Intraoperative cerebral microembolisation and neuropsychological outcome following Total Hip and Knee Arthroplasty

by

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Abstract

Objective

A prospective controlled clinical trial assessing intraoperative cerebral microembolisation during total hip (THA) and total knee (TKA) arthroplasty and neuropsychological outcome. Detection of a patent formaen ovale (PFO) was performed to determine whether its presence or absence affected cerebral microembolic incidence and load. Examination of microemboli load in relation to specific surgical activity was performed.

Methods

Ninety-five patients were recruited who underwent neuropsychological assessment (NP group): a battery of tests administered pre-operatively, 6 weeks and 6 months post-operatively. Roughly equal numbers underwent total hip or total knee arthroplasty. Intraoperative cerebral microembolisation was recorded by transcranial Doppler monitor over the middle cerebral artery. Evidence of PFO was sought using agitated saline injected into a large peripheral vein (a validated technique). Orthopaedic and Quality of Life outcome was also measured.

Results

The groups proved well balanced in pre-operative variables. The incidence of cerebral microembolisation for THA was 23% and 45% for TKA. During THA the median number and range of microemboli was 0 (0 – 438); for TKA this was 0 (0 – 83). Mean microemboli load for THA was 2.80 (excluding one outlier) and for TKA 3.76. The overall prevalence of PFO was 29%. PFO did not appear to influence microemboli load or incidence. More microemboli were seen during femoral component impaction in the THA group and after tourniquet release in the TKA group. Overall, patients showed an improvement in total NP change scores at both post-operative intervals. No relationship between microemboli and neuropsychological outcome was found. Good orthopaedic and Quality of Life outcome was recorded.

Conclusion

Intraoperative cerebral microembolisation occurs in a significant proportion of patients during THA and TKA recorded by transcranial Doppler. The microemboli load is low and is not influenced by the presence of PFO. Certain surgical acvtivities seem to be responsible for greater cerebral microemboli generation. However, in this study neuropsychological outcome was not affected post-operatively by microemboli or other operative or patient variables.

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Introduction

Intra-operative cerebral microembolisation during surgery may in some patients result in a global cerebral injury which can be noticed as a decline in post-operative neuropsychological (NP) performance. This decline is defined as an impairment of concentration, memory, learning or the speed of mental and visuomotor responses (although not necessarily all of these).

There is a large body of published work on cardiothoracic surgery patients; the incidence of cerebral microembolisation and the consequent NP decline after coronary artery bypass grafting surgery (CABG), is well recognised [1, 5-7, 9, 10]. This has led to a number of significant changes both in the technique of the surgery, in the control of peri-operative factors, and in the recognition of physiological factors which may be influential, such that the procedure has become more neuroprotective[9].

The risk of stroke following CABG surgery is reported to be between 1.5% and 5.2% [7]. Emboli production is due to the inherent nature of the procedure and thus interest has arisen in other fields of surgery, namely orthopaedic surgery, where emboligenic procedures are commonplace.

The incidence of fat embolism after long bone fracture has been recognised for over a hundred years but the clinical manifestation of this, Fat Embolism Syndrome (FES) was described by Gurd as recently as 1974 [4]. Moreover, it has only been recently recognised in endoprosthetic surgery, where due to the insertion of an arthroplasty component into the intramedullary canal, the pressure within that canal increases. This seems to be the decisive pathogenic factor for development of FES. Furthermore, with the use of conventional cementing techniques, the intramedullary pressures are raised further and the major component of cement, polymethylmethacrylate, has been implicated in producing a hypercoaguable state both local to the site of the operation and systemically via marrow embolisation of tissue thromboplastin into the veins. Activation of clotting, cytokine and kinin cascades occurs and thrombogenesis ensues.

The ultimate fate of these microemboli and their effect is unknown. Presence of embolic material in the right heart is well known during hip and knee surgery, but animal studies have shown microemboli deposition in several end organs including the brain [2]. The route by which microemboli reach the end organs is under investigation and hypotheses have been put forward but much work thus far has been in the animal model.

