheaths were 23cm in length and short sheaths were 13cm in length, with and without a hydrophilic coating. After introducer sheath insertion, a weight-adjusted dose of heparin, when required, was administered into the central circulation. The routine use of a vasodilator cocktail was avoided and vasodilators were only used in the event of radial artery spasm. In the event of spasm 100 to 200μg of nitro-glycerine and/ or 2.5 to 5mg of verapamil were administered via the radial artery sheath, at the operator's discretion. The rest of the procedure was performed according to the operator's preference.

Procedural success via the radial route was defined as successful radial artery puncture and completion of the intended coronary procedure.

Figure 2-4 The hydrophilic-coated short (13 cm) introducer sheath with dilator and guide wire.

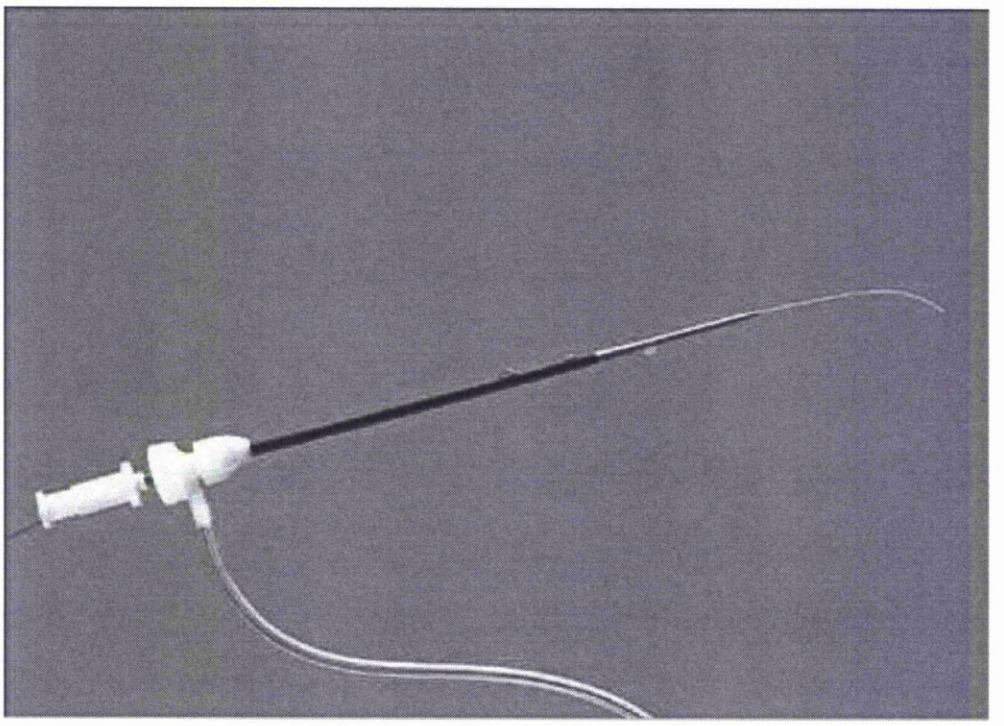
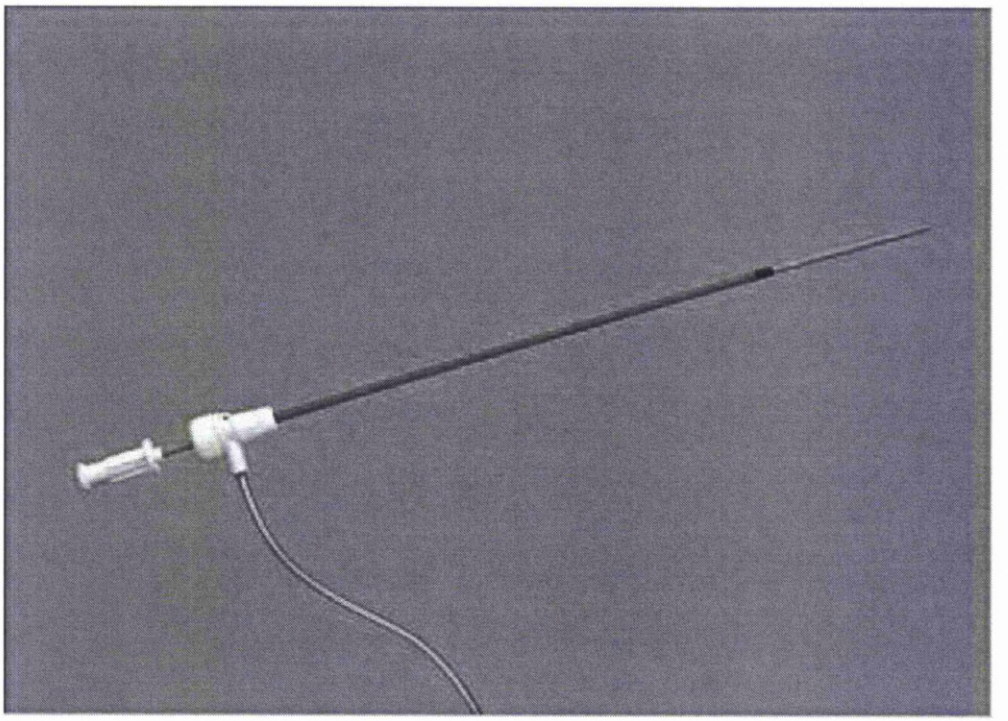


Figure 2-5 The uncoated long (23 cm) introducer sheath with dilator.



2.10.2 Introducer sheath removal and haemostasis

All introducer sheaths were removed immediately after the procedure and haemostasis achieved in the catheterisation laboratory using either a TR band or a Radistop according to randomisation. Only enough pressure was applied to just stop the bleeding and maintain forward flow in the radial artery. The TR band and Radistop devices were removed using the following protocols.

2.10.2.1 TR Band application and removal

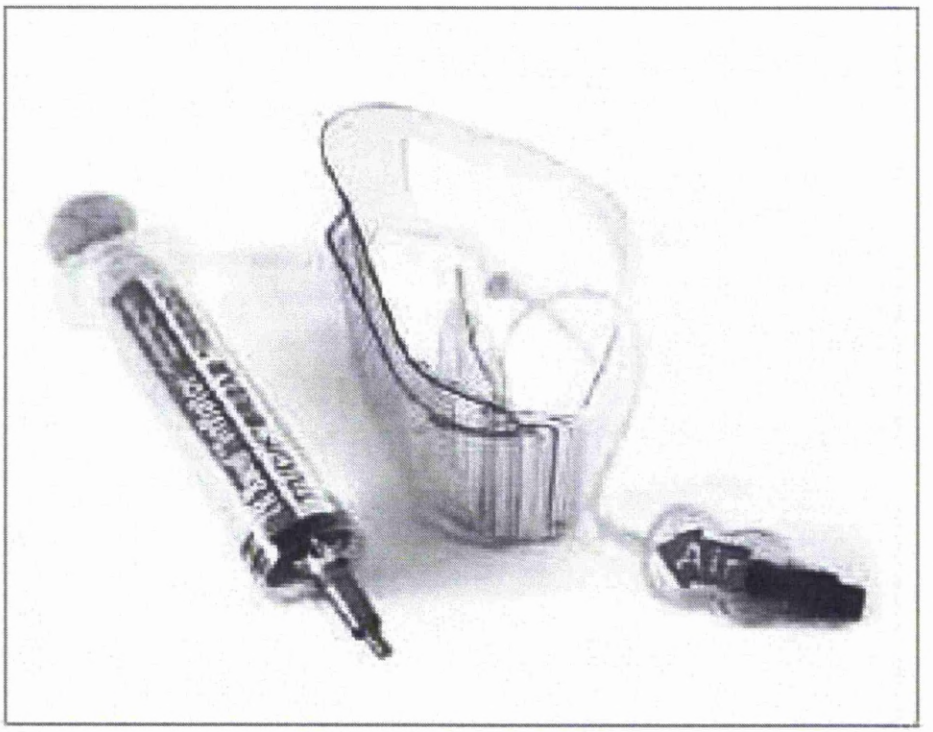
On completion of the procedure introducer sheath is withdrawn by 2-3cm and the green marker on the TR Band is positioned over the arterial puncture site, approximately 0.5-1.0cm above the skin incision. Thereafter, the Velcro® strap

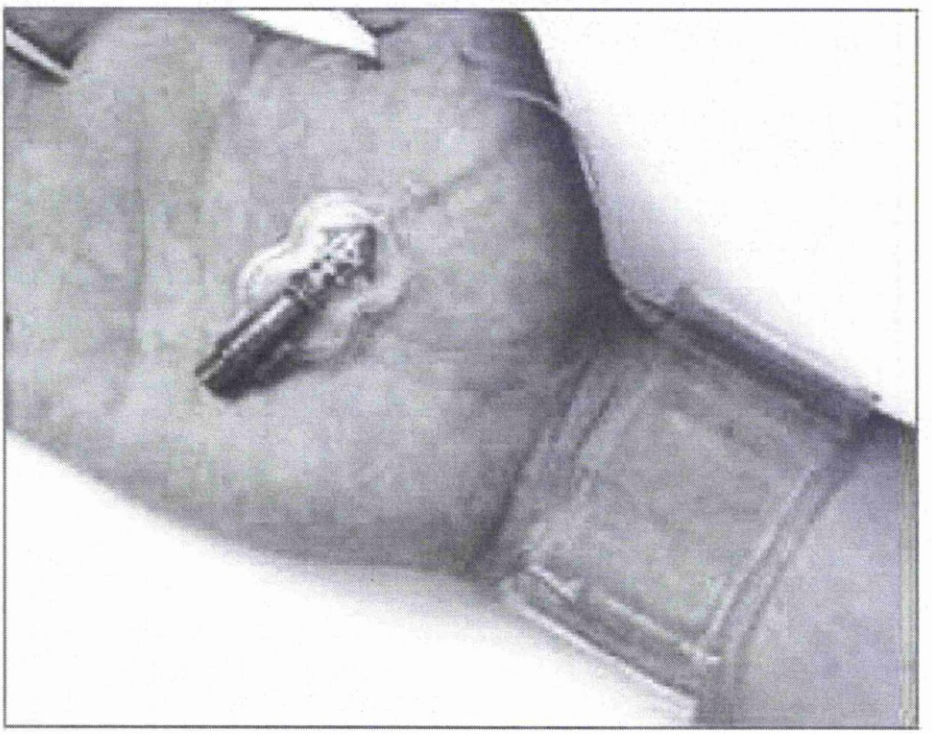
is wrapped around the wrist and 15-18ml of air is injected through the valve to inflate the compression pad. The introducer sheath is then removed, observing for any bleeding. The syringe is then re-attached to the valve and air is slowly removed, watching for any bleeding. When bleeding occurs 2-3ml of air is re-injected and the syringe removed. At this stage radial pulsation distal to the device should be detectable.

On return to the ward, air is slowly removed from the device, 2ml at a time, starting one hour after the procedure. Evidence of bleeding is watched for at all times and, if bleeding occurs, the device is re-inflated with 1-2ml of air. Further air is removed every thirty minutes until the pad is completely deflated and the band is then removed. (Appendix 3) (Figure 2-6)

Figure 2-6 The TR Band compression device

Showing the band, and syringe used to inflate and deflate compression pad, top panel. Bottom panel shows its application on the wrist at the radial artery puncture site.



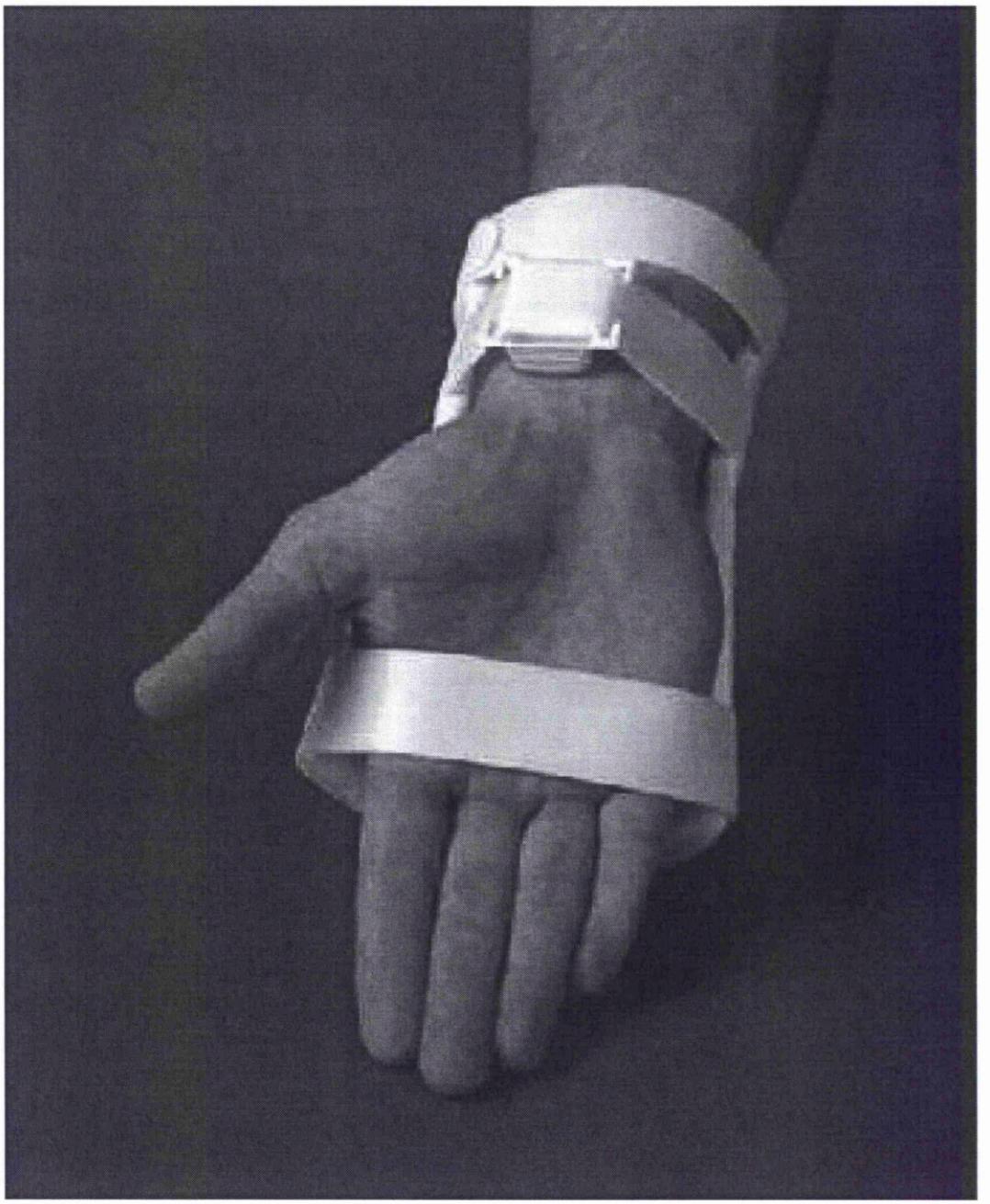


2.10.2.2 Radistop application and removal

The hand and the wrist are placed in the support plate and the distal and proximal Velcro® straps are fixed. Then centre of the compression pad is placed directly over the radial artery puncture site, continually applying pressure while removing the introducer sheath. The compression pad is secured with the third Velcro® strap while continual pressure is applied. The radial pulse should be palpable after the application of the device.

After one hour of return to ward, pressure is reduced gradually, observing for haemostasis and checking this every thirty minutes until the device can be removed completely (Appendix 4, Figure 2-7).

Figure 2-7 Radistop application over the radial artery puncture site after a transradial procedure.



The procedure time was considered as the period ranging from sheath insertion to sheath withdrawal. The time taken to achieve haemostasis was defined as the period from application of the compression device to its complete

removal. The results of time taken to achieve haemostasis are recorded as the time to which the device was removed, in units of 0.5 hours as the devices are only checked every 30 minutes.

2.10.3 The assessment of radial artery spasm (Operator)

Clinical radial artery spasm was defined as pain reported by the patient to the operator and /or advanced difficulty perceived by the operator during insertion, manipulation, and/or withdrawal of the introducer sheath and catheter.
This was assessed by a questionnaire completed by the operator.

Operators were asked to report the presence of radial artery spasm on the following criteria:

1. The patient reported presence of continuous forearm pain.
2. The patient reported forearm pain only during catheter manipulation.
3. The patient reported forearm pain during sheath retrieval.
4. Firm grip of the catheter during manipulation.
5. Augmented resistance to sheath retrieval.

The operators were allowed to score on multiple criteria. This scoring system excludes cases of difficult manipulation due to severely tortuous radial or subclavian arteries, therefore only identifying those patients in whom difficulty was likely to be due to radial artery spasm.
Clinical radial artery spasm was defined as meeting at least two criteria from the above scoring or, only one criterion and the need for intra-arterial vasodilators. This qualitative definition has been used by other investigators in the past and correlates well with quantitative measures of radial artery spasm.

2.10.4 The assessment of discomfort experienced by the patient

Each patient was approached soon after the procedure and asked to complete a questionnaire on their experience during the procedure. They were requested to comment on degree of discomfort felt, if any, during introduction of the sheath at the beginning and pull-back at the end of procedure.

The pain score denotes the patient's assessment of pain during the pullback of sheath:

1. Nothing felt during procedure.
2. Noticeable sensation but no pain.
3. Mild pain.
4. Significant pain (Moderate)
5. Unbearable pain (Severe)

Radial artery spasm was defined as any moderate or severe discomfort during the manipulation of the introducer sheath reported following the procedure.

2.10.5 Assessment of the compression devices

Each patient included in the study was randomised to either a TR band or a Radistop device to achieve haemostasis. The compression device is applied at the end of procedure and the removed over time as per protocol. All patients were assessed by investigator (SR) to evaluate the discomfort, if any, caused by the use of the haemostatic device. Patients were asked to describe the level of discomfort as none, mild, moderate, or severe while the compression device was *in situ*. If the randomised compression device was changed to the other compression device, the reason for this was documented.

2.10.6 Assessment of radial artery patency

Each patient included in study was examined by investigator (SR) or another experienced physician to assess the patency of the radial artery after removal of haemostatic compression device and before the patient was discharged. Pulsation of the radial artery was examined by palpation proximal and distal to the original entry site. When equivocal, patency was confirmed by using a hand held Doppler device (10MHz) to detect flow proximal and distal to the original entry site. Each patient also had a reverse Allen's test performed to assess the patency of radial artery. A reverse Allen's test is performed in a similar way to an Allen's test but after compression of both arteries at the wrist, the pressure over the radial artery is released first to demonstrate patency of the radial artery. In equivocal cases a PL & OX test was performed to assess the patency of the radial artery by applying pressure on ulnar artery and measuring PL & OX from the patient's thumb.

Radial artery occlusion was defined as the absence of palpable radial pulsation distal to the puncture site, confirmed by an abnormal reverse Allen's test and/or absent Doppler flow signals. When patency of the radial artery was assessed by measuring PL and OX, and radial artery was considered occluded when the oxygen saturation and pulse pressure tracing during ulnar artery compression were absent.

2.10.7 Assessment of local complications

Local vascular complications were assessed after removal of the compression device. Vascular complications were defined as following:

1. Oozing from the puncture site was defined as any leakage of blood from the puncture site requiring re-application of pressure.
2. Ecchymosis was defined as bleeding into the subcutaneous tissue planes causing bluish-purple discoloration of more than 4cm in diameter without visible swelling.
3. Local haematomas were classified as small if they were less than 2cm in their largest diameter.
4. Local haematomas were classified as large if they were 2cm or more in any diameter.
5. Any evidence of access site inflammation or infection at discharge was also noted.
6. Radial, brachial or subclavian artery dissection was documented if proven by angiography.

Patients were advised to contact the investigator or the on-call doctor immediately if any late complication occurred and were reviewed by the investigator [SR].

2.10.8 Follow-up

The majority of patients undergoing transradial PCI were routinely reviewed in the outpatient clinic after four to six months. In those attending, the patency of the radial artery and any late access site complications were assessed. Follow-up

assessment was performed as per protocol and in the majority of cases by the investigator (SR).

Radial artery patency at follow up was assessed using the same techniques as the assessment before discharge.

A history of late access-related complication, particularly any evidence of local allergic reactions, was sought and documented. Any access site vascular complications were documented and evidence of functional impairment was recorded.

2.11 Analysis of Data

2.11.1 Computers and software

All data was collected on a case record form (Appendix 5) and subsequently transferred on to a Microsoft Access database for storage and analysis.

2.11.2 Statistical analysis

Continuous variables are expressed as percentages and described as mean ± standard deviation and comparisons were made using Student's t test. Categorical variables are expressed as frequencies and compared using the chi-squared test or Fisher's exact test where appropriate. The comparison was done between long introducer sheaths and short introducer sheaths and between coated and uncoated introducer sheaths in the factorial design. Multivariate analysis was performed using logistic regression analysis to assess predictors of clinical radial artery spasm and radial artery occlusion rates. A secondary analysis was

performed as an extension to the multivariate regression analysis, by introducing a term for interaction. Analysis of variance (ANOVA) was applied to detect any interaction between coating and length of the introducer sheaths for the primary outcome of radial artery spasm. Similarly, there was a comparison done between the two different compression devices. All analysis was performed using SPSS Version 15. In all tests p values of less than 0.05 were considered significant.

2.11.3 Presentation of results from a factorial trial

Interaction tests were not applied for the secondary outcomes as the sample size was powered to test the primary outcome. The results are presented as the primary outcome analysis relating to the main interventions (hydrophilic coating and length of introducer sheath) investigated in the trial. A common misunderstanding is that outcome measures should be analysed and presented separately for each of the four factorial cells (long coated, long uncoated, short coated, and short uncoated in our study), but to do so would fail to realise the full efficiency and purpose of the factorial design (152). Even in trials powered for main effects, a test for the interaction should be provided (152, 154). Going with this guidance, we have presented our primary outcome results comparing all patients receiving coated versus uncoated sheath and long versus short sheath.

Chapter 3 Methods: Physiological study

3.1 Aims and objectives of the study

- Assessment of changes in the vascular function of the radial artery following a transradial coronary procedure.

- Assessment of the impact of the length and coating of the transradial introducer sheath on changes in the vascular function of the radial artery.

3.2 Study design

Patients in this study were a selected subgroup of patients enrolled in the larger prospective randomised study, where patients were assigned to one of two different introducer sheaths: a hydrophilic coated (coated sheath) or a sheath without coating (uncoated sheath).

Patients were tested on three occasions: the day of the transradial procedure (immediately before the catheterization, "pre"), the day after catheterization ("post") and approximately three months after catheterization ("recov"). Volunteers were requested to abstain from alcohol or caffeinated beverages and cigarettes for 12 hours prior to each testing session. Assessments were taken in a quiet, temperature-controlled room. Patients rested in a supine position for a minimum of 20 minutes to ensure that all hemodynamic variables had stabilized. The radial artery was assessed with the arm extended and supported at an angle of approximately 80° from the torso. A rapid inflation/deflation pneumatic cuff was positioned on the imaged arm around the wrist. A standard catheter sheath was then used to mark the length of the catheter on the surface of the arm, from

the scaphoid process. Care was taken to image the same section of the artery during repeat measurements. We assessed both arms to determine whether changes as a consequence of catheterization were specific, or more generalized, throughout the vascular system. On each occasion flow-mediated [endothelial-dependent] dilatation (FMD) was assessed over a distal section of the radial artery, within the zone that would contain the sheath. A minimum of 20 minutes rest was observed between repeated FMD assessments in the same arm. Endothelium-independent function was assessed as the vascular response to a sublingual dose of glyceryl trinitrate (GTN). A minimum of 30 minutes elapsed between repeat doses of glyceryl trinitrate.

3.3 Study outline

Visit 1 (pre-assessment clinic)

1. Information sheet provided (Appendix 6) and informed consent obtained.

Visit 2 (On the day of the procedure)

1. Baseline demographics were recorded and Allen's test performed.

2. Vascular function of the radial artery was assessed before the transradial procedure. Endothelium-dependent and endothelium-independent vasodilatation was measured on both radial arteries as described in section 3.9.

3. Following assessment of vascular function, the transradial procedure was performed.

Visit 3 (24 hours after the procedure)

1. Patients were invited for repeat assessment of vascular function of the radial artery one day after the procedure

Visit 4 (Follow-up after three to four months)

1. Patients were reviewed and followed-up to repeat the assessment of vascular function of the radial artery.

3.4 Inclusion and exclusion criteria

3.4.1 Inclusion criteria

1. Intended transradial coronary procedure
2. Patient at least 18 years old and able to give informed consent.

3.4.2 Exclusion criteria

1. Previous ipsilateral or contralateral transradial procedure or coronary artery bypass surgery.
2. Myocardial infarction during the previous three months.
3. Valvular heart disease.
4. Left ventricular ejection fraction less than 40%.
5. Chronic obstructive lung disease.
6. Renal or hepatic dysfunction.

3.5 End-points

The end-points were the change in flow-mediated and GTN-mediated vasodilatation between the initial assessment ("pre") and the assessments the day after ("post") and at follow-up ("recov") stages. The sample size was calculated considering the change in endothelium-dependent vasodilatation between "pre and "post" stages as a primary end-point..

3.6 Sample size

The sample size estimation was based on historical studies performed by Woodman and Green et al (128), using a novel computerised edge-detection and wall-tracking software system. We have used this software to reliably and reproducibly measure the change in radial artery diameter in our study subjects. In this study (128) the standard deviation (SD) for determining sample size was calculated by using the SD of the mean of visits 1 and 2 (between-subject variance) for parallel design. Sample size was then calculated using the following formula:

For a paired t-test; sample size = $\sqrt{2.SD}$.

Woodman and Greens study (128) showed the mean absolute difference between visits was 1.6±1.0% in the flow-mediated dilatation (FMD) measurement in normal subjects. Similarly there was a between-visit difference in the GTN-mediated dilatation of 3.8±3.3%. Based on this study we assumed that detection of 2.0% change in FMD will be clinically relevant. Therefore, assuming a power of 90% (alpha= 0.05), a parallel design study would require 16 patients in each

arm. We recruited 40 patients to account for loss in follow-up and completing all three visits.

3.7 Randomisation

The patients for this sub-study were recruited form main clinical study randomisation and after thorough discussion with the patients. Consecutive patients fulfilling inclusion and exclusion criteria that agreed and gave consent to attend for all three visits to undergo vascular function testing were included in the physiology sub-study.

3.8 Radial artery access and transradial procedural details

The radial artery was approached with the arm extended and supported with the wrist in mild hyperextension. Local anesthesia was achieved with 2% lignocaine after disinfection at the puncture site. The radial artery was punctured with a 21 gauge arterial needle through which a 0.118 inch platinum-tipped nitinol guidewire was introduced. Following this, the needle was withdrawn and a small skin incision was made. A 6 F introducer sheath (13 or 23 cm in length, external diameter 2.6 mm, Cook Medical Inc. Bloomington, IN, U.S.A) with a dilator tip length of 2.5 cm was inserted. Routine use of vasodilator cocktail (arterial vasodilators like, nitroglycerine, verapamil, or diltiazem) was avoided and a weight-adjusted dose of heparin was introduced into the central circulation following the introduction of the first catheter. All introducer sheaths were removed at the end of the procedure and haemostasis achieved in the

catheterization laboratory by a compression device. The patients were mobilized immediately and the compression device was removed after two to four hours.

3.9 Experimental procedural details

3.9.1 Experimental design

All studies were performed under standardized conditions and preferably at the same time of day. All measurements were performed by one experienced investigator (ED), who is a post-doctoral fellow (Research Institute for Sports and Exercise Sciences, Liverpool John Moore's University, Liverpool) with experience in performing vascular function studies. This operator was blinded to the randomisation data. All procedures were performed after six hours of fasting and patients were asked to abstain from caffeine or alcohol for 12 hours before the assessment. Patients were advised to continue with their medications as normal. Each patient had flow-mediated dilatation (FMD) and glyceryl trinitrate-mediated dilatation assessed using high resolution B-mode ultrasound imaging of the radial artery. There were six examinations performed during each visit, in the following order:

1. Flow-mediated dilatation (FMD) distally on the ipsilateral forearm (a few cm above the flexor retinaculum): Distal FMD, treatment arm.
2. Flow-mediated dilatation (FMD) distally on the contralateral forearm, similar in location to the treatment arm: Distal FMD, control arm.
3. Flow-mediated dilatation (FMD) at least 13 cm above the intended radial puncture site on the ipsilateral forearm: Proximal FMD, treatment arm.

4. Flow-mediated dilatation (FMD) similar in location on the contralateral forearm: Proximal FMD, control arm.
5. Glyceryl trinitrate (GTN)-mediated dilatation distally on the ipsilateral forearm: GTN-mediated dilatation, treatment arm.
6. Glyceryl trinitrate (GTN)-mediated dilatation distally on the contralateral forearm: GTN-mediated dilatation, control arm.

Two different lengths (23cm and 13cm) of introducer sheaths were used to assess their impact on vascular function of the radial artery. With the use of the 13cm length introducer sheath guide, catheters used during procedure come into contact with the radial artery beyond the sheath. Therefore there is the potential for radial artery injury and an effect on vascular function of the proximal radial artery. In contrast, the 23cm long sheath comes into contact with a large area of the radial artery and reduces guide catheter irritation of the proximal portion. These two lengths can potentially have different effects on the vascular function. Therefore, to test the effect of different length, the vascular function is tested at two different points, the distal being covered by the sheath in all cases. The proximal area assessed would be covered by the sheath when the long sheath was used, but would be exposed to catheter movements in patients receiving the short sheath.

3.9.2 Vascular measurements

Patients were rested supine with the test arm extended and immobilised with the foam supports at an angle of approximately 80 to 90 degrees from the torso. Heart rate (HR) and mean arterial blood pressure (MAP) were determined from

an automated sphygmomanometer (Dinamap; GE Pro 300V2, Tampa, Florida) on the contralateral arm. A rapid inflation/deflation paediatric pneumatic cuff was positioned on the imaged forearm at the level of the wrist to provide the stimulus to hand ischaemia. A 12MHz multi-frequency linear array probe attached to a high resolution ultrasound machine (T3000, Terason, Burlington, MA) was used to image the radial artery in the forearm. The radial artery was imaged just above the inflator cuff and at a second point which was around 13cm above first measurement. These measurements were performed on both forearms in the order described in section 3.9.1. Ultrasound parameters were set to optimise longitudinal B- mode images of the lumen/arterial wall interface. Continuous pulsed wave Doppler velocities were obtained using the ultrasound machine, and data were collected using the lowest possible isonation angle (always less than 60 degrees), which did not vary during each study.
After adjusting for gain and compression settings, the images were acquired and archived for later measurements.

3.9.3 Flow-mediated dilatation (endothelium-dependent NO-mediated function).

To examine the radial artery FMD response, a rapid inflation/deflation paediatric pneumatic cuff was used to provide the ischaemic stimulus. After an initial 15 minute resting period, baseline scans assessing resting vessel diameter and flow were recorded over one minute. The cuff was then inflated to > 200 mm Hg for five minutes. Diameter and flow recordings resumed 30 seconds before cuff deflation and continued for five minutes thereafter as described by Black et al

(198). Peak artery diameter and flow, and the time taken to reach these peaks after release of the occlusion, were recorded.

These measurements were repeated after 20 minutes on the contralateral arm at a similar location on the forearm. Following this a repeat measurement is performed on the test arm at a higher point on the forearm to measure the FMD, and also repeated a higher point on the contralateral arm after a wait of 20 minutes. This whole process gave FMD measurements at two locations (proximal and distal) on each forearm.

3.9.4 Glyceryl trinitrate-mediated dilatation (endothelium-independent NO-mediated function)

Following a further 15 minute recovery period, 400 μg of GTN was administered sublingually and the diameter of the radial artery and the peak blood flow were measured for the following five minutes. Blood pressure and pulse rate were measured simultaneously on the contralateral forearm before and after the administration of GTN. The ultrasound measurements were performed on the test arm at the distal point at the wrist corresponding to the FMD site measurements. Following a further 20 minute recovery period, GTN-mediated dilatation measurement was performed at a similar location on the contralateral forearm.

3.9.5 Radial artery diameter measurement and blood flow analysis

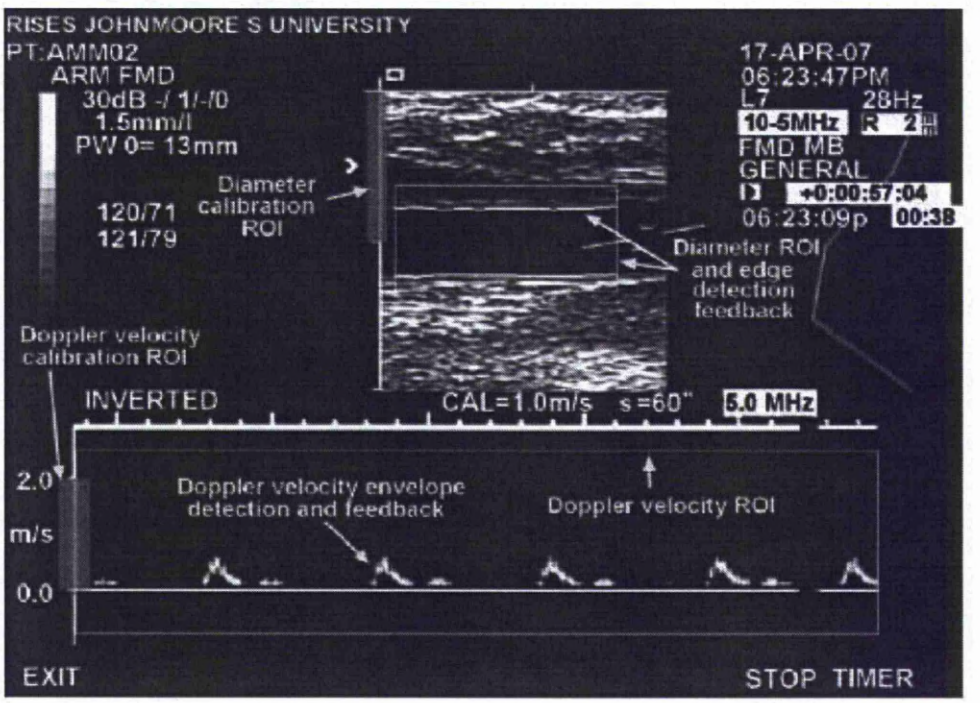
Post-test analysis of radial or brachial artery diameter was performed using custom-designed edge detection and wall-tracking software, which is independent of investigator bias as shown by Woodman et al (128). This study

has shown a significantly lower (6.7%) mean intra-observer coefficient of variation compared to traditional manual measurements using the intima-lumen interfaces (32.5%, $p<0.05$) and intima-media interfaces (32.5%, $p<0.05$). This study also shows significantly lower coefficients of variation for between-visit reproducibility of FMD and GTN-mediated dilatation of 14.7% and 17.6% respectively. Assuming 80% power and an alpha of 0.05, eight subjects with matched controls would be required, in a parallel design study, to detect an absolute change of 2.5% in flow-mediated dilatation.

In this technique the video signal is taken directly from the ultrasound machine, and, using an IMAQ-PCI-1407 card, is encoded and stored as a DICOM (Digital Images and Communication in Medicine) file on a personal computer. Subsequent software analyses of this data were performed at 30Hz using an icon-based graphical programming language and toolkit (Lab VIEW 6.02, National Instruments). The initial phase of image analysis involved the identification of regions of interest (ROI) on the first frame of every individual study (Figure 3-1). These ROI's allowed automated calibration for diameter on the B-mode image and velocity on the Doppler strip. An ROI was then drawn around the optimal area of the B-mode image. Within this ROI a pixel density algorithm automatically identified the angle-corrected near and far wall e-lines for every pixel column within the ROI. The algorithm begins by dividing the ROI into the upper half, containing the near wall lumen-intima interface, and the lower half containing the far wall interfaces. The near wall intimal edge is identified by a rake routine that scans from the bottom to the top of the upper half of the ROI. The position of the edge is established by determining the point where the pixel intensity changes most rapidly. Typical B-mode ROIs therefore contained

approximately 200 to 300 diameter measures per frame, the average of which was calculated and stored. This process occurred at 30 frames per second. We did not use the R-wave gating function in our software because of previous observations that at 30MHz the continuous assessments of diameter yields similar results.

Figure 3-1 Still frame of B- mode ultrasound image acquisition software.

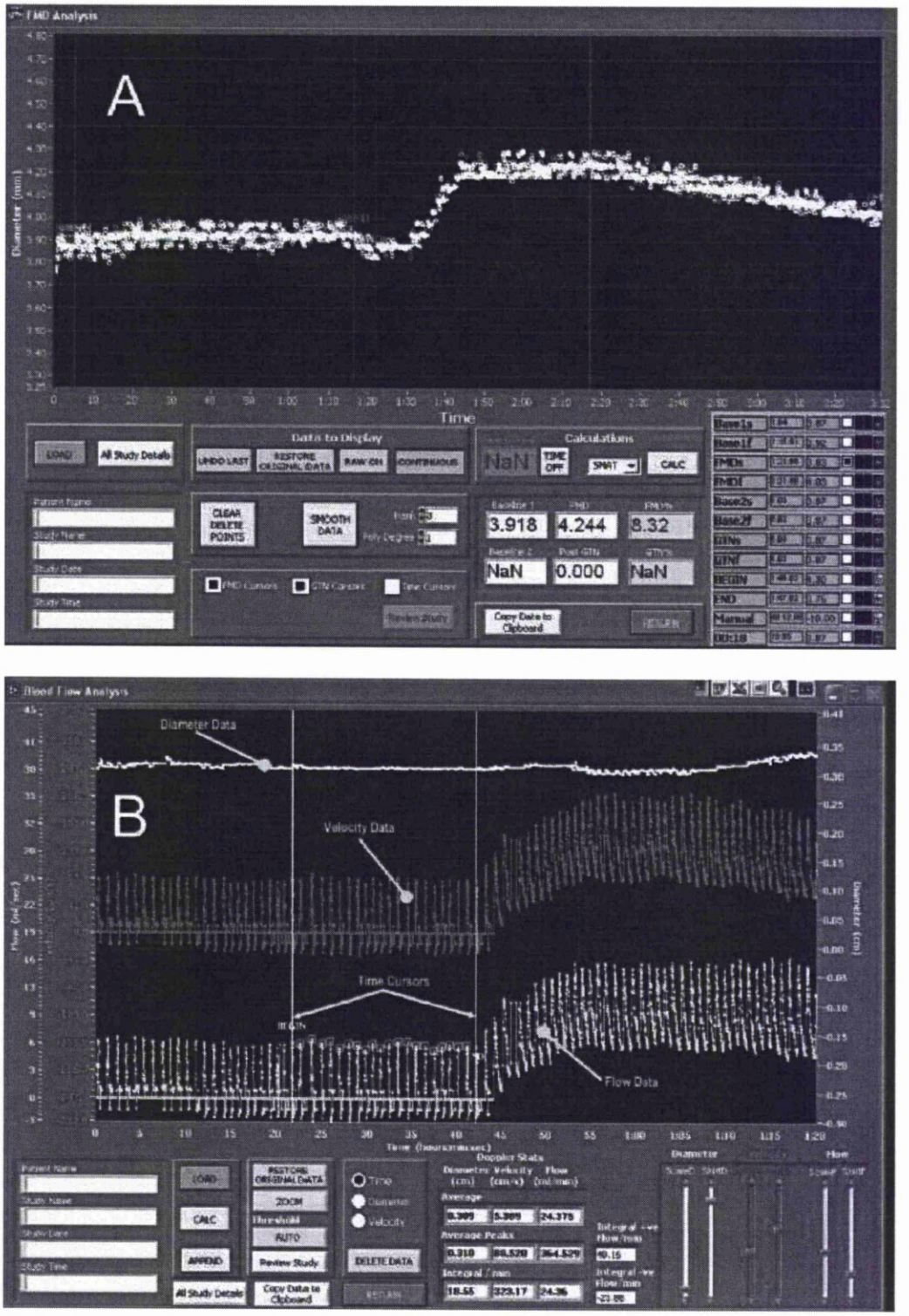


The "Calibrate Diameter," "Calibrate Doppler," "Diameter," and "Doppler" regions of interest (ROIs) are highlighted.

A final ROI was drawn around the Doppler waveform and the peak of the waveform was automatically detected (Figure 3.1). The mean diameter measure derived from within the B-mode ROI (above) was synchronized with the velocity measure derived from the Doppler ROI at 30 frames per second. Ultimately, from this synchronized diameter and velocity data, blood flow (the product of cross sectional area and Doppler velocity [v]) and shear rate (four times velocity

divided by diameter) were calculated at 30Hz. All data were written to file and retrieved for analysis in a custom-designed analysis package (Figure 3-2). Our method of blood flow assessment is closely correlated with actual flow through a "phantom" arterial flow system (129).

Figure 3-2 Upper panel, The flow-mediated dilatation (FMD) edge detection and wall tracking software "output screen".
Lower panel, still frame of B-mode ultrasound data "Display" software.



3.10 Data analysis

Baseline diameter, flow and shear rate were calculated as the mean of data acquired across the one minute preceding the cuff inflation period (Figure 3.2). Each dot in upper panel represents the mean of of 200 to 300 diameter measures for a given frame, with a frame rate of 30 Hz. The vertical cursors are placed at times corresponding to baseline or FMD periods. The peak responses after FMD are calculated by applying a smoothing algorithm which determines the median value of a moving window of consecutive data points. The "peak" of the smoothed median values detected in this way is then used to calculate %FMD via comparison to the preceding baseline. Lower panel in Fig 3-2 shows continuous traces of radial artery diameter (white), velocity (red), and flow (yellow) against time. Vertical "begin" and "end" cursors are placed to zoom in on selected data and, ultimately, calculate mean (MBF) blood flows, area under the flow curve, and similar data foe shear rate. After cuff deflation, a custom-designed software program was used to determine peak diameter from the 30Hz of mean diameter data derived according to the methods described above. Peak diameter after cuff deflation was automatically detected according to an algorithm which identified the maximum bracket of data subsequent to performance of a moving window smoothing function. This smoothing routine calculates the median value from 100 consecutive samples, before the window shifts to the next bracket of data which shares 20% overlap with the preceding bracket. The maximum value of all the calculated median values is then automatically detected and chosen to represent the peak of the diameter curve (Figure 3.2).

Flow-mediated dilatation was calculated as the percentage rise of this peak diameter from the preceding baseline diameter. The time to peak diameter (in

seconds) was calculated from the point of cuff deflation to the maximum post-deflation diameter. Calculation of FMD and time to peak were therefore observer-independent and based on standard algorithms applied to data which had undergone automated edge detection and wall tracking. In accordance with recent findings (130), we expressed FMD data normalised to the shear rate stimulus responsible for endothelium-dependent FMD. The post-deflation shear rate data, derived from simultaneously acquired velocity and diameter measures at 30Hz (Figure), was exported to a spreadsheet and the area under the shear rate curve (AUC) calculated for data up to the point of maximal post deflation diameter (FMD) for each individual. In this way an individual's FMD was normalised to the area under their own shear rate curve between the point of deflation and maximal dilatation for that individual.

Similarly the GTN-mediated vasodilatation is measured as the percentage rise in the peak diameter from the preceding baseline diameter.

3.11 Statistical analysis

The responses initially were assessed using 3-way ANOVAs with linear mixed models. This was followed-up using 2-way repeated measures ANOVAs on the coated or uncoated groups compared over time and between arms. The differences between coated and uncoated groups were compared using a 2-way ANOVA on time and coating in either the catheterized or non-catheterized arms separately. Post-hoc analysis was carried out using paired t-tests. The effects of the FMD test or GTN administration on blood pressure were assessed using a 1-way ANOVA. Baseline characteristic differences were determined using t tests

or chi-square tests. Results are expressed as means ± SD. A p value <0.05 was considered significant.

Chapter 4 Results: Clinical study

4.1 Summary of the results

The success rate of the clinical procedure was high at 96% and was not affected by different introducer sheaths. Radial artery spasm prevented the completion of the procedure in 2.2% of cases.

Operator-defined radial artery spasm was observed in 29.4% patients and 21.8% patients reported discomfort of moderate or severe intensity during the procedure. There was significantly less radial artery spasm and patient-reported discomfort observed in patients receiving a hydrophilic sheath. No significant difference was observed between the groups receiving long and short sheaths.

Radial artery occlusion at the time of discharge was observed in 9% of the patients, similar in the two groups. A large local haematoma or arterial dissection was seen in 2.2%. Minor complications, such as a small haematoma, ecchymosis, or oozing were observed in about 20% of the patients in each group.

There were significantly more patients reporting no discomfort in the TR band group compared to the Radistop group. Patients in the Radistop group reported significantly more pain across all levels of severity. Local vascular complications were similar in both groups. The time taken to achieve haemostasis was significantly longer in the TR Band group compared to the Radistop group.

4.2 Study population

Between November 2006 and January 2008, 794 patients were included in the study. During the initial five months, 570 patients were screened and 505 patients

were included in the study. The most common reason for exclusion was previous ipsilateral transradial procedure (60 patients) and five patients refused to consent. The recruitment for the remaining patients was slow due to an interim analysis and recruitment of patients for the vascular function sub-study. During this period 350 patients were screened and 295 patients were included in the study. Forty patients were excluded because they had had a previous ipsilateral transradial procedure, 10 patients refused to participate in the study and another five patients were not included because the treating physician excluded them from the trial. Out of these 794 patients, four patients underwent a femoral approach without an attempt at radial artery cannulation (protocol violation) and the results from 790 patients are included in this analysis on an intention-to-treat basis.

4.3 Baseline characteristics of the study population

Baseline characteristics of the whole population are shown in Table 4-1 and are typical for a population with ischaemic heart disease. The mean age of the patients included in the study was about 63. Approximately three quarters of the patient in the study were male and one quarter female. Nearly 70% of the patients were hypertensive and 91.0% were hyperlipidaemic on treatment, as expected in patients with coronary artery disease. About a fifth of the patients were diabetic and about 75% of the patients were either ex-smokers or current smokers.

We measured other physical parameters in our study population such as height, weight and wrist circumference. Body mass index (BMI) and wrist/BMI ratio were calculated, as shown in Table 4-1.