A proposed route of passage for microemboli is across a patent foramen ovale (a congenital / neonatal conduit between the right and left chambers of the heart which may persist asymptomatically in adult life). This is one factor this study aims to investigate. In addition, few studies have been performed assessing the true incidence of intra-operative cerebral microembolisation during total joint arthroplasty and no study exists comparing the two commonest types: total hip arthroplasty (THA) and total knee arthroplasty (TKA). The incidence until now has been reported to be between 40% and 60%[3-8], but neither of these studies investigated the effect of microemboli on cerebral function post-operatively.

The aim of this thesis is to investigate the incidence of intra-operative cerebral microembolisation during THA and TKA and the effect on neuropsychological function (primary endpoint). Presence of patent foramen ovale and differences between types of arthroplasty are secondary and potentially mediating outcomes.

Original Hypotheses

The null hypotheses tested were: -

There will be no decline in neuropsychological outcome after total hip and knee arthroplasty.

There will be no significant difference in neuropsychological outcome post-operatively between total hip arthroplasty and total knee arthroplasty.

Patent foramen ovale does not influence cerebral microembolisation incidence or load.

Review of the relevant physiology and literature

The first eight chapters of this thesis consist of a review of the relevant physiological mechanisms which play a role and current literature. The specific areas discussed are: -

1. Thromboembolism in Orthopaedic surgery
2. Patent Foramen Ovale
3. Transcranial Doppler Ultrasound and detection of Patent Foramen Ovale
4. Primary Total Hip Arthroplasty
5. Primary Total Knee Arthroplasty
6. Mechanisms of cerebral injury during Orthopaedic surgery
7. The assessment of neuropsychological function after Orthopaedic surgery

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Chapter 1

Thromboembolism in Orthopaedic Surgery

1.1 Overview of Haemostasis

The ability of the body to control the flow of blood following vascular injury is paramount to continued survival. The process of blood clotting and then the subsequent dissolution of the clot, following repair of the injured tissue, is termed haemostasis.

Haemostasis involves a concerted and complex series of reactions, integrating vascular, endothelial cell, platelet and plasma factor responses that regulate thrombus formation. In response to injury, or other prothrombotic stimuli, such as endoprosthetic surgery, rapid changes in vascular endothelial cells will lead to both the release of intracellular proteins that participate in the haemostatic process and an alteration of cell-surface properties, promoting a thrombogenic environment. Platelet adhesion and activation and concurrent activation of the plasma clotting cascade will rapidly promote thrombin formation and fibrin deposition. Almost simultaneously, reactions are set in motion to limit the thrombotic process. The dynamic balance between procoagulant reactions and their down regulation by natural anticoagulants in conjunction with the fibrinolytic system should function within normal parameters to prevent abnormal thrombus propagation. However, in some instances, alteration of just one variable in this complex series of interacting components will bring about a significant hypercoagulable state, which can manifest clinically as venous thromboembolism. More often, changes in multiple variables are required in a combined fashion to lead to a clinically significant hypercoagulable state. In addition to laboratory alterations, clinical factors will also affect a patient's overall thrombotic risk.

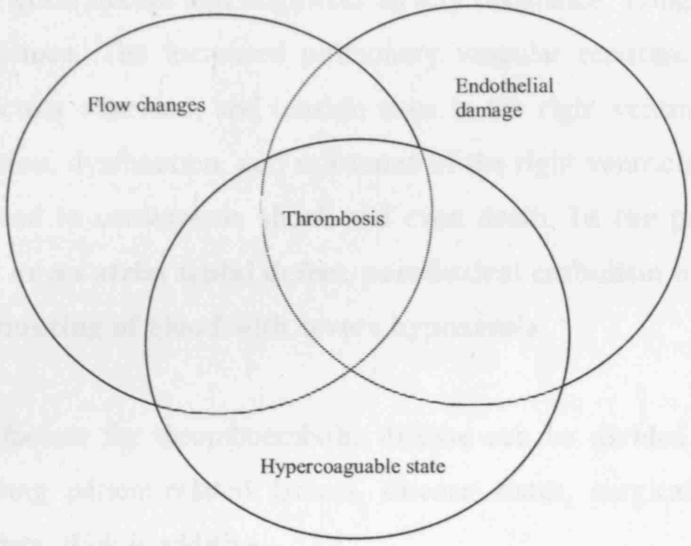
1.2 Introduction

Thromboembolism traditionally encompasses two interrelated conditions that are part of the same spectrum, deep venous thrombosis (DVT) and pulmonary embolism (PE). Deep venous thrombosis affects mainly the veins in the pelvis, thigh and the lower leg. It involves the formation of a clot (thrombus) in the larger veins of the area. This thrombus may interfere with circulation of the area, and it may break off and travel through the blood stream (embolise). The embolus thus created can lodge in the lungs, heart, or another area, such as the brain, causing severe damage to that organ. PE is the obstruction of blood flow to one or more arteries of the lung by a thrombus lodged in a pulmonary vessel. PE and DVT can occur in the setting of disease processes, spontaneously in

predisposed patients, following hospitalization for serious illness, or following, or during, **major surgery**.

In 1856, Virchow demonstrated that 90% of all clinically important pulmonary embolisms result from DVT occurring in the deep veins of the lower extremities, proximal to and including the popliteal veins. However, emboli also can originate from the pelvic veins, the inferior vena cava, and the upper extremities.

Figure 1.1 Virchow's triad



1.3 Aetiology

Thromboembolic disease is the third most common acute cardiovascular disease, second to cardiac ischemic syndromes and stroke. Both DVT and PE frequently remain undiagnosed because they may be clinically unsuspected. The spectrum of disease ranges from clinically slient, to clinically unimportant, to massive embolism causing death. Untreated acute proximal DVT causes clinical PE in 33-50% of patients [94]. Untreated PE often is recurrent over days to weeks and can either improve spontaneously or cause death. Pulmonary embolism is a major clinical problem that contributes to over 150,000 deaths per year in the United States. [31]

1.4 Pathophysiology

Hypercoagulability or obstruction leads to the formation of thrombus in the deep veins of the legs, pelvis, or arms. As the clot propagates, proximal extension occurs, which may dislodge or fragment and embolise to the pulmonary arteries. This causes pulmonary artery obstruction and the release of vasoactive agents (i.e. serotonin) by platelets increases pulmonary vascular resistance. The arterial obstruction increases alveolar dead space and leads to redistribution of blood flow, thus impairing gas exchange due to the creation of low ventilation-perfusion areas within the lung.

Stimulation of irritant receptors causes alveolar hyperventilation. Reflex broncho-constriction occurs and augments airway resistance. Lung oedema decreases pulmonary compliance. The increased pulmonary vascular resistance causes an increase in right ventricular afterload, and tension rises in the right ventricular wall, which may lead to dilatation, dysfunction, and ischaemia of the right ventricle. Right heart failure can occur and lead to cardiogenic shock and even death. **In the presence of a patent foramen ovale or an atrial septal defect, paradoxical embolism may occur, as well as right-to-left shunting of blood with severe hypoxemia.**

Risk factors for thromboembolic disease can be divided into a number of categories, including patient-related factors, disease states, surgical factors, and haematological disorders. Risk is additive.

- Patient-related factors include obesity, varicose veins, use of oral contraceptives or oestrogen, and immobility.

- Disease states such as malignancy, congestive heart failure, nephrotic syndrome, recent myocardial infarction, inflammatory bowel disease, spinal cord injury with paralysis, and pelvic, hip, or long-bone fracture confer increased risk of thromboembolic disease.

- Surgical factors are related to procedure type and procedure duration. Approximately fifty percent of patients who have undergone hip surgery have **asymptomatic** venous thromboemboism (VTE) on the same side as the hip

surgery. The incidence of VTE is reported to be higher in patients who have undergone knee surgery. [125]

- The risk for thromboembolic disease has been shown to be increased with coronary artery bypass grafting, urological surgery, and neurosurgery.