Table 4-1 Baseline and procedural characteristics of the study patients. Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	Study population n=790
Age (years)	62.9±11.1
Male	586 (74.2%)
Hypertension	547 (69.2%)
Hyperlipidaemia	719 (91.0%)
Diabetes mellitus	155 (19.6%)
Current smoker	188 (23.8%)
Allen's test: 'not at all'	46 (5.8%)
PL+OX test: type D	56 (7.1%)
Clinical presentation: Stable angina Acute coronary syndrome	 549 (69.5%) 241 (30.5%)
Wrist circumference (cm)	17.2±1.2
Height (cm)	168.8±9.8
Weight (kg)	83.7±16.4
BMI (kg/m^2)	29.2±4.9
Number of catheters used	1.6±0.9
Time sheath in situ (minutes)	50.4±28.3
Procedure: Diagnostic Intervention	 61 (7.7%) 729 (92.3%)

4.4 Ulno-palmar Circulation

The ulno-palmar collateral circulation was assessed in each patient at the baseline prior to the procedure. Each patient underwent an Allen's test and a plethysmography and oximetry (PL&OX) test, the results of which are shown in Table 4-2, Figure 4-1and Figure 4-2.

Table 4-2 Ulno-palmar circulation assessed by Allen's test and PL&OX test

	All n=790	Long n= 396	Short n=394	p value	Coated n= 397	Uncoated n=393	p value
Allen's Test							
< 5s	282(35.7)	138(34.8)	144(36.6)	0.83	125(31.5)	157(40.0)	0.66
5-10s	348(44.1)	183(46.2)	165(41.9)	0.56	182(45.8)	166(42.2)	0.82
10-20s	72(9.1)	37(9.3)	35(8.9)	0.73	44(11.1)	28 (7.1)	0.06
>20s	42(5.3)	22(5.6)	20(5.1)	0.81	23(5.8)	19(4.8)	0.89
not at all	46(5.8)	16(4.0)	30(7.6)	0.03	23(5.8)	23(5.9)	1.0
PL&OX Test							
Type A	676(85.6)	348(87.9)	328(83.3)	0.77	335(84.4)	341(86.8)	0.82
Type B	40(5.1)	17(4.3)	23(5.8)	0.81	24(6.0)	16(4.1)	0.42
Type C	18(2.3)	6(1.5)	12(3.0)	0.16	10(2.5)	8(2.0)	0.92
Type D	56(7.1)	25(6.3)	31(7.9)	0.34	28(7.1)	28(7.1)	1.0

Figure 4-1 Allen's test results

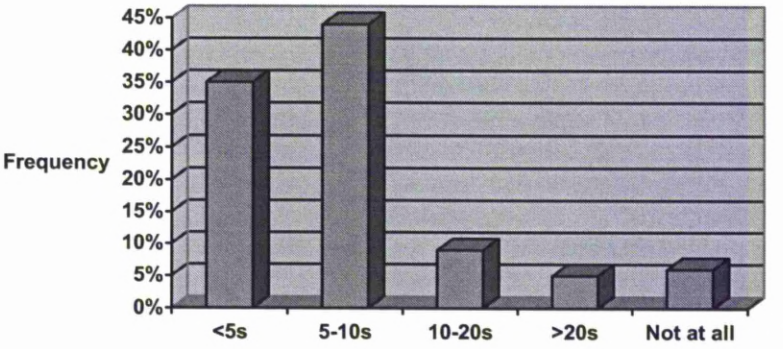


Figure 4-2 Plethysmography and oximetry test results

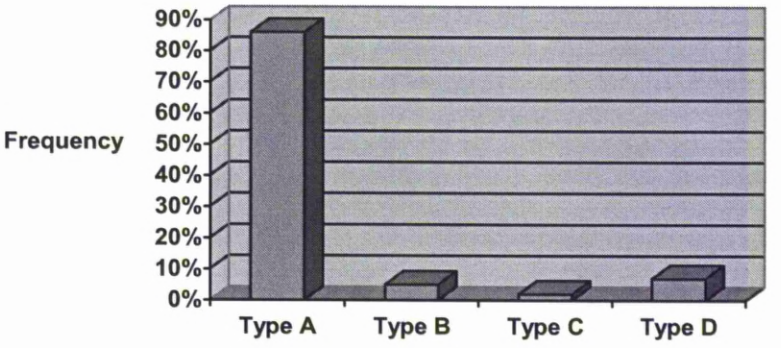
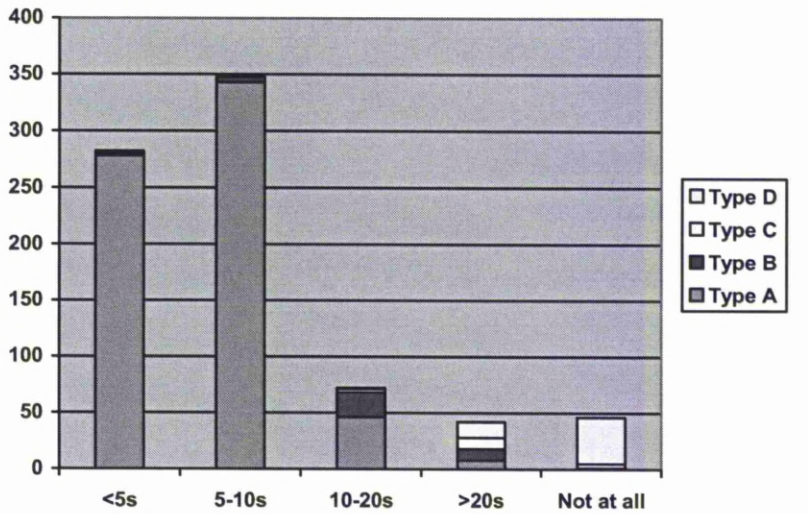


Table 4-3 The correlation between the Allen's test and the PL&OX test

Allen's test	PL+ OX TEST				Total
	Type A	Type B	Type C	Type D	
< 5s	278	3	1	0	282
5-10s	343	5	0	0	348
10-20s	46	22	3	1	72
>20s	8	10	10	14	42
Not at all	1	0	4	41	46
Total	676	40	18	56	790

Figure 4-3 Correlation between Allen's test and PL&OX Test



The correlation between the Allen's test and the PL&OX test is shown in Table 4-3and Figure 4-3. As shown in the table the majority of patients with an Allen's test up to 20s have a PL&OX test type A, B or C, which reflects physiologically normal ulno-palmar collateral circulation. On the other hand the majority of patients with a negative Allen's test have a PL&OX test type D showing inadequate ulno-palmar circulation. However, up to two thirds of patients with an Allen's test of more than 20s show a PL&OX test of type A, B or C, reflecting

adequate ulno-palmar circulation and only one third of the patients show inadequate ulno-palmar circulation by the PL&OX test. Patients were not excluded from our study or deemed unsuitable for a procedure via the radial artery on the basis of the ulno-palmar circulation test results.

4.5 Clinical presentation of the study patients

The majority of the patients included in our study presented with stable angina with 549 (69.5%) of the patients undergoing a procedure for stable angina pectoris and 241(30.5%) patients undergoing a procedure for the investigation and treatment of an acute coronary syndrome. This reflects the standard percutaneous coronary intervention activity at a tertiary cardiac centre.

4.6 Treatment allocation

Table 4-4 Treatment allocation of the study patients.

Treatment allocation	Number of patients	%
Sheath+compression device		
1.Long hydrophilic + TR band (LH+TR)	101	12.8
2.Long hydrophilic + Radistop (LH+RADI)	99	12.5
3.Long uncoated + TR band (LU+TR)	98	12.4
4.Long uncoated + Radistop (LU+RADI)	98	12.4
5.Short hydrophilic + TR band (SH+TR)	97	12.3
6.Short hydrophilic + Radistop (SH+RADI)	100	12.6
7.Short uncoated + TR band (SU+TR)	99	12.6
8.Short uncoated + Radistop (SU+RADI)	98	12.4
Length		
Long	396	50.1
Short	394	49.9
Coating		
Coated	397	50.3
Uncoated	393	49.7
Compression Device		
TR Band	395	50
Radistop	395	50

4.7 Procedural characteristics

4.7.1 Operators

All the procedures were performed by consultant interventional cardiologists (41%) or specialist registrars in the advanced stage of training in coronary intervention under the direct supervision of a consultant (59%).

4.7.2 Procedural success

Procedural success via the ipsilateral radial route was achieved in 757 (96.0%) patients. The procedure could not be completed via the ipsilateral radial route in 33 (4.0%) patients. The reasons for procedural failure in the different treatment

arms are shown in Table 4.5. There were a higher number of procedural failures with short sheaths compared to long sheaths but there was no significant difference seen between coated and uncoated sheaths.

In the study population as a whole, radial artery spasm (RAS) was the reason for procedural failure in 17 (2.1%) cases, radial loop and subclavian tortuosity in two (0.25%) cases each, inability to pass the guide wire up the radial artery in eight (1.0%) cases, failure to puncture the radial artery in three (0.37%) cases, and poor guide catheter back up in one (0.12%) case. The majority of these procedures were completed without any problem from the contralateral radial artery. Only five cases (0.63%) crossed over to a femoral approach to complete the procedure.

Table 4-5 Procedural failure by study group

	Long sheath n= 396	**Short sheath n= 394**	**Coated sheath n= 397**	**Uncoated sheath n= 393**
Radial artery spasm (17)	6	11	7	10
Radial loop (2)	0	2	1	1
Subclavian tortuosity (2)	1	1	1	1
Unable to pass sheath guide wire (8)	2	6	4	4
Unable to puncture radial artery (3)	0	3	1	2
Poor guide catheter back-up (1)	1	0	1	0
Total (33)	10	23	15	18

4.7.3 Procedure time

The procedure time ranged from 10 to 234 minutes with a median value of 45 minutes. The mean procedure time was 50.2 minutes with a SD of 28.4 minutes.

4.7.4 Number of catheters used

The number of catheters used during the procedure ranged from one to five with a median of one and a mean (SD) of 1.7(0.9)

4.7.5 Procedures performed

The total number of procedures performed via the radial approach in this study was 790 which included 61 diagnostic procedures (7.7%) and 729 procedures that involved coronary intervention (92.3%)

4.7.6 Heparin use

A weight-adjusted dose (70units/kg) of unfractionated heparin was given to patients undergoing coronary intervention. The administration of heparin was left to the operator's discretion in patients undergoing diagnostic coronary procedures. A total of 60 (7.6%) procedures were performed without administration of heparin and one patient was given 1000 units of heparin. The remaining 729 (92.3%) patients received heparin ranging from 3000 units to 14000 units during the procedure as part of our routine clinical practice.

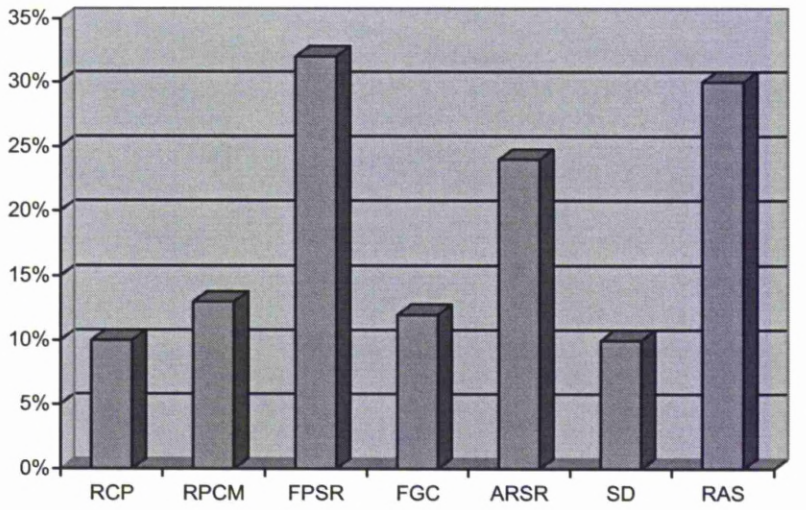
4.8 Study end-points

The study endpoints in the whole study cohort are shown in Table 4-6, Figure 4-4 and Figure 4-5.

Table 4-6 Outcomes following transradial procedures

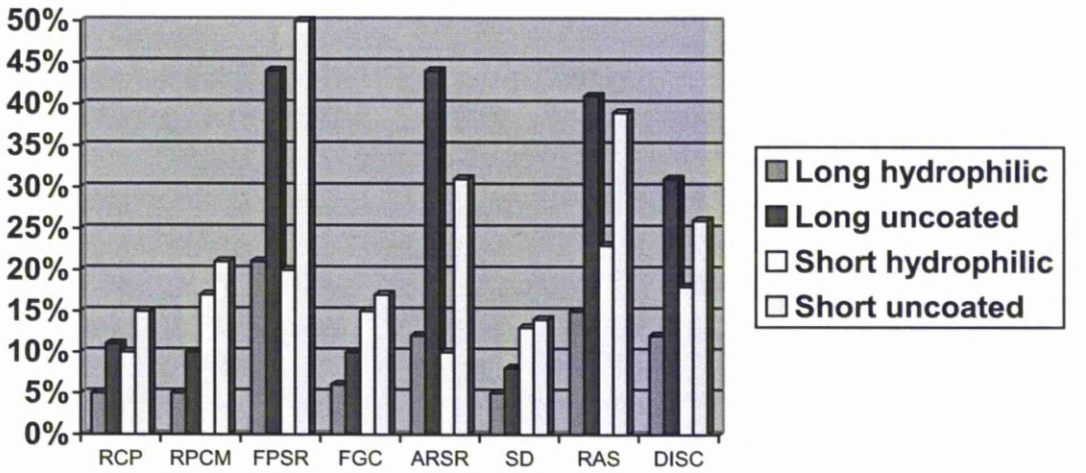
End points	Number of cases, (%)
Operator's assessment of spasm:	
Patient-reported continuous pain (RCP)	79 (10.0%)
Patient-reported pain during catheter manipulation (RPCM)	103 (13.0%)
Forearm pain during sheath retrieval (FPSR)	250 (31.6%)
Firm grip of catheter (FGC)	93 (11.8%)
Augmented resistance to sheath removal (ARSR)	193 (24.4%)
Operator-defined spasm	**230 (29.4%)**
Use of spasmolytic drugs during procedure (SD)	81 (10.4%)
Patient assessment of pain	
Nothing felt during procedure	366 (46.3%)
Noticeable sensation but no pain	112 (14.2%)
Mild pain	140 (17.7%)
Moderate pain	107 (13.6%)
Severe pain	65 (8.2%)
Moderate or severe pain	**172 (21.8%)**
Patient assessment of compression device	
No discomfort	555 (70.3%)
Mild discomfort	161 (20.4%)
Moderate discomfort	51 (6.5%)
Severe discomfort	20 (2.5%)
Severe discomfort causing cross-over	3 (0.4%)
Radial artery patency (at hospital discharge)	
Patent	717(90.5%)
Occluded	73(9.5%)
Local vascular complications	
No complications	588 (74.4%)
Oozing	52 (6.6%)
Ecchymosis	87 (11.0%)
Small haematoma	43 (5.4%)
Large haematoma	17 (2.2%)
Radial or brachial artery dissection	2(0.3%)
Subclavian artery dissection	1(0.1%)
Time taken to achieve haemostasis (hours, median and interquartile range)	5.0 (4.0-6.0)
Radial artery patency (at follow up), n= 625	
Patent	582(93.1%)
Occluded	43(6.9%)
Late access site complications, n=625	
Swelling and infection	21(3.4%)
Pseudo-aneurysm	1 (0.15%)

Figure 4-4 Operator-defined radial artery spasm scores



RCP: Reported continuous pain; RPCM: Reported pain during catheter manipulation; FPSR: Forearm pain during sheath retrieval; FGC: Firm grip of catheter; ARSR: Augmented resistance to sheath removal;
SD: Use of spasmolytic drugs during procedure; RAS: Operator-defined spasm.

Figure 4-5 Operator-defined radial artery spasm with the different sheaths.



4.8.1 Operator-defined radial artery spasm

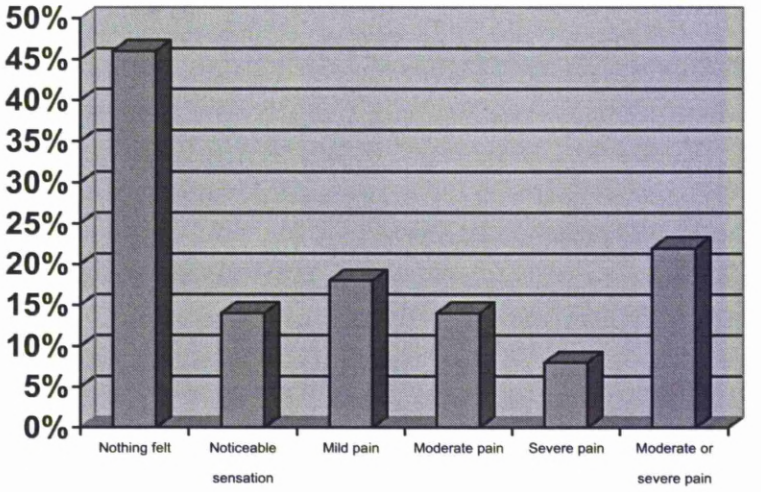
Operator defined radial artery spasm was observed in 230 (29.4%) of the patients included in the study. Spasmolytic drugs were used in 81 (10.4%) patients to treat radial artery spasm. Further breakdown of the different individual scores of radial artery spasm as defined by the operators are shown in Figure 4-4 and Figure 4-5.

4.8.2 Forearm pain during the procedure

Moderate or severe discomfort during introduction or pull-back of the introducer sheath was observed in 172 (21.8%) patients in the study population. Nearly half of the patients 366 (46.3%) reported feeling nothing during the pullback or insertion of the introducer sheath. 112 patients (14.2%) reported noticeable sensation but no discomfort during the pull back or insertion of the introducer sheath and 140 patients (17.7%) reported mild discomfort.

Nearly one quarter of the patients (22%) reported moderate or severe discomfort during the pull back or insertion of the introducer sheath. Moderate discomfort was experienced by 107(13.6%) patients and severe discomfort was experienced by 65(8.2%) (Figure 4-6).

Figure 4-6 Discomfort felt by the patient during sheath retrieval



4.8.3 Radial artery patency

Radial artery occlusion was seen in 73 (9.2%) patients before discharge from hospital after removal of the compression device. In 717 (90.8%) patients the radial artery was patent. However, none of the patients with radial artery occlusion reported any symptoms of hypoperfusion or functional impairment of the hand.

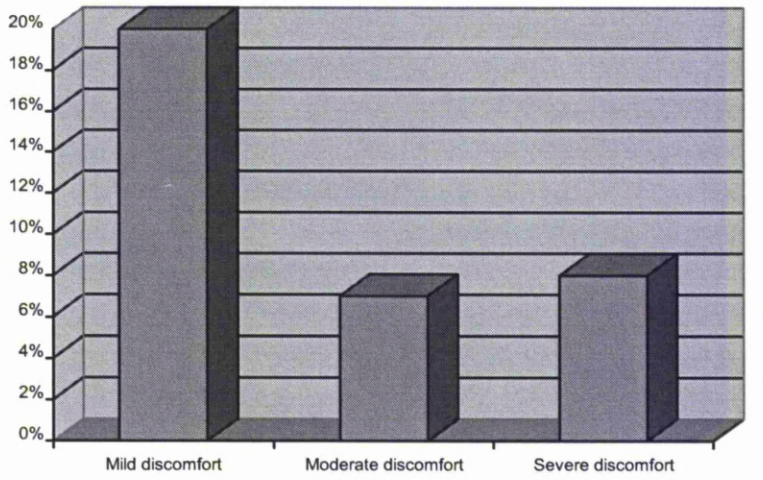
4.8.4 Time taken to achieve haemostasis

As shown in Table 4-6, the time taken to remove the compression device ranged from one to 19 hours with a median and interquartile range of five and four to six hours respectively.

4.8.5 Patient tolerance of the haemostatic device

As shown in Table 4-6, most patients did not report any discomfort during the time period when the compression device was in place. A mild or moderate degree of discomfort was reported by 161 (20.4%) and 51 (6.5%) patients respectively during the application of the compression device (Fig 4.7). Twenty (2.5%) patients reported severe discomfort with the application of the compression device and in three cases (0.4%) patients with a Radistop were changed over to the other available compression device (TR Band). No crossover from TR band to Radistop occurred.

Figure 4-7 Patient tolerance of the haemostatic device.

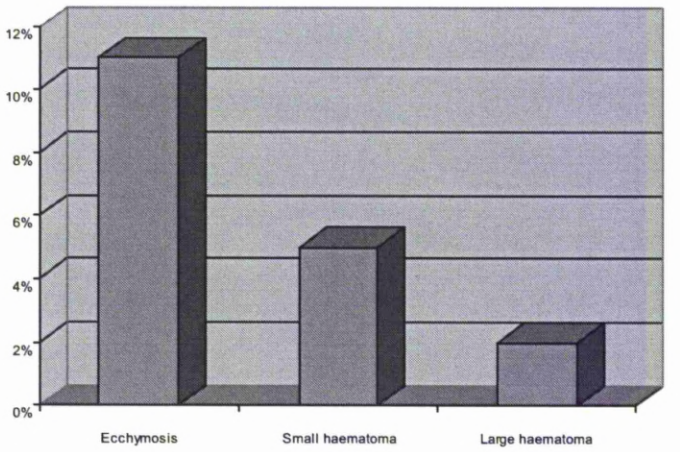


4.8.6 Local vascular complications

There were no access site complications seen in 588 (74.4%) patients after the removal of the compression device. Oozing needing manual pressure to stop bleeding after removal of the compression device was seen in 52 (6.6%) patients. Ecchymosis was seen in 87 patients (11.0%) and small and large haematomas

were seen in 43(5.4%) and 17(2.2%) patients respectively (Figure 4-8). Radial or brachial artery dissection and subclavian artery dissection was seen in two (0.3%) and one (0.1%) patients respectively. None of these local vascular complications required any further interventions or blood transfusion and they were all managed conservatively without adverse sequelae.

Figure 4-8 Local vascular complications



4.8.7 Radial artery occlusion rates at follow up

Radial artery patency was assessed in 625 patients during routine follow-up between four and six months. The radial artery was patent in 582 (93.1%) patients and occluded in 43 (6.9%) patients. None of the patients reported any vascular compromise or functional impairment.

4.8.8 Late access site complications at follow up

Twenty-one (3.4%) patients reported late swelling or discharge following discharge from the hospital. Twelve patients were treated by antibiotics or

surgical drainage. These patients usually sought treatment for their access site inflammation elsewhere and we do not know the quality of the diagnosis of infection. One patient developed a pseudo-aneurysm of the radial artery at the puncture site and needed surgical intervention.

4.9 Interaction between length and coating of the introducer sheath

We have described primary endpoints of the study for the different introducer sheaths in previous sections. Univariate analysis of variance (UNIANOVA) was applied to the data to assess any interaction between length and coating of the introducer sheath on operator-defined spasm and patient-reported discomfort during the radial procedure. There was no significant interaction observed between length and coating for operator-defined radial artery spasm ($F=1.213$, $p= 0.108$) or patient-reported discomfort ($F=2.085$, $p= 0.631$). The results of comparisons between long and short introducer sheaths and hydrophilic coated and uncoated sheaths are described in the following sections.

4.10 Comparison between long and short introducer sheaths

4.10.1 Baseline characteristics

As shown in Table 4-7, the baseline characteristics including risk factors and physical profile were well matched between long and short introducer sheath groups. The patients' age and sex distribution was similar between the two groups. There were more patients with a negative Allen's test in patients who received a short introducer sheath compared to those who received a long introducer sheath but there was no difference seen in the PL&OX test between

the two groups. The clinical presentation was similar in both groups, as was the physical profile including wrist circumference, height, weight, and body mass index.

Table 4-7 Baseline and procedural characteristics of the long and short introducer sheath groups.
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	Long n=396	Short n=394	p value
Age (years)	62.7±11.5	63.0±10.8	0.73
Male	293 (74.0)	293 (74.4)	0.93
Hypertension	275 (69.4)	272 (69.0)	0.94
Hyperlipidaemia	360 (90.9)	359 (91.1)	1.0
Diabetes mellitus	68 (17.2)	87 (22.1)	0.09
Current smoker	95 (24.0)	93 (23.7)	1.0
Allen's test: 'not at all'	16 (4.0)	30 (7.6)	0.03
PL&OX test: type D	25 (6.3)	31 (7.9)	0.41
Clinical presentation: Stable angina Acute coronary syndrome	 280 (70.7) 116 (29.3)	 269 (68.3) 125 (31.7)	0.49
Wrist circumference (cm)	17.2±1.2	17.3±1.2	0.82
Height (cm)	168.7±10.1	169.0±9.4	0.68
Weight (kg)	83.2±16.6	84.1±16.2	0.43
BMI (kg/m^2)	29.2±4.8	29.4±5.0	0.54
Number of catheters used	1.7±0.86	1.7±0.85	0.96
Time sheath *in situ* (minutes)	50.2±27.7	50.6±28.9	0.88
Compression device: Radistop TR band	 196 (49.5) 200 (50.5)	 199 (50.5) 195 (49.5)	0.83
Procedure: Diagnostic Intervention	 32 (8.1) 364 (91.9)	 29 (7.4) 365 (92.6)	0.79

4.10.2 Procedural characteristics

The majority of the patients underwent coronary intervention and the proportion undergoing intervention was similar between both groups. The total number of

catheters used during the procedure and the procedure time were similar in the two groups. Haemostasis following procedure was achieved by TR Band or RADISTOP in equal proportion (by randomisation).

4.10.3 Outcomes

Table 4-8 Outcomes with long and short introducer sheaths
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

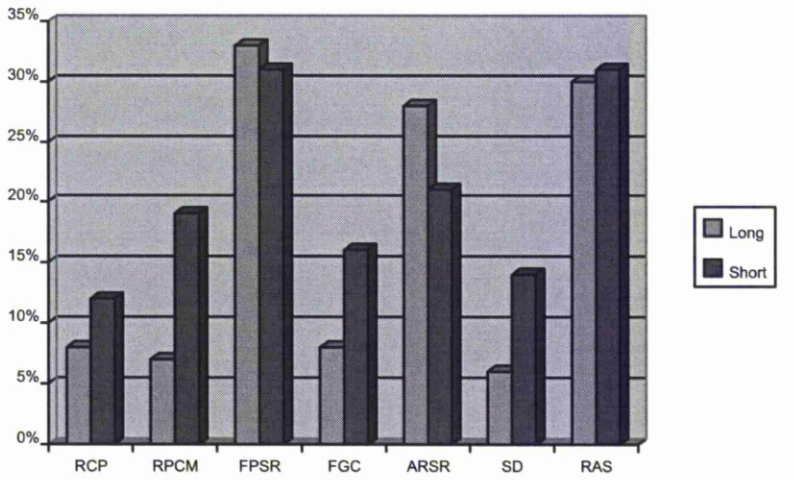
	Long n=396	**Short n=394**	**p value**
Operator-defined spasm	110 (27.9)	120 (30.8)	0.39
Patient discomfort	85 (21.5)	87 (22.2)	0.41
Use of spasmolytic drugs	26 (6.6)	55 (14.1)	0.001
Local Complications			
Ecchymosis	43 (10.8)	44 (11.2)	1.00
Oozing	31 (7.8)	21 (5.3)	0.20
Small haematoma	21 (5.3)	22 (5.6)	1.0
Large haematoma	8 (2.1)	9 (2.3)	0.81
Dissection	0 (0)	3 (0.8)	1.0
Occlusion	31 (8.0)	42 (10.9)	0.18
Late complications	**Long n=324**	**Short n=301**	
Abscess or infection	11 (3.3)	10 (3.3)	1.0
Pseudo-aneurysm	0 (0)	1 (0.3)	0.51
Occlusion	27 (8.3)	16 (5.3)	0.12

4.9.3.1: Radial Artery Spasm

There was no difference in the rate of operator-defined radial artery spasm between patients receiving long and short introducer sheaths. Similarly, there were no differences in the patients' discomfort level during insertion or retrieval of the introducer sheath between the two groups. However, there was a greater

use of intra-arterial spasmolytic drugs in patients receiving short introducer sheaths (Table 4-8, Figure 4-9).

Figure 4-9 Operator-defined spasm rates by sheath length



***RCP**: Reported continuous pain; **RPCM**: Reported pain during catheter manipulation; **FPSR**: Forearm pain during sheath retrieval; **FGC**: Firm grip of catheter; **ARSR**: Augmented resistance to sheath removal; **SD**: Use of spasmolytic drugs during procedure; **RAS**: Operator-defined spasm.*

4.9.3.2: Local access site complication

There were similar rates of access site complications in both groups. Both small and large haematomas were infrequent and similar in incidence in patients receiving long and short introducer sheaths. Radial artery occlusion at the time of hospital discharge were seen in 8.0% and 10.9% (p=0.18) of patients receiving long and short sheaths respectively.

4.9.3.3: Late access site complications

Persistent radial artery occlusion was observed in 8.3% and 5.3% of the patients at the time of long term follow up in the long and short sheath groups. There were marginally higher rates of radial artery occlusion in patients receiving the

long introducer sheath, but this was not statistical significant (p=0.18). Late local access site swelling or infection were observed similarly in both groups (3.3% vs. 3.3%, p=1.0).

4.11 Comparison between hydrophilic coated and uncoated introducer sheaths

4.11.1 Baseline characteristics

As shown in Table 4-9, the baseline characteristics including risk factors and biophysical profile were well matched between the coated and uncoated introducer sheath groups. Patient age and sex distribution were similar in both groups. The Allen's test and PL&OX test results were similarly distributed in each group. The clinical presentation was also similar in both groups with two thirds of the patients presenting with stable angina. The biophysical profile, including wrist circumference, height, weight, and body mass index were comparable between patients receiving coated and uncoated sheaths.

Table 4-9 Baseline and procedural characteristics in the coated and uncoated introducer sheath groups
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	Coated n=397	Uncoated n=393	p value
Age (years)	62.7±11.2	63.1±11.1	0.57
Male	292 (73.6)	294 (74.8)	0.22
Hypertension	283 (71.3)	264 (67.2)	0.22
Hyperlipidaemia	366 (92.2)	353 (89.8)	0.26
Diabetes mellitus	79 (19.9)	76 (19.3)	0.86
Current smoker	93 (23.4)	95 (23.9)	1.00
Allen's test: 'not at all'	23 (5.8)	23 (5.9)	1.00
PL+OX test: type D	28 (7.1)	28 (7.1)	1.00
Clinical presentation: Stable angina Acute coronary syndrome	 279 (70.3) 118 (29.7)	 270 (68.7) 123 (31.3)	0.64
Wrist circumference (cm)	17.2±1.3	17.2±1.1	0.98
Height (cm)	169.1±10.4	168.6±9.1	0.44
Weight (kg)	83.6±16.6	83.8±16.2	0.88
BMI (kg/m^2)	29.2±4.8	29.4±4.9	0.52
Number of catheters used	1.67±0.88	1.69±0.82	0.74
Time sheath in situ (minutes)	47.4±26.0	53.6±30.2	0.003
Compression device: Radistop TR band	 198 (49.9) 199 (50.1)	 197 (50.1) 196 (49.9)	1.00
Procedure: Diagnostic Intervention	 37 (9.3) 360 (90.7)	 24 (6.1) 369(93.9)	0.11

4.11.2 Procedural characteristics

The majority of the patients underwent coronary intervention, the rates of intervention and the total numbers of catheters used during the procedure were similar in the two groups. The procedure time was significantly higher in patients receiving an uncoated introducer sheath compared to patients receiving a hydrophilic-coated sheath. Compression device use was similar in the two groups.

4.11.3 Outcomes

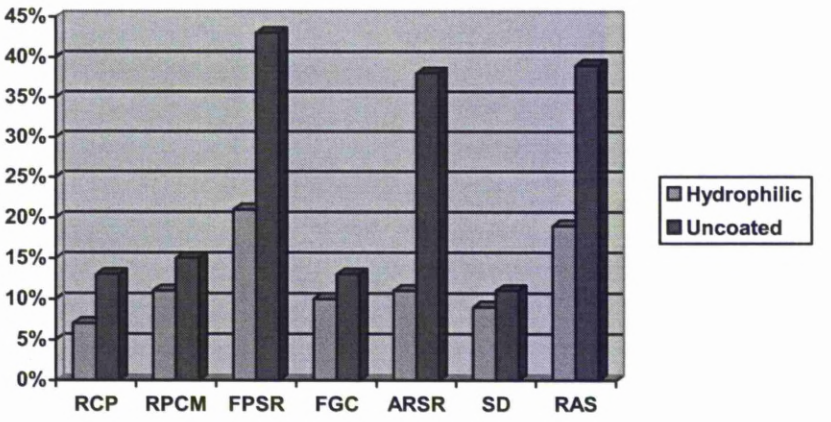
Table 4-10 Outcomes with coated and uncoated introducer sheath. Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	Coated (n=397)	**Uncoated (n=393)**	**p value**
Operator-defined spasm	75 (19.0)	155 (39.9)	<0.001
Patient discomfort	60 (15.1)	112 (28.5)	<0.001
Use of spasmolytic drugs	37 (9.4)	44 (11.4)	0.41
Local complications:			
Ecchymosis	39 (9.8)	47 (11.9)	0.30
Oozing	28 (7.1)	24 (6.1)	0.67
Small haematoma	22 (5.5)	21 (5.3)	1.0
Large haematoma	3 (0.8)	14 (3.7)	0.006
Dissection	1 (0.3)	2 (0.5)	1.0
Occlusion	35 (8.9)	28 (10.0)	0.62
Late complications	**Coated (n=315)**	**Uncoated (n=310)**	
Abscess or infection	20 (6.3)	1(0.3)	0.0001
Pseudo-aneurysm	1 (0.3)	0 (0)	0.57
Occlusion	24 (7.6)	19 (6.1)	0.44

4.10.3.1: Radial artery spasm

There was less operator-defined radial artery spasm and patient-reported discomfort observed in patients receiving a hydrophilic-coated sheath (Figure 4-10, Table 4-10). There was a 50% relative reduction in the occurrence of operator- defined radial artery spasm in patients receiving a hydrophilic-coated introducer sheath compared to those receiving an uncoated sheath. However, the use of intra-arterial spasmolytic drugs was similar in both groups.

Figure 4-10 Operator-defined radial artery spasm scores by sheath coating



***RCP**: Reported continuous pain; **RPCM**: Reported pain during catheter manipulation; **FPSR**: Forearm pain while sheath retrieval; **FGC**: Firm grip of catheter; **ARSR**: Augmented resistance of sheath removal; **SD**: Use of spasmolytic drugs during procedure; **RAS**: Operator-defined spasm*

4.10.3.2: Local access site complication

There were similar rates of small haematoma seen in the two groups but large haematomas were significantly more common in patients receiving uncoated introducer sheaths. All haematomas were managed conservatively by compression bandage and none needed surgical intervention. Radial artery occlusion rates at the time of hospital discharge were similar in patients receiving coated and uncoated sheaths (Table 4-10).

4.10.3.3: Late access site complications

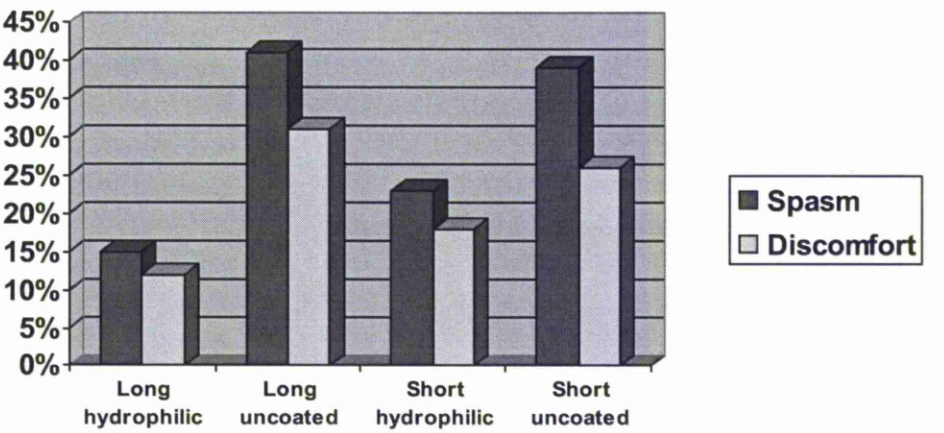
Persistent radial artery occlusion was observed in 7.6% and 6.1% of the patients at the time of long term follow up in the coated and uncoated sheath groups. There was a higher occurrence of local swelling or infection at the arterial puncture site in patients receiving a hydrophilic coated sheath as compared to those receiving uncoated sheaths (Table 4-10).

4.12 Comparison between different introducer sheaths

4.12.1 Operator-defined clinical radial artery spasm

The operators described the highest incidence of spasm in patients receiving long uncoated sheaths and the lowest in those receiving the long hydrophilic-coated sheath. Short sheaths had intermediate incidences with less spasm when the sheath was coated (Figure 4-11).

Figure 4-11 Radial artery spasm and patient discomfort by sheath type



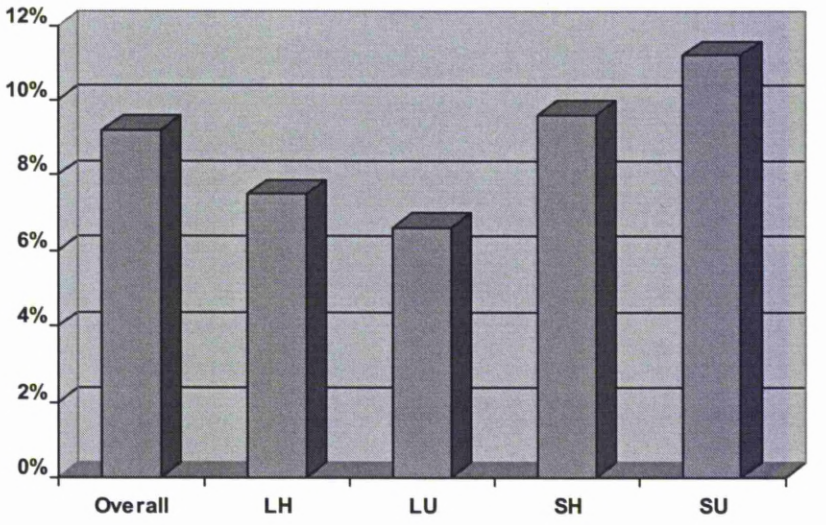
4.12.2 Forearm pain during the procedure

The patient experience of pain was similar to the operators' definition of spasm, occurring most frequently when a long uncoated sheath was used and least frequently when a long hydrophilic-coated sheath was used (Figure 4-11).

4.12.3 Radial artery patency

Figure 4-12 shows the incidence of radial artery occlusion early after discharge in the different sheath types used in study. The incidence of radial artery occlusion was highest when short uncoated sheaths were used and lowest with long uncoated sheaths. Short hydrophilic sheaths had a higher occlusion rate than long hydrophilic sheaths.

Figure 4-12 Radial artery occlusion rates with different sheaths



LH: Long hydrophilic sheath, LU: Long uncoated sheath, SH: Short hydrophilic sheath, SU: Short uncoated sheath.

4.13 The comparison between TR Band and Radistop haemostatic compression devices

4.13.1 Baseline characteristics

As shown in Table 4-11, the baseline risk factors, including physical profile, are similar among both groups of patients who were treated with the TR Band and the Radistop haemostatic compression devices. Age and sex distribution was similar between both groups. The results of the Allen's test and PL&OX test were equally represented in each group. Clinical presentation was also similar in the two groups and two thirds of the patients presented with stable angina. Biophysical profile including wrist circumference, height, weight, and body mass index was comparable between the patients receiving a Radistop or a TR Band.

Table 4-11 Baseline and procedural characteristics and type of compression device used.
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	Radistop n= 395	TR Band n=395	p value
Age (years)	63.1±10.7	62.7±11.6	0.66
Male	290 (73.4)	298 (75.4)	0.30
Hypertension	268 (67.8)	279 (70.6)	0.44
Hyperlipidaemia	364 (92.2)	355 (89.9)	0.32
Diabetes mellitus	77 (19.5)	78 (19.7)	1.0
Current smoker Ex-smoker	90 (22.8) 209 (52.9)	97 (24.5) 196 (49.6)	0.62 0.39
Allen's test: Not at all	24 (6.1)	22 (5.6)	0.71
PL+ OX Test: Type D	26 (6.6)	30 (7.6)	0.82
Clinical syndrome: Stable angina Acute coronary syndrome	279 (70.6) 116(29.4)	276 (69.9) 119 (30.1)	0.91 0.82
Length of sheath: Long Short	196 (49.6) 199 (50.4)	200 (50.6) 195 (49.4)	0.83
Coating of sheath: Hydrophilic Uncoated	198 (50.1) 197 (49.9)	199 (50.4) 196 (49.6)	1.0
Wrist circumference (cm)	17.2±1.2	17.3±1.2	0.41
Height (cm)	168.7±9.6	169.0±10.0	0.63
Weight, (kg)	83.1±15.5	84.2±17.2	0.37
BMI (kg/m^2)	29.2±5.1	29.3±4.7	0.81
Procedure time (minutes)	51.2±28.4	49.6±28.2	0.43
Number of catheters used	1.7±0.8	1.7±0.9	0.28
Heparin used during procedure	374 (94.7)	355 (89.9)	0.016

4.13.2 Procedural characteristics

The majority of the patients underwent coronary intervention and the rates of intervention were similar in the two groups. The total number of catheters used during the procedure and the procedure times were similar for both groups. Various introducer sheaths were used in similar proportions in both groups by

randomisation. The frequency of heparin use during the procedure was lower in patients receiving a TR Band (Table 4-11).

4.13.3 End Points

4.11.3.1: Time taken to achieve haemostasis

As shown in Table 4-12, the time taken to achieve haemostasis was significantly longer in patients receiving a TR Band compression device compared to patients receiving a Radistop (Figure 4-13). However haemostasis was achieved in all patients with the designated compression device except for three patients in the Radistop group who crossed over to a TR Band because of severe discomfort.

Figure 4-13 Time taken to achieve haemostasis

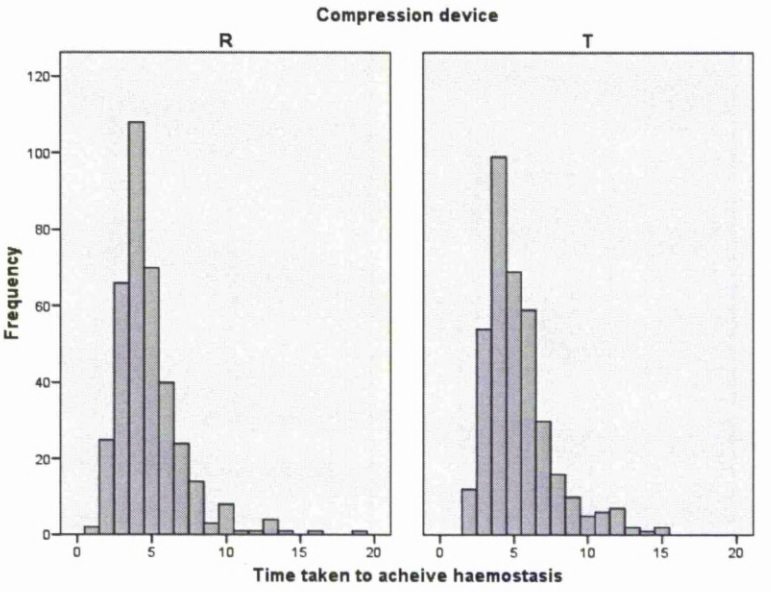


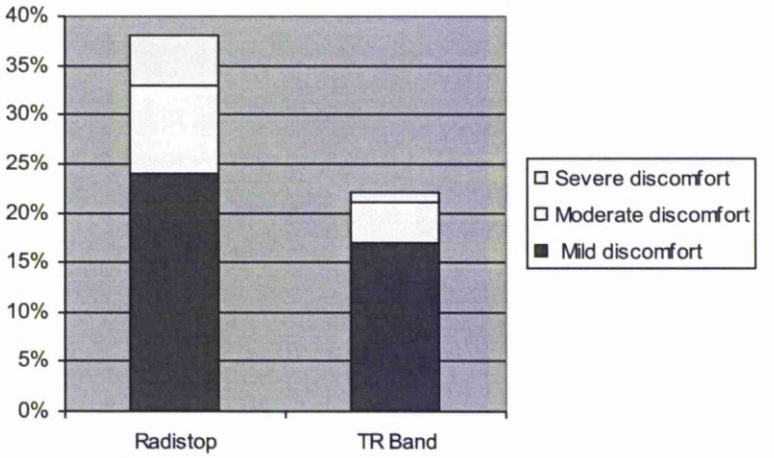
Table 4-12 Outcomes with different compression devices
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	Radistop n= 395	**TR Band n= 395**	**p value**
Time taken to achieve haemostasis(hours)	4.8±2.3	5.3±2.3	0.004
Patient discomfort			
Moderate	34 (8.6)	17 (4.3)	0.019
Severe	18 (4.6)	2 (0.5)	0.0003
Crossover to alternate device	3 (0.8)	0 (0)	0.25
Local complication			
Ecchymosis	42 (10.6)	45 (11.4)	0.92
Oozing	28 (7.1)	24 (6.1)	0.57
Large haematoma	6 (1.5)	11 (2.8)	0.33
Small haematoma	19 (4.8)	24 (6.1)	0.32
Occlusion at discharge	38 (9.6)	35 (8.9)	0.89
Occlusion at follow-up	25 (8.0)	18 (5.6)	0.27

4.11.3.2: Patient tolerance of compression device

Overall both compression devices were well tolerated. However, significantly more patients complained of moderate or severe discomfort during compression with a Radistop device compared to the TR Band group (Figure 4-14). Three patients (0.4%) in Radistop group were crossed over to a TR Band because of severe discomfort.

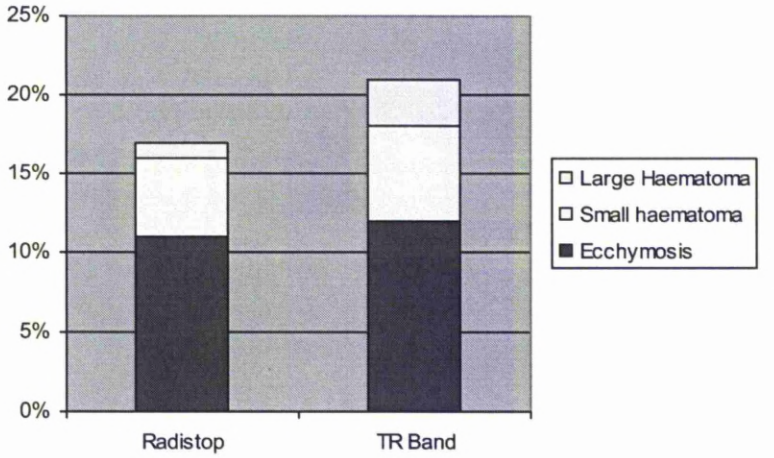
Figure 4-14 Patient tolerance of the haemostatic device



4.11.3.3: Access site complications

There were similar rates of small and large haematomas seen in each group (Figure 4-15). All haematomas were managed conservatively by compression bandage and none needed surgical intervention. Oozing of blood and ecchymosis after removal of compression device was seen in equal proportions in both groups of patients. Radial artery occlusion rates at the time of hospital discharge and at the time of follow-up were similar in the two groups.

Figure 4-15 Access site bleeding complications



4.14 Predictors of Radial Artery Spasm

Table 4-13 shows the baseline and procedural characteristics in patients with and without operator-defined radial artery spasm during their transradial coronary procedure. Patients experiencing spasm were significantly younger and spasm was more likely in females. There were significantly more patients with diabetes experiencing spasm, but other risk factors were similar in the two groups.

The wrist circumference was significantly lower in patients experiencing spasm during the procedure. Similarly, the patients experiencing spasm were shorter, lighter, and had a lower body mass index.

There was a higher frequency of patients with abnormal ulno-palmar circulation in patients experiencing spasm. There was an equal distribution of an unstable clinical presentation in each group.

There was a significantly higher incidence of spasm in patients receiving uncoated introducer sheaths compared to those receiving coated sheaths. There was no significant impact of the length of the introducer sheath used on incidence of spasm.

The number of catheter exchanged or used during the procedure did not influence the incidence of spasm.

Table 4-13 Baseline and procedural characteristics of patients with and without radial artery spasm
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	No Spasm n=553	Spasm n=230	p value	O.R/S.E*	95% C.I
Age (years)	63.7±10.9	60.9±11.5	0.001	0.87*	1.16-4.59
Females	115 (20.8)	87 (37.8)	<0.001	1.75	1.41-2.16
Hypertension	383 (70.7)	159 (69.1)	1.0	1.004	0.79-1.27
Hyperlipidaemia	507 (91.7)	207 (90.0)	0.49	1.15	0.80-1.63
Diabetes mellitus	97 (17.5)	58 (25.2)	0.018	1.59	1.09-2.29
Current smoking	127 (23.0)	61 (26.5)	0.81		
Allen's test: Not at all	37 (6.7)	9 (3.9)	0.18		
PL+OX:Type D	46 (8.3)	10 (4.3)	0.04		
Clinical syndrome: Stable angina Acute coronary syndrome	 392 (70.9) 161 (29.1)	 156 (67.8) 74 (32.1)	 0.39		
Sheath length: Long Short	 284 (51.4) 269 (48.6)	 110 (47.8) 120 (52.2)	 0.39	 1.15	 0.84-1.56
Sheath coating: Hydrophilic Uncoated	 320 (57.9) 233 (42.1)	 75 (32.6) 155 (67.4)	 <0.001	 2.84	 2.05-3.92
Height (cm)	169.6±9.7	166.8±9.5	<0.001	0.77*	1.37-4.38
Weight (kg)	85±16.2	80.3±16.3	<0.001	1.30*	2.11-7.21
BMI (kg/m^2)	29.5±5.0	28.8±4.6	0.067	0.39*	-0.04-1.47
Wrist circumference (cm)	17.4±1.2	16.9±1.2	<0.001	0.093*	0.27-0.64
Time sheath in situ (minutes)	51.1±28.0	48.7±29.0	0.001	0.87*	1.16-4.59
Number of catheters used	1.7±0.9	1.7±0.8	0.83	0.06*	-0.11-0.14

A multivariate analysis of the independent predictors of spasm during transradial procedures was performed and the results are shown in Table 4-14. Female sex, young age, diabetes mellitus, small wrist circumference, and low BMI were found to be independent predictors of spasm in our study patients.

Table 4-14 Independent predictors of radial artery spasm

	Odds ratio	95% C.I.	p value
Female sex	2.01	1.31-3.09	0.001
Age (years)	0.96	0.95-0.98	<0.001
Diabetes mellitus	1.84	1.22-2.76	0.003
Wrist circumference (cm)	0.86	0.72-1.02	0.096
BMI (kg/m^2)	0.96	0.92-1.00	0.059

4.15 Predictors of radial artery occlusion at the time of discharge

Table 4-15 shows the baseline variables, procedural characteristics and outcome measures associated with radial artery occlusion at the time of the patient's discharge from hospital. Patients with occlusion were younger at the time of procedure and occlusion was more frequent in females. Other risk factors (hypertension, hyperlipidaemia and diabetes mellitus) did not influence this outcome in our study.

There was no significant influence of the length and the coating of the introducer sheath on the incidence of occlusion. Occlusion rates were also similar in the Radistop and the TR Band groups.

There was a significantly higher rate of occlusion seen in patients experiencing radial artery spasm during the transradial procedure. There was also a significant negative correlation between the use of heparin during the procedure and the risk of occlusion. When heparin was used the rate of occlusion was 7.2% but when heparin was not used the rate was 22% (p=<0.0001).

Wrist circumference was significantly smaller in patients who had occlusion after the procedure and patients with occlusion were shorter in height. There was no impact of weight and body mass index on the risk of occlusion.

Procedure time, or the duration that the introducer sheath remained in situ, and the time taken to achieve haemostasis were not related to the risk of occlusion in our study.

Table 4-15 Baseline correlates and procedural characteristics of patients with radial artery occlusion at the time of discharge.
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	Occlusion n=73	**No occlusion n=707**	**p value**
Age	60.4±11.2	63.1±11.1	0.05
Female	31 (42.5)	170 (24.0)	0.001
Hypertension	48 (65.8)	492 (69.6)	0.80
Hyperlipaedemia	63 (86.3)	648 (91.7)	0.15
Diabetes mellitus	14 (19.2)	141 (19.9)	0.29
Sheath length: Long Short	 31 (42.5) 42 (57.5)	 361 (51.1) 346 (48.9)	0.31
Sheath coating: Coated Uncoated	 35 (47.9) 38 (52.1)	 360 (50.9) 347 (49.1)	0.14
Compression device: Radistop TR Band	 38 (52.1) 35 (47.9)	 351 (49.6) 356 (50.4)	 0.76
Operator-defined spasm	33 (45.2)	196 (27.7)	0.008
Heparin administered	53 (72.6)	666 (94.2)	<0.0001
Height (cm)	167.0±8.5	169.0±9.9	0.056
Weight (kg)	82.4±17.2	83.8±16.4	0.52
Wrist circumference (cm)	16.8±1.2	17.3±1.2	0.001
BMI (kg/m^2)	29.4±5.0	29.3±4.9	0.79
Time sheath in situ (minutes)	46.6±28.2	50.6±28.4	0.26
Time taken to achieve haemostasis (hours)	4.94±2.05	5.08±2.30	0.59

The results of a multivariate analysis showing independent predictors of occlusion are shown in Table 4-16. Younger age, smaller wrist size, operator

defined spasm and failure to administer heparin were shown to be independent predictors of radial artery occlusion.

Table 4-16 Independent predictors of radial artery occlusion at the time of discharge

Variables	O.R	95% C.I	p value
Younger age (per year)	1.02	1.00-1.04	0.036
Smaller wrist size (per cm)	1.39	1.06-1.80	0.014
No operator-defined spasm	0.53	0.31-0.90	0.021
No heparin use	7.12	3.75-13.52	<0.0001

Chapter 5 Results: Physiological study

5.1 Summary of the results

There was a significant reduction in flow-mediated dilatation (FMD) (endothelium-dependent) and glyceryl trinitrate (GTN)-mediated dilatation (endothelium-independent) of the radial artery in the catheterized arm with no change in the non-catheterized arm following a transradial procedure.

There was no significant difference in the magnitude of change in FMD between the use of coated and uncoated sheaths in the catheterized arm, with a significant effect of time, but no interaction of time and coating.

In the subjects who participated at the three month follow up, matched data revealed that FMD and the GTN-mediated vasodilatation decreased non-significantly and then returned towards baseline at three months in the coated sheath group and the uncoated group. There was no significant change in the FMD in the contralateral arm during the study period.

5.2 Study population

Thirty-five subjects (32 male) were recruited from the list of patients requiring radial artery catheterization for coronary angiography or coronary angioplasty. All were randomized in the main clinical study. The following were excluded: patients who had previously undergone coronary artery bypass surgery or coronary intervention via either radial route or had myocardial infarction during the previous three months, valvular heart disease, a left ventricular ejection

fraction less than 40%, chronic obstructive lung disease, and renal or hepatic dysfunction.

Fifteen of the patients had been randomized to a coated sheath; one patient had an occluded artery post-procedure that remained occluded at the three month recovery period. Occlusion was confirmed by a reverse Allen's test and the existence of impaired SR_{AUC} following ischaemia (shear rate area under curve) as explained in methods section (Chapter 3). This subject's data was removed from subsequent analysis. The other 14 subjects in the coated sheath group had FMD data collected pre-catheterization and post-catheterization and 12 of these had GTN-mediated vasodilatation at similar time points. A subgroup of six subjects was retested approximately three months after the procedure.

Twenty subjects were recruited in the uncoated group: all had FMD assessed before and after the procedure, with 19 able to complete the GTN testing. From this group 13 subjects were re-tested for the FMD and 12 for the GTN protocols approximately three months later.

5.3 Baseline and clinical characteristics of the study patients

Baseline and clinical characteristics of the patients who underwent assessment of the vascular function of the radial artery are shown in Table 5.1. Risk factors were standard for coronary artery disease populations. All patients in this group presented with chronic stable angina. All these variables were well matched in the coated and uncoated introducer sheath groups.

Various biophysical parameters and the procedure time, defined as the duration of the introducer sheath staying in the radial artery were also similar in the two groups.

Table 5-1 Clinical characteristics of the study patients (n=35).
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

	All patients n=35	**Coated n=15**	**Uncoated n=20**	**p value**
Age (years)	64.4±7.8	64.8±8.1	64.1±7.8	0.82
Male	32 (91.4)	13 (86.0)	19 (95.0)	0.99
MAP (mmHg)	94±12	95±11	93±13	0.88
Heart rate (beats/minute)	62±12	62±13	62±13	
Hypertension	25 (71.4)	10 (66.7)	15 (75.0)	0.71
Hyperlipidaemia	32 (91.4)	13 (86.7)	19 (95.0)	0.56
Diabetes mellitus	8 (22.8)	3 (20.0)	5 (25.0)	1.00
Height (cm)	171.0±8.6	169.5±8.7	172.1±8.5	0.37
Weight (kg)	88.2±16.0	83.6±9.5	91.6±19.0	0.23
Wrist circumference(cm)	17.1±0.9	16.3±3.9	17.1±1.0	0.36
Smoking:				
Current	5 (14.3)	2 (13.3)	3 (15.0)	
Ex-smoker	24 (68.6)	10 (66.7)	14 (70.0)	0.26
Stable angina	35 (100)	15 (100)	20 (100)	1.00

5.4 Clinical outcomes of the study patients

There was significantly higher occurrence of operator-defined radial artery spasm and patient discomfort in patients receiving uncoated sheaths. Minor access site vascular complications were seen in one third of the patients and at

similar rates in the two groups. One patient had documented radial artery occlusion at the time of hospital discharge which remained occluded at follow up with no vascular compromise or functional impairment of the hand.

Table 5-2 Clinical outcomes of the study patients (n=35).
Continuous variables are presented as mean ± standard deviation, discrete variables as n (%)

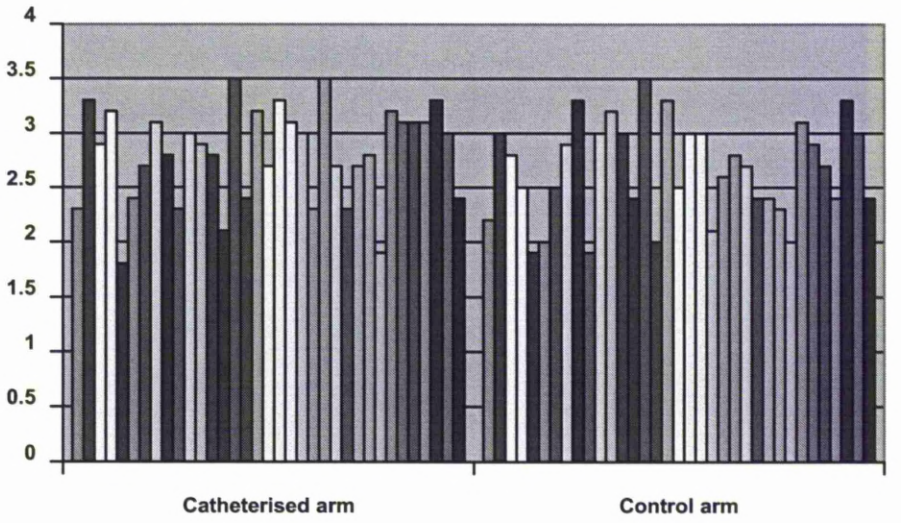
	All patients n=35	Coated n=15	Uncoated n=20	p value
Operator-defined spasm	9 (25.7)	0 (0)	9 (45.0)	<0.001
Patient discomfort	6 (17.1)	0 (0)	6 (30)	<0.001
Time sheath in situ (minutes)	66.4±27.3	70.4±30.3	64.2±24.0	0.54
Vascular complications:				
Ecchymosis	5 (14.3)	2 (13.3)	3 (15.0)	
Oozing	5 (14.3)	4 (26.7)	1 (5.0)	0.18
Radial artery occlusion	1 (2.8)	1 (6.7)	0 (0)	0.42
Late local infection	1 (2.8)	1 (6.7)	0 (0)	0.42
Radial artery occlusion at follow up	1 (2.8)	1 (6.7)	0 (0)	0.42

5.5 Baseline radial artery diameter in the catheterised and non-catheterised arms

The baseline radial artery diameter in the catheterized and non-catheterized arms is shown in figure 5.1. The radial artery diameter ranged from 1.8 to 3.5mm in the catheterised arm with a mean diameter of 2.79mm and standard deviation of 0.43mm. These measurements were similar to those obtained in the control arm (2.65±0. 45 mm, range: 1.9-3.5 mm).

Figure 5-1Baseline radial artery diameter in control and catheterised arm

Radial artery diameter on y axis (mm).



Baseline radial artery diameters were similar in the coated and uncoated groups, both in the catheterized and control arms. There was significant increase in the baseline diameter in the catheterised arm immediately after the procedure, which returned to baseline at follow up at three months.

Table 5-3 Baseline and post-procedure radial artery diameters

	Catheterized arm		p	Control arm		p
	Coated n=15	Uncoated n=20		Coated n=15	Uncoated n=20	
Baseline radial artery diameter (mm)	2.68±0.50	2.88±0.37	0.20	2.62±0.50	2.68±0.42	0.73
Post-procedure radial artery diameter (mm)	3.01±0.44	3.10±0.42	0.56	2.59±0.46	2.89±0.42	0.23

5.6 Baseline endothelium-dependent vascular function (flow-mediated dilatation)

Baseline flow-mediated dilatation of the radial artery at the distal and proximal sites in both arms is shown in Table 5-4. There was no significant difference between the proximal and distal sites in the catheterized or the control arms.

Table 5-4 Baseline-flow mediated dilatation of the radial artery.

Patient number	Catheterized arm FMD (%)		Control arm FMD (%)	
	Distal	Proximal	Distal	Proximal
1	6.99	-	16.82	-
2	10.94	9.25	11.15	11.18
3	8.62	10.86	15.11	13.25
4	9.32	11.75	7.33	7.67
5	15.00	13.40	13.30	-
6	10.59	10.22	11.62	10.33
7	6.23	5.69	7.29	8.45
8	10.16	10.67	8.53	8.14
9	4.26	4.36	7.83	6.47
10	13.36	16.20	14.36	22.17
11	9.80	4.60	14.62	3.98
12	16.90	8.23	10.53	7.73
13	6.65	9.28	6.60	7.27
14	6.85	6.40	6.20	7.21
15	7.20	8.82	8.12	10.00
16	5.96	4.01	11.11	10.55
17	8.81	7.89	9/94	10.43
18	11.81	15.47	7.97	7.92
19	9.94	10.43	10.07	10.61
20	9.12	7.18	6.25	8.96
21	7.77	8.75	7.73	7.80
22	8.84	10.76	9.65	12.73
23	6.82	4.79	8.87	6.29
24	7.01	9.97	7.01	7.09
25	16.02	8.10	10.37	11.42
26	6.23	5.69	6.72	6.84
27	11.97	10.50	10.39	11.24
28	13.02	13.17	12.87	12.15
29	5.08	5.98	6.73	-
30	10.78	12.24	10.88	8.18
31	5.56	5.45	6.59	4.83
32	5.50	5.03	5.50	4.80
33	5.09	6.15	5.21	4.54
34	7.38	5.65	7.24	7.09
35	9.13	10.50	6.25	13.13
Mean	**8.98**	**8.74**	**9.33**	**9.07**
Median	**8.81**	**8.78**	**8.53**	**8.16**
S.D	**3.18**	**3.20**	**2.99**	**3.48**
Range	**4.26-16.90**	**4.01-16.20**	**5.21-16.82**	**3.98-22.17**

Table 5-5 Baseline glyceryl trinitrate-induced dilatation of the radial artery.

Patient No	Catheterized arm (%)	Control arm (%)
1	21.25	15.5
2	14.95	11.6
3	13.00	10.1
4	15.61	8.7
5	16.06	13.7
6	8.90	-
7	15.50	8.5
8	9.60	8.6
9	11.04	9.9
10	-	12.7
11	6.19	7.6
12	14.37	14.9
13	15.73	11.5
14	24.64	7.6
15	11.62	7.9
16	14.23	12.2
17	11.28	14.7
18	5.98	7.3
19	14.72	12.5
20	7.21	8.6
21	10.96	13.2
22	16.94	13.3
23	11.23	13.3
24	5.36	7.3
25	24.79	18.6
26	15.50	8.0
27	15.25	17.8
28	27.06	10.1
29	10.03	10.2
30	10.43	12.8
31	8.08	13.4
32	7.07	7.6
33	7.58	9.4
34	10.86	8.3
35	29.18	19.9
Mean	**13.59**	**11.39**
Median	**12.31**	**10.82**
S.D	**6.02**	**3.40**
Range	**5.36-29.18**	**7.3-19.9**

5.7 Baseline glyceryl trinitrate-induced dilatation of the radial artery

Baseline GTN-mediated vasodilatation of the radial artery is shown in Table 5-5. The GTN-mediated dilatation of individual patients in both catheterized and control arms were highly variable. GTN-mediated vasodilatation of the radial artery was significantly higher in the catheterised arm at baseline.

5.8 The impact of transradial catheterization on vascular function of the radial artery

As shown in Figure 5-2, the FMD reduces significantly post-procedure in the catheterized arm and returns back to normal at three month follow up. These results were similar at the distal and proximal sites of the radial artery. Similarly, the GTN-mediated vasodilatation reduces significantly post-procedure in the catheterised arm and returns back to normal at follow-up.

FMD and GTN mediated vasodilatation remained unchanged in the control arm during the study period (Figure 5-3).

Figure 5-2 Flow-mediated and GTN-mediated dilatation in the catheterised arm (mean ± SD)

Distal site

	Pre-procedure	Post-procedure	3 month F/U
FMD (%)	8.98±3.18	5.19±3.45	7.80±3.74

P= <0.001

P = 0.012

P= 0.71

Proximal site

	Pre-procedure	Post-procedure	3 month F/U
FMD (%)	8.74±3.20	4.86±3.38	7.90±4.50

P= <0.001

P = 0.002

P= 0.85

	Pre-procedure	Post-procedure	3 month F/U
GTN (%)	13.59±6.02	8.53±4.22	13.37±6.19

P= <0.001

P = <0.001

P= 0.51

Figure 5-3 FMD at the distal site (a), proximal site (b), and GTN-mediated dilatation (c) in the control arm

(a)

	Pre-procedure	Post-procedure	3 month F/U
FMD (%) Mean ± SD	9.33±2.99	8.92±3.01	9.01±3.40

P= 0.06

P = 0.53

P= 0.32

(b)

	Pre-procedure	Post-procedure	3 month F/U
FMD (%) Mean ± SD	9.07±3.48	9.19±4.21	8.99±2.57

P= 0.52

P = 0.69

P= 0.41

(c)

	Pre-procedure	Post-procedure	3 month F/U
GTN (%) Mean ± SD	11.39±3.40	12.02±4.10	11.54±4.07

P= 0.39

P = 0.15

P= 0.61

5.9 Comparison of the baseline radial artery diameter and vascular function in the catheterised and control arms

As shown in table 5.6, the baseline radial artery diameter was significantly larger in the catheterised arm (right forearm in our study) both at the distal and proximal sites. The baseline endothelium-dependent vasodilatation was similar in both the catheterised and control arms, but we observed higher baseline GTN-induced vasodilatation in the catheterised arm.

There was a significant negative correlation between baseline radial artery diameters and flow-mediated dilatation ($r=-0.361$, $p=0.033$), which is abolished at follow up ($r=-0.191$, $p= 0.294$). Similarly, there was a significant negative correlation between baseline radial artery diameters and GTN-induced vasodilatation ($r=-0.685$, $p<0.01$).

Table 5-6 The baseline radial artery diameter and vascular function in catheterized and control arms

Measurements	Catheterised arm	Control arm	p value
Artery diameter-distal (mm)	2.79±0.43	2.65±0.45	0.025
Artery diameter-proximal (mm)	3.03±0.52	2.85±0.54	0.013
FMD distal (%)	8.98±3.18	9.33±2.99	0.480
FMD proximal (%)	8.74±3.20	9.07±3.48	0.295
GTN-mediated dilatation (%)	13.59±6.02	11.39±3.40	0.020

5.10 The impact of sheath coating on endothelium-dependent vasodilatation

In the coated group there was a reduction in FMD in the catheterized arm with no change in the non-catheterized arm. The repeated measures were compared over time (pre, post and follow up) and between arms (catheterized and control arms)

as discussed in methods section in Chapter 3. There was a significant effect of time ($p=0.04$), arm ($p=0.02$) and interaction between arm and time ($p=0.003$). The FMD changed significantly with time after catheterization in catheterized arm.

In the uncoated group there was also a significant reduction in the FMD with no change in the non-catheterized arm. There was a significant effect of time ($p=0.005$), arm ($p=0.001$) and interaction between arm and time ($p<0.001$) (Figure 5.4). There was no significant difference between the time to peak hyperaemia and the shear rate area under the curve between the coated and uncoated sheath at different study time (Table 5.7).

Figure 5-4 Changes in flow-mediated dilatation in the catheterized and non-catheterized arms pre and post-procedure

Top panels are coated sheath and lower panels are uncoated sheath. Data are presented as mean ± SD. * significantly different from pre ($p<0.05$)

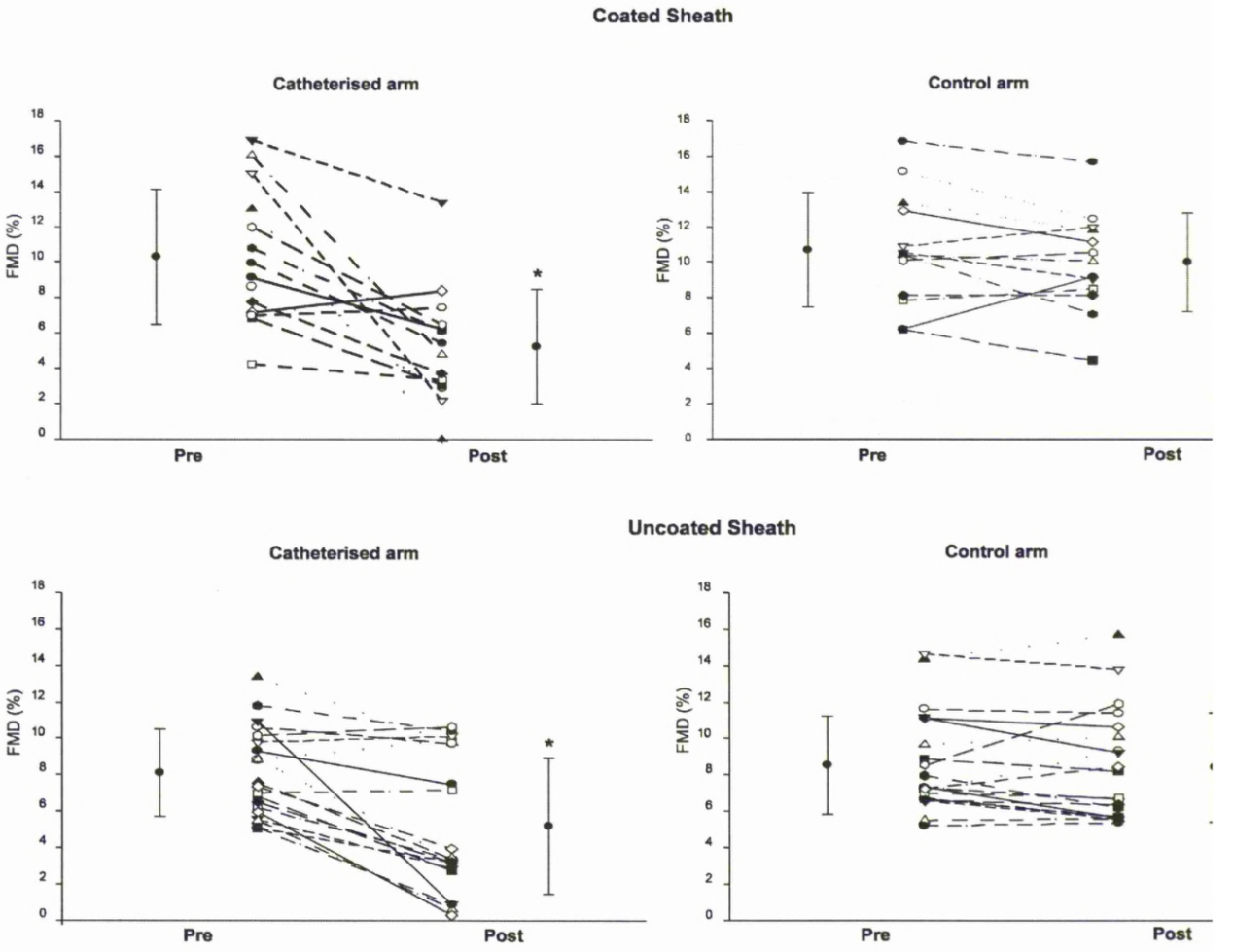


Table 5-7 Time to peak, baseline diameter and shear rate area under the curve (SR_{AUC}) pre-procedure (pre), the day following the procedure (post) and three months post–procedure (Recov) in the catheterized (cath) and non-catheterized (contr) arms

n=6 for FMD and GTN in the coated group. n=13 for FMD and n=12 for GTN in the uncoated group.
*Endothelium-dependent flow-mediated dilatation (FMD) and endothelial-independent function (GTN-mediated dilatation) was assessed in the coated and uncoated catheter sheath groups. Cath; catheterized arm. Contr; non-catheterized control arm. *significantly different from "pre" ($p<0.05$); $ significantly different from "post".*

Data are presented as mean ± SD.

		Baseline diameter (mm)			Time to peak (s)			SR_{AUC} (s^{-1} 10^3)		
		Pre	Post	Recov	Pre	Post	Recov	Pre	Post	Recov
					FMD PROTOCOL					
CATH	Coated	26±5	29±4	27±6	94±49	100±54	113±27	25.2±19.2	28.5±17.3	27.2 ±13.8
	Uncoated	29±4	32±4	27±4$	109±46	86±44	90±56	31.7±17.9	20.6±14.0	33.2±23.8
CONTR	Coated	26±5	24±4	26±5	67±50	66±25	81±45	17.2±8.6	24.8±10.9	32.5±22.3
	Uncoated	26±4	29±4*	28±4$	87±24	103±68	89±48	23.0±7.1	27.3±15.7	26.8±16.9
					GTN PROTOCOL					
CATH	Coated	27±05	29±5	25±3	316±110	372±63	343±100			
	Uncoated	30±5	32±2	27±3$	353±84	250±128	278±104$			
CONTR	Coated	27±2	29±5	28±3	323±148	303±103	293±131			
	Uncoated	29±3	29±3	31±4$	245±105	297±109	266±114$			

5.11 The impact of sheath coating on non-endothelium-dependent vasodilatation

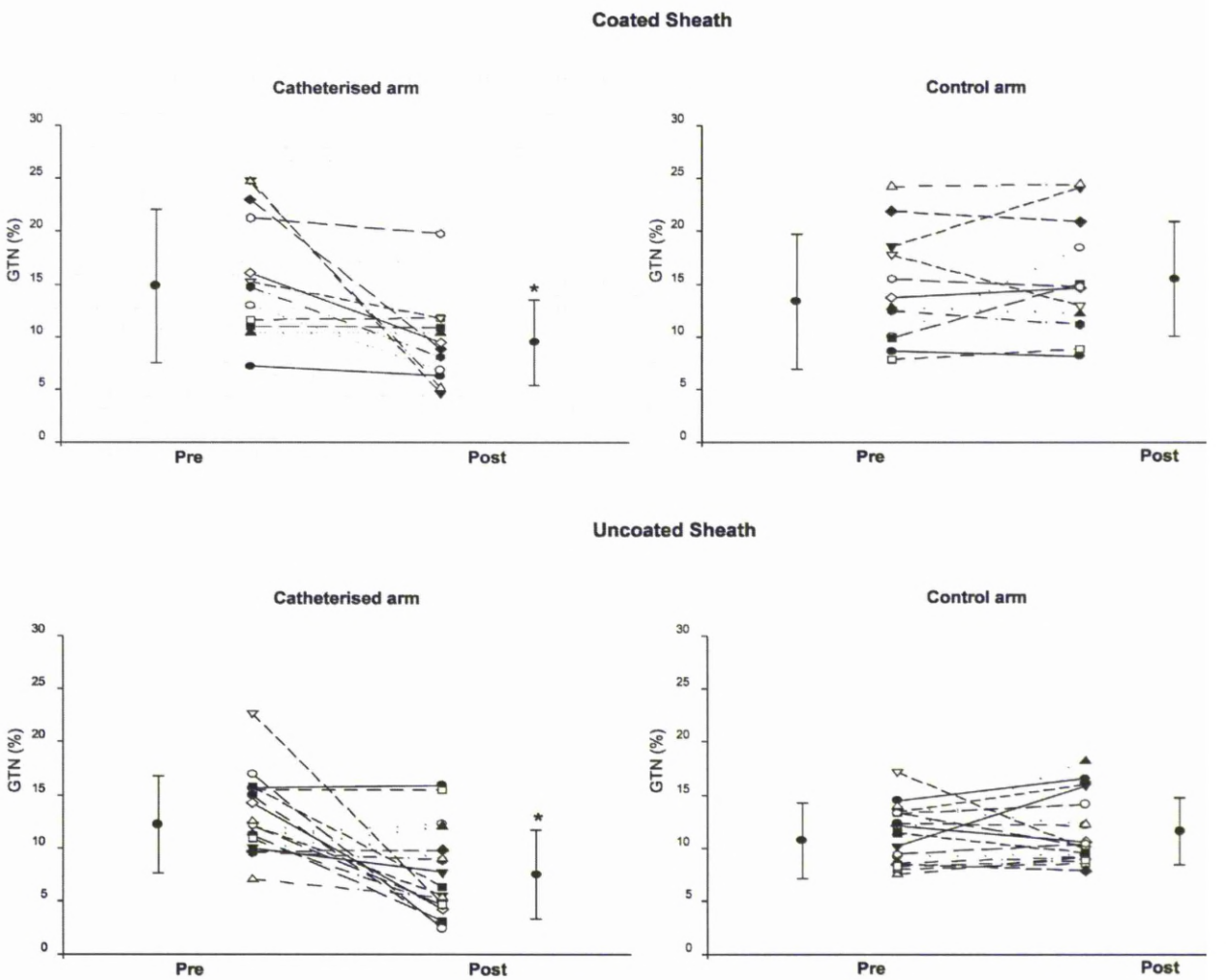
In the coated group there was a reduction in the GTN response in the catheterized arm, with no change in the non-catheterized arm. ANOVA revealed no

significant effect of time, but there was a significant effect of arm and interaction between arm and time.

In the uncoated group there was a reduction in GTN in the catheterized arm with no change in the non-catheterized arm. There was no significant effect of time, but there was a significant effect of arm and interaction between arm and time (Figure 5.5).

Figure 5-5 Changes in GTN-mediated dilatation.

Top panels are coated sheath and lower panels are uncoated sheath. Data are presented as mean ± SD. * significantly different from pre ($p<0.05$)



Although there was significant interaction among arm, time, and coating with the three-way ANOVA, there was no significant difference in the magnitude of change in FMD between the coated and uncoated conditions in the catheterized arm, with a two-way ANOVA demonstrating a significant effect of time, but no interaction of time and coating. Likewise, an ANOVA on the GTN data comparing the effect of time and coating in the catheterized arm showed a significant effect of time but no interaction between time and coating.

5.12 The impact of sheath coating on the recovery of endothelium-dependent vasodilation

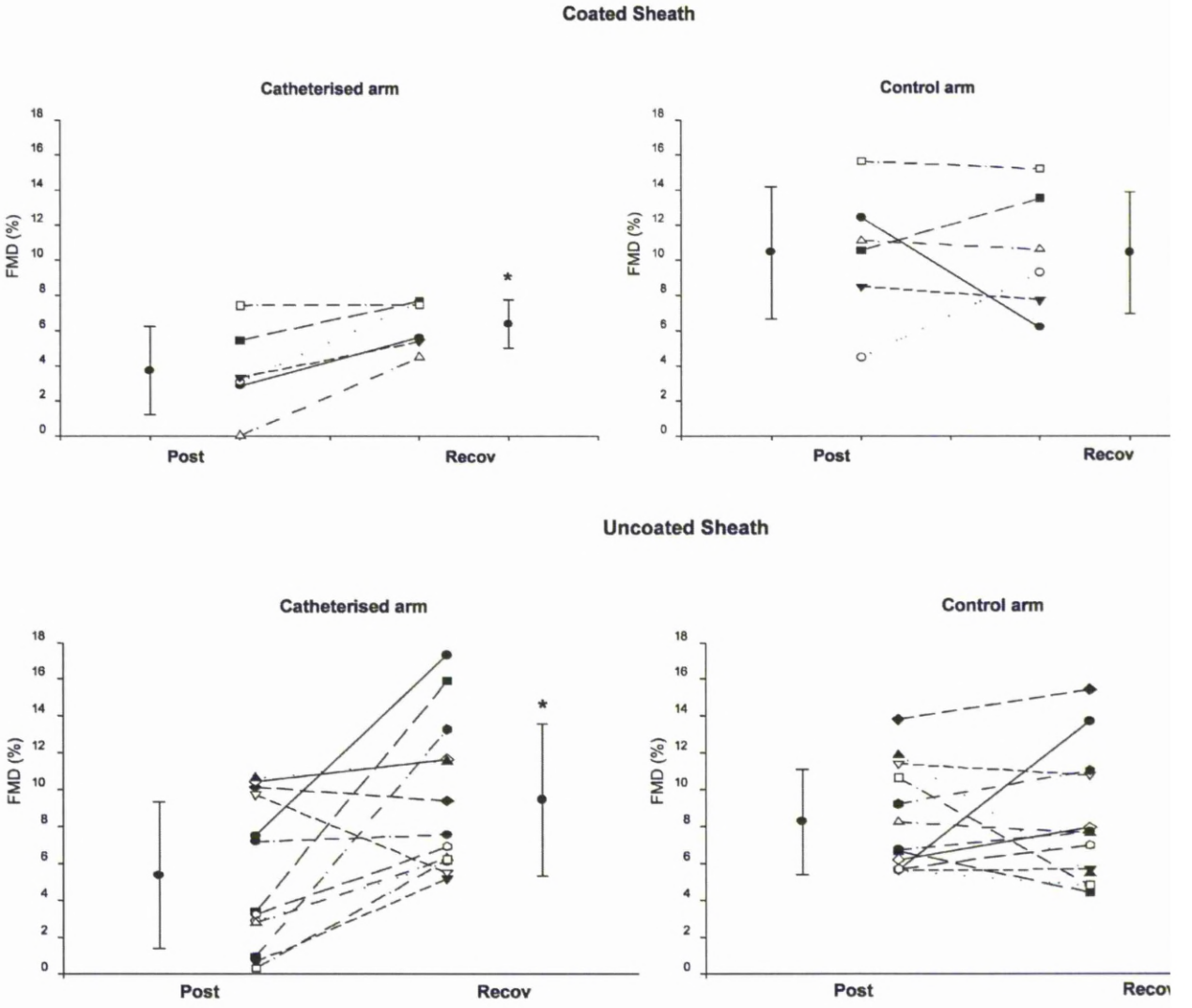
In the subjects who participated in the three month follow up, matched data revealed that FMD decreased non-significantly and then returned towards baseline at three months in the coated sheath group. In the control limb, FMD was similar at all three time points. ANOVA on the post-procedure vs. recovery data comparing time and arm revealed no significant effect of time, a significant effect of arm, but no significant interaction. In the uncoated group, the FMD decreased significantly and returned to baseline at three months. In the contralateral control limb, FMD was similar at all three time points (Table 5.8). ANOVA on the post-procedure vs. recovery data comparing time and arm revealed no significant effect of time, a nearly significant effect of arm and a significant interaction.

Table 5-8 FMD before, after and at follow-up in coated and uncoated sheaths

Sheath type	Arm	"pre"	"post"	"recov"
Coated sheath	**Catheterized arm**	8.3±3.0%	3.7±2.5%	6.4±1.4%
	Control arm	11.5±4.2%	10.5±3.8%	10.4±3.4%
Uncoated sheath	**Catheterized arm**	8.2±2.4%	5.4±4.0%	9.4±4.1%
	Control arm	8.8±2.6%	8.3±2.8%	8.2±3.5%

Figure 5-6 Changes in flow-mediated dilatation from post-procedure to three month follow-up

Top panels are coated sheath and lower panels are uncoated sheath. Data is presented as mean ± SD. * significantly different from post ($p<0.05$)



5.13 The impact of sheath coating on the recovery of non-endothelium-dependent vasodilation

The GTN data in the coated group decreased significantly and then returned to baseline at three months. In the contralateral limb, GTN-mediated function was similar at all three time points. ANOVA on the post-procedure vs. recovery data comparing time and arm revealed no significant effect of time or arm, but a

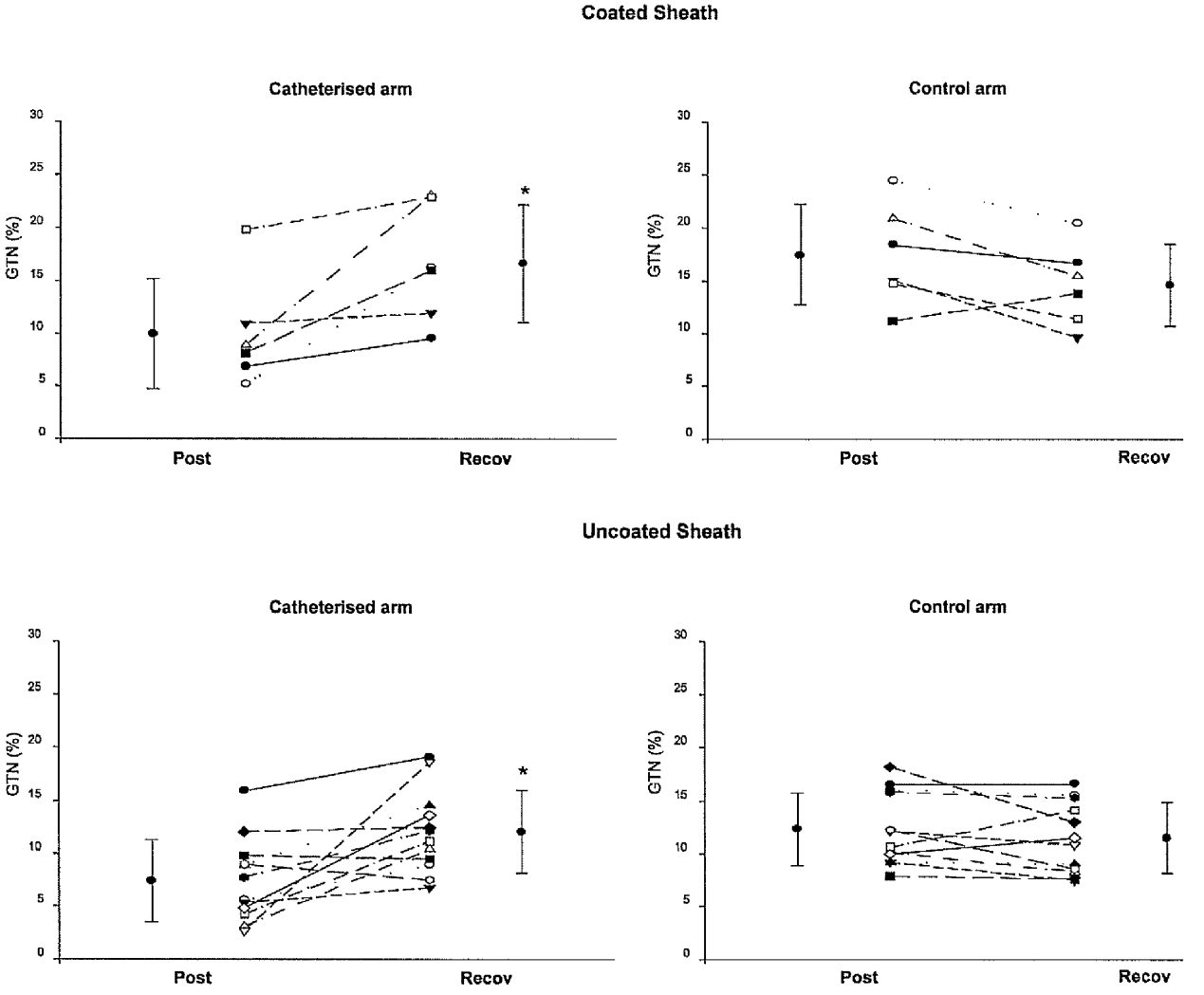
significant interaction between arm and time. In the uncoated group, GTN-mediated dilatation decreased significantly post-procedure and returned towards baseline levels at three months. In the control limb, GTN-mediated function was similar at all three time points (Table 5.9). ANOVA on the post-procedure vs. recovery data comparing time and arm showed a significant effect of time, an almost significant effect of arm and a significant interaction between arm and time (Figure 5.6).

Table 5-9 GTN-mediated vasodilatation before, after and at follow-up in the coated and uncoated sheath groups.

Sheath type	Arm	"pre"	"post"	"recov"
Coated sheath	**Catheterized arm**	17.9±5.7%	10.0±5.2%	16.6±5.6%
	Control arm	15.7±5.6%	17.5±4.8%	14.6±3.9%
Uncoated sheath	**Catheterized arm**	12.5±4.1%	7.4±3.9%	12.1±3.9%
	Control arm	11.9±2.8%	12.3±2.4%	11.5±3.3%

Figure 5-7 Changes in GTN-mediated dilatation from post-procedure to three-month follow-up.

Top panels are coated sheath and lower panels are uncoated sheath. Data is presented as mean ± SD. * significantly different from post ($p<0.05$)



A two-way analysis of variance was used to examine whether recovery of flow-mediated and GTN-mediated dilatation differed in the groups receiving coated and uncoated sheaths. There was no significant difference in the recovery of FMD from the post-procedure study to the follow-up study between the coated and uncoated conditions in the catheterized arm, with a two-way ANOVA

demonstrating a significant effect of time but no interaction of time and coating. There was also no significant difference in the recovery of the GTN-mediated dilatation from the post-procedure study to the follow-up study between the coated and uncoated sheaths in the catheterized arm, with two-way ANOVA demonstrating a significant effect of time but no interaction between time and coating. Baseline arterial diameters, time to peak, and shear rate area under the curve are presented in Table 5.7.

5.14 Hemodynamic measurements during the study

Mean arterial pressure during the study period is shown in Table 5.8. The mean arterial pressure was similar during various stages of flow-mediated dilatation measurement. In contrast the mean arterial pressure was significantly lower following administration of glyceryl trinitrate.

Table 5-10 Mean arterial pressure (MAP) during baseline measurements and post-cuff release or after glyceryl trinitrate (GTN) administration

pre-procedure (pre), the day following the procedure (post) ***and three months follow-up (Recov) in the catheterized (cath) and non-catheterized (No cath) arms.***
*Mean arterial pressure (MAP) was assessed in the contralateral arm. Measurements were taken during the baseline period and one minute after cuff release or three minutes after GTN administration. *significantly different from baseline ($p<0.05$). Data are presented as mmHg (mean ± SD).*

COATED

	Catheter				Control			
	Baseline FMD	**During FMD**	**Baseline GTN**	**During GTN**	**Baseline FMD**	**During FMD**	**Baseline GTN**	**During GTN**
Pre	95±11	95±10	96±10	89±11*	95±9	96±11	94±11	89±12*
Post	97±12	93±8	94±12	91±11	93±10	94±10	90±12	86±10*
Recov	89±11	83±10	83±14	75±9	85±16	81±18	83±12	77±11*

UNCOATED

	Catheter				Control			
	Baseline FMD	**During FMD**	**Baseline GTN**	**During GTN**	**Baseline FMD**	**During FMD**	**Baseline GTN**	**During GTN**
Pre	93±13	94±14	92±14	85±10*	93±14	93±11	93±14	90±11
Post	91±11	88±11	88±12	82±10*	91±16	88±13	88±12	82±12*
Recov	94±15	93±18	94±15	92±15	93±19	99±12	94±18	91±17

5.15 The impact of radial artery to introducer sheath diameter ratio on vascular function

There was significantly greater reduction in flow-mediated dilatation in patients with a radial artery to introducer sheath ratio of less than one compared to patients with a ratio more than one at the distal measurement site (Table 5-11). This was similar at the proximal measurement site (Table 5-12).

Similarly, there was a significantly greater impairment of GTN-mediated vasodilatation in patients with a radial artery to introducer sheath ratio of less than one (Table 5-13 and Table 5-12).