- Haematological disorders that increase thromboembolic risk include activated protein C-resistance (factor V Leiden), protein C or protein S deficiency, anti-thrombin III deficiency, lupus anticoagulant, polycythaemia vera, paroxysmal nocturnal haemoglobinuria, and dysfibrinogenaemia.

Thromboembolic complications frequently begin intra-operatively quietly and extend post-operatively and often present as sudden death[76]. Apparently changes which correlate with the magnitude of the surgical intervention are maximal during the first two days of the post-operative course, but are not related to increases in common neuroendocrine hormones or cytokines. Instead they appear to be more related to surgical tissue trauma and liberation of tissue factor, leading to thrombin formation. In addition, inflammatory (leucocyte) reactivity and hypercoagulability interact to increase the contribution to each other to thromboembolism [98].

1.5 Risk after Orthopaedic surgery

The occurrence of thromboembolism during and as a result of orthopaedic surgery is well known and documented. With particular relevance to this study, venous thromboembolic disease is a major complication of both total hip and knee arthroplasty, and it has potentially life-threatening consequences. In the absence of prophylactic measures, the risk of DVT for total hip arthroplasty (THA) has been reported to range from 39% to 74% and the risk of fatal PE from 0.19% to 3.4% [37]. For total knee arthroplasty (TKA), risk of DVT has been reported to range from 31% to 82% and the risk of fatal PE from 0% - 0.4% [10].

Although early mobilisation, compressive stockings, external pneumatic compression and chemical prophylaxis are widely used as anti-thrombotic agents after elective hip and knee arthroplasty[23,24,38,47,95,99], a better understanding of the factors that stimulate

thrombogenesis during these procedures might provide a more focused approach to prevent or minimise the occurrence of DVT and PE.

Fat and bone marrow contained in the intramedullary canal of long bones are considered potential activators of the clotting cascade and are potential factors in the creation of endothelial lesions of the peripheral veins [109,122]. In fact, fat embolism during long bone fractures has been recognised for over one hundred years, although not fully understood until recently. Moreover, since 1974 it has been recognised in **endoprosthetic surgery** [40] e.g. joint replacement surgery, the clinical manifestation of which, in both settings, has been described as Fat Embolism Syndrome (FES).

1.6 Fat Embolism Syndrome

FES classically refers to the constellation of clinical manifestations that may develop after trauma, and particularly after fractures, when fat droplets acting as emboli, become impacted in the pulmonary microvasculature and other microvascular beds, especially in the brain. Embolism begins rather slowly and attains a maximum in about 48 hours. Open fractures furnish less emboli than closed fractures.

Other forms of trauma that rarely result in fat embolism include massive soft tissue injury, severe burns and liposuction. Non-traumatic settings occasionally lead to fat embolism. These include conditions associated with fatty liver, prolonged corticosteroids therapy, acute pancreatitis, osteomyelits, and conditions causing bone infarcts, such as sickle cell disease.

The principal clinical features of fat embolism syndrome are: respiratory failure, cerebral dysfunction and petechiae. The initial symptoms are probably caused by mechanical occlusion of multiple blood vessels with fat globules that are too large to pass through the capillaries. Unlike other embolic events, the vascular occlusion in fat embolism is often temporary or incomplete since fat globules do not completely obstruct capillary blood flow because of their fluidity and deformability. The late presentation is thought to be a result of hydrolysis of the fat to more irritating free fatty acids which then migrate to other organs via the systemic circulation.

Many aspects of the fat embolism syndrome remain poorly understood, and disagreement about its aetiology, pathophysiology, diagnosis and treatment persists.

Two events promote entrance of marrow contents into the circulation following a fracture: movement of unstable bone fragments and reaming of the medullary cavity during placement of an internal fixation device. Both of these cause distortion of and increased pressure within the medullary cavity, permitting entry of marrow fat into torn venous channels that remain open even in shock because they are attached to the surrounding bone.