5.16 The impact of hydrophilic coating of the introducer sheath on the vascular function

There was no significant difference in the degree of impairment of flow-mediated dilatation between coated and uncoated introducer sheaths at either the distal or proximal measurement sites. Impairment of GTN-mediated vasodilatation was also similar after coated and uncoated introducer sheaths.

Table 5-11 Flow-mediated dilatation at the distal radial site before and after the procedure

	n	FMD-D pre-procedure (%)	FMD-D post-procedure (%)	p value
Artery:sheath ratio				
<1	10	10.57±3.59	4.49±3.50	
>1	25	8.35±2.83	5.48±3.46	0.01
Coating of the sheath				
Coated	15	10.23±3.68	5.18±3.14	
Uncoated	20	8.05±2.45	5.20±3.74	0.06

Table 5-12 Flow-mediated dilatation (FMD-P) at the proximal radial site before and after the procedure

	n	FMD-P pre-procedure (%)	FMD-P post-procedure (%)	p value
Artery:sheath ratio				
<1	8	10.28±4.00	4.30±1.97	
>1	24	8.16±2.92	5.05±3.75	0.06
Coating of the sheath				
Coated	12	9.46±2.78	6.67±3.29	
Uncoated	20	8.22±3.55	3.78±3.01	0.24

5.17 The impact of length of the introducer sheath on the vascular function

There was no significant difference in the degree of impairment of flow-mediated dilatation between long and short introducer sheaths at either the distal or proximal measurement sites. Impairment of GTN-mediated vasodilatation was also similar with long and short introducer sheaths.

Table 5-13 GTN-mediated vasodilatation before and after the procedure

	n	GTN-mediated dilatation pre-procedure (%)	GTN-mediated dilatation post-procedure (%)	p value
Artery:sheath ratio				
<1	9	20.33±6.71	8.34±5.10	
>1	25	11.16±3.41	8.51±4.00	<0.001
Coating of the sheath				
Coated	15	16.77±6.85	9.56±4.00	
Uncoated	19	11.08±3.86	7.60±4.37	0.10

Chapter 6. Discussion

6.1. Introduction

The benefits of a transradial approach have clearly been documented in numerous studies in the past two decades (2, 101, 103-108, 111, 112,). Access site bleeding complication rates are lower and early ambulation results in a significant reduction in patient morbidity and lower total procedure costs (101, 112). Both patients undergoing the transradial procedure, and the staff caring for these patients, overwhelmingly prefer the transradial approach (120).

As a result of these benefits, there has been a worldwide increase in the use of radial artery for interventional procedures in the past several years. This experience has led to an understanding of the problems and complications that can result from the transradial approach. These complications often cause discomfort to the patient and can result in an inability to complete the intended procedure via the transradial approach. The ramifications of temporary or permanent radial artery injury are important not only in patients undergoing repeat interventional procedures, but also in patients in whom the radial artery may be used as a conduit for coronary artery bypass surgery.

As the transradial approach is evolving, there has been an influx of a variety of equipment including introducer sheaths, radial artery puncture needles, guide wires and guide catheters, manufactured by different commercial companies in the market. This equipment intends to facilitate the procedure by reducing

complications rates and improving procedural success rates. Despite the significant volume of research on the transradial approach in the setting of different clinical syndromes, there is a paucity of data making comparison between different designs of introducer sheath and compression device. Moreover, there is very limited data on vascular injury caused by the transradial approach.

In this study I have investigated the impact of length and coating of the introducer sheath on clinical outcomes and complications in patients undergoing coronary procedures via a transradial approach. I have also studied the effect of two commonly-used haemostatic compression devices. In order to understand the mechanism of the clinical impact of the different types of equipment used, we have studied in greater detail the effect of radial catheterisation on vascular function in a selected subset of patients.

6.2. Study design and sample size

The randomised controlled trial is often seen as the gold standard in study design and it provides the best quality evidence in medical research (144). This trial was an intervention study with different treatment arms. Hydrophilic-coated and uncoated, and long and short introducer sheaths are widely used by physicians during transradial coronary catheterisation with no definite evidence of one being superior to the other. I have used a randomised allocation of the various different introducer sheaths and randomisation was performed in the blocks of eight to keep nearly equal number of patients in each intervention group. An independent

researcher carried out the randomisation procedure and the treating physician was informed of the allocated treatment before the procedure. This helped to reduce any bias on the part of the treating physician. Randomisation is also important in avoiding the effects of known and unknown confounding factors that may affect the results e.g. age, sex, biophysical profile, or clinical condition of the patient. This trial was single-blinded and the patient was unaware of the type of introducer sheath allocated, but the treating physician was necessarily aware of the type of the introducer sheath at the time of the procedure. The physician could not be blinded to the sheath type as the long and short sheaths are obviously different to look and the coated sheaths differ in colour to the uncoated sheaths. Lack of blinding of the physician could potentially induce bias in the reported results; however, both physician-reported and patient-reported end-points were used in the study. I found good correlation between patient-reported discomfort and physician-reported measures of radial artery spasm (Patient-reported discomfort was seen in 63% of the patients with physician reported spasm as compared to only 4.2% in the no spasm group, odds ratio: 19.84; C.I: 13.38-30.67, $p< 0.0001$).

I have used a factorial design to calculate the sample size and the analysis of results. Factorial designs provide an efficient method of evaluating more than one intervention (three interventions in our study) without loss of power. The important requirement of factorial design is that there is no interaction between the different interventions. I found no significant interaction between the length and coating of the introducer sheath.

6.3. Radial artery spasm

6.3.1. Definition of radial artery spasm

Radial artery vasospasm is induced by the introduction of a sheath or catheter into the radial artery and is usually manifest as difficulty in manipulating the catheter and/or the experience of discomfort in the forearm or arm by the patient. This is usually caused by the friction between the outer lining of the arterial sheath and the radial artery wall or pressure due to the overstretching of the arterial wall. Several operator- and patient-specific questionnaires have been developed and used to qualitatively assess radial artery spasm. These questionnaires rate the difficulty perceived by the operator and the discomfort experienced by the patient during the procedure. Some investigators have tried to quantify radial artery spasm using an automated pull-back device (13). They have shown that all patients who experienced clinical radial artery spasm, as assessed subjectively by the difficulty perceived by the operator /or pain perceived by the patient during the procedure, had an mean pull back force of greater than 1 kg-force, while all other patients without a clinical spasm has mean pull back force of less than 1 kg-force. However, this study used a small number of patients. Similarly, Saito et al (21) tested *in vitro* friction resistance as a surrogate for radial artery spasm. They concluded that a hydrophilic coating on the introducer sheath results in significantly less friction resistance. Objective methods of assessing radial artery spasm are cumbersome and impractical in a clinical setting.

We have used a combination of definitions using operator- and patient-completed questionnaires used in previous studies (12, 13, 14) to quantify radial artery spasm both objectively and subjectively. Kiemeneij et al (14), using 6F 23cm long radial sheaths has shown a direct correlation between the patient's assessment of pain during withdrawal of the radial artery sheath and the maximum pull back force using an automated pull back device. We have used the same pain score and considered a pain score of IV and V (severe pain and unbearable pain respectively) as patient-defined radial artery spasm. In a previous study (14) these scores correlate with significant radial artery spasm measured objectively.

We have used a definition of operator-defined radial artery spasm similar to the one used in a previous validation study by Salmeron et al (13). They demonstrated radial artery spasm in 18% of cases using this definition and found a correlation with radial artery diameter response to different spasmolytic agents.

In these studies, we have used outcomes which are clinically relevant and take into account both operator-defined difficulty and patient-experienced discomfort to define the incidence of clinical radial artery spasm. These methods of assessing radial artery spasm are subjective and an important limitation of our study, but we used a standard questionnaire in all patients. We attempted to eliminate difficulty in manipulating catheters experienced during the procedure due to vascular tortuousity and other external or patient related factors to try to get a true assessment of radial artery spasm.

6.3.2. Mechanism of and factors predisposing to radial artery spasm

The radial artery has a prominent medial layer, composed of smooth muscle, which is largely dominated by alpha-1 adrenoreceptor function (61). Thus, increased levels of circulating catecholamines predispose to radial artery spasm. It has also been well established that the vascular endothelium synthesizes and releases potent vaso-active factors that play active roles in vascular biology and pathophysiology. Among the various compounds formed in the endothelium are nitric oxide (NO) and endothelin-1 (ET-1), vasoactive factors that strongly influence the modulation of vascular tone (155). In the intact blood vessel wall, there is continuous basal release of both NO and ET-1, Mechanical forces such as shear stress and the activation of various receptors regulate the release of these vasoactive substances (156). However, the balance between the two antagonistic substances, together with other released factors and the reactivity of smooth muscle cells, play an important role in the determination of vascular tone and various other physiological processes. In the vascular wall, endothelial cells and smooth muscle cells also generate superoxide, which is involved in the pathogenesis of radial artery spasm through its effects on NO scavenging, on peroxynitrite generation, and on redox-sensitive cell-signaling pathways (157). An *in vitro* study by Aksungar et al (158) has shown that basal and thrombin-stimulated release of NO from the internal mammary artery is higher than from the radial artery, while the release of ET-1 from the internal mammary artery is less than from the radial artery. This observation shows the functional difference between the two arterial beds and the higher tendency to spasm in the radial artery in reaction to various stimuli. Similarly, a better understanding of the

contractile properties of radial artery smooth muscle will help address the critical question of radial artery spasm and its pathogenesis. Vascular smooth muscle tone is directly dependent on intracellular calcium concentration, which in turn is largely determined by the regulation of calcium–influx through voltage-gated calcium channels. Potassium and calcium currents also play important roles in regulating the vascular tone. Several factors including stretching and injury to the radial artery following radial artery manipulation could effect ion channel function and subsequently interfere with the vasomotor response. It is known that potassium channel function is intricately regulated by endothelium-released autocoids, including prostaglandin I2, nitric oxide and endothelium-derived hyperpolarising factors (159).

Local anaesthesia and adequate sedation to control anxiety during sheath insertion and catheter manipulation are potentially important preventative measures. Moreover, the friction or pressure caused by the mismatch between the outer diameter of the introducer sheath and the inner diameter of the radial artery could result in radial artery spasm by the various mechanisms discussed above. Therefore, increasing the mismatch between the size of radial artery and the radial sheath could potentially cause more irritation, damage and stimulation of the endothelium and smooth muscle cells. This would result in increased secretion of procoagulant and other vasoactive agents (ET-1 and superoxide radicals) causing radial artery spasm and injury. The length and coating of the introducer sheath could also impact on the occurrence of radial artery spasm. A long sheath, extending into the larger diameter brachial artery, allows insertion, manipulation and withdrawal of multiple catheters, without friction between the moving catheter and the surface of the radial artery. This results in less

mechanical stimulation of the wall and also less irritation and damage to the endothelium and smooth muscle cells, and therefore could be associated with less spasm. However, if spasm develops it could be more difficult to retrieve a longer sheath. Sheaths coated with hydrophilic or lubricious coating may be easier to retrieve in the event of spasm.

There are other factors, such as the radial artery puncture needle and guide wire used to gain access to the radial artery, which can provoke radial artery spasm. To reduce any confounding bias we used introducer sheaths from the same manufacturer (Cook Vascular Inc), thereby keeping all ancillary equipment constant.

Patient-related factors which might play a role in the genesis of radial artery spasm, such as fixed atherosclerotic lesions (160-162), vessel tortuousity, reduced radial artery diameter or erroneous entrance into small side branches.

6.3.3. The incidence of radial artery spasm

The routine use of vasodilator spasmolytic cocktails is widespread and several studies have shown radial artery spasm rates ranging from 10% to 20% (11-14, 16) with the routine use of a vasodilator cocktail during introducer sheath insertion. In the placebo arm (where no vasodilator cocktail was used) of the SPASM study (16) 22.2% of the patients experienced moderate or severe discomfort during a transradial procedure compared to 4.5%-8.3% in the treatment arm. We deliberately avoided the use of vasodilator cocktail, to assess the effects of sheath design on the radial artery spasm without the confounding

influence of vasodilators. In our study radial artery spasm was observed in 29.4% of patients and 21.8% of patients experienced significant discomfort during the procedure, with 10.4% of patients deemed to require treatment with a vasodilator because of spasm. Our results are similar to the placebo arm of the SPASM study. However, three quarters of the patients in the SPASM study underwent a transradial procedure using a 5F introducer sheath and we used a 6F introducer sheath in all patients.

6.3.4. The impact of hydrophilic coating of the introducer sheath on radial artery spasm

There was significantly less clinical radial artery spasm observed in patients receiving a hydrophilic coated sheath. There was significantly less operator-defined radial artery spasm and patient-reported discomfort in patients receiving a hydrophilic coated sheath. This is the largest study to date evaluating the impact of a hydrophilic coating on radial artery spasm. Hydrophilic coating on the introducer sheath reduces the friction force between the radial artery wall and the introducer sheath resulting in less radial artery spasm and patient discomfort. The hydrophilic coating could potentially reduce irritation of the vascular wall and therefore also reduces occurrence of radial artery spasm as compared to uncoated introducer sheaths. This reduction in radial artery spasm is due to the reduced mechanical irritation of the radial artery by the hydrophilic coated sheath. This in turn results in diminished release of vasoactive agents and procoagulants resulting in less radial artery spasm as discussed in the previous section. Previous small studies have shown a similar beneficial effect of a hydrophilic coating on the incidence of radial artery spasm. A study of 90 patients by

Kiemeneij et al (23) showed that there was a significant reduction in the incidence of radial artery spasm with the use of a hydrophilic-coated long (23cm) introducer sheath. These rates of spasm in this study were lower than in our study, which could be due to the routine use of vasodilator cocktail. Saito et al (21) have shown a similar reduction in radial artery spasm with a hydrophilic coated 16 cm long sheath compared to an uncoated sheath of similar length. The main limitation of this study was the small number of subjects (n=30). These two studies showed that a hydrophilic coating was associated with a significant reduction in the friction resistance measured quantitatively during pull-back of the introducer sheath. Recently, Caussin et al (163) have also shown that radial spasm was significantly reduced when using the long hydrophilic coated sheath compared to short sheath (4% vs. 18%) in a series of 351 patients. However, other factors, such as a different patient population, operator experience and material of the introducer sheath could have influenced the results. More recently, Hemetsberger et al (164) evaluated the effect of nitric oxide-coating of introducer sheath on local complications in juvenile porcine femoral arteries of similar size to human radial artery. They reported significantly less spasm, as measured by the femoral artery diameter at the access site, when using the nitric oxide-coated sheaths. They have showed significantly less luminal thrombosis and a reduced intima inflammation score on histopathology after their use. This study demonstrates the beneficial role of NO-coating in causing less complication during trans-arterial manipulation.

6.3.5. The impact of length of the introducer sheath on radial artery spasm

No difference was observed between long and short sheaths in the incidence of radial artery spasm and the patients discomfort level. Before concluding that sheath length has no effect it is necessary to consider the possibility of a type II error (acceptance of null hypothesis when it is false). As well as the absence of a statistically significant difference, a study should be sufficiently powerful to detect a physiologically meaningful difference between the mean control value and the intervention group, based on previous consideration of what constitutes a physiologically meaningful change. This also depends on the incidence of the outcome and, given a 10%-20% incidence of radial artery spasm, to make an intervention worthwhile we judged we would need to reduce the incidence by 50% to be clinically relevant.

The measurements of clinical radial artery spasm and patient discomfort level were adequately powered to detect a difference of 50%. It is therefore unlikely that these results represent a type II error, and it may be concluded that there is no difference, at a level that may be important, in the occurrence of clinical radial artery spasm in the long and short introducer sheath groups.

6.3.6. Predictors of radial artery spasm

We identified younger age, female sex, diabetes mellitus, smaller wrist circumference, low body mass index, and the use of uncoated introducer sheaths as predictors of radial artery spasm in univariate analysis. Younger age, female

sex, diabetes mellitus, smaller wrist circumference, and low body mass index remained significant independent predictors of clinical radial artery spasm in multivariate analysis.

Previous studies, using fewer patients, have also identified younger age (16, 18), and female sex (16, 19), as independent predictors of radial artery spasm. Coppolla et al (18) also identified radial artery size, radial artery size to height ratio, radial artery size to sheath diameter ratio, and radial artery size to body mass index ratio as predictors of radial artery spasm. Our results are similar to these studies and we identified additional predictors of radial artery spasm such as wrist size, diabetes mellitus, and body mass index. However, as for simplicity's sake we did not measure the size of radial artery, we cannot comment on morphometric indices involving measured artery size.

Morphometric indices might reflect mismatch between the radial artery size and the outer diameter of the introducer sheath, resulting in more friction resistance and over-stretching, thereby causing more radial artery spasm and patient discomfort. Younger patients could be more anxious with higher resting sympathetic tone and this could play a role in inducing radial artery spasm. Female patients generally have smaller wrist circumference, and a smaller radial artery diameter and this could predispose them to radial artery spasm. Whether differences in hormone status, pain tolerance or anxiety between men and women will lead to different levels of catecholamine release, resulting in different rates of radial artery spasm is unknown. Similarly, in diabetic patients, there could be a smaller internal diameter of the radial artery due to generalised atherosclerosis

or increased intima-media thickness, which could predispose to radial artery spasm.

6.4. Procedural success and the impact of radial artery spasm

The intended coronary procedure was successfully completed via the ipsilateral radial route in 96% of the patients. The majority of failed cases were successfully completed via the contralateral radial artery but in five cases (0.63%) the procedure was completed via the transfemoral route.

Radial artery spasm was the most common reason (2.1%) for failure to complete the procedure via the intended route (and is therefore important) but the overall failure rate, even in the absence of routine use of a vasodilator cocktail, was very low.

6.4.1. How the results from this study relate to other studies

Other studies have compared the procedural success rates using the transradial and transfemoral approaches in a randomised fashion. In 1997 Kiemeneij et al (101) reported successful coronary cannulation in 93.0% of patients in the transradial group. They reported that the procedure failed because of inability to puncture the radial artery in 4.6% of cases, failure to advance a 6F sheath in the radial artery in 0.7% of cases, and an inability to advance the guide wire towards the ascending aorta in 1.7% of cases. They also mentioned that twenty patients (6.7%) crossed over to a femoral approach and one patient (0.3%) crossed over

to a left radial approach to complete the procedure. This study did not mention the incidence of radial artery spasm resulting in procedural failure, and failure to puncture the radial artery and crossover to a femoral approach was significantly higher than seen in our study. Our results suggest a significant improvement in procedural success compared to this earlier study, which could be related to improved equipment, techniques and accumulating operator experience over the years.

More recently, Agostoni et al (9) performed a meta-analysis to compare the clinical and procedural outcomes of transradial and transfemoral approaches. They reported a higher number of procedural failures with a transradial approach in comparison to a femoral approach (7.2% vs. 2.4%; OR 3.30, 95% CI 1.63 to 6.71; $p < 0.001$). There was significant heterogeneity present in the rate of procedural failure over years. They divided the trials into those completed before and after the year 1999. In more recent trials (after 1999) procedural failure was seen in 3.9% of the patients in the transradial group. This review did not report the reasons for procedural failure and the equipment used and patient population was different, but the recent results are very similar to those seen in our study. Radial arterial anatomic variations could also be a potential cause for procedural complications and failure. Lo et al (165) have reported the influence of radial artery anomalies on transradial coronary procedure outcome. Their reported incidence of radial artery anomaly was 13.8%. Seven percent of patients had a high-bifurcating radial artery origin, 2.3% had a radial loop, 2.0% had extreme radial artery tortuousity and 2.5% had other miscellaneous anomalies such as radial atherosclerosis and accessory branches. Procedural failure was more

common in patients with anomalous anatomy (14.2% vs. 0.9%, $p < 0.001$). Similarly, Norgaz et al (166) have shown anatomic variations in 18.6% of patients and these patients were significantly older, more commonly female, and with significantly higher procedural failure rates (8.8% vs. 5.5%, $p = 0.006$). Anomalous radial artery anatomy could have been the cause of some of the procedural failures in our study, particularly in the eight cases where it was difficult to pass the wire after an apparently successful radial artery puncture. We did not systematically perform radial angiography to ascertain the impact of anatomic variations.

6.4.2. The impact of length and coating of the introducer sheath on procedural success rates

The study failed to demonstrate any statistically-significant difference between the rates of procedural failure in the long versus short sheath groups or the coated versus uncoated sheath groups. The higher incidence of radial artery spasm with the use of an uncoated sheath did not result in higher rates of procedural failure in our study. The procedure could still be completed successfully in the event of radial artery spasm, albeit causing some discomfort to the patients and with more frequent use of an intra-arterial vasodilator cocktail (verapamil and/or glyceryl trinitrate). However, considering the low overall incidence of this outcome, a study would need to have sample size of 2000 patients to detect a 50% reduction with a confidence level of 80%. This study therefore cannot exclude the possibility of a difference (type II error).

6.5. Radial artery occlusion

Radial artery occlusion after a transradial procedure is a major concern, although the immediate consequences of radial artery occlusion are usually benign. The collateral blood supply to the hand effectively prevents significant ischaemia. However, occlusion of the radial artery prevents its use as an arterial conduit for aorto-coronary bypass surgery, as the preferred artery for use in the creation of an arterio-venous fistula for haemodialysis access and as the access route for future percutaneous procedures.

6.5.1. The definition of radial artery occlusion

The radial pulse is frequently present even after occlusion of the artery at or more proximal to the access site. The occluded radial artery distal stump has been found to have up to 70% of mean arterial pressure because of macro-collateral circulation from the palmar arches (167), leading to a palpable pulse. Hence palpation of radial pulse does not prove radial artery patency. A reverse Allen's test and plethysmographic evaluation of palmar circulation has provided a rapidly available and reliable means to detect radial artery occlusion (41, 118). It has shown equivalent diagnostic accuracy in the diagnosis of radial artery occlusion, with extremely high correlation with duplex Doppler ultrasonography (41). Doppler ultrasound is not easily available and is time-consuming in the clinical setting. Therefore, we have developed a clinical algorithm to detect radial artery patency which could be performed quickly and cheaply. We used the reverse Allen's test to assess radial artery patency in all patients, confirmed in equivocal cases by plethysmography and oximetery or Doppler ultrasound. This

could have potentially led to an underestimate of the actual incidence of radial artery occlusion as the gold standard is Doppler ultrasound. However, there are no established criteria for radial artery occlusion and most of the historical data comes from coronary graft assessment studies. Kamienski and Barnes (168) have shown that arterial obstruction results in distal arterial velocity signals which are attenuated with a resultant decrease in the systolic component and loss of normal diastolic sounds. Using these abnormal criteria of Doppler ultrasonography, the reverse Allen's showed complete concordance with the findings obtained by Doppler ultrasonography.

6.5.2. The mechanisms of radial artery occlusion

The Virchow's triad (146) for thrombogenesis postulate that three features predispose to thrombus formation: abnormalities in blood flow, abnormalities of the vessel wall and abnormal blood constituents. 'Abnormal blood flow' is evident in patients undergoing transradial procedures by various mechanisms. Firstly, mismatch between the introducer sheath size and the radial artery diameter can result in stagnation of blood flow through the radial artery during the procedure and this can predispose to thrombus formation. Secondly, non-thrombotic occlusion secondary to severe prolonged spasm or dissection of radial artery could predispose to thrombus formation. Similarly, abnormalities of the vessel wall secondary to damage to the endothelium could initiate the cascade of thrombus formation resulting in radial artery occlusion. This could also be contributed to by compression devices used to achieve haemostasis after the procedure. In a classical Virchow's triad, vascular damage has been considered to be of prime importance in arterial thrombosis (169). Mechanical trauma

induced by a transradial sheath might lead to dysfunction of endothelium and consequently to the loss of its antithrombotic properties and represent a trigger to thrombus deposition. A pathogenic role of endothelial dysfunction has been shown for arterial thrombosis (170).

The endothelium, a thin monolayer of cells covering the inside of both arteries and veins, has emerged as one of the pivotal regulators of haemostasis through its ability to express anticoagulant and vasodilatory molecules in healthy conditions, and, in diseased conditions, to release vasoconstrictors and to express procoagulant and cell adhesion molecules and cytokines. Under normal conditions endothelial cells exert a vasodilatory, antiplatelet and local fibrinolytic tone that prevents platelet adhesion, leukocyte attachment, as well as blood coagulation. A non-thrombogenic endothelial surface is maintained through a number of mechanisms, including the production of thrombomodulin (TM), an activator of anticoagulant protein C, the expression of heparin and dermatan sulphate, which accelerate the thrombin-inhibitory activity of antithrombin III and of heparin cofactor II, the constitutive expression of tissue factor pathway inhibitor (TFPI), an inhibitor of tissue factor, and the local production of tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), the main effectors of physiological fibrinolysis. Crucial to many of the antithrombotic activities of endothelium are the synthesis of prostacyclin (PGI 2) and nitric oxide (NO).

Nitric oxide is a powerful vasodilatory agent, but also has strong anti-aggregatory effects on platelets, is an inhibitor of leukocyte adhesion and

activation and a suppressor of smooth muscle cell proliferation (171). Prostacyclin is a vasodilator, an inhibitor of platelet activation and a suppressor of leukocyte adhesion and activation (171). Noxious stimuli, either physical (trauma by sheath) or functional (stasis of blood), provoking a disturbance of the endothelial monolayer, turn the endothelium into a prothrombotic and proinflammatory surface favouring platelet and leukocyte deposition, local blood clotting activation and smooth muscle cell proliferation. In particular, upon activation, endothelial cells respond with an increased surface expression of cell adhesion molecules (such as P- or E-selectin, ICAM-1 or VCAM-1) that promote the adhesion and activation of leukocytes, an event that initiates and amplifies inflammation and contribute to thrombosis. Activated leukocytes, in particular monocytes, express tissue factor (TF), a strong trigger of blood clotting. Endothelial dysfunction has been conclusively shown to be an early event in the progression of thrombosis and smooth muscle proliferation (170, 172). In the context of arterial thrombosis, endothelial dysfunction, and in particular a reduction of the biosynthesis or the biologic activity of NO, has been identified as fundamental component of the pathophysiology of atherothrombotic complications and shown to be associated with risk factors such as diabetes, hypercholesterolemia, smoking and hypertension (170, 172). Endothelial dysfunction is associated with increased oxidative stress and with inflammatory changes that play a role in the development of intimal thickening in the early stages, while later they increase the vulnerability of thrombosis (172).

Transradial procedures result in endothelial dysfunction as a result of mechanical injury to the intimal lining of radial artery, stasis of blood during the procedure

and during achieving haemostasis, resulting in triggering of the thrombotic cascade as described. In Virchow's triad of the twenty-first century, endothelial dysfunction emerges as the most important component of thrombosis.

6.5.3. The incidence of radial artery occlusion

Clinical evidence of radial artery occlusion was seen in 9.2% of patients at the time of discharge from hospital in our study. However, none of these patients reported any symptoms of vascular compromise or functional impairment of the hand. Similar early radial artery occlusion rates are reported in other studies ranging from 5% to 9% (28, 35). We have found no difference in the incidence of radial artery occlusion between long and short introducer sheaths and between coated and uncoated sheaths. There is a paucity of data available relating to this effect in literature.

6.5.4. Predictors of radial artery occlusion

We have identified younger age, female sex, occurrence of radial artery spasm, failure to use heparin during the procedure, smaller wrist size, and shorter height as predictor of radial artery occlusion in univariate analysis. The type of introducer sheath, compression device, procedure time, and the time taken to achieve haemostasis had no impact on the incidence of radial artery occlusion.

Several variables have previously been shown to influence the incidence of radial artery occlusion. Catheter size has been shown to be an important predictor of

post-procedure radial artery occlusion. Saito et al (29) have shown that the incidence of occlusion was 4% in patients with a radial artery internal diameter to introducer sheath outer diameter ratio of greater than one, compared to 13% in those with the ratio of less than one. We did not measure the radial artery diameter in our study population but did find several morphometeric factors like wrist size, shorter height, and female sex as predictors of radial artery occlusion. These factors potentially reflect smaller radial artery size and the introducer sheath outer diameter (2.4 mm) were fixed in our study population.

When the radial artery is used for haemodynamic monitoring in critically ill patients, the incidence of radial artery occlusion is significantly higher in patients with cannulation duration of more than 24 hours, compared to those with one of less than 24 hours (31, 32, and 33). Catheters and the introducer sheaths are usually removed immediately after cardiac catheterisation and interventional coronary procedures. However, prolonged post-procedure compression force and duration may play an important role in the pathogenesis of radial artery occlusion. We will discuss this effect in future sections.

6.5.5. The impact of radial artery spasm on radial artery occlusion

This is the first study to demonstrate that there was a higher incidence of early radial artery occlusion in patients experiencing radial artery spasm during the procedure. The risk of radial artery occlusion in those experiencing spasm was 14.3% (33/230), compared to 5.2% (40/560) in those not experiencing spasm. Nearly half of patients experiencing radial artery spasm demonstrated radial

artery occlusion at the time of discharge from the hospital. There are several potential mechanisms predisposing to this association; firstly, spasm could cause endothelial trauma leading to a thrombogenic surface; secondly, spasm of a section of the artery could lead to stasis in the rest of the artery and thereby predispose to thrombosis; thirdly, a reduced diameter due to spasm will cause an increase in blood flow velocity and shear strain, resulting in increased platelet activation; fourthly, traction on a introducer sheath in a spastic radial artery can lead to transection or avulsion of the artery resulting in radial artery discontinuity. This suggests that measures taken to avoid spasm should have beneficial effect on subsequent occlusion rates.

Endothelial dysfunction is a predisposing factor for both vasospasm and thrombus generation. In addition to regulating vascular tone and blood pressure, vascular endothelium has antithrombotic properties and modulates interaction between the blood vessel wall, circulating leukocytes, and platelets. Nitric oxide is a powerful antithrombotic molecule and vasodilator produced by endothelial nitric oxide synthase (e-NOS) through L- arginine (173, 174, 175). Endothelial dysfunction contributes significantly to vasospasm and thrombosis (176, 177, 178). In addition to e-NOS, L-arginine is also a substrate of arginase, the final enzyme of the hepatic urea cycle hydrolyzing L-arginine to urea and L-ornithine (179, 180). This cycle could potentially be a therapeutic target for preventing vasospasm and thrombosis. Using acetylcholine-stimulated endothelium-dependent relaxation (EDR), initial studies in several animal models revealed that acute arterial thrombosis causes endothelial dysfunction. Lack of blood flow (ischaemia) alone without intraluminal thrombus did not affect EDR. Nitric

oxide levels are decreased accordingly, and L-arginine administration restored EDR, suggesting normal e-NOS function and that impaired L-arginine availability underlies arterial thrombosis-induced endothelial dysfunction (181, 182, 175). It has been shown in these studies that thrombin plays a central role in thrombus-induced endothelial dysfunction. They have also investigated the molecular mechanisms of arginase changes after thrombin exposure. Thrombin is a coagulation system protease present at the sites of vascular injury (caused by radial sheath manipulation and compressive device application in our study). In addition to catalyzing the conversion of soluble fibrinogen into an insoluble fibrin clot, thrombin is a potent endothelial cell function agonist inducing several genes in endothelial cells (183, 184). Endothelial cells are the first cells in an artery to encounter circulating thrombin, one of the key stimuli leading to the activation of multiple signalling pathways. Zhu et al (185) have shown in the exposure to rat aortic endothelial cells and provided with the evidence supporting a key role for the transcription factor activating protein-1 in mediating endothelial arginase, an enzyme that can modulate L- arginine levels. Their findings highlight the arginase pathway as a potential therapeutic target in limiting endothelial dysfunction and thereby vasospasm and thrombosis.

6.5.6. Anti-thrombotic therapy and radial artery occlusion

Antithrombotic therapy has been found to influence radial artery occlusion (34, 28). Patients undergoing interventional procedures are routinely given systemic antithrombotic therapy, but this is not universal in patients undergoing diagnostic angiography. The incidence of radial occlusion can be as high as 30% in patients receiving only 1000 units of heparin during diagnostic catheterisation (34). The

incidence of radial occlusion is reduced significantly by administering at least 5000 units of heparin during the procedure (34, 28). The importance of treatment with heparin during the procedure is further confirmed in our study. In our study weight-adjusted heparin was used in all interventional cases, while the use of heparin was left to the operator's discretion in diagnostic catheterisation cases. A total of 61(7.7%) patients in our study did not receive any heparin during the procedure and radial artery occlusion was seen in 20 patients (32%), a similar rate to that reported in the literature.

Heparin is a sulfated polysaccharide with a molecular weight range of 3000 to 30000 Da (mean 15000 Da). It produces its major anticoagulant effect by inactivating thrombin and activated factor X (factor Xa) through an antithrombin (AT) -dependent mechanism (186). Heparin binds to AT through a high-affinity pentasaccharide, which is present on about a third of heparin molecules. For inhibition of thrombin, heparin must bind to both the coagulation enzyme and AT, whereas binding to the enzyme is not required for inhibition of factor Xa. By inactivating thrombin, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of platelets and of factors V and VIII. The anticoagulant response to heparin varies among patients. It is standard practice to adjust the dose of heparin and monitor its effect by measurement of the activated thromboplastin time (APTT) or, when very high doses are used, by the activated clotting time (ACT). Similarly, low molecular weight heparin (LMWH) is derived from heparin by chemical or enzymatic depolymerisation to yield fragments approximately one third the size of heparin. LMWH's have a mean molecular weight of 4500 to 5000 Da with the distribution of 1000 to 10000 Da.

All the anticoagulant, pharmacokinetic, and other biological differences between unfractionated heparin and LMWH can be explained by the relatively lower binding properties of LMWH.

The use of a weight-adjusted dosage of heparin has shown a significant reduction in radial artery occlusion rates as discussed above. More recently, investigators have investigated low molecular weight heparin and bivalirudin (a direct thrombin inhibitor) to assess their impact on radial artery occlusion rates following transradial procedures. Bertrand et al (187) have compared bivalirudin (bolus 0.75mg/kg, infusion 1.75mg/kg/h) and standard heparin (70units/kg) during transradial procedures. In a study involving 400 patients they have reported radial artery occlusion rates of 5.3% at 4-8 weeks with no significant difference between the two groups (3.5% bivalirudin vs. 7.0% heparin, p= 0.18). The incidence of radial artery occlusion in our study is 7.2% early post-procedure and 5.7% late (at 4-6 months post procedure) with the use of weight-adjusted unfractionated heparin and this is similar to Bertrand's study. Pancholy (188) has compared the outcomes following intravenous or intra-arterial administration of unfractionated heparin in 500 patients. Early radial artery occlusion was seen in 5.5% of the intravenous group and 6% of the intra-arterial group. They have concluded that intra-arterial and intravenous heparin administration provide comparable efficacy in preventing radial artery occlusion, suggesting a systemically mediated mechanism of action, rather than a local effect. We used heparin directly into the aorta in our study to avoid the local irritant effect of administration directly into the radial artery.

There have been some attempts recently to treat radial artery occlusion seen following transradial procedures. Zanki et al (189), has assessed the effect of therapeutic low molecular weight heparin for four weeks in patients with documented radial artery occlusion following transradial procedures. They reported radial artery thrombosis in 10.5% of patients one day after procedure. After four weeks 86.7% of affected patients showed partial or complete recanalization of the radial artery after treatment with low molecular weight heparin. Bernat et al (190) have evaluated the efficacy and safety of transient ipsilateral ulnar artery compression to achieve acute radial artery recanalization. Radial artery patency was assessed by duplex ultrasonography three to four hours after haemostasis, and, in patients with occluded arteries, immediate ulnar artery compression was applied for one hour. After ulnar artery compression, the final incidence of radial artery occlusion was reduced to 4.1% from 5.9% in the 2,000-IU Heparin group and 0.8% from 2.9% in the 5,000-IU Heparin group (p=0.03). Therefore, all patients should receive weight-adjusted heparin to reduce the incidence of radial artery occlusion following transradial procedures and pharmacological and non pharmacological measures can be applied to the select group of patients with documented radial artery occlusion.

6.6. Ulno-palmar collateral circulation

The original recommendation by Kiemeneij (2) was that a transradial procedure should only be performed in patients with a documented patent ulnar artery and palmar arch. This has traditionally been evaluated using the Allen's test, but

Doppler ultrasound and plethysmography prior to the procedure are more accurate methods (27).

6.6.1. Allen's test

In the original description of his test used for examining patients with thromboangitis obliterans,(121) Allen did not define the test results as positive or negative, nor did he give a time limit for the appearance and maximal blushing. Obviously, time to maximal blushing becomes more difficult to judge when it occurs over a longer period. Also, pallor, inadequate patient cooperation, patient unconsciousness, overextension of the wrist, or contralateral ulnar compression by skin stretching adds to the difficulty and subjectivity of this test.

In the available literature, the upper limit of the time taken for blushing to occur during Allen's test suggested as acceptable before radial artery cannulation, varied from five to 15 seconds. With various upper limits for Allen's test, absence or inadequate hand collaterals during radial artery compression varied between 1% and 27% (1, 31, 32, and 45). In our study 79.8 % of patients had blushing within 10 seconds, 89.9% with 20 seconds, and in 11% it took more than 20 seconds or did not occur at all. These values are consistent with what is reported in the literature.

6.6.2. Plethysmography and oximetry test

Plethysmography and oximetry tests were recorded with a pulse oximeter as previously described. Barbeau et al (27) have shown that that a finding of PL&OX type A, B, or C on either side was more frequent and would exclude

fewer patients from eligibility for a transradial procedure than an Allen's test, while being a more objective test to assess ulno-palmar collateral circulation. In this study of 1000 patients a type A, B, or C pattern, which was considered indicative of adequate collateral circulation, was seen in 95% of the patients. Similar results are shown in our study, a type A or B pattern was seen in 90.7%, a type A, B, or C pattern was seen in 93%, and a type D or inadequate pattern was seen in 7% of patients.

6.6.3. Comparison of the Allen's test and the plethysmography and oximetry test

In our study, we have identified more patients with the use of PL&OX test than with the Allen's test as fulfilling the criteria for adequate collateral supply. Two thirds (65%) of the patients with an unfavourable Allen's test (more than10s) showed a PL&OX type A, B, or C, suggesting adequate collateral supply. All patients showing a favourable Allen's test (less than 10s) showed PL&OX type A, B, or C. Similar results were shown by Barbeau et al (27).

6.6.4. The relation between ulno-palmar circulation adequacy and ischaemic complications

No study to date has demonstrated a relationship between the time to maximal blushing using the Allen's test and ischaemic symptoms or complications in the hand, although Greenwood et al (47) reported that among patients with an abnormal Allen's test, occlusion of the radial artery results in an immediate reduction in blood flow to the principal artery of the thumb as measured by

lactate levels. The Allen's test has nevertheless been advocated to avoid acute and long-term ischaemia of the hand in cases of radial artery occlusion.

The radial artery approach has been widespread and is used at hundreds of cardiac centres. Many centres have abandoned the use of the Allen's test, though there is no published data to support this relaxed approach. Therefore, it is important not to deny this access site to patients with an abnormal Allen's test and a more objective test (PL&OX) should be performed. This is even more important in patients in whom a femoral procedure carries increased risk. We assessed ulno-palmar circulation in all patients before the procedure, but this was not used to deny the patients a radial approach. None of our patients with apparently-inadequate collaterals suffered ischaemic complications after radial artery cannulation.

6.7. Access site complications

The most important benefit of transradial procedures is the virtual elimination of significant access site bleeding complications (9, 110-113,). The radial artery puncture site is located over bone and can easily be compressed with minimal pressure. Thus, significant bleeding from the radial access site can virtually always be prevented. Although manual pressure from an experienced operator is the ideal method to achieve haemostasis, several compression devices have been developed in an attempt to maximize operator and staff efficiency. Local haematomas may occur as a result of improper device application or device failure. It should be emphasized that compression of the radial artery both

proximal and distal to the puncture site must be performed because of retrograde flow from the palmar arch collaterals.

Bleeding after a transradial approach may occur from a site in the radial artery remote to the access site. The most common cause is perforation of a small side branch by the guide wire. Avulsion of a small radial recurrent artery arising from a radial loop is another important cause of remote bleeding (113,114). Hydrophilic guide wires preferentially select this small arterial remnant in patients with a radial loop and forceful advancement of the guide catheter can result in avulsion of the vessel. Radial artery perforation has been described in about 1% of patients. One should have a low threshold to perform a radial artery angiogram when any resistance to guide wire or catheter insertion is encountered to prevent this complication. Remote access site bleeding should be recognised early and pressure should be applied at remote site with the help of compressive bandage. A blood pressure sphygmomanometer may also be utilized.

Very rarely, compartment syndrome can develop due to radial artery haemorrhage (147). A large haematoma causes hand ischaemia due to pressure-induced occlusion of both the radial and ulnar arteries. Fasciotomy with haematoma evacuation must be performed as an emergency procedure to prevent chronic ischaemic injury.

6.7.1. Results from our study

A large local haematoma of more than 2cm diameter was seen in 17 patients (2.2%) and a small haematoma was seen in 5.4% of patients. Radial, brachial, or subclavian artery dissection was seen in one patient each (0.4%). All these complications were managed conservatively by compression bandage where necessary and observation, and none of these patients needed surgery or blood transfusion or suffered long term sequelae. However, superficial ecchymosis and oozing was frequently encountered and was seen in 17% patients, with no sequelae. Agostoni et al (9) has reported a 0.3% incidence of major bleeding complications needing blood transfusion or surgical intervention in a meta-analysis involving 1472 patients. Similarly, Keimeneij et al (14) has reported no major entry-site complications in a series of 300 patients.

Large local haematomas have been reported in literature and are frequently due to injury or perforation of the radial artery or its branches. We have not observed any difference in vascular complications between long and short introducer sheaths. However, large local haematomas were more frequent in patients receiving an uncoated introducer sheath. This could be related to excess radial artery spasm or friction in this group, thereby increased movement of the artery during sheath manipulation, avulsing small branches.

6.8. Late access site vascular complications

Permanent radial artery injury presenting late after discharge from hospital, with or without occlusion, may occur following transradial coronary procedures in

some patients. Spontaneous recanalization is reported in 40% to 60% of patients with radial artery occlusion by clinical evaluation and colour Doppler measurement respectively (27, 34). Late radial artery occlusion was seen in three to five per cent of patients at follow-up of one to three months in these studies. We have evaluated late vascular site-related complications in 625(79.1%) of our patients at the time of routine follow-up at four to six months. Persistent radial artery occlusion was observed in 43 (6.9%) patients with no evidence of vascular compromise or functional impairment of the hand. These results are similar to those reported in the literature. However, we have used a clinical evaluation of radial artery patency and Doppler ultrasound was not systematically used. This could potentially underestimate the true incidence in our study as Doppler ultrasound is the gold standard to identify radial artery occlusion.

6.8.1. Late access site inflammatory reactions

There have been reports of late sterile abscesses or allergic reactions at the site of introducer sheath insertion (62, 116). This complication has been reported in 1.6% of patients who had catheterisation via the transradial approach (62). In this study radial access site reactions occurred in 2.8% of patients in whom a hydrophilic coated sheath was used (and no patients in whom uncoated sheaths were used). The hydrophilic coating is believed to facilitate passage of the sheath, perhaps with the shedding of the coating at the time of sheath retrieval or insertion resulting in this complication. The inflammatory lesion is usually noted two to three weeks after the procedure with a relapsing and remitting clinical course. Cultures are reported as sterile in most patients, and biopsy specimens

show the presence of an amorphous material compatible with the sheath coating. The exact pathogenesis is unknown but it is particularly seen with one brand of gel-coated hydrophilic sheaths, suggesting a coating-specific reaction.

We have used similar introducer sheaths from the same manufacturer with or without coating in our study. We have found patient-reported late swelling or abscess at the radial artery puncture site in 21 patients (3.4%) in the entire cohort. The majority of these are associated with the use of hydrophilic coated introducer sheaths. The results of our study are similar to other reported studies and further confirm the causal relationship between the hydrophilic coating of the introducer sheath and the incidence of this complication.

These sterile abscesses cause discomfort to the patient and in some patients unneeded surgical incision and drainage is carried out. From the evidence accumulated so far, management of individual patients with this type of reaction should be conservative with local wound care and drainage if abscess formation is present. The manufacturer has now changed the materials used to make the coating and the impact of this needs to be tested.

6.9. Assessment of haemostatic compression devices

There are a number of devices that have been developed in last two decades to obtain haemostasis after transradial catheterisation. Earlier, tourniquet-related devices were used because of their simplicity and easy availability. However, marked venous congestion and compression of the ulnar artery could occur with

this method and could be the cause of patient discomfort and additional complications. To avoid this problem several devices have been developed to provide selective compression of the radial artery. The TR band and the Radistop compression devices are the commonest devices used to achieve haemostasis after transradial procedures.

6.9.1. Potential advantages of TR Band and Radistop

The TR band selectively provides compression of the radial artery and the transparent band allows visualisation of the puncture site during the post-procedure period. The pressure in the compression pad can be controlled by releasing air from or adding air to the pad. Moreover, this device does not limit the wrist movement, which could reduce discomfort and improve mobility of the patient.

The Radistop also provides selective compression of the radial artery puncture site with no effect on the ulnar artery flow and the venous circulation. The use of this device involves immobilisation of the wrist until haemostasis is achieved.

6.9.2. Comparison of the time taken to achieve haemostasis by TR Band and Radistop

Both the TR band and Radistop provide effective haemostasis following transradial procedures and the devices are removed over a period of time. The aim of these devices is to secure haemostasis and remove the device as soon as possible to reduce local discomfort and vascular complications. This is the first

study comparing the time taken to achieve haemostasis with two different devices allocated in a randomised fashion. The time taken to achieve haemostasis could be dependent on several variables such as baseline patient-related factors, procedure-related factors, the use of anticoagulants, procedure duration, and device-related factors. Baseline characteristics, including risk factors, wrist size and other morphometeric factors, were similar in both device groups. Procedural characteristics such as procedure time, coronary procedures performed, number of catheters used, type of introducer sheath used, and heparin use was well balanced between both groups. To control for device-related factors we have used similar protocols (Appendix 3 and 4) for the application and removal of the devices after a transradial procedure.

In our study we have observed that the time taken to achieve haemostasis was significantly longer with the TR Band compared to the Radistop. However haemostasis was achieved successfully in all patients. There is limited literature regarding compression devices used and the time taken to achieve haemostasis in contemporary settings. Chatelain et al (38) have described the initial use of the Radistop device and reported a compression time ranging from two to four hours with this device. However, the majority of the procedures were performed using a 5F introducer sheath and were diagnostic coronary angiography. The time taken to achieve haemostasis is longer in our study and could be explained by the use of 6F introducer sheaths in all patients, with more than 90% patients undergoing coronary intervention procedure with a high rate of use of heparin.

6.9.3. Comparison of patient tolerance of the TR Band and Radistop devices

The other important factors in deciding on the type of compression device to use is patient tolerance. A compression device could cause patient discomfort as mechanical pressure is needed to achieve haemostasis. This pressure can vary from patient to patient. In our study population more patients complained of moderate or severe discomfort with the Radistop compared to the TR Band and three patients initially treated with a Radistop crossed over to a TR Band because of severe discomfort. In the initial clinical evaluation of the Radistop (38) the authors reported that 18% of patients reported the device as uncomfortable or painful, but in no patient was it necessary to interrupt compression for that reason.

This could potentially influence the decision of choosing one or the other haemostatic device in an individual patient. The high success rate with both devices is reassuring and the patient tolerance should be considered in making this decision.

6.9.4. Comparison of access site-related complications with the use of the TR Band and Radistop devices

The main advantage of the transradial approach is to reduce access site-related complications. Local access site-related bleeding complications, patency of the radial artery and other complications could be influenced by the type of compression device used following transradial procedure. Other factors such as the size of the introducer sheath, the dose of heparin used and adjuvant treatment could also influence this outcome. Chatelain et al (38) have reported that 15% of

patients developed a small or large local haematoma after the use of Radistop, and no specific treatment was required. In our study 5.4% of patients developed a small haematoma and 2.2% patients developed a large haematoma with all being managed conservatively. These results are a significant improvement over the early description in the above mentioned study. There was no difference seen in the local complications between the TR Band and the Radistop groups. There were no serious bleeding complications needing blood transfusions or surgical intervention, and no deaths as a result of bleeding complications. More recently Bernat et al (190) has evaluated the incidence of haematomas larger than 15cm with very low dose (2000 IU) or low dose (5000 IU) heparin following a transradial procedure and using the TR band as a haemostatic compression device. The incidence of local haematoma was 2.3% and 3.7% in the 2000 and 5000 IU groups respectively (p=0.42).

Radial artery occlusion is an important complication of transradial catheterisation and the haemostatic device could contribute to the risk of this. Radial artery occlusion after transradial approach appears to be a complex interplay of processes such as local trauma and compression post-procedure. Radial artery compression is required to achieve haemostasis and this could potentially initiate the process of thrombus formation by interrupting forward blood flow in the radial artery.

Some studies (41, 118) have shown that occlusive compression of the radial artery is a predictor of subsequent radial artery occlusion. Pancholy et al (118) showed that a guided haemostasis strategy, with careful prevention of

interruption of radial artery flow during haemostatic compression, is highly effective in decreasing radial artery occlusion after transradial catheterisation (5% vs. 12%). There has been an accumulation of data supporting the "patent haemostasis" approach. Only enough compression should be applied to achieve haemostasis and at the same time forward flow in the radial artery should be preserved. We have applied patent haemostasis concepts in our study population and early radial artery occlusion was seen in 9.2% of cases with no difference observed between the TR Band and Radistop group. Our radial artery occlusion rates are slightly higher than described in the above study by Pancholy et al (118). This could be related to the use of 4F introducer sheath in Pancholy's study and a 6F sheath in our study.

The overall access site bleeding complications in our study are similar to that reported in other studies with conventional pressure haemostasis as compared to patent haemostasis in our study. As no increase in bleeding complications was noted in our population, there appears to be no drawback of a lower pressure haemostasis and maintaining forward flow in the radial artery as opposed to the poorly tolerated higher pressure approach used conventionally. Another important factor is that the haemostatic device should be progressively loosened over time, increasing the likelihood of non-occlusive radial artery compression. Haemostatic devices allowing application of measured pressure adjusted to a value less than patient's systolic blood pressure that provides local haemostasis may be ideal. Frequent access site evaluation (every 30 minutes in our study) and application of the shortest duration of compression needed to achieve

haemostasis may also be of help in reducing the occurrence of radial artery occlusion.

6.10. The impact of the introducer sheath on vascular function following transradial procedures

6.10.1. Introduction

Studies have demonstrated that permanent radial artery injury without occlusion may occur following transradial coronary procedures. The mean radial artery diameter, as measured by ultrasound, was smaller in patients undergoing repeat transradial interventional procedures compared to that measured before the initial procedure (30). This smaller diameter was not present on the day following the procedure, but developed during a mean follow up of 4.5 months. Wakeyama et al (36) have demonstrated with intravascular ultrasound that this progressive narrowing is due to intimal hyperplasia, presumably induced by trauma from the cannulation, sheath or catheter. The degree and incidence of significant intimal injury in patients undergoing transradial procedures is yet to be determined.

It is possible that insertion of the introducer catheter sheath has a direct physical impact on the endothelial lining of the vessel wall, a squamous monolayer which is easily damaged as a consequence of mechanical disruption. Removal of or damage to the endothelial lining has been shown in animals to impair endothelium-dependent arterial relaxation by decreasing nitric oxide bioavailability. They may also promote intimal hyperplasia, thrombus formation and the development of atherosclerotic plaques (122, 123). This could have implications for the use of the artery as a donor graft for coronary artery bypass

surgery, as graft longevity is, in part, related to the capacity to remodel and dilate in response to changes in metabolic demand and blood flow. Several studies have observed immediate and long term trauma in the radial artery following transradial coronary angiography; transradial catheterisation can lead to tissue necrosis and adventitial inflammation (124) and has been shown to cause intimal hyperplasia and reduce early graft patency (35, 48, 124), with reductions in radial artery diameter noted as late as 12 months after catheterisation (35, 36,).

Several variables in the design of introducer sheaths, including the hydrophilic coating and the length of the sheath, could impact on arterial dysfunction, damage or occlusion.

6.10.2. Flow-mediated dilatation and its measurement techniques

The endothelium regulates vascular haemostasis through the release of a variety of autocrine and paracrine substances, such as nitric oxide, prostacyclin, and the endothelium-derived hyperpolarising factors (74). Beyond its vasodilator effects, nitric oxide has anti-atherogenic properties, inhibits platelet aggregation and adhesion, smooth muscle proliferation, leucocyte adhesion, vascular permeability, and inflammatory mechanisms (74). Flow-mediated dilatation is an *in vivo* bioassay of largely NO-mediated endothelial function (84, 125). It was demonstrated by Celermejer and colleagues (85) that using cuff occlusion, endothelial function could be tested by inducing arterial shear stress. Several studies since then have shown that human conduit arteries dilation response to increased blood flow (83, 85), that in animals this response is dependent on an

intact endothelium (88) and that shear-sensitive ion channels exist in endothelial cells (90). Joannides and colleagues (90) showed for the first time that an L-N Monomethyl-Arginine (L- NMMA) infusion blocks nitric oxide production after cuff inflation and abolishes flow-mediated dilatation, thus providing strong evidence that flow-mediated dilatation is an endothelium-dependent process, mediated by nitric oxide.

Doshi et al (91) and Mullen et al (92) have shown the importance of placement of the cuff distal to the measurement site and that this provides a true reflection of nitric oxide mediated dilatation. An important collaborative guideline was published in 2002 aimed at standardizing approaches for measurement of flow-mediated dilatation (97). In keeping with this literature and guidelines, we assessed FMD at various sites at the forearm by placing the cuff at the level of the wrist and measurements of the radial artery were performed proximal to the cuff following five minutes of ischaemia.

6.10.3. Analysis of radial artery ultrasound to detect FMD using novel edge-detection software

Brachial or radial artery flow mediated dilatation (FMD), as assessed by high resolution ultrasound, reflects endothelial-dependent vasodilator function (84). The technique for measurement and analysis of brachial FMD (126) has generally relied on a manual assessment of vessel diameter using visual inspection of single frames and placement of ultrasonic callipers (126). Manual assessment is subject to significant error (84, 126) and hence may be inappropriate for measurement of the arterial diameter response to increased flow,

which is generally of the order of 0.2- 0.4 mm and less in the presence of impaired endothelial function. Computer-assisted analysis utilizing edge detection permits multiple measurements along the vessel wall and would be expected to increase the sensitivity of the measurements.

We used a computerised edge-detection and wall-tracking software program to allow accurate and reproducible measurement of arterial diameter for assessing endothelial function (128). The reproducibility of measurements by this method was significantly better than traditional manual methods. These findings are important because previous reproducibility studies suggest that observer error for analysis of FMD may account for as much as 60% of the within-subject variation (84, 127). In addition, because the use of the software allows continuous monitoring of arterial diameter, true peak response is more reliably assessed. This is limited only by image quality, the processing power of the computer (16-17 frames/s), and/ or the frame rate of the recording medium (25 frames/s).

6.10.4. FMD data corrected to shear-rate stimulus

The peak of the shear stress stimulus profile created with reactive hyperaemia occurs four to seven seconds after cuff release and then rapidly decreases, returning to baseline within two minutes. In contrast, the peak diameter adaptation is typically not observed until 45-75 seconds after cuff release (97). Thus the vessel is exposed to the peak stimulus and then an additional 35-65 seconds of continued elevated shear stress prior to development of the peak response. Recently, Pyke et al (129) have shown that the independent

contribution of the peak shear stimulus is minimal, and it is the shear rate area under the curve (AUC), and not the peak itself, that is the critical determinant of peak FMD response. Therefore, AUC is the best method of quantifying reactive hyperaemia shear stimulus for FMD normalisation. We have used the FMD corrected for shear rate stimulus in our observations.

6.10.5. Endothelium-independent vasodilatation

Endothelium-independent vasodilatation can be evaluated in the peripheral circulation after administration of agents that directly relax smooth muscle cells, such as glyeceryl trinitrate or sodium nitroprusside. This technique allows the investigator to assess the ability of the artery to maximally dilate. The role of vascular smooth muscle cells in vasodilatation has important implications for endothelial function testing. It is unclear whether factors that result in endothelial damage and dysfunction also lead to abnormalities in relaxation mediated by vascular smooth muscle cells. Because vascular smooth muscle cells are the final common pathway mediating vasodilatation, it is important realize that processes that cause decreased endothelium-independent vasodilatation responses, by definition, will also decrease endothelium-dependent vasodilatation. We have used glyceryl trinitrate administration sublingually to evaluate endothelium-independent vasodilatation with the methods described above.

6.11. Vascular function after transradial catheterisation and recovery in our study

Our findings indicate that endothelium-dependent and -independent functions were decreased acutely as a result of radial artery catheterisation, impairment that largely resolved during three months of recovery. There was around a 40% to 50 % relative reduction in endothelium-dependent vasodilatation and a similar reduction in endothelium-independent vasodilatation measured the next day after the transradial procedure. There was no difference seen in vascular function recorded simultaneously in the contralateral (non-catheterised) arm. This impairment in vascular function returned towards normal at the time of a follow-up evaluation after three to four month. There is limited previous data on the impact of radial artery catheterisation on vascular function in vivo. One previous study has examined the impact of transradial catheterisation on FMD and found it was impaired immediately post-procedure and up to nine weeks after catheterisation (49). They noticed a more than 70% reduction in vascular function after the procedure and at follow up to nine weeks. Our data largely reinforce this previous experiment, with the addition that our data show recovery of endothelium-dependent and-independent function three months post-procedure, whereas Burstein et al (49) reported depressed function at nine weeks. These findings suggest that up to three months may be required for the arterial function to normalize after catheterisation and sheath insertion.

Our data, and that of Burstein et al (49), indicate that although FMD is reduced, it is not completely abolished. This might suggest that there is not complete denudation of the endothelium. Nonetheless, the substantial depression in FMD

we observed suggests that sheath insertion may have resulted in mechanical damage to the endothelial layer which, given the fragile nature of this monolayer, is a likely mechanism for impaired vasodilator function. It is also likely that the insertion of an introducer sheath into a relatively small radial artery may also result in structural damage to the wall, which in turn impairs GTN-mediated responses post-procedure. The acute increase in baseline radial artery diameter in the cannulated radial segment post-procedure further supports this hypothesis.

6.12. Radial artery diameter at baseline and at follow up

Radial artery luminal diameters ranged from 1.8 to 3.2mm in both catheterised and the control arm. We have found a negative correlation between the baseline radial artery diameter and the percentage vasodilatation in response to shear stress. Therefore, smaller the radial artery size greater the percentage change in the diameter of the radial artery in response to shear stress and GTN administration. Our results reinforce the published literature documenting an inverse relationship between radial artery diameter and the degree of vasodilatation (84, 85). Moreover, this negative correlation is abolished acutely after transradial catheterisation for both FMD and GTN-mediated vasodilatation. This is potentially due to significant vascular impairment acutely after the transradial procedure.

The mean radial artery diameter significantly increased from 2.79 to 3.02mm immediately after the procedure in the catheterised arm, with no difference in the control arm. The radial artery diameter returned back to its baseline size at long

term follow-up. This potentially explains the reversible effects on the vessel wall tone induced by transradial catheterisation. Similar changes in the radial artery diameter were observed by Burstein et al (49) following transradial catheterisation. Zhenxian et al (191) have evaluated the radial artery diameter and injury to the radial artery before, one day and one month after a transradial procedure, using ultrasound. They have reported the mean diameter of the right radial artery was 2.37±0.57, 1.95±0.50 and 2.23±0.41 mm, before the procedure, one day, and one month after the procedure respectively ($p < 0.01$ at one day, $p < 0.05$ at one month). The mean intima-media thickness of the radial artery was 0.25±0.12, 0.69± 0.31 and 0.38±0.17mm before the procedure, one day, and one month after the procedure respectively.

Patel et al (192) have assessed the histological changes induced by catheterisation on the radial artery. They have compared the histopathological changes between previously catheterised radial arteries and non-catheterised arteries. The distal ends of the catheterised radial arteries showed significantly more intimal hyperplasia (73.3% vs. 21%, $p=0.03$), peri-arterial tissue or fat necrosis (26% vs. 0%, $p=0.02$), and more adventitial inflammation (33.3% vs. 0%, $p=0.01$) than the distal ends of the non-catheterised radial arteries.
This study has therefore confirmed that transradial catheterisation induces changes in the radial artery size and the injury to the vessel wall which seems to recover towards baseline, as previously shown in limited studies. In addition we have shown substantial recovery in vasodilatory function three months after catheterisation.

6.13. The impact of hydrophilic coating of the introducer sheath on vascular function

A novel and unique aspect of the present study was the examination of the impact of hydrophilic coating of the introducer sheath on vascular function. We assessed endothelial-dependent and -independent function in sections of arteries subjected to placement of coated and uncoated introducer catheter sheaths. Measures were collected before and after sheath placement and, in a subgroup, at approximately three months after catheterisation to determine whether arterial vascular function recovered. Within-subject control measures were also collected from the contralateral non-catheterised limb. Our findings indicate that there was no significant difference between the hydrophilic-coated and uncoated sheath groups in terms of the acute impact of catheterisation or recovery from this procedure. No changes in arterial function were observed in the non-catheterised arm at any point. These data indicate that a hydrophilic coating does not ameliorate the dysfunction associated with catheter sheath insertion *in vivo*.

The development of hydrophilic coating has purportedly led to a reduction in the force required to remove the sheath and a reduction in friction and likelihood of damage during removal (21). Indeed, there is evidence from our study and other studies that a coated introducer sheath has beneficial clinical effects including reduced spasm and discomfort to the patient (21, 22, and 23). We therefore hypothesised that coating of the introducer sheath would limit the impact of the friction on the vessel wall and that diminished impact on the endothelial lining may preserve its well established anti-atherogenic properties. However, our data show that there was no difference between hydrophilic-coated and uncoated introducer sheaths in terms of their impact upon endothelium-dependent and -

independent function after sheath placement. Furthermore, we observed no evidence of a beneficial effect of sheath coating on the recovery of the artery following sheath removal. These data indicate that, if clinical outcome benefits from coating sheath do indeed exist, then the mechanisms responsible are unlikely to be attributable to preserved endothelial or vascular smooth muscle function. In addition, several recent papers have suggested that subjects can develop a granulomatous inflammation, due to shedding of some of the hydrophilic coating into the artery (62, 116, 130, 131) These findings, in combination with our data, support the suggestion of Tharmaratam et al (131), that the increased cost of the hydrophilic coated sheaths, the cost of treatment of sterile inflammation and the apparent lack of difference in spasm and depressed function need to be carefully balanced against the benefits of reduced spasm and pain on removal.

6.13.1. Type II error

When concluding that there is no difference between two groups, it is necessary to consider the possibility of a type II error (acceptance of null hypothesis when it is false). As well as the absence of a statistically significant difference, a study or result should be sufficiently powerful to detect a physiologically meaningful change from the mean control value in the intervention group, based on previous consideration of what constitutes a physiologically meaningful change. Previous detailed analysis by Woodman et al (128) of power requirements using the edge-detection software indicates that, at an alpha level of 0.05, seven subjects are required in crossover design and 16 subjects are required in parallel design to

ensure 90% power to detect a 2% improvement in FMD. A measurement of 2% reduction in the clinical end point (FMD) is likely to have a significant clinical impact and would be considered clinically relevant. We assumed that the results in this study for a primary end-point of reduction in FMD would therefore be considered adequately powered if a difference can be detected that would result in a reduction of FMD by 2%.

The measurement of change in FMD was adequately powered to detect a difference of 2%. It is therefore unlikely these results represent a type II error, and it may be concluded that there is no difference, at a level that may be important, in the occurrences of impairment of vascular function as measured by percentage change in FMD between uncoated and coated introducer sheath groups.

6.14. The impact of length of the introducer sheath on vascular function

Different lengths of the introducer sheaths cover different lengths of the radial artery during introducer sheath placement. The long introducer sheath (23 cm) extends for a longer length in the radial artery and thereby reduces contact of the catheter on the wall of the radial artery during the catheter manipulation. There is a possibility of a different degree of endothelial and radial artery injury with the use of long and short introducer sheaths during transradial catheterisation. We therefore measured vascular function at both proximal and distal sections of the radial artery in order to determine whether function was affected within the region of the introducer sheath alone, or whether transradial catheterisation has

more generalised effects on vasodilator function. Our findings indicate that endothelium-dependent and -independent function is decreased acutely as a result of catheterisation, both within and above the site of the sheath. This impairment largely resolved during three months of recovery. No changes in arterial function were observed in the non-catheterised arm at any time point. These data indicate that the impact of catheterisation extends beyond the site of sheath placement, but is not generalised to the entire circulation and resolves after a period of recovery.

We have not observed any difference in the degree of vascular impairment at the proximal and distal measurement sites with the use of long or short introducer sheaths. While the long sheath might protect the more proximal part of the radial artery from damage from the catheter movements, it has a greater diameter than the catheter and may therefore cause more damage in this area due to vessel-sheath size mismatch.

6.15. The impact of radial artery to introducer sheath diameter ratio on vascular function

Impairment of vascular function of the radial artery following transradial catheterisation is due to the interaction between the internal lining of the radial artery and the outer lining of the introducer sheath. This results in endothelial and deeper damage to the radial artery following transradial catheterisation. It is plausible that in patients with a radial artery diameter to introducer sheath outer diameter ratio of less than one would experience a greater degree of friction and damage to the endothelial lining of the radial artery during introducer sheath

manipulation. Saito et al (29) have shown a greater degree of radial artery spasm and the patient discomfort when the artery to sheath ratio is less than one during transradial catheterisation.

We have observed a significantly higher degree of vascular impairment in patients with a radial artery diameter to introducer sheath ratio of less than one as compared to the patients with a ratio of greater than one. These findings were seen in both endothelium-dependent and -independent arterial function. These findings further reinforce the hypothesis that radial artery size and introducer sheath size mismatch results in greater degree of vascular impairment and more radial artery spasm and discomfort to the patient (29).

6.16. The clinical impact of vascular dysfunction following tansradial catheterisation

The recovery of endothelial-dependent and -independent function in the catheterised arm indicates that transradial catheterisation should not be considered an absolute contraindication to the subsequent use of the radial artery as a donor graft for coronary artery bypass surgery (CABG). We have shown for the first time that the vascular function improves and returns towards normal after three to four months.

Some caution is warranted, however, as cannulation of the radial artery, in particular repeat cannulation, has been shown to reduce arterial lumen size and result in intima-medial thickening (35, 36, 37, and 133). Damage to smooth muscle may also be associated with intimal hyperplasia, cell proliferation and

collagen synthesis (132) leading to inward vascular remodelling (133). Furthermore, transradial catheterisation has been shown to induce intimal hyperplasia, medial inflammation and tissue necrosis at the puncture site (124). Despite good clinical outcomes (136) caution in using the radial artery as a graft is advocated by several groups due to propensity to spasm, increased likelihood of development of atherosclerosis and damage induced by transradial catheterisation (36, 48, 58, 133-135).

The mechanism of injury is suggestive of injury to the endothelium and the vessel wall as reflected by impairment of both endothelium-dependent and -independent vascular function.

6.16.1. Limitations of the vascular function study

The present study has a number of limitations. There were a relatively small number of subjects in each group and not all patients attended for follow-up studies after the three month recovery period. This limitation is somewhat mitigated by our within-subject design and analysis. We did not control for age, pre-existing vascular disease, history of smoking or drug treatment. However, the use of the contralateral arm as an internal control helped to negate this limitation and our data set has the advantage of representing responses in typical unselected patients

6.16.2. Conclusions and future directions

In conclusion, transradial catheterization results in reversible depression in NO-mediated endothelial and smooth muscle function in the catheterized arm. This effect is not mitigated in subjects who received a hydrophilic-coated sheath. The purported benefits of hydrophilic-sheath coating need to be weighed up against the increase cost, possible increased risk of inflammation and lack of reduction in arterial dysfunction. Future research and technological development should seek to minimise the effects of the catheter as well as the sheath on the vasculature. It is also possible that optimising the function and size of the artery prior to its cannulation may improve the outcome and recovery of the artery and reduce the chance of graft failure if the artery is removed for CABG (138,). To this end, exercise training has been shown to improve arterial function and induce outward remodelling as shown by Hornig et al (139) Hambrecht et al.(138), Gokce et al. (140), Green et al.(141), and Tinken et al. (142)). Therefore, exercise training before the radial catheterisation could improve the endothelial function of the radial artery and might also reduce the degree of endothelial damage and dysfunction following the procedure.

Conclusions

Radial artery spasm is commonly encountered in patients undergoing transradial cardiac catheterisation or coronary intervention. This can cause discomfort to the patient and may prevent completion of the procedure in some patients. We performed a study to see if the length and coating of the radial artery sheath affected the incidence of spasm and other complications of transradial catheterisations. We observed radial artery spasm in 30% of our patients and this resulted in procedural failure in 17 (2.2%) patients. We also investigated the tolerability and safety of two different compression devices used to achieve haemostasis after radial sheath removal.

Hydrophilic coated introducer sheaths significantly reduce clinical radial artery spasm and the discomfort experienced by the patients when compared to uncoated introducer sheaths. There were similar rates of radial artery occlusion rates (9%) and early access site complications in both sheath types. There was a significantly higher incidences of late local access site complication, predominantly an inflammatory reaction seen with the use of a hydrophilic coated introducer sheath (3%).

There was no impact of the length of the introducer sheath on clinical outcomes observed in our study.

We have identified younger age, female gender, diabetes, smaller wrist size, lower body mass index, and use of uncoated introducer sheath as independent predictors of clinical radial artery spasm.

Haemostasis after transradial procedures was successfully achieved by TR Band or Radistop compression devices in all patients. The time taken to achieve

haemostasis was longer with the use of the TR Band but the discomfort experienced while the device was applied, was greater with Radistop. However, access site complications were similar in both groups.

We have identified younger age, female gender, smaller wrist size, occurrence of radial artery spasm, and failure to use heparin during the procedure as independent predictors of radial artery occlusion at the time of discharge from the hospital.

We have evaluated the impact of transradial catheterisation on endothelium-dependent and -independent vascular function of the radial artery acutely and at follow up. We have shown that transradial catheterisation results in reversible impairment of endothelial-dependent and -independent function in the catheterised arm. Our findings indicate that vascular function is severely decreased acutely (24 hours after procedure) and that this dysfunction has largely resolved following 3 months of recovery. We have not found any correlation between hydrophilic coating and the length of the introducer sheath on vascular function impairment after trasradial catheterisation. However, we have observed higher degree of endothelium-dependent and -independent vascular function impairment in the patients with radial artery internal diameter to introducer sheath outer diameter ratio of less than one. This reflects a higher degree of injury to the radial artery in these patients.

The thesis will provide important insight into clinical information and problems encountered during transradial catheterisation in contemporary clinical practice. This work will also help clinicians in choosing between various different introducer sheaths and compression devices available to be used during transradial catheterisation. Operators should be aware of physiological impact of

these procedures on the vasculature and its clinical impact. The work of this thesis could be expanded with further studies investigating the impact of other patient and device related characteristics on vascular function. Further studies looking into optimisation and improving the endothelial function during this procedure may improve patient outcome.

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Appendix 1

PATIENT INFORMATION SHEET

Randomised Comparison Of Introducer Sheaths And Compression Devices In Patients Undergoing Transradial Coronary Procedures

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it would involve for you. Your cardiologist and the study doctor would like to ensure that you completely understand the study and the study requirements. Please take your time to read the following information carefully and discuss it with others if you wish. Ask your study doctor if there is anything that is not clear or if you would like more information. Taking part in the study is entirely voluntary. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

As you are aware you have been diagnosed with coronary artery disease. The procedure that is recommended by your cardiologist is coronary angiography or coronary balloon angioplasty. The procedure could be performed by gaining access through the artery in your wrist or through the artery in your groin. Both access sites have been widely used for many years. Arterial access from wrist has been increasingly used and it has shown to cause less local complications and be better tolerated by patients. To gain vascular access different sheath types are licensed and commercially available and are widely used. After the procedure is completed the bleeding from the wrist is stopped by applying pressure by compression devices.
The TR Band and the Radistop are compression devices that are widely used.

The main objective of this study is to compare the performance of four different types of sheath with different length with and without slippery coating. We will also be comparing the performance of two different kinds of compression devices used to stop bleeding at the end of procedure. We will be studying the impact of these devices on radial artery spasm, radial artery blockage, patient tolerance and local vascular complications.

If you choose to participate in this study, the type of sheath and the type of compression device will be randomly chosen. The rest of the procedure will be performed as it would be normally.

Why have I been chosen?

Your treating consultant cardiologist has advised the research team to approach you for this study. All patients like you who need treatment for coronary artery disease via radial route are being invited to take part. A total of 800 patients will be recruited and treated from this centre [The Cardiothoracic Centre, Liverpool].

What will happen to me if I take part?

If you agree to participate in this study you will undergo your procedure using either of the long coated, long uncoated, short coated or the short uncoated sheaths. At the end of procedure you will receive either the TR band or the Radistop to stop bleeding from wrist. The type of sheath and the type of compression device you receive will be randomly assigned [equal chance of being in any of the groups] so neither you nor your physician will be able to choose which sheath or compression device you will receive. You have an equal chance of receiving either sheath or either compression device.

The risks and benefits of this technique will be explained to you as per usual hospital practice. The procedure will be performed according to your study doctor's usual practice.

Your progress will be monitored throughout your hospital stay. You will have your wrist assessed for any complication or blockage of radial artery.

A summary of the study tests and procedures is provided in the table below.

Before the procedure	Information sheet and consent form provided in Pre-assessment clinic or on wards
After the procedure	Assessment of radial artery spasm, wrist examination by hand held Doppler ultrasound and clinical examination.
At four months	Assessment of wrist by ultrasound examination.

Day 1- Consent taken and procedure performed

Day 1- Assessment of radial artery spasm by questionnaire.
Day 1/2 [pre discharge] - Assessment of the wrist by Doppler ultrasound to detect radial artery patency and any local vascular complications.

4 month [follow up] - Assessment of wrist by Doppler ultrasound to detect patency of radial artery.

It is important for you to understand that participation in the study is entirely voluntary. In addition if you agree to participate initially and reconsider at a later date then you may decline to continue with the study follow up.

What are the possible disadvantages and risks of taking part?

There are some potential known risks involved with transradial coronary procedures. These include: the risk of radial artery blockage [3-7%], radial artery spasm [15-30%], bleeding from wrist [1-2%] and haematoma [2-3%] in the forearm or arm.

All these risks are the known complications from the transradial coronary procedure and are not specific to this study. The study is intended to explore the ways to minimise the above risks.

What are the risks associated with pregnancy?

Pregnant women are excluded from this study. If you are or think you could be pregnant please inform the doctor treating you.

What are the possible benefits of taking part?

It is important for you to understand that the information obtained during this study may be used to help others. You should also understand that there may be some benefits to you, as some sheaths or compression device used during study may cause less discomfort.
The study will help determine and compare the performance of four different sheaths and two different compression devices used in this trial.

Do I have to take part?

You have the right to choose whether you wish to participate in this trial. In addition you have the right to withdraw from this trial at any time, without having to provide a reason. This will not affect your relationship with your cardiologist or with any of the nursing staff at any time. This will also not affect your normal treatment and care.

Your cardiologist may also withdraw you from the study without your permission, if she/he deems it is in your best interest or if the investigator decides to end the study.

What are the alternatives?

If you prefer not to participate in this study your study doctor can discuss the alternative treatments for you. These may include the sheath and compression device routinely used.

Who is organising and funding the research?

You will not be paid for participation in this study. The routine costs for this procedure will be billed to your insurance company or National Health Service as normal. Your study doctor is not paid for your participation in this study.
You can ask the study co-ordinator for any additional costs as result of your participation in this study.

What if something goes wrong?

In the event of an injury during your participation in this study as a result of the procedure, you will be treated by your cardiologist according to local hospital practice. It is important however that you inform your cardiologist via the study co-ordinator of any change in your health, or any other medical treatment that you may require during the course of this study.

If you have any problems, concerns, complaints or other questions about any aspect of the way you have been approached or treated during the course of this study, the normal complaints mechanisms of the NHS are available to you. You should preferably contact the investigator first, Dr Sudhir Rathore on telephone 0151 228 1616 Bleep-760. Alternatively you may contact the hospital complaints department on telephone number 0151 600 1257.

Will my taking part in this study be kept confidential?

The ethics committee, which reviews research projects for this hospital, has approved our participation in this study. With your permission your GP will be notified of your participation in this study. When signing the consent form you will be asked to give approval for this to happen. Please be assured that confidentiality of your records will be maintained at all times.

Any data that is collected in this trial will be managed in accordance with current codes of practice and data protection legislation such as the Data Protection Act 1998. The trust will archive the data for 10 years. If you withdraw from the trial at any time the data collected from your participation will be included in the final trial results up until the time that you withdrew from this study.

What will happen to the results of the study?

The results of this study will be reported in medical journals and/or at medical meetings. When this occurs the identification of individuals taking part is not

disclosed. If you wish to receive a copy of these, you should let your study doctor know so that it may be sent to you when it is ready.

What if new information becomes available?

If any new information becomes available that could affect your participation in the study we will let you know as soon as possible.

Who has reviewed the study?

The study has been approved by the Local Research Ethics Committee responsible for this hospital. Their role is to check that the study is acceptable from an ethical and safety point of view in the interests of the patients participating.

Contact for further information?

If you wish to obtain more information regarding this study or its risks, advantages or medical alternatives, please contact your study doctor. You should also inform your study doctor via the study co-ordinator, if you have been unwell or hospitalised for any reason during the study. Should any problem or question arise with regard to this study, either concerning your rights as a participant in clinical research, or with any research related injury, you should contact the

Principal Investigator, Dr-John Morris on 0151 228 2264.
Principal Co-Investigator and Co-ordinator, Dr Sudhir Rathore on 0151 228 1616 Bleep-760.

Appendix 2

PARTICIPANT CONSENT FORM

Patient Identification Number for this trial (CRF No.):

Study Number: 719. 06/Q1502/94

Title of Project: Randomised Comparison Of Introducer Sheaths and Compression Devices In Patients Undergoing Transradial Coronary Procedures

Name of Researcher : Dr Sudhir Rathore

	Please initial b
1. I confirm that I have read and understand the information sheet dated 27 July, 2006 (final version)for the above study and have had the opportunity to ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Clinical Trials Unit at cardiothoracic centre NHS Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
4. I agree to take part in the above study and agree to my GP being informed of my participation in the study.	☐

Name of Patient _____ Date _____ Signature _____

Name of Person taking consent _____ Date _____ Signature _____

(if different from researcher)

Researcher _____ Date _____ Signature _____

When completed, 1 for patient, 1 for researcher file; 1 [original] to kept in medical records.

Appendix 3

Protocol for the Application and Removal of the TERUMO TR BAND at the Cardiothoracic Centre, Liverpool.

Application [IN CATH LAB]

1. On completion of the procedure withdraw the introducer sheath by 2-3 cm.

2. Align the green marker [which is located on the centre of the compression balloon] over the arterial puncture site, approximately 0.5 to 1.0 cm above [proximal] the skin incision. Wrap the Velcro strap around the wrist leaving a space over the ulnar artery [not too tight].

3. Using the syringe provided, inject 15-18 cc of air through the side arm to inflate the compression pad. After inflation immediately remove the syringe.

4. Remove the arterial sheath and observe for any bleeding.

5. Re-attach syringe and remove air slowly, watching through the transparent band. When a show of blood is visible re- introduce 1-2 ml of air. Note final residual air volume.

6. At this stage there will be palpable radial pulsation distal to device and early forward flow is achieved.

Removal [ON THE WARDS]

7. After one hour of return to ward, using the dedicated syringe, slowly start to remove the air from the TR BAND. Observe the local bleeding at all times. If bleeding shows, simply re inflate the compression pad by 1- 2 ml of air and recheck in 30 minutes.
8. Thereafter check every 30 minutes and repeat the process that has just been described, as required.

9. Completely remove the TR BAND when bleeding stops and check the puncture site for any complications. Then apply dressing over wound.

10. Note the time when TR BAND is removed.

Appendix 4

Protocol for the Application and Removal of RADISTOP at the Cardiothoracic Centre, Liverpool

Application [IN CATH LAB]

1. **Place the hand in the support plate, with the distal Velcro strap at the base of the thumb. Adjust the distal strap to fit.**

2. **Wrap the proximal strap around the patients forearm and secure.**

3. **Thread the compression pad onto the separate Velcro strap. NOTE! Fluffy side of the Velcro strap will be facing down, towards the patients skin.**

4. **Centre the compression pad directly over the puncture site. Apply pressure while removing the sheath. NOTE! Positioning directly over the puncture site will help prevent bleeding from collateral blood supply.**

5. **Continue to apply manual compression while tightening and securing the strap. NOTE! Hold the thumb firmly on the pad and the fingers securely around the support plate, in C-grip.**

6. **Pulse should be checked after application and if no pulse is palpable the Velcro should be loosened slightly until the pulse is palpable or bleeding starts.**

Removal [ON THE WARDS]

7. **After one hour of return to ward consider reducing pressure maintaining haemostasis with no local oozing. Observe for local bleeding at all times. If bleeding shows, simply re tighten the strap and recheck in 30 minutes.**

8. **Thereafter check every 30 minutes, and repeat the process that has just been described, as required.**

9. **Completely remove the RADISTOP when bleeding stops and check the puncture site for any local complication. Then apply dressing over the wound.**

10. **Note the time when RADISTOP was removed.**

Version02/rathore **09/10 /2006**

Appendix 5

	PATIENT DETAILS	
1	Patient's name	
2	Hospital / Unit number	
3	Address: House no./Street	
4	Address line 2	
5	City	
6	Post code	
7	Country	
8	Telephone number	
9	NHS number	
	DETAILS OF RELATIVE OR FRIEND NOT AT THE SAME ADDRESS	
10	Relative's or friend's name	
11	Address: House no./Street	
12	Address line 2	
13	City	
14	Post code	
15	Country	
16	Telephone number	
	DETAILS OF G.P.	
17	GP name	
18	Surgery name	
19	Street	
20	Address line 2	
21	City	
22	Post code	
23	Country	
24	Telephone number	

SCREENING PHASE - ELIGIBILITY CRITERIA			
Inclusion Criteria			
25	Referral for coronary angiography or coronary angioplasty via Transradial route	Yes [ ]	No [ ] ***stop*** ***If 'no', stop, patient not eligible.***
Exclusion Criteria			
26	Previous ipsilateral transradial procedure	Yes [ ] ***stop***	No [ ]
27	Haemodynamically unstable patient- Cardiogenic shock,	Yes [ ] ***stop***	No [ ]
28	Chronic renal failure**	Yes [ ] ***stop***	No [ ]
29	Patient on Haemodialysis with A-V Fistula	Yes [ ] ***stop***	No [ ]
If 'yes' to any of above, patient should not be randomised.			
CONSENT			
30	Has patient been fully informed and received patient information sheet	Yes [ ]	No [ ]
31	Has patient signed consent form	Yes [ ]	No [ ]
32	Date of consent	(dd/mm/yyyy) __ __ / __ __ / __ __ __ __	
33	Name of person obtaining consent		
34	Is copy of consent form in medical records and site file	Yes [ ]	No [ ]

	SCREENING PHASE – CLINICAL HISTORY					
35	Gender	Male [ ]			Female [ ]	
36	D.O.B. (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __				
37	Documented hypertension	Yes [ ]			No [ ]	
38	Documented hyperlipidaemia	Yes [ ]			No [ ]	
39	Diabetes mellitus :	No history of diabetes [ ]		Type I [ ]		Type II [ ]
40	Cigarette smoking	Current [ ] (Within last month)		Ex-smoker [ ] (Stopped > 3 months)		Never smoked [ ]
41	Height [cm]					
42	Weight [Kg]					
43	Wrist circumference [cm]					
44	**ALLENS Test****	< 5 sec [ ]	5-10 sec [ ]	10-20sec [ ]	>20 sec [ ]	Not at all [ ]
45	**Plethysmography and Oximetery** Test**	Type A [ ]		Type B [ ]	Type C [ ]	Type D [ ]

IN-HOSPITAL PHASE				
46	Date of procedure	dd/mm/yyyy --- --- /---- ---- / --- --- --- ---		
47	Clinical Syndrome	Stable angina [ ]	ACS [ ]	Acute MI [ ]
48	Priority of Procedure	Elective [ ]	Urgent [ ]	Emergency [ ]

RANDOMISATION			
Please contact Sudhir Rathore Bleep 2760			
49	Date of randomisation	(dd/mm/yyyy) __ __ / __ __ / __ __ __ __	
50	Randomisation code		
51	**Treatment allocation-** *Introducer Sheath + Compression Device*	**[1] Long Hydrophilic + TR Band**	**[ ]**
		[2] Long Hydrophilic + Radistop	**[ ]**
		[3] Long Uncoated + TR Band	**[ ]**
		[4] Long Uncoated + Radistop	**[ ]**
		[5] Short Hydrophilic + T R Band	**[ ]**
		[6] Short Hydrophilic + Radistop	**[ ]**
		[7] Short Uncoated + T R Band	**[ ]**
		[8] Short Uncoated + Radistop	**[ ]**
52	Randomised by	Name:	

** IN HOSPITAL PHASE – PROCEDURE [COMPLETED IN CATH LAB BY OPERATOR]						
53	Name of operator	Name :				
54	Radial artery access successful	Yes [ ]		No [ ]		
55	If No why? [Please give reason]	RA puncture unsuccessful [ ]				
		Unable to pass wire [ ]				
		Recurrent RA [ ]				
		Difficult anatomy [ ]				
		Other [Specify]				
56	Time Transradial sheath Inserted	[24 hr clock] : __ / __ hrs				
57	Time Transradial sheath removed and compression device applied	[24 hr clock] : __ / __ hrs				
58	Total number of catheters used	1 [ ]	2 [ ]	3 [ ]	4 [ ]	>4 [ ]
59	Radial spasm questionnaire completed by Operator	Yes [ ]		No [ ]		
60	**Operator's Questionnaire- [Please indicate one or more features]**					
	Patient reported presence of continuous pain	Yes [ ] No [ ]				
	Patient reported forearm pain only during catheters manipulation	Yes [ ] No [ ]				
	Patient reported forearm pain while sheath retrieval	Yes [ ] No [ ]				
	Firm grip of the catheters during manipulation	Yes [ ] No [ ]				
	Augmented resistance to sheath retrieval	Yes [ ] No [ ]				
61	Spasmolytic drugs needed	Yes [ ]		No [ ]		
62	If Yes, spasmolytic drug used describe the dose and agent used	Verapamil	Nitroglycerine	Other [specify]		

63. Coronary anatomy and outcomes			
Coronary arteries attempted	**Successful**	**Failure**	**Number of catheters**
LCA Diagnostic Imaging			
LCA Intervention Imaging			
LCA PCI Outcome			
RCA Diagnostic imaging			
RCA Intervention Imaging			
RCA PCI Outcome			

64	Procedure completed via radial route	Yes [ ]	No [ ]	
65	If No , Reason why	Radial artery spasm [ ]	Difficult Anatomy [ ]	Other [Specify]
66	Heparin Dosage	_ _ _ _ _ _ units		
67	If Coronary Intervention, ACT at the end of the procedure	_ _ _ sec		

PRE DISHARGE ASSESSMENT						
68	Time Compression device removed	[24 hr clock] __ __ / __ __ hrs				
69	Patient questionnaire for spasm completed	Yes [ ]		No [ ]		
70	If No Reason why?					
71	Is completed patient questionnaire in site file	Yes [ ]		No [ ]		
72	Patient assessment of radial artery spasm	1 [ ]	2 [ ]	3 [ ]	4 [ ]	5 [ ]
73	Questionnaire regarding compression device completed	Yes [ ]		No [ ]		
74	If No, Give reason					
75	Questionnaire regarding compression device in site file	Yes [ ]		No [ ]		
76	Local vascular complications	Yes [ ]		No [ ]		
77	If Yes Describe	**Oozing** [Leakage of blood from puncture site requiring digital pressure] [ ]				
		Ecchymosis [Bleeding into s/c plane causing bluish purple discoloration > 4cm] [ ]				
		Local small haematoma [< 2 cm] [ ]				
		Local large haematoma [> 2 cm] [ ]				
		Radial or Brachial artery dissection [ ]				
		Subclavian artery dissection [ ]				
78	Radial artery pulsation felt distal to puncture site after compression device removal	Yes [ ]		No [ ]		
79	Radial artery pulsation felt proximal to puncture site after device removal	Yes [ ]		No [ ]		
80	If No, Confirm by hand held Doppler	Doppler flow present [ ]		Doppler flow absent [ ]		
81	Reverse Allen's test*	< 5 sec [ ]	5-10sec [ ]	10-20 sec [ ]	> 20 sec [ ]	Not at all [ ]

82	**Reverse Plethysmography and Oximetery test ****	Type A [ ]	Type B [ ]	Type C [ ]	Type D [ ]
83	**Radial artery Occlusion ****	Yes [ ]		No [ ]	

INVESTIGATOR'S DECLARATION		
I declare that the information presented in the Case Record Form (pages 1 to 12) accurately reflects the medical records, including the results of tests and evaluations performed on the dates specified.		
84	Name of person completing form (capitals)	
85	Signature of person completing form	
86	Date form completed (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __

4-6 Month follow up			
87	Any local access site complication after discharge	Yes [ ]	No [ ]
88	**If Yes , Please describe**		
Local Infection [ ]		Medical Treatment	Vascular surgery
Local allergic reaction [ ]		Medical Treatment	Vascular surgery
Pseudoaneurysm [ ]		Medical Treatment	Vascular surgery
A V Fistula [ ]		Medical Treatment	Vascular surgery
Local pain [ ]		Medical Treatment	Vascular surgery
Other [specify]			

89	Radial artery pulsation felt distal to puncture site	Yes [ ]			No [ ]	
90	Radial artery pulsation felt proximal to puncture site	Yes [ ]			No [ ]	
91	If No, Confirm by hand held Doppler	Doppler flow present [ ]			Doppler flow absent [ ]	
92	Reverse Allen's test**	< 5sec [ ]	5-10sec [ ]	10-20sec [ ]	>20 sec [ ]	Not at all [ ]
93	Radial artery occlusion**	Yes [ ]			No [ ]	
94	Any Functional impairment of hand	Yes [ ]			No [ ]	
95	If YES, Please describe					

INVESTIGATOR'S DECLARATION		
I declare that the information presented in the Case Record Form (follow up) accurately reflects the medical records, including the results of tests and evaluations performed on the dates specified.		
96	Name of person completing form (capitals)	
97	Signature of person completing form	
98	Date form completed (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __

Supporting Publications

DOI: 10.1111/j.1540-8183.2008.00382.x

The Radial Approach: Is This the Route to Take?

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The benefits of the transradial approach have clearly been demonstrated over the years in various studies. The reduced incidence of access site complications and early mobilization are some of the benefits making this technique popular with interventional cardiologists worldwide. With increasing experience and availability of dedicated equipment this technique is now been increasingly used for complex catheter interventions. However, there still remain some potential problems and complications with the transradial approach and it needs further research. The main purpose of this review is to highlight the benefits, complications, and potential problems with the transradial approach. (J Interven Cardiol 2008;21:375–379)

Introduction

The transradial approach for coronary angiography was first described by Campeau in 1989[1] and the technique was extended to percutaneous transluminal coronary angioplasty and stenting by Kiemeneij and Laarman.[2] Since then a widespread proliferation of coronary procedures via the radial artery has taken place.[3–9]

The safety of the transradial approach, compared to the conventional femoral approach for coronary procedures, is mainly due to its favorable anatomic relations. No major veins or nerves are located near the radial artery at the wrist, minimizing the chance of neurological or vascular injury. Hemostasis is easily achieved because of the superficial course of the radial artery. Thrombotic or traumatic radial arterial occlusion does not endanger the viability of the hand if an adequate collateral blood supply from the ulnar artery is present.

Comparison with the Transfemoral Approach

A recent meta-analysis published by Hamon et al.[10] considered 12 randomized trials published between 1989 and 2003, including a total of 3,224 patients, comparing transradial and transfemoral approaches for coronary procedures. The risk of major adverse cardiac events was similar for the radial versus the femoral approach (2.1% vs. 2.4%, OR 0.92, 95% CI 0.57–1.48, $P = 0.07$), but radial access was associated with a significantly lower rate of entry site complications (0.3% vs. 2.8%, OR 0.20, 95% CI 0.09–0.42: $P \leq 0.0001$), although at the price of a higher rate of procedural failure in comparison to femoral access (107[7.2%] of 1472 vs. 33[2.4%] of 1,373 subjects; OR 3.30, 95% CI 1.63–6.71: $P < 0.001$). The authors concluded that the transradial approach for coronary procedures is a safe and effective technique and virtually abolishes entry site complications.