There are two theories which have gained acceptance with regard to pathophysiology:

- **The mechanical theory**: FES results from physical obstruction of the pulmonary and systemic vasculature with embolised fat. Increased intramedullary pressure after injury forces marrow into injured venous sinusoids, from which the fat travels to the lung and occludes pulmonary capillaries. Fat emboli can cause cor pulmonale if adequate compensatory pulmonary vasodilation does not occur.

- **The biochemical theory**: Circulating free fatty acids are directly toxic to pneumocytes and capillary endothelium in the lung, causing interstitial haemorrhage, oedema and chemical pneumonitis. It is also possible that coexisting shock, hypovolemia and sepsis, all of which reduce liver flow, facilitate the development of FES by exacerbating the toxic effects of free fatty acids.

During total joint arthroplasty, showers of bony spicules, marrow fat, cement particles (if used), debris and thrombus are carried by venous blood to the lungs[16] creating conditions not unlike those present in patients who have suffered traumatic long bone fractures, through the mechanisms described above.

Penetration into the medullary canal during endoprosthetic procedures and during intramedullary stabilisation of fractures of the long bones with subsequent release of bone marrow into the circulatory system, have been well documented [64,72,87].

1.7 Mechanisms of Thromboembolism in Orthopaedic Surgery

Total hip or knee replacement orthopaedic surgery requires the insertion of joint prosthesis components into the bone (cemented or non-cemented). When these components are inserted with the use of standard surgical techniques, tissue thromboplastin from the bone marrow is forced into the draining veins of the long bone, leading to activation of the clotting cascade, thromboembolism and cardiopulmonary impairment [7,52,91,104].

It is the increase in intramedullary pressure in the bone which is the decisive pathogenic factor for the migration of bone marrow, fat and bone debris and the embolisation of those elements through the venous system [8,45,50,90]. Furthermore, embolisation of bone marrow elements can produce direct venous endothelial lesions. The study by Stewart et al.[108] showed that total hip arthroplasty in dogs was ultimately responsible for the production of frequent identifiable endothelial tears infiltrated with leucocytes and platelets in veins around and distant to the hip joint. These changes were not observed in veins in control animals. Stewart et al.[109] suggested that total hip arthroplasty causes the release of vasoactive substances and that these substances enter the circulation and survive long enough to influence veins distant from the surgical site. Kinking and occlusion of the femoral vein caused by excessive flexion and rotation of the leg during the operation also may disrupt the endothelium and cause venous stasis [6,104,116]. A later study by the same investigator in the canine model postulated that surgical trauma resulted in circulating vasoactive substances which caused venous dilation and that dilation of smooth muscle and connective tissue beyond the yield point of intima resulted in intimal rupture[108]. Furthermore, the intra-operative venodilation was noticed in veins distant from the site of operation (jugular and femoral veins following total hip replacement). These observations support the recommendation that the prevention of deep venous thrombosis associated with total hip arthroplasty (and probably total knee arthroplasty also) be focused on the intra-operative period rather than during the postoperative period, where well established prophylaxis exists.

It is not only prostheses which increase the intramedullary pressure, but also instrumentation introduced into the intramedullary space as part of the surgical technique; this is temporary but often repetitive, as in the case of femoral broaching or reaming for THA and the use of a femoral alignment rod in TKA [15].

1.8 Cement and Thromboembolism

The current rationale for the use of cement in total hip and knee arthroplasty will be discussed in later sections. The role of cement in the pathophysiology of thromboembolism remains unclear. Most investigations related to the prevalence of DVT have involved cemented components [18,93]. It is possible that cement may have inherent thrombogenic properties and thus influence the prevalence of thrombosis of the deep venous system. Reports concerning this possibility are conflicting; activation of the clotting cascade and concurrent fibrinolysis have been described during and after total hip and knee arthroplasty, but it is uncertain whether this activation differs according to whether the prosthesis is inserted with or without cement [7,39,52]. A previous echocardiographic investigation showed a low risk of fat and bone marrow embolism during THA performed without cement [91]. While the majority of studies assessing the rate of DVT associated with THA or TKA performed with or without cement were not randomised [36,125], Laupacis et al, who randomised 250 patients undergoing THA to receive a femoral component either with or without cement, found no marked difference between the two groups with respect to the frequency of DVT (50% compared with 47% respectively) [58]. With regard to TKA, Berman et al identified thrombus, not fat and no polymethylmethacrylate monomer (the main constituent of cement used in orthopaedics) in the central circulation in fifty-nine patients undergoing cemented TKA[5]. This finding is consistent with that of Healy et al.[43]. Such findings may reflect a complex pathophysiology in which the release of free fatty acids from marrow debris into the central circulation is implicated in the activation of the clotting system [43, 89,107]. However, several studies have argued that bone cement may activate the clotting cascade and subsequently contribute to the formation of fresh thrombus [101,115].