There is also a clear trend toward equalization of the rate of procedural success over the years, mainly due to technological progress in equipment and increased operator experience. The transradial approach has been found to be safe and feasible in a large spectrum of clinical practice[11–13] and in the setting of aggressive pharmacologic treatments such as glycoprotein IIb/IIIa inhibitors[8] and oral anticoagulants.[14]

Most of the trials included in the meta-analysis utilized devices compatible with 6F or smaller catheters. The safety of transradial access with devices requiring catheters with a larger internal diameter (7F or greater) need to be evaluated in large trials. Initial

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results are encouraging in selected patients by experienced operators.[15–18]

The procedural failure is rare with modern practice, experience, and availability of the new equipment. There could be several reasons for procedural failure: Firstly, there may be failure to successfully puncture and cannulate the radial artery, because of the small vessel size, tortousity, or spasm. Secondly, it may be impossible to cannulate the coronary ostia due to difficulty in rotating and manipulating the catheters. Thirdly, the procedure may fail because of inadequate guide catheter support. These problems can be overcome in the majority of cases with recent advances and availability of equipment dedicated to the transradial approach.

Complications of the Transradial Approach

Radial Artery Occlusion. Although this was a major concern of the early transradial operators, the consequences of radial artery occlusion are usually benign. The dual supply to the hand appears robust and the absence of ischemic complications is promoted by the original recommendation by Kiemeneij that transradial procedures be performed only in patients with a documented patent ulnar artery and palmar arch. This has traditionally been evaluated using Allen's test, but ultrasound, Doppler, and plethysmography prior to the procedure are more accurate.[19]

Several variables influence the incidence of radial artery occlusion. Adequate anticoagulation is extremely important. The incidence of radial artery occlusion was as high as 30% in patients receiving 1,000 units of heparin during diagnostic catheterization.[20] Stella et al.[21] have shown radial artery occlusion rates of around 5% demonstrated by ultrasonography at 1 month in patients undergoing coronary angioplasty with 6F guiding catheters. Many other operators have shown radial artery occlusion rates varying from 3% to 10% in anticoagulated patients.

Catheter size has also been shown to be a predictor of radial artery occlusion. Studies have shown that the ratio between the diameter of the radial artery and the radial sheath has an impact on the rate of radial artery occlusion.[22] The incidence of occlusion was 4% in patients with a ratio of greater than 1, compared to 13% in those with a ratio of less than 1.

In clinical practice, variable (short and long) length introducer sheaths with and without hydrophilic coatings are available. There are also several different hemostatic compression devices available (Radistop, TR band, Tourniquet, etc). These are widely used clinically but their impact on clinical outcomes and radial artery injury has not been tested in a randomized trial.

Nonocclusive Radial Artery Injury. Recent studies have demonstrated that permanent radial artery injury without occlusion may occur following transradial intervention in some patients. Mean radial artery internal diameter as measured by ultrasound was smaller in patients undergoing repeat transradial interventional procedures as compared to the first-time procedure.[23] Nagai et al. evaluated the vascular complications following transradial coronary procedures by two-dimensional echo and color Doppler ultrasonic studies before and late after catheterization.[24] Early after the procedure, segmental stenosis was noted in 22% and no flow in 9% of patients. Late after the procedure, segmental stenosis was seen in 1%, diffuse stenosis in 22%, and no flow in 5% of patients. Further studies have shown that this progressive narrowing is due to intimal hyperplasia.[25] Recently Edmundson and Mann have shown that nonocclusive radial artery injury is common after transradial interventional procedures.[26] Intravascular ultrasound evaluation revealed a variable degree of intima-media hyperplasia in all patients who had had a previous transradial procedure. Although luminal cross-sectional diameter and area were significantly smaller than a control group, vasoreactivity was maintained.

These studies have involved a small number of patients in cross-sectional fashion. The incidence and predictors of intimal hyperplasia in patients undergoing transradial procedures are yet to be determined.

The ramifications of radial artery occlusion and injury are important not only in patients undergoing repeat interventional procedures, but also in patients in whom the radial artery may be used as a conduit for coronary artery bypass surgery or for the creation of arteriovenous fistulae for hemodialysis.

Radial Artery Spasm. The radial artery is a muscular artery with a prominent medial layer that is largely dominated by alpha-1 adrenoreceptor function.[27] Much of the discomfort and difficulty of the transradial procedure is related to vasospasm induced by the introduction of a sheath or catheter into the radial artery. Circulating levels of catecholamine play a role in radial artery spasm; therefore local anesthesia and adequate sedation to control anxiety during catheter insertion may be important preventative measures. The

incidence of radial artery spasm has been reported to be around 10–20%, and in about 2–5% of patients prevents the successful completion of the procedure by the transradial route.[28–30]

It has been demonstrated in isolated radial artery ring segment that nitroglycerine and verapamil are effective agents in preventing arterial spasm.[31] Attempts have been made to quantify radial artery spasm using an automatic pullback device.[32] Studies using this device have shown that an intraarterial cocktail of verapamil and nitroglycerine reduces the incidence of pain from 14% to 34%. The mean pullback force (MPF) was also significantly lower (0.53 ± 0.52 kg vs. 0.76 ± 0.45 kg) compared to patients not receiving any vasodilating drug.[29] Clinically important radial artery spasm was seen in 8% of patients receiving a spasmolytic cocktail compared to 22% in the control group ($P = 0.029$). Salmeron et al. have shown in a randomized controlled trial that verapamil is more effective in preventing radial artery spasm than phentolamine.[30] Both vasodilator agents induced a significant increase in radial artery diameter (2.22 ± 0.53 to 2.48 ± 0.57 mm for verapamil and 2.20 ± 0.53 to 2.45 ± 0.53 mm for phentolamine). However, verapamil was more effective in preventing radial artery spasm (13.2% vs. 23.2% in phentolamine-treated patients).

The size (both diameter and length) of the radial artery sheath may have an impact on radial artery spasm and also a hydrophilic coating might reduce the incidence of radial artery spasm by reducing friction and irritation of the endothelium. The exact role of these factors in pathogenesis and prevention of radial artery spasm are yet to be established.

Local Access Site Bleeding. The most important benefit of transradial procedures is the elimination of access site bleeding complications.[33–35] The radial artery puncture site is located over bone and can be easily compressed with minimal force. Several compression devices have been developed to maximize operator and staff efficiency. Local hematomas may occur as a result of improper device selection, application, or device failure. It is of paramount importance to understand that the radial artery should be compressed both proximally and distal to puncture site, to prevent retrograde flow from palmar arch collaterals.

Forearm Hematoma. Bleeding may occur from the radial artery remote from the access site. This may be due to perforation of a small side branch by the guide wire in patients receiving aggressive antiplatelet agents, or due to avulsion of small branches during sheath or catheter manipulation.[36,37] This can rarely lead to compartment syndrome[38] and can lead to pressure-induced occlusion of radial and ulnar artery. Fasciotomy and hematoma evacuation should be performed as an emergency procedure to prevent ischemic injury.

Access Failure. Failure to cannulate the radial artery now occurs in less than 5% of patients with improvements in equipment. It should be emphasized that the puncture site should be proximal to the styloid process of the radius bone. Beyond this the radial artery usually bifurcates and becomes less superficial and attempting to puncture the vessel in this area is a common cause of access failure.

Aberrancies of the Radial Artery. A radial loop is the most common congenital anomaly and may be a cause of access failure.[36,39] Some attempts have been made to delineate the radial artery anatomy in patients going for transradial procedures.[40] At angiography, anatomic variations are noted in 22.8% patients and include tortuous configuration (3.8%), stenoses (1.7%), hypoplasias (7.7%), radioulnar loop (0.8%), abnormal origin of radial artery (8.3%), and lusoria subclavian artery (0.45%). However, the procedure was successfully performed by radial approach in 99.8% of patients with tortuous configurations, 91.9% of radial stenosis, 93.9% of hypoplastic radial artery, 83.35 of radioulnar loop, 96.7% of radial axillary origin, and 60% of lusoria subclavian artery setting. Clinicians need to be aware of these anatomic variations and in most cases the procedure could be completed via radial route.

Rare Complications. There are some rare complications of transradial procedures which are worth discussing, Firstly, radial artery avulsion[38] due to intense spasm has been described but this could be avoided by modern equipment and antispasm measures. Secondly, mediastinal hematoma[41] has been reported and should be considered as differential diagnosis of chest pain following transradial cardiac catheterization. This needs prompt diagnosis and thoracotomy might be needed to evacuate hematoma and decompression.

Late Complications. Sterile abscess formation is reported in about 2–3% of patients in whom a sheath with hydrophilic coating is used.[42–44] The time course for the development of such an abscess is typically 2–3 weeks after the procedure. Biopsy specimens have shown granulomatous reaction and a few have also shown an amorphous extravascular substance

consistent with the catheter coating. No infectious agent could be implicated and all patients had good long-term outcomes with conservative treatment.

Physiological Changes in the Radial Artery Following Transradial Procedures

Besides causing anatomical changes, transradial catheterization may also cause physiological changes by injuring the radial artery endothelium. A small study has examined by ultrasound both endothelium-mediated and nonendothelium-mediated vasodilatation of the radial artery before and after transradial catheterization.[45] This study showed that hyperemia-induced vasodilatation did not change significantly; whereas nitroglycerine-induced vasodilatation was significantly attenuated at 24 hours, but had improved at 1 week and 1 month. This is probably related to the local trauma provoked by sheath and catheters. The exact extent of endothelial damage and its impact on radial artery physiology in the long term are not known.

Use of the Radial Artery as a Graft after Transradial Procedures

In view of anatomical and physiological changes caused by transradial catheterization, concerns have been raised regarding the suitability of the use of the radial artery as a bypass conduit after transradial catheterization. There are limited studies available looking into this issue. Kamiya et al. reported in a retrospective cohort study that there was significant intimal hyperplasia (68% vs. 39%) and reduced early graft patency (77% vs. 98%) in patients who had had previous transradial procedures.[46] However, this did not affect early clinical outcomes. The authors concluded that use of the radial artery as a bypass conduit after transradial catheterization should be undertaken cautiously, particularly when multiple previous procedures have been performed. The impact of endothelial damage and long-term outcome following the use of radial artery as a bypass conduit are not yet known in prospective studies.

Conclusion

The transradial approach for coronary procedures is safe and yields clinical results similar to transfemoral access. The transradial approach virtually abolishes vascular entry site complications and allows us to perform a wide range of diagnostic and therapeutic interventions. However, further research into methods of reducing the incidence of radial artery spasm and minimizing anatomical and physiological changes in the radial artery following transradial procedure are needed.

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JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 3, NO. 5, 2010

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2010.03.009

CLINICAL RESEARCH

Impact of Length and Hydrophilic Coating of the Introducer Sheath on Radial Artery Spasm During Transradial Coronary Intervention

A Randomized Study

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Objectives The aim of this study was to assess the impact of length and hydrophilic coating of the introducer sheath on radial artery spasm, radial artery occlusion, and local vascular complications in patients undergoing transradial coronary procedures.

Background Radial artery spasm is common during transradial procedures and the most common cause for procedural failure.

Methods We randomly assigned, in a factorial design, 790 patients scheduled for a transradial coronary procedure to long (23-cm) or short (13-cm) and hydrophilic-coated or uncoated introducer sheaths. The primary outcome measure was clinical evidence of radial artery spasm, and secondary outcome measures were patient discomfort and local vascular complications.

Results Procedural success was achieved in 96% of the cases, and radial artery spasm accounted for 17 of 33 failed cases. There was significantly less radial artery spasm (19.0% vs. 39.9%, odds ratio [OR]: 2.87; 95% confidence interval [CI]: 2.07 to 3.97, $p < 0.001$) and patient reported discomfort (15.1% vs. 28.5%, OR: 2.27; 95% CI: 1.59 to 3.23, $p < 0.001$) in patients receiving a hydrophilic-coated sheath. No difference was observed between long and short sheaths. Radial artery occlusion was observed in 9.5% of the patients and was not influenced by sheath length or coating. A local large hematoma or arterial dissection was seen in 2.6% of the patients with no difference in groups allocated at randomization. Younger age, female sex, diabetes, and lower body mass index were identified as independent predictors of radial artery spasm.

Conclusions Hydrophilic sheath coating, but not sheath length, reduces the incidence of radial artery spasm during transradial coronary procedures. (J Am Coll Cardiol Intv 2010;3:475–83) © 2010 by the American College of Cardiology Foundation

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Manuscript received December 14, 2009; revised manuscript received February 18, 2010, accepted March 4, 2010.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 5, 2010
MAY 2010:475–83

Transradial coronary artery access has been employed for diagnostic and interventional procedures since it was first described by Campeau in 1989 (1) and its improvement described by Kiemeneij and Laarman in 1993 (2). Improvement in the technique and the equipment has led to the use of the radial approach for diagnostic and interventional procedures in varied coronary syndromes (3–8). The radial approach has become increasingly popular due to lower vascular complications rates, reduced procedural costs, high procedural success, early patient mobilization, and reduced hospitalization when compared with the femoral approach

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(9,10). Transradial intervention has been found to be safe and feasible in a large spectrum of clinical practice (11–14). Radial artery spasm (RAS) is one of the most common complications of the technique, causing significant discomfort to the patient and reducing the procedural success rate (15–21). A number of small studies have shown that sheaths and catheters with hydrophilic coating can reduce spasm and cause less discomfort to the patient (22–25). Long introducer sheaths are used by some operators to reduce spasm and difficulty in catheter manipulation. However, there are no studies assessing the impact of introducer sheath length on the incidence of RAS during transradial angiography and intervention.

Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
OR = odds ratio
RAO = radial artery occlusion
RAS = radial artery spasm

The objectives of this study are to assess the impact of length and hydrophilic coating of the introducer sheath on the incidence of RAS, radial artery occlusion (RAO) rates, and local vascular complications in patients undergoing coronary angiography or intervention via the radial artery.

Methods

Patient population. Patients considered for coronary catheterization and intervention by the transradial approach were screened for participation. Exclusion criteria were kept to a minimum but were as follows: hemodynamically unstable patients; patients with forearm arteriovenous fistulae or with chronic renal failure, previous ipsilateral transradial procedure; and patients unwilling to participate. All patients had an Allen test performed, but were not excluded on the basis of an unfavorable result.

The study conformed to the standards set by the Declaration of Helsinki, and ethical approval was obtained from the Liverpool Local Research Ethics Committee. All patients gave written informed consent.

Study protocol and randomization. This is a prospective randomized study and patients were assigned in a factorial design to 1 of 4 different introducer sheaths: long (23-cm) hydrophilic-coated, long uncoated, short (13-cm) hydrophilic-coated, and short uncoated (Cook Medical, Inc., Bloomington, Indiana). Randomization was performed by computer-generated random numbers from a proprietary database. The randomization was performed in the blocks of 8 to keep an equal number of patients in different groups throughout the study period. The randomization list was generated and patients were assigned to the randomized intervention on an intention-to-treat basis. The person responsible for patient registration and randomization (S.R.) was not in any way concerned or involved in the treatment of the patient. The treating doctor was informed by the investigator of the randomization code prior to the procedure.

RADIAL ARTERY CANNULATION. The radial artery was approached with the arm extended and supported, with the wrist in mild hyperextension. Local anesthetic (2% lignocaine) was given after skin preparation at the puncture site. The radial artery was punctured with a 21-gauge arterial needle through which a 0.018-inch platinum-tipped nitinol guidewire was introduced. Following this, the needle was withdrawn and a small skin incision was made. A 6-F introducer sheath with a dilator taper length of 2.5 cm was inserted over the guidewire. The sheath length was determined by the randomization. All introducer sheath kits used were from the same manufacturer (Cook Medical Inc.). A weight-adjusted dose of heparin was administered into the central circulation following the introduction of the first catheter. Routine use of a vasodilator cocktail was avoided (to abolish the impact of vasodilator agent on primary end point, and this is also a standard practice at our institution), and intra-arterial vasodilators (nitroglycerin and verapamil) were only used in the event of RAS. The rest of the procedure was performed according to the operator's preference.

All introducer sheaths were removed immediately after the procedure and hemostasis was achieved in the catheterization laboratory by either TR Band (Terumo Medical Corp., Somerset, New Jersey) or Radistop (RADI Medical Systems, St. Paul, Minnesota).

Patients were followed up clinically according to usual post-procedural care with most patients reviewed as outpatients after 4 to 6 months. At the time of follow-up, complications related to radial artery patency and late access site were reassessed.

Outcome measures. The primary outcome measure was the incidence of operator-defined RAS. Secondary end points were the discomfort experienced by the patient during sheath manipulation, procedural success rates, rates of RAO, local vascular complications, and local inflammatory reactions.

Definitions. RAS. Clinical RAS was defined as pain perceived by the patient and or difficulty perceived by the operator during insertion, manipulation, and/or withdrawal

of the introducer sheath or catheter. This was assessed by questionnaires completed by operators and patients separately.

Operators reported the presence of spasm on the following scores:

1. Patient reported presence of continuous forearm pain.
2. Patient reported forearm pain only during catheter manipulation.
3. Patient reported forearm pain during sheath insertion or retrieval.
4. Firm grip of the catheters during manipulation.
5. Augmented resistance to sheath retrieval.

This excludes cases of difficult catheter manipulation because of severely tortuous radial or subclavian artery. Radial artery spasm was defined as the occurrence of at least 2 features or only 1 feature and a need for intra-arterial vasodilators.

Patients reported the pain perceived during removal of the introducer sheath on the following score:

1. Nothing felt.
2. Noticeable sensation but no pain.
3. Mild pain.
4. Significant (moderate) pain.
5. Unbearable (severe) pain.

Radial artery spasm was considered present when patient reported moderate or severe pain on sheath withdrawal.

ASSESSMENT OF RADIAL ARTERY PATENCY. Radial artery patency was assessed before patient's discharge and at follow-up. Patients were assessed at the time of routine follow-up scheduled for 4 to 6 months. RAO was defined as the absence of palpable radial artery pulsation confirmed by an abnormal reverse Allen test (26), plethysmography and oximetery test or absent flow signal on handheld Doppler. In brief, reverse Allen test is performed by compressing both radial and ulnar arteries and having the patient make a fist several times. In contrast to Allen test in which pressure on the ulnar artery is released, for the reverse Allen test, occlusion of the ulnar artery is maintained while pressure on the radial artery is released. If there is return of blush to the palm within 10 s, the test is considered positive and indicates patency of radial artery. Similarly, plethysmography and oximetry test was performed as described, and the test was recorded with the occlusion of the ulnar artery to assess radial artery patency.

ACCESS SITE HEMOSTASIS AND LOCAL COMPLICATIONS. Vascular complications were assessed after the removal of compression device and were defined as oozing (leakage of blood from puncture site requiring digital pressure), ecchymosis (bleeding into subcutaneous tissue planes causing bluish-purple discoloration >4 cm in diameter); local hematomas were classified as small (<2 cm in all diameter) and large (>2 cm in diameter). Radial, brachial, and subclavian artery dissections were reported if proven angiographically.

ASSESSMENT OF ULNO-PALMAR CIRCULATION. All patients were assessed for ulno-palmar arch circulation with the use of modified Allen test and the use of plethysmography and oximetry test as described by Barbeau et al. (27). The time taken for Allen test was recorded in seconds and plethysmography and oximetry test was graded in 4 categories. Plethysmography readings were divided into 4 types: A = no damping of pulse tracing immediately after radial artery compression; B = damping of pulse tracing; C = loss of pulse tracing followed by recovery of pulse tracing within 2 min; D = loss of pulse tracing without recovery within 2 min. Oximetry results were either positive or negative during radial artery compression.

Procedural success was defined as successful completion of the intended coronary procedure via the radial route.

Statistical analysis. Clinical RAS is reported to occur in 20% to 30% of cases in studies in the literature, using several qualitative and quantitative definitions. We assumed that a 50% reduction in the incidence of RAS would be clinically significant. A factorial design was used to compare hydrophilic-coated and uncoated sheaths and short and long sheaths. We calculated that we needed 375 patients in each of the 2 arms of different introducer sheath types to detect this difference with significance level of 0.02 (alpha error) and power of 95% (beta error 0.05). We decided to recruit 400 patients in each arm to compensate for missing cases.

Continuous variables are described as mean ± SD and compared using Student *t* test. Categorical variables are expressed as frequencies and compared using chi-square tests and, where appropriate, Fisher exact test. The comparison between long introducer sheaths and short introducer sheaths and between coated and uncoated introducer sheaths uses a factorial design. Analysis of variance was applied to detect any interaction between coating and length of the introducer sheaths. Multivariate analysis was performed using logistic regression model to assess predictors of clinical RAS. Variables included in the model were age, sex, height, body weight, body mass index (BMI), diabetes, procedure time, and number of catheters used during the study. Variables were entered through forward stepwise analysis. All analyses were performed using SPSS version 15 (SPSS Inc., Chicago, Illinois).

Results

Patient population. Between November 2006 and January 2008, 794 patients were included in the study. During the initial 5 months, 570 patients were screened and 505 patients were included in the study. The most common reason for exclusion was previous ipsilateral transradial procedure (n = 60) and 5 patients refused to consent. The recruitment occurred in 2 distant time periods with a gap

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imposed by external factors. The remaining patients were recruited between July 2008 and January 2008; during this period, 344 patients were screened and 289 patients were included in the study: 40 patients were excluded because they had had previous ipsilateral transradial procedure, 10 patients refused to participate in the study, and another 5 patients were not included because of physician's preference. Out of these 794 patients, 4 patients underwent primary femoral approach (physician preference, protocol violation), and the results from 790 patients are included in this analysis.

Baseline characteristics. Patients were compared in 2 different analyses considering length and coating of the introducer sheath. Baseline characteristics as stratified by length and coating of the sheath are shown in Table 1.

The mean age was 62.88 years, and 74.2% of the patients were men. Patient age, height, weight, wrist circumference, BMI, male sex, hypertension, diabetes, hypercholesterolemia, and smoking incidence were similar in both groups. About two-thirds of patients presented with stable angina, and the proportion of patients with unstable presentations was similar in all groups. The procedure time and compression device usage were also similar in all groups.

Ulno-palmar circulation was assessed in all patients but was not an exclusion criterion. Ninety-four percent of the patients had a favorable Allen test and plethysmography and oximetry test, and 6% to 7% of patients had apparently unfavorable ulno-palmar circulation, which was similar in both groups.

Procedural success. Procedural success was high in both groups at 758 of 790 (96%) patients. RAS prevented the completion of the procedure in 17 (2.2%) cases. In 15 patients, we were unable to enter the radial artery or advance the catheter into the aorta because of unfavorable vascular anatomy, and 1 case was abandoned because of poor backup from the guide catheter.

Radial artery spasm. Operator-defined RAS was observed in 230 (29.4%) of the patients and 172 (21.8%) patients reported discomfort of moderate or severe intensity. There was significantly less clinical RAS (relative reduction 50%) observed in patients randomized to a hydrophilic sheath (Table 2). There was significantly less RAS (19.0% vs. 39.9%, odds ratio [OR]: 2.87; 95% confidence interval [CI]: 2.07 to 3.97, $p < 0.001$) and patient-reported discomfort (15.1% vs. 28.5%, OR: 2.27; 95% CI: 1.59 to 3.23, $p < 0.001$) observed in patients receiving a hydrophilic sheath.

Table 1. Baseline and Procedural Characteristics of the Study Population

Variables	All (N = 790)	Long (n = 396)	Short (n = 394)	p Value	Coated (n = 397)	Uncoated (n = 393)	p Value
Age, yrs	62.88 ± 11.14	62.74 ± 11.45	63.02 ± 10.83	0.732	62.66 ± 11.24	63.11 ± 11.05	0.573
Men	586 (74.2)	293 (74.0)	293 (74.4)	0.933	292 (73.6)	294 (74.8)	0.215
Hypertension	547 (69.2)	275 (69.4)	272 (69.0)	0.939	283 (71.3)	264 (67.2)	0.218
HL	719 (91.0)	360 (90.9)	359 (91.1)	1.00	366 (92.2)	353 (89.8)	0.264
DM	155 (19.6)	68 (17.2)	87 (22.1)	0.089	79 (19.9)	76 (19.3)	0.858
Current smoker	188 (23.8)	95 (24.0)	93 (23.7)	1.00	93 (23.4)	95 (23.9)	1.00
Allen test							
Not at all	46 (5.8)	16 (4.0)	30 (7.6)	0.031	23 (5.8)	23 (5.9)	1.00
PL+OX test							
Type D	56 (7.1)	25 (6.3)	31 (7.9)	0.409	28 (7.1)	28 (7.1)	1.00
Clinical presentation							
Stable angina	549 (69.5)	280 (70.7)	269 (68.3)		279 (70.3)	270 (68.7)	
ACS	241 (30.5)	116 (29.3)	125 (31.7)	0.487	118 (29.7)	123 (31.3)	0.643
Wrist circumference, cm	17.24 ± 1.20	17.23 ± 1.23	17.25 ± 1.16	0.817	17.24 ± 1.27	17.24 ± 1.12	0.984
Height, cm	168.84 ± 9.76	168.69 ± 10.07	168.98 ± 9.44	0.681	169.05 ± 10.36	168.61 ± 9.10	0.445
Weight, kg	83.65 ± 16.39	83.18 ± 16.63	84.13 ± 16.15	0.426	83.56 ± 16.60	83.75 ± 16.20	0.876
BMI, kg/m^2	29.27 ± 4.87	29.16 ± 4.79	29.38 ± 4.96	0.539	29.16 ± 4.83	29.38 ± 4.92	0.524
Number of catheters used	1.68 ± 0.85	1.68 ± 0.86	1.68 ± 0.85	0.961	1.67 ± 0.88	1.69 ± 0.82	0.740
Time sheath in situ, min	50.40 ± 28.28	50.24 ± 27.72	50.55 ± 28.89	0.880	47.36 ± 25.98	53.57 ± 30.21	0.003
Compression device							
Radistop	395 (50.0)	196 (49.5)	199 (50.5)		198 (49.9)	197 (50.1)	
TR Band	395 (50.0)	200 (50.5)	195 (49.5)	0.831	199 (50.1)	196 (49.9)	1.00
Procedure							
Diagnostic	61 (7.7)	32 (8.1)	29 (7.4)		37 (9.3)	24 (6.1)	
PCI	729 (92.3)	364 (91.9)	365 (92.6)	0.790	360 (90.7)	369 (93.9)	0.109

Values are mean ± SD or n (%).

ACS = acute coronary syndromes; BMI = body mass index; DM = diabetes mellitus; HL = hyperlipidemia; PCI = percutaneous coronary intervention; PL+OX = plethysmography and oximetery test.

Table 2. Outcomes of the Study Patients

Variables	All (N = 790)	Long (n = 396)	Short (n = 394)	p Value	Coated (n = 397)	Uncoated (n = 393)	p Value
Operator RAS	230 (29.4)	110 (27.9)	120 (30.8)	0.389	75 (19.0)	155 (39.9)	<0.001
Patient discomfort	172 (21.8)	85 (21.5)	87 (22.2)	0.414	60 (15.1)	112 (28.5)	<0.001
Local complication							
Large hematoma	17 (2.2)	8 (2.1)	9 (2.3)	0.812	3 (0.8)	14 (3.7)	0.006
Noncoronary dissection	3 (0.4)	0 (0)	3 (0.8)	1.00	1 (0.3)	2 (0.5)	1.00
RAO at discharge	73 (9.5)	31 (8.0)	42 (10.9)	0.178	35 (8.9)	28 (10.0)	0.624
Late complication (n = 625)	625	324	301		315	310	
Abscess	9 (1.4)	5 (1.5)	4 (1.3)		9 (2.8)	0 (0)	
Infection	12 (1.9)	6 (1.8)	6 (2.0)	1.00	11 (3.5)	1 (0.3)	0.0001
Pseudoaneurysm	1 (0.1)	0 (0)	1 (0.3)	0.510	1 (0.3)	0 (0)	0.570
RAO at follow-up (n = 625)	43 (6.9)	27 (8.3)	16 (5.3)	0.116	24 (7.6)	19 (6.1)	0.436

Values are n (%) or n.
RAO = radial artery occlusion; RAS = radial artery spasm.

No significant difference was observed between the groups receiving long and short sheaths.

An interaction test was applied to investigate the interaction between length and coating of the introducer sheath. There was no significant interaction observed between length and coating for operator-defined RAS ($p = 0.108$) and patient-assessed RAS ($p = 0.631$).

Local vascular complications. RAO at the time of discharge was observed in 9% of the patients, which was similar in both groups as shown in Table 2 (9.6% vs. 8.9%, $p = 0.892$, in Radistop and TR Band groups). None of these patients exhibited any clinical evidence of compromised perfusion of the hand.

A large local hematoma or arterial dissection was seen in 17 patients (2.2%) as shown in Table 2. The rates were similar in all groups and all access-related complications were managed conservatively. There was a slightly higher incidence of a large local hematoma in patients randomized to an uncoated sheath. Minor complications such as small hematoma, ecchymosis, and oozing were observed in about 20% of the patients in each group.

Predictors of clinical RAS. As shown in Table 3, several factors were associated with occurrence of operator-defined RAS during transradial procedures. Patients with spasm were younger and were more frequently female. There was a significantly higher incidence of spasm when an uncoated sheath was used. Patients with spasm were more frequently diabetic, had smaller wrist circumferences, and had lower body weight. Other baseline characteristics, ulno-palmar circulation, clinical presentation, introducer sheath length, procedure time, and number of catheters used were not found to be associated with RAS.

In logistic regression analysis, the use of uncoated sheath, young age, female sex, diabetes, and lower BMI were shown to be independent predictors of RAS in patients undergoing transradial coronary procedures (Table 4).

Long-term follow-up for late complications. Follow-up was completed in 625 patients (79.1%) and persistent RAO was observed in 43 patients (6.9%) (8.0% vs. 5.6%, $p = 0.273$, in Radistop and TR Band groups). There was no difference seen in RAO rates between the groups receiving hydrophilic and uncoated sheaths; however, there was a higher incidence of RAO at follow-up in patients receiving longer sheaths (8.3% vs. 5.3%, $p = 0.042$). In all affected patients, the RAO was asymptomatic.

Local infection or abscess at the radial artery puncture site was reported by 21 patients (3.4%) with no difference between the long and short sheath groups. There was a significantly higher incidence of late local access site swelling and discomfort in patients randomized to hydrophilic sheaths (5.1% vs. 0.3%, $p = 0.001$). These symptoms were usually noticed after 2 to 4 weeks, often with a remitting and relapsing course, and a majority were treated conservatively with antibiotics. One patient underwent local surgical drainage with no long-term adverse effects.

Discussion

To our knowledge, this is the first prospective, large, randomized study comparing the clinical efficacy of several introducer sheaths in the prevention of RAS during unselected coronary procedures. The primary aim of our study is to assess the impact of length and coating of introducer sheath on the incidence of clinically relevant spasm during transradial coronary procedures. In the current study, there was a 50% reduction in RAS with a hydrophilic sheath, with 40.5% of patients assigned to an uncoated sheath experiencing RAS compared with only 19.1% in the hydrophilic sheath group. There were higher occurrences of forearm pain and the augmented resistance during sheath retrieval with the use of uncoated sheath as compared to hydrophilic sheath (42.4% vs. 20.9%, $p < 0.001$; and 37.4% vs. 11.5%,

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Table 3. Baseline Correlates of Patients With RAS

Variables	All (N = 783)	No RAS (n = 553)	RAS (n = 230)	p Value	OR	95% CI
Age, yrs	62.88 ± 11.14	63.74 ± 10.87	60.86 ± 11.52	0.001	1.041	1.01–1.07
Sex						
Male	581 (74.2)	438 (79.2)	143 (62.2)			
Female	202 (25.8)	115 (20.8)	87 (37.8)	<0.001	1.750	1.41–2.16
Hypertension	542 (69.2)	383 (70.7)	159 (69.1)	1.000	1.004	0.79–1.27
Hyperlipidemia	714 (91.2)	507 (91.7)	207 (90.0)	0.489	1.150	0.80–1.63
Diabetes	155 (19.8)	97 (17.5)	58 (25.2)	0.018	1.585	1.09–2.29
Current smoking	188 (24.0)	127 (23.0)	61 (26.5)	0.808		
Allen test						
Not at all	46 (5.9)	37 (6.7)	9 (3.9)	0.180		
PL+OX						
Type D	56 (7.2)	46 (8.3)	10 (4.3)	0.049		
Clinical syndrome						
Stable angina	548 (70.0)	392 (70.9)	156 (67.8)			
ACS	235 (30.0)	161 (29.1)	74 (32.1)	0.898		
Length of the sheath						
Long	394 (50.3)	284 (51.4)	110 (47.8)			
Short	389 (49.7)	269 (48.6)	120 (52.2)	0.389	1.152	0.84–1.56
Coating of the sheath						
Hydrophilic	395 (50.4)	320 (57.9)	75 (32.6)			
Uncoated	388 (49.6)	233 (42.1)	155 (67.4)	<0.001	2.838	2.05–3.92
Height, cm	168.84 ± 9.76	169.6 ± 9.7	166.8 ± 9.5	<0.001	1.022	1.01–1.03
Weight, kg	83.65 ± 16.39	85 ± 16.24	80.3 ± 16.32	<0.001	1.056	1.02–1.09
BMI, kg/m^2	29.27 ± 4.87	29.48 ± 4.95	28.76 ± 4.64	0.067	1.021	1.00–1.05
Wrist circumference, cm	17.24 ± 1.20	17.37 ± 1.17	16.92 ± 1.19	<0.001	1.021	1.01–1.03
Time sheath in situ, min	50.40 ± 28.28	51.13 ± 27.95	48.69 ± 29.04	0.001	1.05	0.96–1.15
Number of catheters used	1.68 ± 0.85	1.69 ± 0.87	1.67 ± 0.82	0.829	1.01	0.93–1.09

Values are mean ± SD or n (%).
CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

$p < 0.001$, respectively). These results are similar to those in previous small studies (23,24,28). These reductions in spasm were also reflected in the level of discomfort experienced by the patient during withdrawal of the introducer sheath. In the uncoated group, 29.1% of patients experienced moderate to severe discomfort compared with only 15.3% experiencing this discomfort in the hydrophilic sheath group. Dery et al. (23) demonstrated significant reduction in peak traction force (265 ± 167*g* vs. 865 ± 318*g*) and mean maximal pain score (0.6 ± 1.2 vs. 4.8 ± 2.9) during withdrawal of hydrophilic-coated sheath. However, there is a potential for bias in this study as they used introducer sheaths of different lengths. Similarly, Kiemeneij et al. (22) demonstrated a significant reduction in maximal pull-back force (0.24 ± 0.31 kg vs. 0.44 ± 0.33 kg, p = 0.003) and patient discomfort (7% vs. 27%, p = 0.02) with the use of a hydrophilic-coated sheath in a randomized study of 90 patients. Saito et al. (24) have also shown that a hydrophilic coating on the introducer sheath reduced friction resistance by 70% with reduced trends in the incidence of spasm.

Table 4. Independent Predictors of RAS

Variables	OR	95% CI	p Value
Female sex	2.01	1.31–3.09	0.001
Age, yrs	0.96	0.95–0.98	<0.001
Diabetes mellitus	1.84	1.22–2.76	0.003
Wrist circumference, cm	0.86	0.72–1.02	0.096
BMI, kg/m^2	0.96	0.92–1.00	0.059

Abbreviations as in Tables 1, 2, and 3.

We have not demonstrated any significant difference in the overall incidence of spasm between long and short sheaths. In this study, 30.9% of patients assigned to short sheath group experienced spasm compared with 28.9% of the patients in the long sheath group. These results were similar when compared to the level of discomfort noticed by the patient during pull-back of the sheath. We have not come across any study comparing the performance of different length sheaths in the literature.

Overall in our study, we have observed that one-quarter of the patients experienced some degree of RAS, similar to that noticed in other studies (15–21). Although, the proce-

dure was successfully completed via the radial route in 96% of the cases, RAS was the most common cause of procedural failure, accounting for about one-half of failed cases, with tortuous vascular anatomy accounting for another one-third of failures. The radial artery could not be punctured in only 3 cases, and in 1 patient, the procedure could not be completed because of poor guide catheter backup. In the majority of these patients, the procedure was successfully completed via the other radial artery and femoral access was needed in a few patients. These results are consistent with other large studies reported in the literature. The ACCESS study (9) has shown procedural success rates of 93% with radial approach with the major causes of procedural failure being an inability to puncture the radial artery or RAS.

We have also identified factors associated with occurrence of spasm in patients undergoing transradial coronary procedures. Young age and female sex were identified as independent predictors for spasm, which is consistent with previous studies (29,30). Small wrist circumference, lower height, and lower weight were also found to be associated with high incidence of spasm. It could be postulated that all these factors may reflect a small radial artery size in these patients that can predispose to clinically evident spasm. We did not measure the size of radial artery, but 1 previous study (28) has shown that a ratio of radial diameter to sheath size of <1:1 predisposes to spasm. High levels of anxiety and increased circulating levels of catecholamines in the young patients could also predispose to spasm, and females have been reported to have smaller radial artery diameter (28).

Previous studies have reported RAO rates ranging from 3% to 10% (9,31,32). RAO following a transradial coronary procedure was observed before discharge in 9% of our patients. Leferve et al. (33) has reported high (30%) RAO rates with 1,000 U of heparin. In our study, all patients undergoing coronary intervention received weight-adjusted heparin (70 U/kg). The administration of heparin in diagnostic cases was left at the operator's discretion, and 11.8% of patients did not receive any heparin. RAO rate was 7.2% in patients undergoing coronary angioplasty and receiving weight-adjusted heparin, similar to that reported in literature.

Persistent RAO was observed in only 43 (6.9%) patients at follow-up, and no patient reported any symptoms of compromised perfusion. We observed a high incidence of RAO in patients with documented spasm during their procedure (14.5% vs. 7.4%, $p = 0.003$). We have not excluded any patient on the basis of Allen test, and there is an ongoing debate about denying radial access to patients with abnormal Allen test (34,35). There is no evidence so far that a normal Allen test is required for the safe undertaking of transradial procedure (36). However, prospective studies involving a large number of patients looking at the incidence and consequences of RAO based on Allen test are needed to answer this question.

In this study, the incidence of large local hematoma or arterial dissection was low. A large hematoma occurred in 17 (2.2%) patients and radial/brachial or subclavian dissection was observed in 3 (0.3%) cases. However, none of these patients needed blood transfusion or surgical intervention. However, about 20% patients had oozing needing manual pressure after compression device removal, ecchymosis, or small hematoma.

There have been reports of allergic or inflammatory reaction at the radial artery puncture site following the use of hydrophilic-coated sheaths (37,38). In this study, we have found a high incidence of local inflammatory reaction in the patients randomized to a hydrophilic-coated sheath. These reactions usually occurred 2 to 4 weeks after the procedure with relapsing and remitting course and usually presented as a small purple colored painful nodule. A majority of patients with this reaction were treated conservatively with antibiotics and analgesics. This phenomenon is seen with hydrophilic-coated sheaths and can cause considerable discomfort to the patient, though has no known long-term sequelae. It has been postulated that the hydrophilic polymer is left behind at the puncture site following the removal of the sheath, causing a local allergic reaction and inflammatory abscess.

The transradial approach for coronary procedures has become more popular over the years and has been used in all clinical situations. The British Cardiovascular Intervention Society audit returns (39) reported that 28.1% of the coronary interventions performed in the United Kingdom in 2007 were done via the transradial route. RAS is the most commonly encountered complication and can result in significant discomfort to the patient and can result in procedural failure in some cases. A hydrophilic coating on the sheath theoretically induces less friction and trauma to the endothelial lining of the radial artery and therefore causes less spasm and consequent discomfort to the patient. RAS results in difficulty in removing the introducer sheath and causes more damage to the endothelium of the radial artery. Theoretically the physical trauma caused by the spasm and the introducer sheath can result in damage to the endothelium and thereby predispose to thrombus formation. This could be one of the reasons for observing a higher incidence of RAO in patients with documented RAS. This is the first study observing this association and can be hypothesis-generating for future large studies.

The ramifications of RAO and injury are important not only in patients undergoing repeat coronary procedures, but also in the patients in whom the radial artery may be used as a conduit for coronary artery bypass surgery or in patients needing an arteriovenous fistula for hemodialysis.

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Study limitations. First, our study was single-blinded, and this could result in some bias, but we have included both operator- and patient-defined RAS as end points. We have found a statistically significant association between operator-defined RAS and discomfort experienced by the patient ($p < 0.0001$). Second, a qualitative definition of RAS was used in the study, increasing the potential effect of bias. However, a close association has been shown between quantitative measurement of spasm and a qualitative definition (18). Third, avoidance of vasodilator use at the time of introducer sheath insertion might influence the incidence of RAS. However, our study was assessing the impact of different introducer sheaths on the incidence of clinical RAS and the role of vasodilator is previously known.

Conclusions

We have shown in this randomized study that there is a significant reduction in the incidence of RAS and patient discomfort with the use of a hydrophilic coating on the introducer sheath during transradial coronary procedures. We have not found any significant effect of sheath length on the incidence of spasm. We have also identified young age, female sex, diabetes, and low BMI to be independent predictors of RAS.

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Key Words: transradial coronary procedures ■ radial artery spasm ■ randomized study ■ radial artery occlusion ■ introducer sheaths.

Catheterization and Cardiovascular Interventions 76:660–667 (2010)

A Randomized Comparison of TR Band and Radistop Hemostatic Compression Devices After Transradial Coronary Intervention

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Background: The transradial route for coronary intervention has proven to be safe, effective, and widely applicable in different clinical situations. Several compressive hemostatic devices have been introduced that have shown to be safe and are effective in achieving hemostasis. Methods: Seven hundred ninety patients were randomly assigned to receive either TR band or Radistop hemostatic compression devices after transradial coronary procedure. The outcome measures were patient tolerance of the device, local vascular complications, and the time taken to achieve hemostasis. Results: The mean age was 62.88 years, and 74.2% of the patients were men. Patient age, height, weight, wrist circumference, body mass index, male sex, hypertension, diabetes, hypercholesterolemia, and smoking incidences were similar in both groups. There were significantly more patients reporting no discomfort in the TR band group compared to the Radistop group (77% vs. 61%; $P = 0.0001$). Patients in the Radistop group reported significantly more pain across all categories of severity and three patients in the Radistop group were crossed over to TR band because of severe discomfort. Oozing and ecchymosis were seen in about 16% of the patients. Local small hematoma and large hematoma were seen in 5.4% and 2.2% patients respectively, and similar in both groups. Radial artery occlusion at the time of discharge was seen in 9.2% of the patients though only 6.8% showed persistent occlusion at the time of follow-up. The time taken to achieve hemostasis was significantly longer in the TR Band group (5.32 ± 2.29 vs. 4.83 ± 2.23 hr; $P = 0.004$). There was significantly higher incidence of radial artery occlusion in patients with smaller wrist circumference, the patients who experienced radial artery spasm during the procedure, and patients with no heparin administration during the procedure. Conclusions: We have shown in a randomized comparison of Radistop and TR band that both devices are safe and effective as hemostatic compression devices following transradial procedures. However, more patients felt discomfort with the Radistop device and the time taken to achieve hemostasis was longer with TR band.

Key words: TRAD, transradial cath; CLOS, closure–vascular access; PCI, percutaneous coronary intervention; COMP, complications adult cath/intervention

INTRODUCTION

The transradial route for coronary intervention has proven to be safe, effective, and widely applicable in different clinical situations [1–10]. The radial approach has been shown to reduce access site vascular complications when compared to the femoral approach [11,12]. Another advantage is early mobilization and thereby early discharge from the hospital, reducing staff workload and overall cost [11,12]. As the arterial sheath can be removed immediately after the procedure, with mechanical compression applied over the puncture site, early hemostasis can be achieved. This allows early mobilization and discharge from hospital. Several compressive hemostatic devices have been

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Conflict of interest: No conflict of interest.

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Received 12 February 2010; Revision accepted 16 April 2010

DOI 10.1002/ccd.22615
Published online 6 October 2010 in Wiley Online Library (wileyonlinelibrary.com).

introduced that have shown to be safe and are effective in achieving hemostasis [13–15]. However, no studies have compared different hemostatic devices and their impact on the patient comfort, time taken to achieve hemostasis, and on local vascular complications.

Two commonly used compressive devices used to achieve hemostasis after transradial access are the Radistop (RADI, Uppsala, Sweden), and the TR Band (Terumo, Japan). Both have been shown to safely achieve hemostasis in large populations of patients. These devices allow selective application of controlled pressure over the radial artery, thereby allowing sustained arterial flow and venous return. At our center we routinely use TR band compression device following transradial procedures.

The objectives of our study are to compare the effects of Radistop and TR band on patient comfort, time taken to achieve hemostasis, and local vascular complications.

MATERIALS AND METHODS

Patient Population

Patients considered for coronary catheterization and intervention via the radial approach were screened for participation. Hemodynamically unstable patients, patients with forearm arterio-venous fistulae or with chronic renal failure, previous ipsilateral transradial procedure and patients unwilling to participate were excluded from the study. All patients had an Allen's test performed, but were not excluded on the basis of an unfavorable result.

The study conformed to the standards set by the Declaration of Helsinki and ethical approval was obtained from the Liverpool Local Research Ethics Committee.

Study Design

This is a prospective randomized study and patients were assigned to one of the two different hemostatic compression devices: TR Band and Radistop. Randomization was performed by computer-generated random numbers from a proprietary database. The person responsible for patient registration and randomization (SR) was not in any way concerned or involved in the treatment of the patient. The treating doctor was informed by the investigator of the treatment assigned prior to the procedure.

Outcome Measures

The outcome measures were patient tolerance of the device assessed by the questionnaire, local vascular complications, and the time taken to achieve hemostasis.

Assessment of Radial Artery Patency

Radial artery patency was assessed prior to the patient's discharge and at follow-up. Radial artery occlusion was defined as the absence of palpable radial artery pulsation and one of the following three confirmatory tests; abnormal reverse Allen's test, negative plethysmography (PL), and oximetry test during ulnar artery occlusion or absent Doppler flow signal on hand held Doppler.

Access Site Hemostasis and Local Complications

Vascular complications were assessed after the removal of compression device and were defined as oozing (leakage of blood from puncture site requiring digital pressure), ecchymosis (bleeding into subcutaneous tissue planes causing bluish-purple discoloration $\geq$4 cm in diameter), local hematomas were classified as small ($\leq$2 cm in all diameter) and large ($\geq$2 cm in diameter).