It has been clear since 1974 that the use of cement during total hip arthroplasty increases the intramedullary pressure[114]. Kallos et al. went on to report that pulmonary embolism was a direct sequelae of such an increase in the dog model[50]. Although Bredbacka et al. supported the theory held by others (above) that cement itself was not responsible for activating the coagulation, fibrinolytic and kallikrein cascades, they postulated that perhaps it was the reaming of the canal that was responsible[7]. This prompted others to study what systemic effect cementing a prosthesis had on cardiovascular responses during arthroplasty. Clark et al. studied patients undergoing cemented or uncemented

hemiarthroplasty and found that introduction of cement transiently reduced cardiac output by 33% and stroke volume by 44% but did not affect heart rate or mean arterial pressure.[19] Insertion of the prosthesis did not adversely affect cardiac function. This was echoed in the findings by Ereth et al.[33]

However, Hofmann et al.[46] showed that intramedullary pressure increases were not exclusive to cemented implants as demonstrated by rises in intrameduulary pressure in their series of uncemented total hip arthroplasties.

Most recently Pitto et al.[91] have documented embolic events seen in the heart using TOE in 85% of total hip arthroplasties using cement but no embolic events in patients receiving uncemented implants. Moreover Pitto demonstrated that using a bone vacuum as a modified cementing technique reduces the incidence of embolic events dramatically, suggesting that the reduction in intramedullary pressure is the key factor in lowering the incidence of embolisation.

The converse has been recorded by Kim at al.[54] who described no differences in fat or bone marrow embolisation between groups of patients receving either cemented or uncemented total hip arthroplasty, using arterial blood sampling. They also recount no difference between bilateral simultaneous or unilateral hip arthroplasty when examining systemic embolisation.

Thus the argument on whether cement directly affects the incidence and load of embolic material delivered to the heart is ongoing. It seems that an increase in intramedullary pressure is responsible for embolisation which may be irrespective of cement use. However cement may trigger clotting and other physiological cascades which in turn may heighten this response.

1.9 Tourniquet use and Thromboembolism

The pathophysiology of thromboembolism during total knee arthroplasty has also been linked to the use of tourniquet. Intra-operative transoesophageal echocardiography (TOE) has provided reproducible evidence of an echogenic embolic phenomenon associated with total joint arthroplasty and the use of a tourniquet [5,66,98].

Pneumatic tourniquet inflation compresses the femoral artery and vein, leading to venous stasis and acidosis. Furthermore, endothelial disruption or injury, and additional tissue thromboplastin forced into the femoral vein from the femoral cavity, account for thrombosis. This hypercoaguable state completes the Virchow Triad (figure 2.1) of thrombus formation.

The period after tourniquet release during TKA with cement represents a critical time of potential haemodynamic instability and haemodynamic collapse remains one of the most serious complications of total joint arthroplasty [65,66,81]. Embolic showers have frequently been observed after tourniquet release, suggesting that PE and thromboembolism to other end organs may also occur at that time [20,65,81,84]. Histological evidence of consistent fresh venous thrombus released into the circulation at that time has also been confirmed [5,20,66].

It is commonly believed that embolic events can occur while the tourniquet is inflated; sudden decreases in oxygen saturation during TKA, even while the tourniquet is still inflated, have been noticed.

Kato et al. suggested two possible causes for intravasation of embolic material with a tourniquet noticed in their study comparing echogenic material (detected by TOE) in the right atria of patients undergoing TKA with or without tourniquet [53]. Firstly, echogenic material could flow from the drainage veins of the femur to the inferior vena cava. Anatomically, blood that enters the femur can be drained to the surface through the emissary or perforating vein [1]. Furthermore some authors have shown that fluid and even methylmethacrylate monomer particles leave cancellous bone and enter the systemic venous circulation [27,42,113,119]. Because it is impossible to increase the inner pressure of the femur by tourniquet inflation, some of the materials that migrated into the vessels in the medullary cavity could flow centrally through the venous network and exit to the surface of the femur via the drainage veins that were central to the site of application of the tourniquet. Then the material flowed into the inferior vena cava and reached the right atrium. Two patients in their study underwent TKA on the ipsilateral side to previous THA (with a tourniquet); no echogenic material was seen in the atria during surgical activity on the femoral side. This seemed to show that migration of material through the

marrow of the proximal femur is impossible because of an artificial substance that had already been inserted into the intramedullary cavity.

Secondly, since material larger than the size of the drainage veins was noticed echogenically during TKA also, and the movement of that material could not be explained by the mechanism above, they postulated that perhaps thrombi formed in the veins at sites of blood flow congestion proximal to the femur as a result of tourniquet inflation might have been sheared off the vessel walls by foreign material washed out of the blood stream above it, and hence gained passage to the right atrium.

The pattern of echogenic material detected by TOE has been classified according to established criteria [33,56,57]. A simplified version used by Kato et al [53] allows the type of embolic material reaching the right atrium to be determined: grade 0, no emboli, grade 1, a few fine emboli, grade 2, a cascade of fine emboli or embolic masses less than 5mm in diameter and the right atrium opacified with echogenic materials; and grade 3, fine emboli mixed with large embolic masses greater than 5mm in diameter or serpentine emboli.

Previous studies have shown both femoral and tibial prosthesis cementing continously caused small echogenic emboli during TKA **without tourniquet** [53,85], upto grade 1. However, during TKA with tourniquet, after deflation, grade 1 to 3 material was seen; large discrete particles superimposed on a miliary pattern [85,86]. In particular, the large material classified as grade 3 was strongly suspected to be thrombus and it seemed to have formed while the tourniquet was inflated. The material seen after deflation seemed to be a mixture of material seen during reaming and insertion of the prosthesis in cases without tourniquet and material formed while the tourniquet was inflated. Further conclusions from these studies suggest that grade 2 and 3 material only, are responsible for haemodynamic changes and impaired gas exchange. However since reports that emboli reduce the cross-sectional area of the pulmonary arterial bed by at least 40% to produce haemodynamic changes, [62,67] mechanical obstruction alone may not have caused the observed changes, but in combination with the vasoconstrictor effect on the pulmonary vasculature due to the release of neurohumoral substances, such as serotonin released from platelets adhering to embolus [41].

Thus it appears that deflation of the tourniquet causes a high incidence of grade 3 events; the same severity of events is rarely observed during TKA when a tourniquet is not used; when such events are observed, it is after femoral reaming only.

There are concerns regarding the relation between tourniquet use and echogenic emboli. A 5.33-fold greater risk of large venous embolism accompanies the use of tourniquet during TKA[86]. If avoiding tourniquet inflation decreases the occurrence of large emboli, then TKA should be performed without tourniquet especially in patients with cardiopulmonary impairment. The actual rate of PE remains unconfirmed in such cases and with such effective prophylactic methods already in use today, judicious inflation of the tourniquet during TKA (i.e. when cementing the prosthesis) may be a useful option, as dry bone optimises cement fixation. However, it should be noted, there is no evidence that duration of tourniquet inflation influences emboli formation.

One other possible aetiological factor exists in the cause of intravasation of embolic material with a tourniquet which is inadequate tourniquet pressure. If pressure is insufficient to compress the vessels then embolic material may be seen throughout surgery as aforementioned. The duration of tourniquet inflation is reported not to influence the size or volume of echogenic material seen by TOE [5]. The embolic shower appears in the right atrium and ventricle typically, ten to fifteen seconds after tourniquet deflation and peaks in intensity within thirty seconds, lasting several minutes [5,81,85,86].