Assessment of Patient Comfort Following Application of Compressive Device

The patient's comfort level at the site of application of device was assessed during the later wearing of the device using a short form of the McGill Pain Questionnaire (SF-MPQ) [16]. This includes the patient's assessment of the compression device on 15 descriptors, rated on an intensity scale of none, mild, moderate, and severe. Therefore, the patient's discomfort following application of the compression device was categorized as no discomfort, mild discomfort, moderate discomfort, and severe discomfort. The patients were particularly asked to describe the discomfort due to the compression device at the site of application and not mix up with other discomfort in the arm during the procedure.

Assessment of Ulno-Palmar Circulation

All patients were assessed for ulno-palmar arch circulation prior to the procedure with the use of modified Allen's test and the use of PL and oxymetry (OX) testing as described by Barbeau et al. [17]. The time taken for return of color to the hand during an Allen's test was recorded in seconds and PL + OX test was graded in four categories. PL readings were divided into four types: A, no damping of pulse tracing immediately after radial artery compression; B, damping of pulse tracing; C, loss of pulse tracing followed by recovery of pulse tracing within 2 min; D, loss of pulse tracing without recovery within 2 min. Oxymetry results were either positive or negative during radial artery compression.

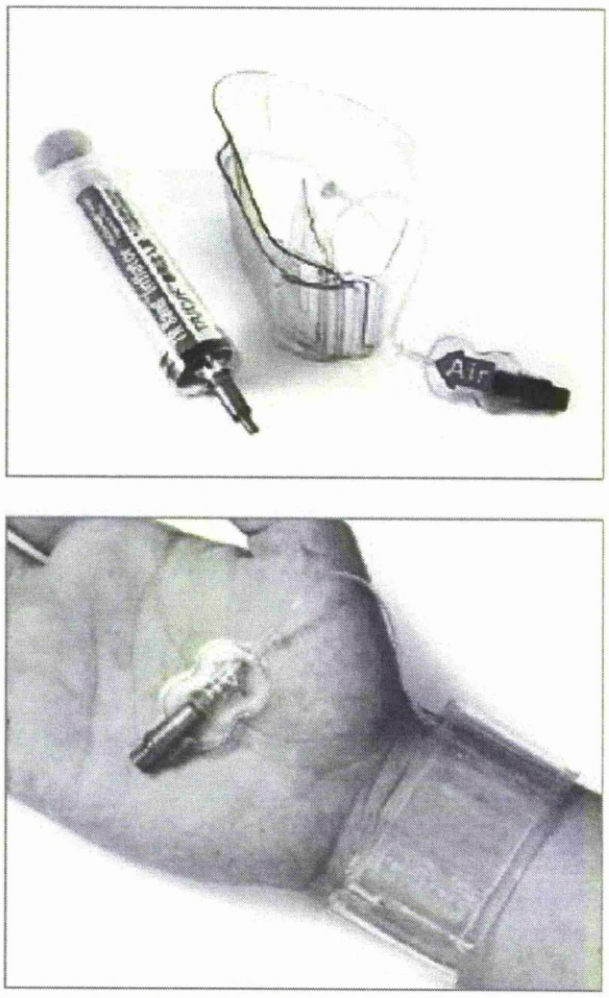

Fig. 1. TR Band compression device: showing the band, and syringe used to inflate and deflate compression pad, top panel. Bottom panel shows its application on the wrist at the radial artery puncture site. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Radial Artery Cannulation

The radial artery was punctured with anterior wall puncture with a 21-gauge arterial needle through which a 0.018-inch platinum-tipped nitinol guidewire was introduced. Following this, the needle was withdrawn and a small skin incision was made. A 6F introducer sheath with a dilator taper length of 2.5 cm was inserted over the guidewire. All introducer sheath kits used were from the same manufacturer (COOK MEDICAL, Bloomington, IN). Routine use of a vasodilator cocktail was avoided and intra-arterial vasodilators (nitro-glycerine and verapamil) were only used in the event of radial artery spasm. The rest of the procedure was performed according to the operator's preference.

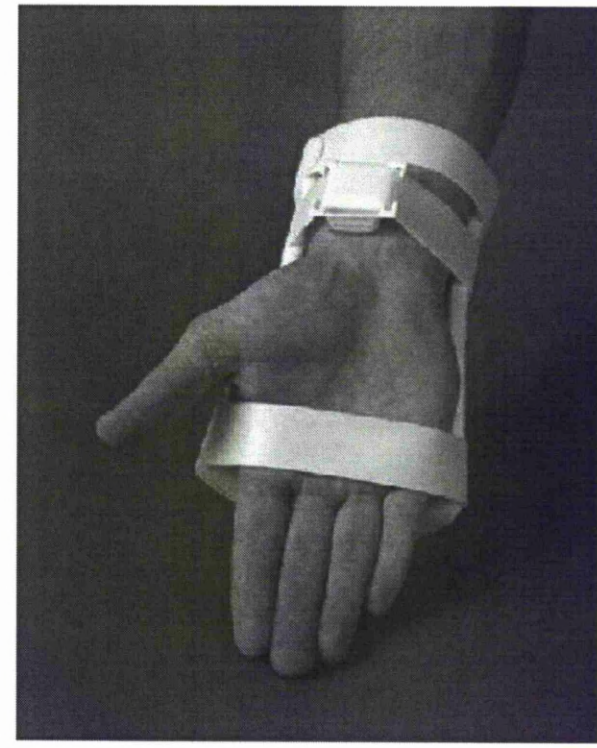

Fig. 2. Radistop application over the radial artery puncture site after a transradial procedure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Introducer Sheath Removal and Hemostasis

All introducer sheaths were removed immediately after the procedure and hemostasis achieved in the catheterization laboratory by the physician using either TR band (Fig. 1) or Radistop (Fig. 2) as per randomization. The aim with each device is to apply just enough pressure to stop the bleeding whilst maintaining forward flow in the radial artery. Radistops were applied according to the manufacturer's instructions. The radial pulse distal to the compression site was checked after application and if the pulse was not palpable the Velcro was loosened slightly until the pulse became palpable or bleeding started. Similarly, the TR Band was applied according to the manufacturer's instructions with air from the occlusive balloon being slowly removed until a show of blood was visible, and then reintroducing 1–2 ml of air.

Reduction in the compressive pressure was started after 1 hr of the procedure observing for any bleeding and thereafter checking every 30 min until hemostasis was achieved and the device was removed. The compression devices were managed by the nursing staff on the wards as per above mentioned protocol.

Baseline characteristics, including age, sex, body mass index, and wrist circumference were recorded, as

were data on the procedure, including the number of catheters used, procedure time, and the time taken to achieve hemostasis. All patients were assessed prior to discharge to determine the outcomes as defined. All data were recorded on a clinical record form and entered into a customized database (Access 2003).

Procedure time was considered as the period ranging from sheath insertion to sheath withdrawal. Time taken to achieve hemostasis was defined as the time period ranging from application of the compression device to its complete removal.

Patients were followed up clinically as usual post-procedural care, with most patients reviewed in outpatients after 4–6 months. At the time of follow-up, radial artery patency and late complications were reassessed.

Statistical Analysis

Continuous variables are described as mean ± SD and compared using Student's *t*-test. Categorical variables are expressed as frequencies and compared using chi-squared tests and, where appropriate, Fisher's exact test. Multivariate analysis was performed to assess predictors of radial artery occlusion. Variables included in the model were age, gender, height, weight, wrist circumference, diabetes, procedure time, use of heparin, occurrence of radial artery spasm, and time taken to achieve hemostasis. All analysis was performed using SPSS Version 15.

RESULTS

Patient Population

Between November 2006 and January 2008, a total of 794 patients were included in the study. During the initial 5 months, 570 patients were screened and 505 patients were included in the study. The most common reason for exclusion was previous ipsilateral transradial procedure (60 patients) and five patients refused to consent. The recruitment occurred in two distant time period with a gap imposed by external factors (interim analysis was performed and the recruitment was stopped temporarily). The remaining patients were recruited between July 2008 and January 2009, during this period 344 patients were screened and 289 patients were included in the study. Forty patients were excluded because they had previous ipsilateral transradial procedure, 10 patients refused to participate in the study and another five patients were not included because of physician's preference. Out of these 794 patients, four underwent femoral approach without an attempt at radial puncture (physician preference, protocol violation) and the results from 790 patients are included in this analysis. We perform 2,500 angioplasty procedures per year and 70% of these procedures are performed via radial route (Five radial operators and two femoral operators).

Baseline Characteristics

The mean age was 62.9 years, and 74.2% of the patients were male. Patient age, height, weight, wrist circumference, body mass index, sex, hypertension, diabetes, hypercholesterolemia, and smoking prevalence were similar in both groups as shown in Table I. About two-thirds of patients presented with stable angina and the proportion of patients with unstable presentations was similar in both groups. The use of long and hydrophilic sheaths was similar in both groups. The majority of the patients in this study received a weight-adjusted dose of heparin (70 U/kg) at the start of their procedure and further heparin as judged necessary by the operator during longer procedures. Coronary intervention was performed in 729 (92.3%) patients and the remaining patients (7.7%) underwent diagnostic procedures. The procedure time was similar in both groups.

Ulno-Palmar Circulation

Ulno-palmar circulation was assessed in all patients but an unfavorable result was not an exclusion criterion. Ninety-four percent of the patients had a favorable Allen's test and PL and oximetry test, and 6–7% patients had apparently unfavorable ulno-palmar circulation, similar in both groups.

Patient Discomfort During Application of Compression Device

There were significantly more patients reporting no discomfort in the TR band group compared to the Radistop group (77% vs. 61%; $P = 0.0001$) (Fig. 3). Patients in the Radistop group reported significantly more pain across all categories of severity and three patients in the Radistop group were crossed over to TR band because of severe discomfort.

Local Vascular Complications

As shown in Table II, local vascular complications were similar in both groups. Oozing and ecchymosis were seen in about 16% of the patients. Local small hematoma and large hematoma were seen in 5.4% and 2.2% patients, respectively. One patient (0.1%) developed pseudo-aneurysm that was treated surgically. Radial artery occlusion at the time of discharge was seen in 9.2% of the patients though only 6.8% showed persistent occlusion at the time of follow-up. No patient had symptoms or signs of ischemia distal to the occlusion.

TABLE I. Baseline and Procedural Characteristics of the Study Patients

Variables	All patients $N = 790$	Radistop $N = 395$	TR band $N = 395$	P value
Age, yrs, mean ± SD	62.9 ± 11.1	63.1 ± 10.7	62.70 ± 11.57	0.660
Male sex, n (%)	588 (74.4)	290 (73.4)	298 (75.4)	0.304
Hypertension	547 (69.2)	268 (67.8)	279 (70.6)	0.441
Hyperlipedemia	719 (91.0)	364 (92.2)	355 (89.9)	0.320
Diabetes Mellitus	155 (19.6)	77 (19.5)	78 (19.7)	1.000
Smoker				
Current	187 (23.7)	90 (22.8)	97 (24.5)	0.615
Ex Smoker	405 (51.3)	209 (52.9)	196 (49.6)	0.393
PL + OX Test				
Type D	56 (7.1)	26 (6.6)	30 (7.6)	0.818
Clinical syndrome				
Stable angina	555 (70.3)	279 (70.6)	276 (69.9)	0.912
ACS	235 (29.7)	116 (29.4)	119 (30.1)	0.823
Length of sheath				
Long	396 (50.1)	196 (49.6)	200 (50.6)	0.831
Short	394 (49.9)	199 (50.4)	195 (49.4)	
Coating of sheath				
Hydrophilic	397 (50.3)	198 (50.1)	199 (50.4)	1.000
Uncoated	393 (49.7)	197 (49.9)	196 (49.6)	
Wrist circumference, cm	17.24 ± 1.20	17.20 ± 1.16	17.27 ± 1.23	0.414
Height, cm	168.8 ± 9.8	168.7 ± 9.6	169.0 ± 9.9	0.632
Weight, kg	83.6 ± 16.4	83.1 ± 15.5	84.2 ± 17.2	0.367
BMI, kg/m^2	29.3 ± 4.9	29.2 ± 5.1	29.3 ± 4.7	0.810
Procedure time, min	50.4 ± 28.3	51.2 ± 28.4	49.6 ± 28.2	0.428
Number of caths used	1.7 ± 0.9	1.6 ± 0.8	1.7 ± 0.9	0.275
Heparin used during procedure	729 (92.3)	374 (94.7)	355 (89.9)	0.016

SD, standard deviation; PL + OX, plethysmography and oximetery; ACS, acute coronary syndrome; BMI, body mass index.

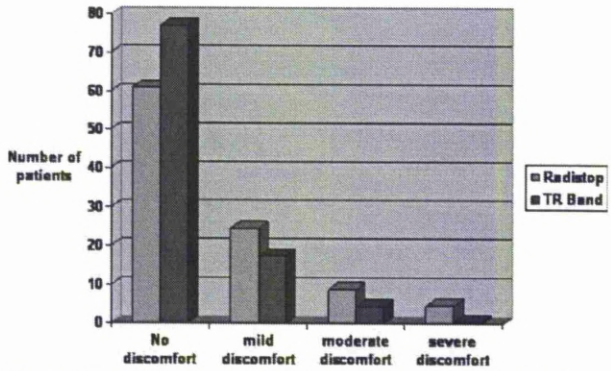

Fig. 3. Comparison of discomfort level during radial artery compression by Radistop and TR Band devices. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Time to Hemostasis

The time taken to achieve hemostasis was significantly longer in the TR Band group (Table II) and Fig. 4.

Predictors of Radial Artery Occlusion

As shown in Table III, several factors were associated with radial artery occlusion at the time of discharge following transradial procedures. Patients with radial artery occlusion tended to be younger and were more frequently female. There was a significantly higher incidence of radial artery occlusion in patients with a smaller wrist circumference, patients who experienced radial artery spasm during the procedure and patients with no heparin administration during the procedure. Other baseline characteristics, ulno-palmar circulation, clinical indication, time taken to achieve hemostasis, length or coating of the introducer sheath and type of hemostatic compression device used were not found to be associated with radial artery occlusion in our study.

In logistic regression analysis (Table IV) young age, smaller wrist circumference, occurrence of radial artery spasm during the procedure, and failure to administer heparin during the procedure were shown to be independent predictors of radial artery occlusion.

DISCUSSION

Both hemostatic compressive devices were effective and well tolerated, but patients complained of discomfort more frequently with the use of the Radistop device. Time taken to achieve hemostasis was significantly longer with the TR Band. Local access site

TABLE II. Outcomes of the Study Patients

Variable	All patients $N = 790$	Radistop $N = 395$	TR band $N = 395$	P value
Time taken to achieve hemostasis, hrs	5.1 ± 2.1	4.8 ± 2.2	5.3 ± 2.3	0.004
Patient discomfort				
Crossover to other device	3 (0.4)	3 (0.8)	0 (0)	0.249
Local complication				
Ecchymosis	87 (11.0)	42 (10.6)	45 (11.4)	0.918
Oozing	52 (6.6)	28 (7.1)	24 (6.1)	0.567
Large hematoma	17 (2.2)	6 (1.5)	11 (2.8)	0.327
Small hematoma	43 (5.4)	19 (4.8)	24 (6.1)	0.321
RAO (at discharge)	73 (9.2)	38 (9.6)	35 (8.9)	0.892
RAO (at F/U)	43 (6.8)	25 (8.0)	18 (5.6)	0.273

RAO, radial artery occlusion; F/U, at follow-up visit.

complications and radial artery occlusion rates were similar in both groups

To our knowledge, this is the first large randomized trial evaluating the efficacy and tolerance of commonly used hemostatic compression devices. Previous studies have evaluated the efficacy of individual hemostatic devices; Chatelain et al. [13] assessed the efficacy of Radistop in 159 patients and reported that 18% of patients found the device uncomfortable or painful. The mean compression time was 151 min and 19.4% had local vascular complications including radial artery occlusion in 4.4%. The compression time is shorter in this study as compared to our study because about two-third of patients in this study had diagnostic angiography with the use of 4F and 5F sheaths, compared to our study where 6F sheaths were used and 92% of the patients had coronary intervention. Ochiai et al. [15] reported the efficacy of another compressive hemostatic device, Adapty (Medikit, Tokyo, Japan) in 199 patients and reported success rates in 99.5% with no vascular complications.

Choi et al. [14] compared the efficacy of a hydrophilic wound dressing (Closur PAD) with a compressive device (Radistop) in 80 patients. They reported significantly less compression time with the use of the dressing (58.7 ± 32.6 min vs. 131.3 ± 59.1 min; $P < 0.001$) and similar vascular complication rates (5% for hydrophilic dressing vs. 2.5% for compressive devices). The majority of procedures in this study were performed using a 5F sheath.

Recently, Pancholy et al. [18] evaluated conventional pressure hemostasis using touniquet with the TR band in a randomized study of 436 patients. They reported a significantly lower incidence of early (at 24 hr) radial artery occlusion for the TR band, compared to conventional pressure compression (4.4% vs. 11.2%, $P < 0.005$) and also late (at 30 days) radial artery occlusions (3.2% vs. 7.2%, $P < 0.05$). They speculated that hemostasis achieved by TR band and guided compression was responsible for better outcomes. All patients underwent diagnostic coronary angiography using 5F sheath. This could explain the difference in the radial artery occlusion rates as sheath size in relation to radial artery diameter plays a significant role [19]. In addition, the procedure time was significantly less than our study group (19 min vs. 54 min).

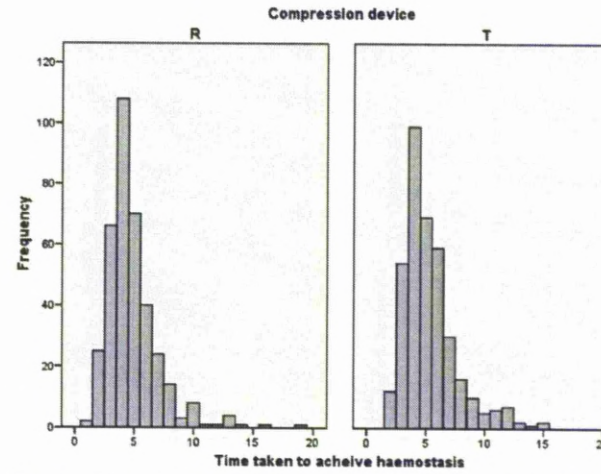

Fig. 4. Comparison of time taken to achieve hemostasis in hours by Radistop and TR Band devices. "R," Radistop compression device; "T," TR band compression device. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The interruption of blood flow by compression devices can also influence the incidence of radial artery occlusion and other vascular complications. Sanmartin et al. [20] has analyzed the possible relationship between compression after transradial procedures and radial artery occlusion in 275 patients by the use of pulse oximeter. In this study, radial artery flow was absent in 174 cases (62%) immediately after entry site compression. After 2 hr of pressure hemostasis, radial artery flow was absent in 162 cases (58%) before bandage removal. At 7-day follow-up, 12 patients (4.4%) had absent pulsation and radial artery flow was absent in 29

TABLE III. Baseline and Procedural Variable Correlates of Radial Artery Occlusion at Discharge

Variables *N* (%)	All pts *N* = 780	RAO *N* = 73	No RAO *N* = 707	*P* value
Age, mean ± SD	62.88 ± 11.14	60.43 ± 11.18	63.12 ± 11.15	0.052
Sex				
Male	586 (74.2)	42 (7.2)	537 (92.8)	0.051
Female	202 (25.6)	31 (15.3)	170 (84.7)	
Hypertension	547 (69.2)	48 (65.8)	492 (69.6)	0.795
Hyperlipidemia	719 (91.0)	63 (86.3)	648 (91.7)	0.148
Diabetes Mellitus	155 (19.6)	14 (19.2)	141 (19.9)	0.287
Sheath length				
Long	396 (50.1)	31 (42.5)	361 (51.1)	0.306
Short	394 (49.9)	42 (57.5)	346 (48.9)	
Sheath coating				
Coated	397 (50.3)	35 (47.9)	360 (50.9)	0.139
Uncoated	393 (49.7)	38 (52.1)	347 (49.1)	
Compression device				
Radistop	395 (50.0)	38 (9.6)	351 (90.4)	0.756
TR Band	395 (50.0)	35 (8.9)	356 (91.1)	
Operator RAS	230 (29.4)	33 (45.2)	196 (27.7)	0.008
Heparin usage	729 (92.3)	53 (72.6)	666 (94.2)	<0.0001
Height, cm	168.8 ± 9.8	166.9 ± 8.5	169.0 ± 9.9	0.056
Weight, kg	83.6 ± 16.4	82.4 ± 17.2	83.8 ± 16.4	0.524
Wrist circumference, cm	17.2 ± 1.2	16.8 ± 1.2	17.3 ± 1.2	0.001
BMI	29.3 ± 4.9	29.4 ± 5.0	29.3 ± 4.9	0.794
Time sheath in situ, min	50.4 ± 28.3	46.6 ± 28.2	50.6 ± 28.4	0.259
Time taken to achieve hemostasis, hrs	5.1 ± 2.1	4.9 ± 2.1	5.1 ± 2.3	0.590

SD, standard deviation; RAO, radial artery occlusion; RAS, radial artery spasm; BMI, body mass index.

cases (10.5%). Logistic regression analysis showed that absent flow before compressive bandage removal was the only independent predictor of radial artery occlusion at follow-up (OR = 6.7, IC 95%:1.95–22.9; $P = 0.002$). Flow-limiting compression was frequently seen in this study and the absent radial artery flow during compression was found to be a predictor of the radial artery occlusion.

Therefore, adequate compression should be applied to reduce local bleeding complications and also to achieve adequate hemostasis. Pressure applied should be limited to the minimum required to achieve hemostasis. This use of lower pressure will allow forward flow during the compressive period and this reduces the risk of vascular complications. The compressive pressure should be reduced as early as possible with careful monitoring for local vascular complications.

Previous studies have reported radial artery occlusion rates ranging from 3 to 10% [11,21,22]. Radial artery occlusion following a transradial coronary procedure was observed before discharge in 9% of our patients. Several factors have been found to be associated with radial artery occlusion including radial artery size at baseline, radial sheath to artery diameter ratio, duration of the sheath placement, prior procedure, and the presence of diabetes mellitus [19,21,23]. We have identified small wrist diameter, female sex, and young age as predictors of radial artery occlusion. However,

TABLE IV. Independent Predictors of Radial Artery Occlusion at Discharge

Variables	O.R	95% C.I	*P* value
Male sex	0.61	0.29–1.28	0.194
Younger age (per yr)	1.02	1.00–104	0.036
Smaller wrist size (per cm)	1.39	1.06–1.80	0.014
No operator RAS	0.53	0.31–0.90	0.021
No heparin usage	7.12	3.75–13.52	<0.0001

we did not measure the diameter of the radial artery. We have for the first time found association between radial artery spasm and radial artery occlusion and this needs to be tested in further large scale studies.

Lefvre et al. [24] have reported high (30%) radial artery occlusion rates with the use of 1,000 U of heparin. In our study, all patients undergoing coronary intervention received weight-adjusted heparin (70 units/kg) and the administration of heparin in diagnostic cases was left at operator's discretion, 61 (7.7%) patients did not receive any heparin. Radial artery occlusion in these patients was observed in 15 (24.1%) patients, similar to that reported in literature. We have found failure to administer heparin as an independent predictor of radial artery occlusion.

In our study, the protocol for application of either hemostatic compression device was to achieve controlled compression and thereby maintain antegrade flow during the period of compression. The ramifications of the

radial artery occlusion and injury are important not only in patients undergoing repeat interventional procedures, but also in patients in whom the radial artery may be used as a conduit for coronary artery bypass surgery or for the creation of arteriovenous fistulae for hemodialysis.

LIMITATIONS

We have used qualitative assessment of the patient comfort level for the compressive devices, this can induce some bias. Second, lack of allocation concealment and neither the patient nor the nurse removing the device could be blinded to the compressive device and this could induce bias due to a perceived superiority of the device over the other. Third, the release of pressure in the TR band can be semiquantitatively controlled by increasing the amount of air released, whereas there is no measure of the amount of pressure reduction as the Radistop is released and potentially can effect the outcomes.

CONCLUSIONS

We have shown in a randomized comparison of Radistop and TR band that both devices are safe and effective as hemostatic compression devices following transradial procedures. However, more patients felt discomfort with the Radistop device and the time taken to achieve hemostasis was longer with TR band.

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Clinical SCIENCE

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Clinical Science (2010) 118, 633–640 (Printed in Great Britain) doi:10.1042/CS20090548

Impact of catheter insertion using the radial approach on vasodilatation in humans

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ABSTRACT

The aim of this study was to determine the impact of catheter sheath insertion, a model of endothelium disruption in humans, on the conventional FMD (flow-mediated dilatation) response *in vivo*. Seventeen subjects undergoing transradial catheterization were recruited and assessed prior to, the day after, and 3–4 months postcatheterization. The catheter sheath's external diameter was 2.7 mm, and the average preprocedure internal radial artery diameter was 2.8 mm, indicating a high likelihood of endothelial denudation as a consequence of sheath placement. Radial artery flow-mediated and endothelium-derived NO (nitric oxide)-dependent function (FMD) was assessed within the region of sheath placement (sheath site) and also above the sheath (catheter site). GTN (glyceryl trinitrate) endothelium-independent NO-mediated function was also assessed distally. Measurements were made in both arms at all time points; the non-catheterized arm provided an internal control. Neither sheath ($4.5 \pm 0.9\%$) nor catheter ($4.4 \pm 0.9\%$) insertion abolished FMD, although both significantly decreased FMD from preintervention levels ($9.0 \pm 0.8\%$ sheath segment; $8.4 \pm 0.8\%$ catheter segment; $P < 0.05$). The impact of sheath and catheter placement on FMD was no longer evident after ~ 3 months recovery (8.0 ± 1.5 and $8.1 \pm 1.7\%$, sheath and catheter, respectively). GTN responses also decreased from 14.8 ± 1.7 to $7.9 \pm 1.0\%$ ($P < 0.05$) as a result of sheath placement, but values returned to baseline at ~ 3 months ($13.0 \pm 1.8\%$). These results suggest that the presence of an intact, functional endothelial layer and consequent NO release may not be obligatory for some component of the FMD response. This raises the possibility of an endothelium-independent contribution to the flow-induced vasodilatation in humans.

INTRODUCTION

In recent years, FMD (flow-mediated dilatation) has become a popular technique in cardiovascular medicine and clinical physiology, as evidence has accrued that depressed FMD is an independent prognostic index of incident and recurrent cardiovascular events, which adds predictive value to established risk factor approaches [1–5]. The physiological rationale for the use of FMD, and a proposed reason for its prognostic relevance, is that it reflects endothelium- and (nitric oxide)-dependent vascular function.

When Celermajer, Deanfield and colleagues introduced the now conventional and widely adopted FMD approach in the *Lancet* in 1992 [6], no direct evidence was available that brachial and femoral dilatation, subsequent to the release of cuff-induced ischaemia, were endothelium- or NO-dependent in humans. The

Key words: catheterization, flow-mediated dilatation, endothelium, nitric oxide, radial approach.

Abbreviations: eNOS, endothelial NO synthase; FMD, flow-mediated dilatation; GTN, glyceryl trinitrate; HR, heart rate; L-NMMA, N^G-monomethyl-L-arginine; MAP, mean arterial pressure; SR_{AUC}, shear rate area under the curve; TTP, time to peak.

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approach was therefore based on evidence available at the time that the endothelium released a labile vasodilator substance [7,8], that increased luminal flow-induced vasodilatation in human conduit arteries [9–12] and, crucially, that FMD in animals was dependent upon the presence of an intact endothelial lining. In these latter studies, insertion of a catheter and balloon inflation was used to denude the endothelial layer, which abolished FMD. Very few studies of this nature have been undertaken in humans to examine FMD after endothelial damage [13–15]. While previous studies have reported a depression in the vasodilator function of the radial artery after it has been catheterized [13,14], the methods used to assess arterial vasodilator function were limited. In particular, discreet time measurements were used to assess the peak diameter, and as such, the 'true' peak is likely to have been missed. Furthermore, these studies did not assess the stimulus the artery received during the FMD test [SR_{AUC} (shear rate area under the curve)]. This has previously been demonstrated to be an important determinant of the FMD response and should be reported in order to elucidate whether any changes in FMD are due to alterations in the artery's ability to dilate, as opposed to a reduction in the stimulus [16]. In addition, the time-course of recovery from endothelial damage remains largely unknown.

The relevance of determining the degree to which FMD responses are endothelium-dependent is heightened by a recent debate over the extent to which FMD represents an endothelium-dependent and NO-mediated response [18,19]. NO blockers have been infused during FMD in humans, with differing effects. Joannides et al. [20] demonstrated that L-NMMA (N^G-monomethyl-L-arginine) infusion converted flow-mediated vasodilatation into constriction in the radial artery in healthy young humans, while Doshi et al. reported abolition of FMD with L-NMMA [21]. Somewhat in contrast, Mullen et al. [22] Lieberman et al. [23] and Koojiman et al. [24] all observed decreased FMD in the presence of L-NMMA, but not FMD abolition by NO blockade in these studies. In addition, eNOS (endothelial NO synthase) knockout mice exhibit preserved FMD responses [25]. These studies suggest that compensatory mechanisms may play a role in the FMD response if the endothelial release of NO is dysfunctional or absent and/or that NO is not obligatory for a dilator response to ischaemia. They also raise the question of to what extent FMD responses are dependent upon the presence of an intact and functional endothelium.

The principal aim of the present study was to use a model of endothelial disruption in humans to determine the impact on FMD acutely. We also examined the impact of sheath compared with catheter placement, the impact of sheath placement on endothelium-independent GTN (glyceryl trinitrate) responses and the time-course of recovery of FMD and GTN responses. We hypothesized that sheath insertion would diminish or abolish the endothelium-dependent and -independent function within, but not above, the sheath site.

MATERIAL AND METHODS

Patients

Seventeen subjects (16 men, one woman) were recruited from the list of patients requiring radial artery catheterization for coronary angiography or coronary angioplasty. The following were excluded: patients who had previously undergone coronary artery bypass surgery or coronary intervention via the radial route or had myocardial infarction during the previous 3 months, valvular heart disease, a left ventricular ejection fraction $< 40\%$, chronic obstructive lung disease, or renal or hepatic dysfunction.

The study conformed to the standards set by the Declaration of Helsinki and ethical approval was obtained from the Liverpool Local Regional Ethics Committee. All patients provided informed written consent.

Study design

Patients were tested on three occasions: the day of the transradial procedure (immediately before the catheterization 'Pre'), the day after catheterization ('Post') and ~ 3 months after catheterization ('Recov'). Volunteers were requested to abstain from alcohol or caffeinated beverages and cigarettes (if they were smokers) for 12 h prior to each testing session. Assessments were taken in a quiet, temperature-controlled room. Patients rested in the supine position for approximately 20 min to ensure that all haemodynamic variables had stabilized. The radial artery was assessed with the arm extended and supported at an angle of approximately 80° from the torso. A rapid inflation/deflation pneumatic cuff was positioned on the imaged arm around the wrist. A standard catheter sheath was then used to mark the length of the catheter on the surface of the arm, from the scaphoid process. Care was taken to image the same section of the artery during repeat measurements. We assessed both arms to determine whether changes as a consequence of catheterization were specific, or more generalized, throughout the vascular system. On each occasion, endothelial-dependent function (FMD) was assessed over a distal section of the radial artery (FMD sheath), within the zone containing the sheath and over a proximal section (FMD catheter), which lay above the sheathed region. A minimum of 20 min was observed between repeated FMD assessments in the same arm. The order in which the arms were tested was randomized for FMD and GTN. Endothelium-independent function was assessed as the vascular response to a sublingual dose of GTN with the scans taken in the distal section of the

radial artery after the FMD assessments. A minimum of 30 min was given between repeat doses of GTN.

Radial artery access and procedural details

In this study, we recruited patients undergoing treatment for coronary artery disease. These patients have their coronary arteries either imaged (angiography) or have the narrow arteries widened (angioplasty). In order to gain access to the coronary circulation, a catheter is placed into a peripheral artery, in this case the radial artery, and the catheter is guided up to the heart. Introducer sheaths are used to gain access to the radial artery and to keep the artery open in order to facilitate the exchange of the guiding coronary catheter to the heart.

The radial artery was approached with the arm extended and supported with the wrist in mild hyperextension. Local anaesthesia was achieved with 2 % lignocaine after disinfection at the puncture site. The radial artery was punctured with a 21-gauge arterial needle through which a 0.118-in platinum-tipped nitinol guidewire was introduced. Following this, the needle was withdrawn, and a small skin incision was made. A 6 F introducer sheath (13 cm in length, external diameter 2.7 mm; Cook Medical) with a dilator tip length of 2.5 cm was inserted. A weight-adjusted dose of heparin was introduced into the central circulation following the introduction of the first catheter. All introducer sheaths were removed at the end of the procedure and haemostasis was achieved in the catheterization laboratory by a compression device. The patients were mobilized immediately, and the compression device was removed after 2–4 h.

Experimental procedures

Ultrasound assessment of conduit artery function

HR (heart rate) and MAP (mean arterial pressure) were determined from an automated sphygmomanometer (Dinamap; GE Pro 300V2) on the contralateral arm. A 12-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (T3000; Terason) was used to assess radial artery function.

FMD (endothelium-dependent NO-mediated function)

Baseline scans assessing resting vessel diameter and flow were recorded in the final minute of the initial rest period. The occluding cuff was then inflated to >200 mmHg for 5 min. Diameter and flow recordings resumed 30 s prior to cuff deflation and continued for 5 min thereafter. Blood pressure and HR were recorded during the resting period and once the cuff had been released.

GTN dilatation (endothelial-independent NO-mediated function)

Vessel diameter was recorded 1-min before and, continuously for 10 min after, sublingual administration of GTN (400 μg). Blood pressure and HR were recorded during the rest period and 5 min after the GTN had been administered.

Data analysis

Posttest analysis was carried out using custom-designed edge detection and wall tracking software [26,27]. Our previous detailed analysis of power requirements using this software indicates that, at an alpha level of 0.05, seven subjects are required to ensure 90 power to detect a 2 % change in FMD [27]. FMD or GTN were calculated as the percentage rise from preceding baseline diameters. The TTP (time to peak) diameter (in seconds) was calculated from the point of cuff deflation to the time of peak postdeflation diameter. Postdeflation shear rate data, derived from simultaneously acquired velocity and diameter measures at 30 Hz, were exported to a spreadsheet SR_{AUC} was calculated for data up to the point of maximal postdeflation diameter (FMD) using the Riemann sum technique for each individual. SR_{AUC} represents the stimulus for FMD [17].

Statistics

The responses were assessed using a two-way repeated measures ANOVA. Where significant interaction was observed, a one-way ANOVA was carried out on each arm separately to identify differences. Results are expressed as means $\pm$ S.E.M. A P value <0.05 was considered significant.

RESULTS

The clinical characteristics of the patients are described in Table 1. The majority of the patients were on aspirin, clopidogrel, a statin, an ACEI (angiotensin-converting enzyme inhibitor) and a β-blocker. Efforts were made to avoid changes to the patients' drug regimes throughout the study. In any event, the within-subjects design, with contemporaneous contralateral limb measures at each time point effectively controlled for any drug effects.

Seventeen subjects completed the pre- and post-scans for the FMD sheath site, and 11 subjects completed all three testing points. For the FMD catheter site (proximal) data, 13 subjects completed the pre- and post-scans, and nine subjects completed all three testing sessions. For the GTN protocol, 15 subjects were tested pre- and post-catheterization, and 11 completed all three testing protocols. The average age of the subjects was 64 ± 10 years, mean blood pressure was 95 ± 15 mmHg and HR was 59 ± 7 beats/min, and the baseline clinical characteristics are shown in Table 1.

Table 1 Clinical characteristics of the study patients (n = 17)

Values are number of patients (percentages). PCI, percutaneous coronary intervention.

Characteristic	
Male	16 (94%)
PCI	17 (100%)
Current smoker	3 (18%)
Ex-smoker	11(65%)
Diabetes mellitus	3 (18%)
Hyperlipidaemia on medication	17 (100%)
Hypertension on medication	13 (77%)

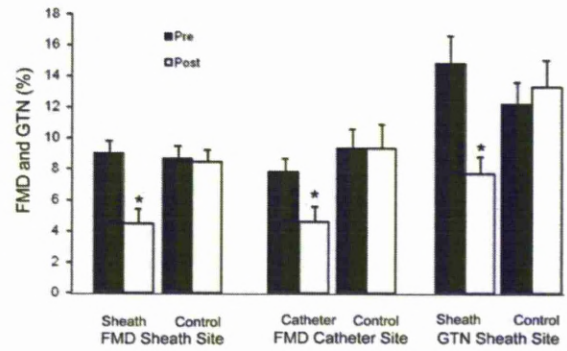

Figure 1 Changes in FMD (%) within the area of the sheath (sheath site, n = 17) and above the area of the sheath (catheter site, n = 13) and changes in GTN (%) within the area of the sheath (n = 15) in the catheterized and non-catheterized (control) arms pre- (Pre) and post- (Post) procedure

Results are presented as means ± S.E.M. *Significantly different from Pre ($P < 0.05$).

There was no significant difference in resting radial artery diameter between arms at the sheath site (distal) prior to catheterization, but diameter was significantly larger ($P < 0.05$) in the catheter (proximal) section of the catheterized arm compared to the control (non-catheterized) arm (Table 2). This may relate to the fact that the catheterized arm was typically the dominant right arm. There was no significant difference in SR_{AUC} or TTP between arms or across time.

There was a significant increase in baseline diameter (Table 2) postprocedure in the catheterized arm (16 ± 5%) in the sheath section only ($P < 0.05$). There was no significant change in baseline diameter in the control arm at either the catheter or sheath sites. The recovery (15 ± 1 week) resting baseline diameters were not significantly different from preprocedure in either the catheterized or non-catheterized control arm.

There was no significant difference in FMD or GTN between arms precatheterization (Figure 1). There was a significant reduction in FMD at both the sheath ($P < 0.01$) and catheter sites ($P < 0.01$) in the catheterized arm (Figure 1), but FMD was not completely abolished at either site. Similarly, there was a significant decrease ($P < 0.05$), but not abolition, of the artery response to the GTN postprocedure in the sheath segment of the catheterized arm. These decreases had returned towards preprocedure values by 3–4 months after the catheterization (Figure 2). In contrast, there was no change in FMD or GTN across any of the time-points in the control arm (Figure 1). One patient had an occluded artery postprocedure that remained occluded at the 3-month recovery period.

There was no change in MAP across time (Table 3). There was a decrease in MAP with administration of GTN, which was significant for both arms at the pre- and posttesting sessions ($P < 0.01$).

DISCUSSION

The aim of the present study was to determine the impact of radial artery sheath and catheter placement on vascular function *in vivo*. There are several novel

Table 2 Baseline diameter and time to peak vasodilation preprocedure (Pre), the day following the procedure (Post) and ~ 3 months postprocedure (Recov) in the catheterized (sheath or catheter site) and non-catheterized (control) arms

Results are presented as means ± S.E.M. Endothelium-dependent FMD was assessed in the distal section of the artery exposed to the catheter sheath (sheath site, n = 17 for Pre and Post and 11 for Recov) and the proximal section of the artery, above the sheath (catheter site, n = 13 for Pre and Post and 9 for Recov). Endothelial-independent function (GTN) was assessed in the distal section (n = 15 for Pre and Post and 11 for Recov) of the artery within the site of the catheter sheath. *Significantly different from Pre ($P < 0.05$); #significantly different from catherterized.

		Baseline diameter (mm)			Time to peak (s)			SR_{AUC} (s^{-1} 10^3)		
Measurement		Pre	Post	Recov	Pre	Post	Recov	Pre	Post	Recov
FMD sheath site	Sheath	2.8 ± 0.1	3.2 ± 0.1*	2.7 ± 0.2	95 ± 10	87 ± 11	77 ± 1	30.0 ± 2.9	20.7 ± 3.8	25.3 ± 3.6
	Control	2.6 ± 0.1	2.8 ± 0.1	2.9 ± 0.2	78 ± 9	79 ± 8	83 ± 14	23.5 ± 3.3	26.6 ± 1.9	32.6 ± 6.6
FMD catheter site	Sheath	3.1 ± 0.1	3.4 ± 0.1	2.8 ± 0.2	73 ± 9	105 ± 11	63 ± 15	20.7 ± 3.5	23.7 ± 3.8	27.5 ± 6.5
	Control	2.8 ± 0.2#	2.8 ± 0.1	2.8 ± 0.2	110 ± 14	90 ± 8	71 ± 13	31.7 ± 6.2	28.3 ± 3.8	24.0 ± 3.9
GTN sheath site	Sheath	2.8 ± 0.1	3.2 ± 0.1	2.6 ± 0.2	308 ± 23	263 ± 31	333 ± 30	–	–	–
	Control	3.0 ± 0.2	2.9 ± 0.1	3.2 ± 0.2	351 ± 30	297 ± 28	276 ± 28	–	–	–

Table 3 MAP during baseline measurements and postcuff release or post-GTN administration preprocedure (Pre), the day following the procedure (Post) and ~ 3 months postprocedure (Recov) in the catheterized (cath) and non-catheterized (control) arms

Results are presented as means ± S.E.M. Mean arterial pressure (FMD) was assessed in the contralateral arm. Measurements were taken during the baseline period and ~ 1 min after cuff release or ~ 3 min post-GTN administration. *Significantly different from baseline ($P < 0.05$); #Significantly different from Pre.

	MAP (mmHg)					
	FMD sheath site		FMD catheter site		GTN sheath site	
	Baseline FMD	During FMD	Baseline FMD	During FMD	Baseline GTN	During GTN
Cath						
Pre	95 ± 4	94 ± 4	91 ± 4	94 ± 3	95 ± 3	87 ± 3*
Post	94 ± 3	92 ± 4	91 ± 3	90 ± 4	89 ± 3	85 ± 3*
Recov	96 ± 4	93 ± 5	88 ± 3	86 ± 2	88 ± 5	84 ± 5
Control						
Pre	95 ± 4	95 ± 12	88 ± 3	91 ± 3	93 ± 3	86 ± 3*
Post	89 ± 4	88 ± 4	88 ± 5	87 ± 3	88 ± 3	83 ± 4*
Recov	95 ± 5	96 ± 5	93 ± 5	92 ± 6	89 ± 4	85 ± 4

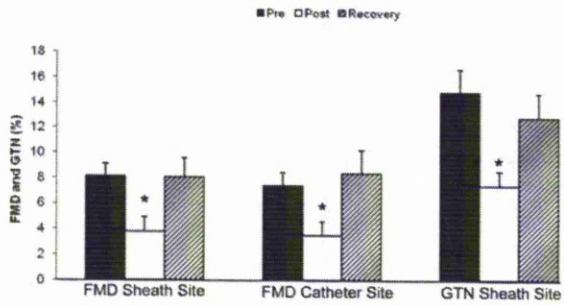

Figure 2 Changes in FMD (%) within the area of the sheath (sheath site, $n = 11$) and above the area of the sheath (catheter site, $n = 9$) and changes in GTN (%) within the area of the sheath ($n = 11$) in the catheterized arm Pre, Post and ~ 3 months (Recovery) postprocedure

Results are presented as means ± S.E.M. *Significantly different from Pre ($P < 0.05$).

findings. This is the only study, to our knowledge, which has assessed both distal and proximal sections of the radial artery in order to determine whether function was affected within the region of the catheter sheath alone or whether catheterization has more generalized effects on vasodilator function. Importantly, continuous measurement of artery diameter and flow allowed us to record the 'true' peak in vasodilatation in addition to the SR_{AUC}, which represents the stimulus the artery receives during the FMD test. We also repeated measures ~ 3 months postcatheterization to determine whether arterial function recovered, and we included within-subjects control measures on the contralateral non-catheterized limb. Our findings indicate that endothelium-dependent function is decreased acutely as a result of catheterization, both within and above the site of sheath, while no changes in arterial function were observed in the non-catheterized control arm at any time-point. This is similar to the work of Heiss et al. [15] who also reported a reduction in brachial as well as radial artery function postcatheterization. The lack of a significant change in the SR_{AUC}, an estimate of the vasodilatory stimulus, supports the notion that the reduction in the FMD was due to an impaired ability of the artery to dilate. Impairment in FMD function was not complete, however, as substantial dilatation occurred despite sheath and catheter placement. Responses largely resolved, i.e. returned to near-baseline levels, following ~ 3 months recovery.

The external diameter of the catheter sheaths used in this study was 2.7 mm and the mean preprocedure internal radial artery diameter above the insertion site was 2.8 mm (range 2.2–3.5 mm). While we cannot say for certain that the artery was denuded, given the fragile nature of the endothelial monolayer, it is highly likely that placement of the sheath disrupted and/or denuded the endothelial layer, in a similar manner to the induction of endothelial denudation by balloon inflation in animal models [28,29]. The suggestion that we induced endothelial disruption or denudation is supported by the finding that baseline arterial diameter in the sheathed radial segment was larger following the procedure (mean 3.2 mm). Studies of the impact of catheterization and subsequent denudation on radial arterial function are scant. Burstein et al. [13] reported that transradial catheterization impaired FMD immediately postprocedure. Recently, Heiss et al. [15] also observed a reduction in FMD in the radial artery 6 h postcatheterization. In contrast to our findings, values recovered after 12 h in non-smokers. Heiss and

colleagues did not assess GTN function, so they were unable to determine whether smooth muscle function was affected. In contrast, Sanmartin et al. reported no change in postischaemic radial artery dilatation immediately after the procedure, although this was probably due to an initial impairment in function [14]. Interestingly, despite a significant reduction in FMD in this study, there was still some vasodilatation in response to the hyperaemic challenge. This suggests that placement of a large sheath and consequent disruption or denudation of the endothelial layer decreases, but does not abolish, FMD. This is in agreement with some previous studies which have blocked NO function and found only partial reductions in FMD [22–24]. Likewise, eNOS knockout mice have been shown to have preserved FMD responses [25]. In these studies, it was assumed that some compensatory mechanisms, including the release of other endothelium-dependent vasodilators such as protoglandins [25], may come into play if the endothelial release of NO is impaired or absent. However, our data raise the possibility that there may be a non-endothelium-dependent vasodilatation in response to increased blood flow and shear stress in humans. Future studies will be required to elucidate the contribution of both the endothelium-dependent and independent vasodilators to the conventionally used FMD technique.

In addition to the assessment of endothelial-dependent function, we measured endothelial-independent NO-mediated responses to GTN. As a NO donor, GTN provides a measure of the smooth muscle component of the vascular NO-dilator system. It is possible that insertion of the relatively large sheath into the radial artery results in disruption of the smooth muscle layer of the vessel wall. Decreased GTN responses in the catheterized, but not the non-catheterized, arm supports the contention that sheath-related impacts may not be limited to the intima and is in agreement with the previous literature [13,14]. As with the FMD data, it is notable that sheath placement did not completely abolish GTN-mediated vasodilatation, suggesting that some smooth muscle cell function remains intact despite the placement of the sheath, and that sheath placement impairs but does not eradicate smooth muscle responsiveness to an NO donor. These observations have implications for the use of nitrovasodilators in the clinical setting soon after percutaneous interventions are carried out.

It is possible that the mechanical stretch induced by the sheath insertion played a role in the depressed vascular function, as diameter is an important determinant of the dilator-response magnitude, at least when large differences exist in the resting diameter. In the present study, artery diameter increased modestly as a result of artery catheterization (0.4 mm). Our previous data suggests that this magnitude of change in resting diameter is unlikely to fully explain the change in FMD observed in the present study, with an expected FMD of 10% in healthy subjects for a radial artery of 2.8 mm and 8% for a radial artery of 3.2 mm [30].

In addition to measuring endothelial function within the region of the catheter sheath, we also examined endothelium-dependent function in the proximal section of the artery, which was exposed to the catheter but not the catheter sheath. As with the distal section of the artery, we observed a reduction in FMD in the section of the artery only exposed to the catheter. From these data, we can suggest that the impact of catheterization extends beyond the site of sheath placement. This is in agreement with Heiss et al. [15] who reported a reduction in brachial artery function 6 h postradial artery cannulation, although this depression recovered after 12 h in non-smokers and remained depressed in smokers. It is feasible that the catheter itself may damage the endothelium as it is advanced. However, we cannot rule out the possibility that the catheter is associated with localized inflammation or irritation as a mechanism for reduced function in the catheterized arm [31]. Reduced function above the sheath site raises questions about injury to the rest of the arterial tree through which the catheter passes, including perhaps the coronary arteries. Since FMD in the contralateral arm was not depressed, a global impact of catheterization, mediated via inflammation or oxidative stress, seems unlikely.

It is interesting to note that both endothelial and smooth muscle responses return to near-baseline levels following a 3-month recovery period. This is in contrast to the study of Burstein et al. who previously reported that the impairment in FMD following transradial catheterization was still evident 6 weeks after surgery [13]. Our findings that vascular function had recovered ~3 months postprocedure suggests that this period may be the minimum required for arterial function to normalize after catheterization and sheath insertion.

Limitations

This is the first study of its type to use automated-edge detection and wall-tracking software to derive operator-independent measures of arterial diameter and FMD. The study of two sites within and above the catheter sheath site along the radial artery also provides novel information, as does the repeated measurement following a recovery period. However, the present study also has some limitations. There were a relatively small number of subjects in each group, and we could not get all patients back for the 3-month recovery period. This limitation is somewhat mitigated by our within-subjects design and analysis. We did not control for age, pre-existing vascular disease, history of smoking or drug treatment. However, the use of contralateral arm as an internal control helped to negate this limitation.

Conclusions

In conclusion, transradial catheterization results in reversible depression in NO-mediated endothelial and

smooth muscle function in the catheterized arm. This effect is evident in the region of the sheath and also above the site of the catheter sheath, suggesting that both sheath and catheter insertion impact upon the vasculature, possibly via a localized inflammatory or irritant response. Although FMD responses were impaired by sheath placement, they were not abolished, suggesting that some endothelium-independent vasodilator mechanisms may contribute to the vasodilatation response to an FMD test in humans. This hypothesis will require further investigation. From a clinical perspective, it is possible that optimizing the function and size of the artery prior to its cannulation may improve the outcome and recovery of the artery. To this end, exercise training has been shown to improve arterial function and induce outward remodelling [32–36], both of which might limit the impact of transradial catheterization and improve the health and recovery of the artery postprocedure.

ACKNOWLEDGEMENTS

We thank Chris Reed for his assistance with the development of the edge detection and wall-tracking software.

FUNDING

D.J.G. received funding support from the National Heart Foundation of Australia [grant number G 08P 3666].

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Received 29 October 2009/22 December 2009; accepted 8 January 2010
Published as Immediate Publication 8 January 2010, doi:10.1042/CS20090548

Impact of Introducer Sheath Coating on Endothelial Function in Humans After Transradial Coronary Procedures

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Background—The aim of this study was to compare the impact of transradial catheterization with hydrophilic-coated catheter sheaths versus uncoated sheaths on NO-mediated endothelial-dependent and -independent vasodilator function.

Methods and Results—Thirty-five subjects undergoing transradial catheterization were recruited and assessed before and the day after catheterization. A subgroup was also assessed 3 to 4 months after catheterization. Subjects received hydrophilic-coated sheaths (n=15) or uncoated sheaths (n=20). Radial artery flow-mediated dilatation and endothelium- and NO-dependent arterial dilatation were assessed within the region of sheath placement. Glyceryl trinitrate endothelium-independent NO-mediated function was also assessed. The noncatheterized arm provided an internal control. Flow-mediated dilatation in the catheterized arm decreased from 10.3±3.8% to 5.3±3.3% and 8.1±2.4% to 5.2±3.7% in the coated and uncoated groups, respectively ($P<0.01$). These values returned toward baseline levels ≈3 months later (coated, 6.4±1.4%; uncoated, 9.4±4.1%; $P<0.05$) versus postprocedure. Glyceryl trinitrate decreased from 14.8±7.2% to 9.5±4.1% ($P<0.05$) in the coated group and from 12.2±4.6% to 7.5±4.2% ($P<0.01$) in the uncoated group. Values returned to baseline at ≈3 months (coated, 16.6±5.6%; uncoated, 12.1±3.9%; $P<0.05$). There was no difference in the magnitude of decrease in flow-mediated dilatation or glyceryl trinitrate between coated and uncoated groups. No changes in function occurred in the noncatheterized arm.

Conclusions—Placement of a catheter sheath inside the radial artery disrupts vasodilator function, which recovers after 3 months. No differences were evident between hydrophilic-coated and uncoated sheaths. **(*Circ Cardiovasc Interv*. 2010;3:148-156.)**

Key Words: flow-mediated dilatation ■ radial artery catheter ■ endothelium

Since its introduction in 1989, transradial catheterization has gained popularity as an approach for diagnostic and coronary interventional procedures.[1] This approach has been associated with lower vascular complication rates, reduced procedural costs, comparable procedural success rates, earlier patient mobilization, improved quality of life, and reduced hospitalization costs.[2–10] However, it is probable that insertion of the catheter sheath into the relatively small radial artery has a direct physical impact on the endothelial lining of the vessel wall, a squamous monolayer that is easily damaged as a consequence of mechanical disruption. Removal or damage of the endothelial lining impairs arterial relaxation by decreasing NO bioavailability. It may also promote intimal hyperplasia, thrombus formation, and the development of atherosclerotic plaques,[11,12] which could have implications for the use of the artery as a donor graft for coronary artery bypass surgery because graft longevity is partly related to the capacity to remodel and dilate in response to changes in metabolic demand and blood flow.

Clinical Perspective on p 156

Recent advances in the development of catheter sheaths include the development of hydrophilic coatings that aim to reduce frictional resistances during sheath placement and removal.[13] Although hydrophilic-coated sheaths have been reported to result in a reduction in the occurrences of discomfort and clinical spasm,[4,14] no previous study has addressed the questions of whether sheath coating results in less endothelial dysfunction. The aim of this study, therefore, was to measure endothelium-dependent and -independent vasodilator function in patients undergoing transradial catheterization with either a hydrophilic-coated or an uncoated sheath.

Methods

Informed written consent was obtained from 35 subjects (32 men) recruited from the list of patients requiring radial artery catheterization for coronary angiography or angioplasty. The exclusion criteria were as follows: previous coronary artery bypass graft or coronary

Received September 25, 2009; accepted February 22, 2010.

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Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org DOI: 10.1161/CIRCINTERVENTIONS.109.912022

intervention through the radial route or myocardial infarction during the previous 3 months, valvular heart disease, left ventricular ejection fraction <40%, chronic obstructive lung disease, and renal or hepatic dysfunction. The study conformed to the Declaration of Helsinki, and ethical approval was obtained from the Liverpool Local Regional Ethics Committee.

Study Design

In this prospective randomized study, patients were assigned to 1 of the 2 different introducer sheath groups: hydrophilic-coated sheath (coated group), sheath without coating (uncoated group). Patients were tested on 3 occasions: the day of the transradial procedure (before catheterization [pre]), the day after catheterization (post), and ≈3 months after catheterization (recov).

Radial Artery Access and Procedural Details

The radial artery was approached with the arm extended and supported with the wrist in mild hyperextension. Local anesthesia was achieved with 2% lignocaine after disinfection at the puncture site. The radial artery was punctured with a 21-gauge arterial needle through which a 0.118-inch platinum-tipped nitinol guide wire was introduced. Next, the needle was withdrawn, and a small skin incision was made. A 6F introducer sheath (length, 13 or 23 cm; external diameter, 2.6 mm) with a dilator tip length of 2.5 cm was inserted. Routine use of vasodilator cocktail (nitroglycerine, verapamil, or diltiazem) was avoided if possible, and a weight-adjusted dose of heparin was introduced into the central circulation after the introduction of the first catheter. All introducer sheaths were removed at the end of the procedure and hemostasis achieved in the catheterization laboratory through a compression device. The patients were mobilized immediately, and the compression device removed after 2 to 4 hours.

Experimental Procedures

Patients were requested to abstain from alcohol, caffeine, and cigarettes for 12 hours before each session. Assessments were taken in a quiet, temperature-controlled room. Patients rested in the supine position for ≈20 min to ensure that all hemodynamic variables stabilized. The radial artery was imaged with the arm extended and supported at 80° from the torso. A rapid inflation/deflation pneumatic cuff was positioned on the imaged arm around the wrist. A standard catheter sheath was used to mark the length of the catheter on the surface of the arm from the scaphoid process. Care was taken to image the same section of the artery during repeat measurements. We assessed both arms to determine whether changes as a consequence of catheterization were specific or more generalized throughout the vascular system. On each occasion, endothelial-dependent function (flow-mediated dilatation [FMD]) was assessed over a distal section of the radial artery, within the zone containing the sheath, and above the cuff. Endothelium-independent function was assessed as the vascular response to a sublingual dose of glyceryl trinitrate (GTN). A minimum of 30 min was given between repeat doses of GTN. The sonographer was blinded to the catheter sheath type during scanning and analysis.

Ultrasound Assessment of Conduit Artery Function

Heart rate and mean arterial pressure (MAP) were determined from an automated sphygmomanometer on the contralateral arm. A 12-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine was used to image the radial artery.

Flow-Mediated Dilatation (Endothelium-Dependent, NO-Mediated Function)

Baseline scans assessing resting vessel diameter and flow were recorded in the final minute of the initial rest period. The occluding cuff then was inflated to >200 mm Hg for 5 min. Diameter and flow recordings resumed 30 sec before cuff deflation and continued for 5 min thereafter.[15] MAP and heart rate were recorded during the resting period and after cuff release.

Table 1. Clinical Characteristics and Outcomes of the Study Patients (n=35)

Variables	Coated (n=15)	Uncoated (n=20)	*P*
Age, y	62.7±9.7	62.0±10.5	0.82
Male	13 (86)	19 (95.0)	1.00
MAP, mm Hg	95±11	93±13	0.89
Heart rate, bpm	62±13	62±13	0.95
Hypertension	11 (73)	16 (80)	0.71
Hyperlipidemia	13 (87)	19 (95)	0.57
Diabetes mellitus	3 (20)	5 (25)	1.00
Height, cm	153.5±9.2	165.3±8.1	0.38
Weight, kg	76.8±9.7	86.5±19.3	0.23
Wrist circumference, cm	16.3±3.9	17.1±1.0	0.37
Smoking			
Current	2 (13)	3 (15)	
Former	10 (67)	14 (70)	0.26
Stable angina	15 (100)	20 (100)	1.00
Time sheath in situ, min	70.4±30.3	64.2±24.0	0.54
Vascular complications			
Ecchymosis	2 (13)	3 (15)	
Oozing	4 (27)	1 (5)	0.18
Radial artery occlusion	1 (7)	0 (0)	0.43
Late local infection	1 (7)	0 (0)	0.43
Radial artery occlusion at follow-up	1 (7)	0 (0)	0.43

Data are presented as n (%) or mean±SD. Hypertension is defined as systolic blood pressure >140 or diastolic blood pressure >90 mm Hg. Hyperlipidemia was considered apparent on treatment for total serum cholesterol >5.0 mm·mol/L. Diabetes mellitus was determined on treatment. Radial artery spasm is defined as discomfort felt by patient or resistance felt during removal of introducer sheath.

Glyceryl Trinitrate Dilatation (Endothelial-Independent, NO-Mediated Function)

Vessel diameter was recorded 1 min before and continuously for 10 min after sublingual administration of GTN (400 μg). Heart rate and MAP were recorded at rest and 5 min after GTN administration.

Posttest analysis was carried out using custom-designed edge detection and wall-tracking software.[15,16] Our previous detailed analysis of power requirements using this software indicated that at an alpha level of 0.05, 7 subjects were required to ensure 90% power to detect a 2% improvement in FMD. FMD and GTN were calculated as the percentage rise from preceding baseline diameters. Time to peak diameter was calculated from the point of cuff deflation to the time of peak postdeflation diameter.[15] Postdeflation shear rate area under the curve was calculated for data up to the point of maximal postdeflation diameter (FMD) using the Riemann sum technique for each patient. Shear rate area under the curve represents the stimulus for FMD.[17] Further detailed methods are available elsewhere.[15]

Data Analysis

The responses initially were assessed using 3-way ANOVAs with linear mixed models. We followed-up with 2-way repeated-measures ANOVAs on the coated or uncoated groups compared over time and between arms. Further post hoc analysis was carried out using paired *t* tests. The effects of the FMD test or GTN administration on MAP were assessed using a 1-way ANOVA. Baseline characteristic

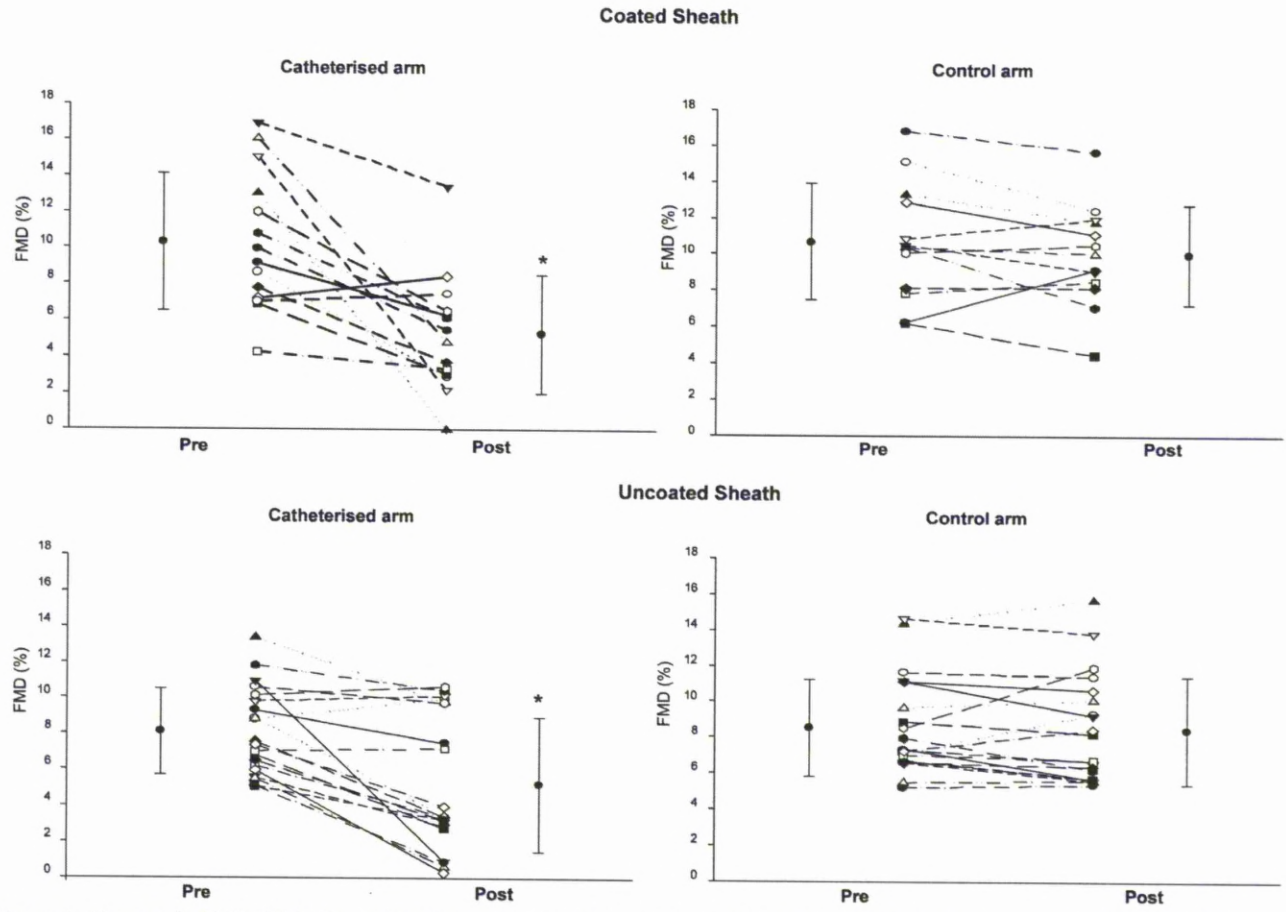

Figure 1. Changes in FMD (%) in the catheterized and noncatheterized control arms before and after procedure. Top panel shows coated sheath, and bottom shows uncoated sheath. Data are presented as mean±SD. *Significantly different from pre $P<0.05$.

differences were determined using t tests or χ^2 tests. Results are expressed as mean±SD, and $P<0.05$ was considered significant.

Results

Study Patients

The clinical characteristics of the patients are described in Table 1. The majority of the patients were taking aspirin, clopidogrel, a statin, an angiotensin-converting enzyme inhibitor, and a β-blocker, and there were no systematic differences between the groups in terms of medication use. Efforts were made to avoid changes to the patients' drug regimens throughout the study. In any event, the within-subject design, with contemporaneous contralateral limb measures at each time point, provided an important experimental control. All patients had successful transradial coronary procedures. Coronary artery angioplasty and stenting was performed in 33 patients, and 2 patients had only coronary angiography. The mean procedure time was 67±27 minutes. Three patients needed intraarterial isosorbide dinitrate to treat radial artery spasm during the procedure (2 in uncoated group and 1 in coated group). One patient in the coated sheath group had an occluded artery postprocedure that remained occluded at 3 months. Occlusion was confirmed by a reverse Allen's test, and the existence of impaired shear rate after ischemia. The data for this patient were removed from subsequent analysis. The other 14 subjects in the coated sheath group had FMD data collected before and after catheterization, and 12 of these had GTN before and after catheterization. A subgroup of 6 patients from the coated sheath group was retested ≈3 months after procedure. Twenty patients were recruited to the uncoated group of whom all had pre- and post-FMDs, whereas 19 completed pre- and post-GTN testing. From this group, 13 patients were retested for FMD and 12 for GTN ≈3 months later. The difference in group size was due to patient drop-out or poor ultrasound images.

Baseline Characteristics and Clinical End Points

The baseline clinical characteristics are shown in Table 1 and were similar in both groups. The incidence of minor access site complications was low in both groups. There was no significant difference in MAP between arms or between catheter sheath coatings.

The 3-way ANOVA produced a significant effect of arm ($P=0.003$); time ($P=0.000$); interaction of arm and time; and coating, arm, and time for the FMD percent. For the GTN percent, there was a significant effect of coating, time, and arm and time. These data were followed up by a simple main effects model using 2-way ANOVAs.

Impact of Sheath Placement on Endothelium-Dependent and -Independent Vasodilation

In the coated group, there was a significant effect of time ($P=0.046$), arm ($P=0.002$), and interaction between arm and

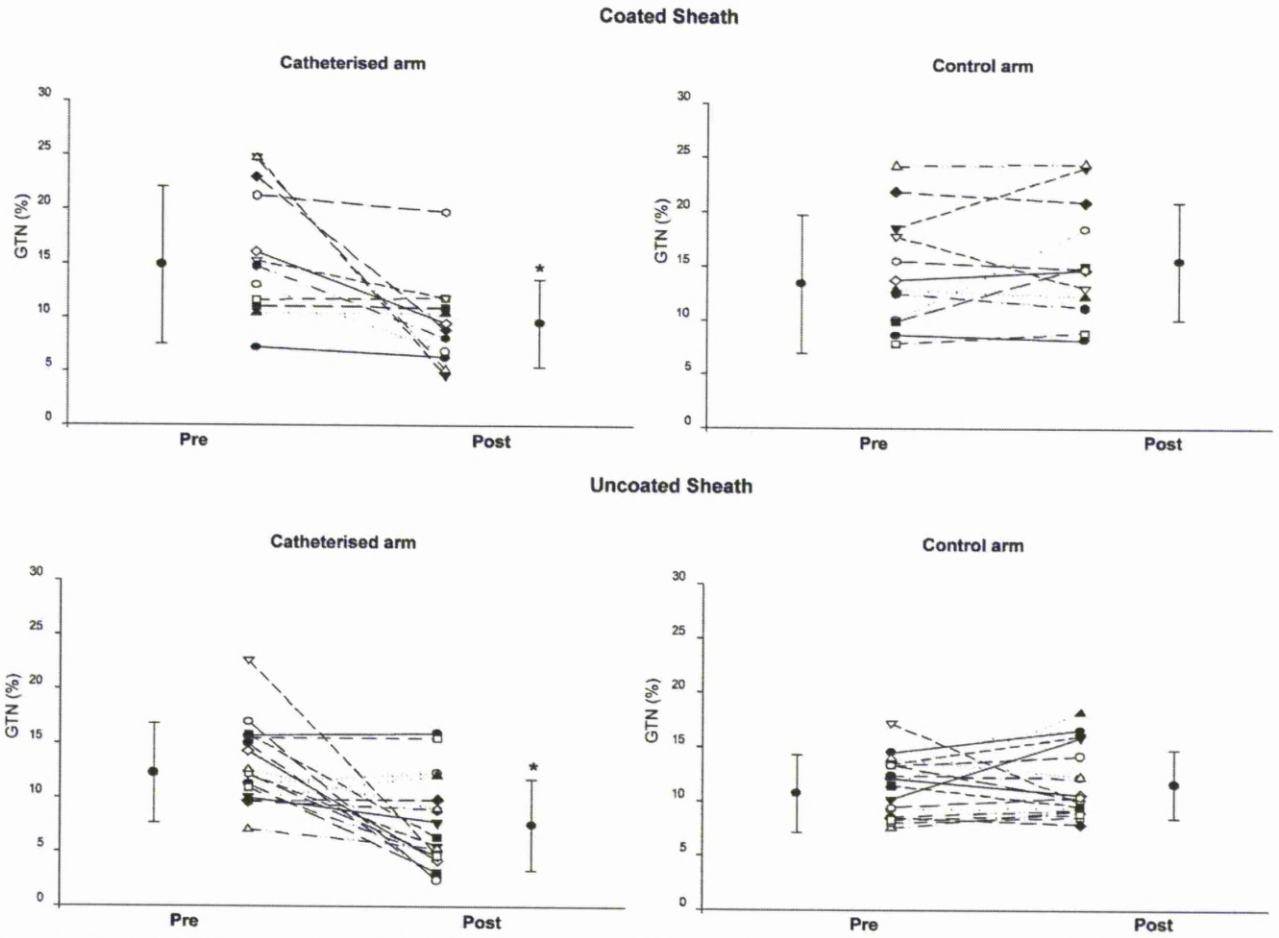

Figure 2. Changes in GTN (%) in the catheterized and noncatheterized control arms before and after procedure. Top panel shows coated sheath, and bottom shows uncoated sheath. Data are presented as mean±SD. *Significantly different from pre $P<0.05$.

time ($P=0.003$) on FMD. There was a reduction in FMD in the catheterized arm pre to post ($P<0.01$), with no change in the noncatheterized arm ($P=0.18$) (Figure 1).

In the uncoated group, there was a significant effect of time ($P=0.005$), arm ($P=0.001$), and interaction between arm and time ($P<0.001$) on FMD. There was also a significant reduction in FMD in the catheterized arm ($P<0.05$), with no change in the noncatheterized arm (Figure 1).

In the coated group, ANOVA revealed no significant effect of time ($P=0.089$), but there was a significant effect of arm ($P=0.029$) and interaction between arm and time for GTN data ($P=0.012$). There was a reduction in the GTN response in the catheterized arm pre to post ($P<0.05$), with no change in the noncatheterized arm ($P=0.32$) (Figure 2).

In the uncoated group, there was no significant effect of time ($P=0.11$), but there was a significant effect of arm ($P=0.017$) and interaction between arm and time for GTN data ($P<0.001$) (Figure 2). There was a reduction in GTN in the catheterized arm pre to post ($P<0.01$), with no change in the noncatheterized arm ($P=0.65$).

Although there was a significant interaction among arm, time, and coating with the 3-way ANOVA, there was no significant difference in the magnitude of change in FMD between the coated and uncoated conditions in the catheterized arm, with a 2-way ANOVA demonstrating a significant effect of time ($P<0.001$) but no interaction of time and coating ($P=0.085$). Likewise, an ANOVA on GTN data comparing the effect of time and coating in the catheterized arm showed a significant effect of time ($P<0.001$) but no interaction between time and coating ($P=0.63$). Baseline arterial diameters, time to peak, and shear rate area under the curve are presented in Table 2.

Impact of Sheath Placement on the Recovery of Endothelium-Dependent and -Independent Vasodilation

In the subjects who participated in the 3-month follow-up, matched data revealed that FMD decreased nonsignificantly ($P=0.063$) as a result of catheterization and then returned toward baseline at 3 months ($P<0.05$ post to recov) in the coated group (n=6) (Figure 3). In the contralateral control limb, FMD was unchanged. ANOVA on the post versus recov data comparing time and arm revealed no significant effect of time ($P=0.21$), a significant effect of arm ($P=0.004$), but no significant interaction ($P=0.14$). In the uncoated group (n=13), the FMD decreased from pre to post ($P<0.01$) and returned toward baseline post to recov ($P<0.05$). In the contralateral control limb, FMD was unchanged. ANOVA on the post versus recov data comparing time and arm revealed no significant effect of time ($P=0.38$), a near significant effect of arm ($P=0.05$), and a significant interaction ($P=0.020$) (Figure 3).

Table 2. Baseline Diameter, Time to Peak, and Shear Rate Area Under the Curve Preprocedure and the Day After the Procedure in the Catheterized and Noncatheterized Arms

	Baseline Diameter, mm		Time to Peak		SR_{AUC}, $s^{-1}\times10^3$	
	Pre	Post	Pre	Post	Pre	Post
FMD protocol						
Cath						
Coated	2.7±0.5	3.0±0.4*	97±42	107±47	28.9±21.6	27.2±13.4
Uncoated	2.9±0.4	3.1±0.4*	106±48	93±45	31.0±15.5	21.5±12.5
Contr						
Coated	2.6±0.5	2.5±0.4	91±50	61±30	26.7±27.8	25.3±9.6
Uncoated	2.6±0.4	2.9±0.4*	86±28	103±58	15.4±8.6	27.7±13.1
GTN protocol						
Cath						
Coated	2.6±0.5	2.9±0.5	316±87	284±93		
Uncoated	2.9±0.4	3.3±0.3*	345±83	254±117*		
Contr						
Coated	2.7±0.5	2.7±0.3	354±125	323±101		
Uncoated	3.0±0.3	2.9±0.3	276±108	297±115		

Data are presented as mean±SD. Coated group, n=14 for FMD and n=12 for GTN. Uncoated group, n=20 for FMD and n=19 for GTN. Endothelium-dependent (FMD) and endothelial-independent function (GTN) in groups. Cath indicates catheterized arm; Contr, noncatheterized control arm, SR_{AUC}, shear rate area under the curve.

*Significantly different from pre $P<0.05$.

The GTN data in the coated group (n=6) decreased from pre to post ($P<0.05$) and then returned toward baseline post to recov ($P<0.05$). In the contralateral control limb, GTN was unchanged. ANOVA on the post versus recov data comparing time and arm revealed no significant effect of time ($P=0.39$) or arm ($P=0.18$) but a significant interaction between arm and time ($P=0.014$). In the uncoated group (n=12), GTN decreased from pre to post and returned toward baseline levels at 3 months post to recov ($P<0.05$). In the contralateral control limb, GTN was unchanged. ANOVA on the post versus recov data comparing time and arm showed a significant effect of time ($P=0.036$), an almost significant effect of arm ($P=0.052$), and a significant interaction between arm and time ($P=0.001$) (Figure 4).

There was no significant difference in the recovery of FMD post versus recov between the coated and uncoated conditions in the catheterized arm, with a 2-way ANOVA demonstrating a significant effect of time ($P=0.005$) but no interaction of time and coating ($P=0.52$). There was also no significant difference in the recovery of the GTN post versus recov between the coated and the uncoated conditions in the catheterized arm, with 2-way ANOVA demonstrating a significant effect of time ($P=0.000$) but no interaction between time and coating ($P=0.58$). Baseline arterial diameters, time to peak, and shear rate area under the curve are presented in Table 3.

Discussion

The aim of this study was to determine the impact of coating of sheaths used during radial artery catheterization on vascular function in vivo. Catheterization may have implications for long-term artery health, as endothelial damage leads to the development of atherosclerotic plaques.[11,12] We assessed endothelial-dependent and -independent function in a section of the artery subjected to sheath placement. Measures were collected before and after catheterization and, in a subgroup, ≈3 months postcatheterization to determine whether arterial function recovered. Within-subject control measures were also collected from the contralateral, noncatheterized limb. Our findings indicate that FMD and GTN decreased as a result of catheterization, impairment that largely resolved after ≈3 months of recovery. There was no difference between the hydrophilic-coated versus uncoated groups in terms of the acute impact of catheterization or recovery. No changes in arterial function were observed in the noncatheterized arm at any time point. These data indicate that a hydrophilic coating does not ameliorate the dysfunction associated with catheter sheath insertion in vivo.

FMD is an in vivo bioassay of NO-mediated endothelial function.[18,19] Depressed FMD is an independent prognostic index of cardiovascular events, particularly in patients with cardiovascular disease.[20,21] There are, however, few data examining the impact of catheterization of vascular function in vivo. One previous study found that FMD was impaired immediately after procedure and up to 9 weeks after surgery.[22] Our data largely reinforce this finding and indicate recovery in endothelial-dependent and -independent function ≈3 months after procedure, whereas Burstein et al[22] reported depressed function at 9 weeks. These findings suggest that 3 months may be the minimum required for arterial function to normalize after sheath insertion.

The question of relative impact of sheath placement on the endothelium versus smooth muscle is difficult to definitively resolve from our data. Although impaired GTN responses indicate that the endothelium is not solely affected, a finding of

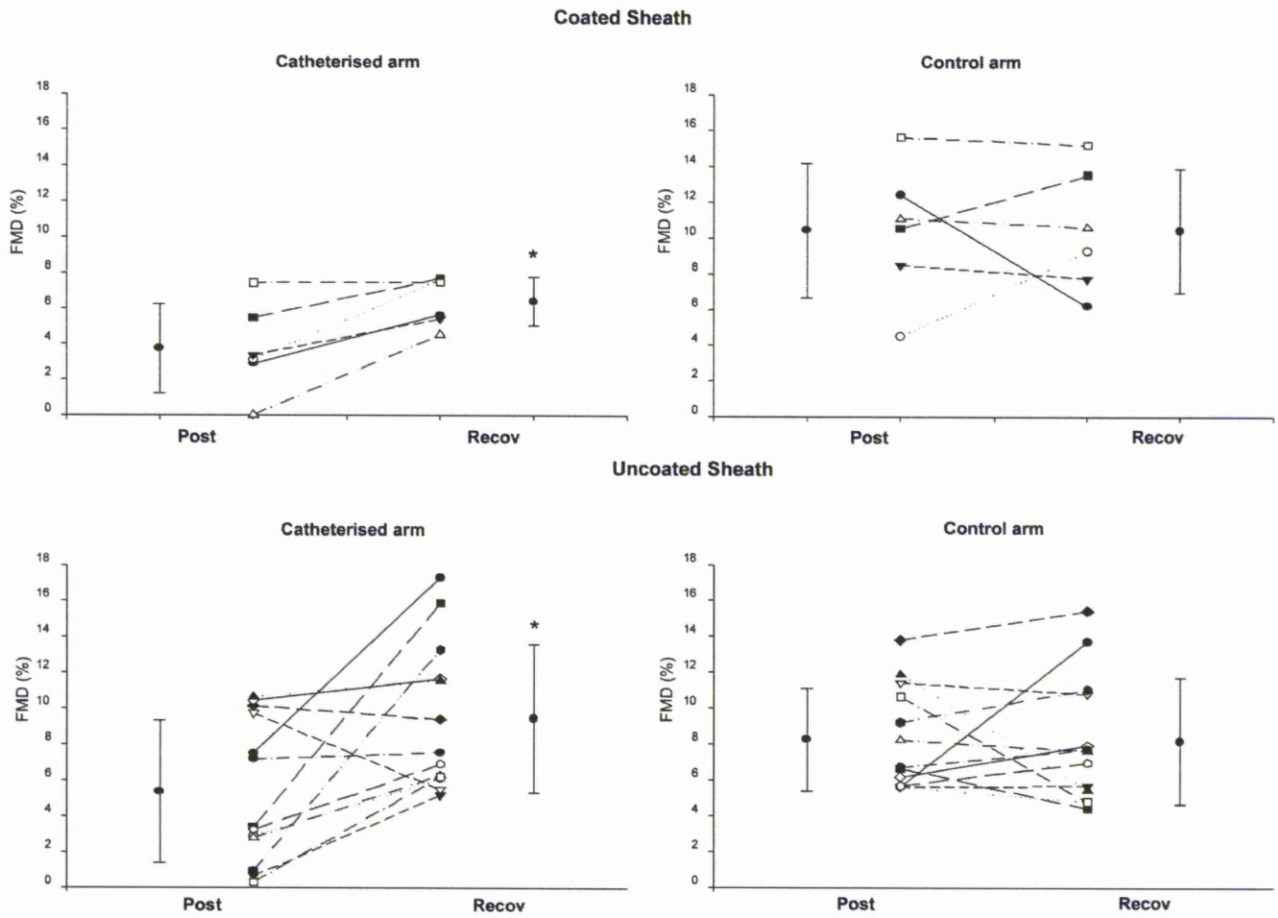

Figure 3. Changes in FMD (%) in the catheterized and noncatheterized arms post and recov. Top panel shows coated sheath data, and bottom shows uncoated sheath data. Data are presented as mean±SD. *Significantly different from pre $P<0.05$.

impaired FMD and GTN function nonetheless allows for the possibility that both endothelial and smooth muscle function were affected. We favor the latter interpretation because we believe that impairment in the function of the middle layer of the wall as a result of the introduction of a sheath, which is of similar outer diameter to that of the artery lumen, is likely to have resulted in endothelial denudation or dysfunction. Although we have no direct evidence of endothelial denudation or damage, it is important to consider that animal studies that established a role for the endothelial function in FMD did so by placing a balloon inside an artery to denude the inner layer.[23,24] We would contend that sheath placement in this study represents a similar, or perhaps even more robust, intervention, which is supported by the significantly larger diameter postprocedure in the catheterized but not in the noncatheterized arm. Therefore, it seems likely that both endothelial and smooth muscle function were affected by sheath placement.

The recovery of endothelial-dependent and -independent function in the catheterized arm indicates that transradial catheterization should not be considered an absolute contraindication to subsequent use of the radial artery as a donor graft. Some caution is warranted; however, as cannulation of the radial artery has been shown to reduce arterial lumen size and result in intima-medial thickening.[25–27] Damage of the smooth muscle also may be associated with intimal hyperplasia, cell proliferation, collagen synthesis,[28] and inward remodeling.[26,29] Furthermore, transradial catheterization has been shown to induce intimal hyperplasia, medial inflammation, and tissue necrosis at the puncture site.[30] Despite good clinical outcomes,[31] caution in using the radial artery as a graft is advocated by several groups due to its propensity to spasm, an increased likelihood of development of atherosclerosis, and damage induced by catheterization.[25,26,32–34]

A unique aspect of this study was examination of the impact of sheath coating on vascular function. The development of hydrophilic coating purportedly leads to reduction in the force required to remove the sheath and the likelihood of damage during removal.[13] There is some evidence that sheath coating has beneficial clinical effects, including reduced spasm and pain.[4,13–14,35] We therefore hypothesized that sheath coating would limit impacts on vessel function and that diminished impact on the endothelium may preserve its well-established antiatherogenic properties. However, our data show that there was no difference between hydrophilic-coated and uncoated sheaths in terms of endothelium-dependent or -independent function after sheath placement. Furthermore, we observed no evidence of a beneficial effect of sheath coating on the recovery of the artery after sheath removal. These data indicate that if clinical and outcome benefits from coating sheaths do exist, then the mechanisms

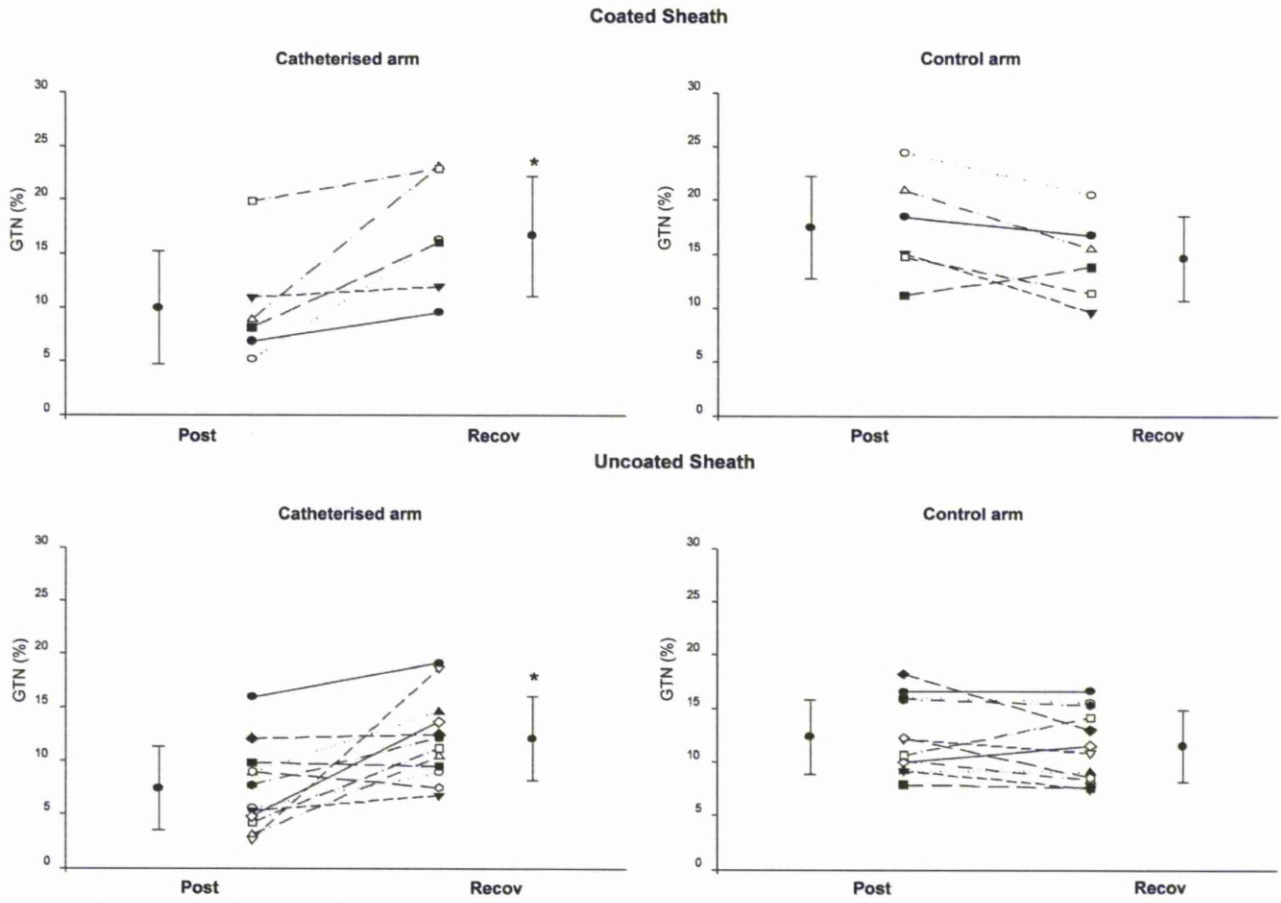

Figure 4. Changes in GTN (%) in the catheterized and noncatheterized arms post to recov. Top panel shows coated sheath data, and bottom shows uncoated sheath. Data are presented as mean±SD. *Significantly different from pre $P<0.05$.

responsible are unlikely to be attributable to preserved endothelial or vascular smooth muscle function. In addition, several recent articles have suggested that patients can develop a granulomatous inflammation due to shedding of some of the hydrophilic coating into the artery.[36–43] These findings, in combination with our data, support the suggestion of Tharmaratnam et al[39] that the increased cost of the hydrophilic-coated sheaths, the cost of treatment of inflammation, and the apparent lack of difference in spasm and depressed function need to be carefully balanced against the putative benefits of reduced spasm and pain on removal.

This study had a number of limitations. There were a relatively small number of patients in each group, and we could not get all to return at 3 months. This limitation is somewhat mitigated by our within-subject design and analysis. We did not control for age, preexisting vascular disease, history of smoking, or drug treatment; however, the use of the contralateral arm as an internal control negated this limitation, and our data set has the advantage of representing responses in typical unselected patients. Finally, sheath insertion increased baseline artery diameter before our postprocedural measures of FMD and GTN. It has been suggested that baseline diameter is an important determinant of the dilator response magnitude, at least between individuals or between arteries, when large differences can exist in the resting diameter.[44] However, the change in diameter we observed is unlikely to explain the magnitude of impairment in FMD. For example, on the basis of our recent article,[44] an FMD difference of 0.2% to 1.5% would be expected for a 0.3-mm change in baseline radial artery diameter. In addition, FMD data collected 3 months after catheterization (Table 3) remained impaired, despite return of the resting diameter to values below that observed before catheterization. Of course, the impact of baseline diameter change per se on FMD and GTN responses is not relevant to the issue of sheath coating because both types of sheath have similar effects on baseline artery diameter. Although our findings are clear and consistent, with a large number of tests, we cannot rule out the possibility of a type I error.

In conclusion, transradial catheterization results in reversible depression in NO-mediated vasodilator function in the catheterized arm. This effect is not mitigated in patients who received a hydrophilic-coated sheath. The purported benefits of hydrophilic-sheath coating need to be weighed against the increased cost, possible increased risk of inflammation, and lack of reduction in arterial function. Future research and technological development should seek to minimize the effects of the catheter and the sheath on the vasculature. It is also possible that optimizing the function and size of the artery before its cannulation may improve the outcome and recovery of the artery and reduce the chance of graft failure if the artery is removed for coronary artery bypass.[45] To this end, exercise training has been shown to improve arterial function and induce outward remodeling,[46–50] both of which might improve the health and recovery of the artery after the procedure.

Table 3. Baseline Diameter, Time to Peak, and Shear Rate Area Under the Curve Preprocedure, the Day After the Procedure, and ~3 Months After Procedure in the Catheterized and Noncatheterized Arms

	Baseline Diameter, mm			Time to Peak, s			SR_{AUC}, $s^{-1}\times10^3$		
	Pre	Post	Recov	Pre	Post	Recov	Pre	Post	Recov
FMD protocol									
Cath									
Coated	2.6±0.5	2.9±0.4	2.7±0.6	94±49	100±54	113±27	25.2±19.2	28.5±17.3	27.2±13.8
Uncoated	2.9±0.4	3.2±0.4	2.7±0.4†	109±46	86±44	90±56	31.7±17.9	20.6±14.0	33.2±23.8
Contr									
Coated	2.6±0.5	2.4±0.4	2.6±0.5	67±50	66±25	81±45	17.2±8.6	24.8±10.9	32.5±22.3
Uncoated	2.6±0.4	2.9±0.4*	2.8±0.4†	87±24	103±68	89±48	23.0±7.1	27.3±15.7	26.8±16.9
GTN Protocol									
Cath									
Coated	2.7±0.5	2.9±0.5	2.5±0.3	316±110	372±63	343±100			
Uncoated	3.0±0.5	3.2±0.2	2.7±0.3†	353±84	250±128	278±104†			
Contr									
Coated	2.7±0.2	2.9±0.5	2.8±0.3	323±148	303±103	293±131			
Uncoated	2.9±0.3	2.9±0.3	3.1±0.4†	245±105	297±109	266±114†			

Data are presented as mean±SD. Coated group, n=6 for FMD and GTN. Uncoated group, n=13 for FMD and n=12 for GTN. Endothelium-dependent (FMD) and endothelial-independent function (GTN) was assessed in both groups. Cath indicates catheterized arm; Contr, noncatheterized control arm; SR_{AUC}, shear rate area under the curve.

*Significantly different from pre $P<0.05$.

†Significantly different from post.

Acknowledgments

We thank Chris Reed for his assistance with development of the edge detection and wall tracking software.

Sources of Funding

Dr Green received funding from the National Heart Foundation of Australia and the Australian Research Council.

Disclosures

None.

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CLINICAL PERSPECTIVE

Since its introduction in 1989, transradial catheterization has gained popularity as an alternate approach for coronary diagnostic and interventional procedures. Recent advances in catheter sheaths include hydrophilic coatings, the aim of which is to reduce friction during sheath insertion and removal. The integrity of this artery is important because it might be harvested as a graft during coronary artery bypass surgery. Although there is evidence of reduced spasm with hydrophilic coating, there is no evidence regarding its impact on vascular function. Our study shows that vascular endothelial and smooth muscle function are reduced after radial artery sheath insertion. This effect is not mitigated by a hydrophilic-coated sheath. The potential benefits of hydrophilic-sheath coating need to be compared with increased cost, risk of inflammation, and reduction in endothelial function.