Embolisation is possible even when the tourniquet is inflated and deflation of the tourniquet is associated with a shower of larger embolic material entering the venous circulation. The size of embolic particles seems to play a role in the severity of pulmonary impairment and haemodynamic instability although this may be in concurrence with metabolic factors. Therefore, thromboembolism is intricately related to tourniquet use during TKA.

1.10 The fate of thromboembolic material

The presence of air emboli in the right heart during hip surgery has been well documented [3,69,70,79]. Emboli consisting of fat, bone marrow, cement, bone debris and thrombus have also been reported in animals [11,12,51,82] and humans alike [26,44,71,121].

Through the mechanisms described earlier in this chapter, we understand how emboli enter the venous circulation, and consequently the right heart, during arthroplasty surgery. The extruded contents of the intramedullary cavity of long bones have traditionally been thought to be effectively filtered by the lungs, in some cases injuriously leading to cardiopulmonary collapse and PE. Intra-operative haemodynamic instability and hypoxaemia have been attributed to right ventricular dysfunction secondary to pulmonary fat embolism and acute pulmonary hypertension [16,123].

Several interesting studies, animal and human, have demonstrated with histopathological evidence, the presence of intravascular fat in end organs such as the brain, heart and kidneys after cemented arthroplasty[13,102,103,120]. Although the origin of fat in pulmonary vessels is the medullary cavity[16,82], the aetiology of intravascular fat in systemic organs is controversial and more importantly, how embolic material is synthesised in or traverses to the systemic (arterial) circulation from the venous circulation remains unclear.

We have already considered one hypothesis, the **biochemical theory** of FES. This theory suggests that fat forms from intravascular chemical reactions[4,89]. Weisz suggested that embolic triglycerides "decompose" in the presence of tissue lipase, causing a chemical reaction as a result of the release of free fatty acids [120]. This theory suggests that the development of an acute pulmonary inflammatory reaction in response to released free fatty acids could cause pulmonary oedema in post-traumatic FES.

The biochemical theory has been contested by investigators who propose that small fat globules may pass through the lung vasculature (**transpulmonary passage**) and enter the systemic circulation, causing peri-operative microembolism [13,35,103]. This theory suggests that, because of the fluidity and deformability of the fat globule, pulmonary vascular occlusion is variable over time [16,103]. Furthermore, Byrick et al. demonstrated that deformable fat globules could traverse the pulmonary vasculature under high pulmonary artery pressure in dogs which had undergone bilateral cemented arthroplasty, within three hours [13]. To contest the biochemical theory further, ultrastructural studies demonstrated no evidence of acute inflammation around fat occluded pulmonary vessels of any of the tissues examined using electron microscopy in their model three hours after arthroplasty. They also found intravascular fat in all the brain, heart and kidney specimens examined

three hours after arthroplasty. Moreover, a control group of dogs were injected 15 micrometer diameter microspheres, twice, labelled with two different isotopes denoting whether the injection was immediately before arthroplasty or within 1 minute of arthroplasty ending. No microspheres from either injection were detected in arterial blood for the 3 hour sampling period following arthroplasty. The number of microspheres per gram lung tissue was significantly greater than the number found in brain, kidney or myocardium (no difference between injections). The total number of microspheres in brain, heart and kidneys represented less than 1% of all microspheres injected. Transpulmonary passage of 15 micrometer microspheres was therefore minimal after arthroplasty at high pulmonary artery pressures in dogs (transpulmonary passage of microspheres previously being proved as minimal at normal pulmonary artery pressures [34]), when substantial intravascular fat deposits were found in all tissues simultaneously. The final most striking finding from this study was the distribution of systemic fat appeared to be primarily in glomerular capillaries in the kidney, cortical tissue of the brain (relevant to this study) and myocardial arterioles in the heart. This is consistent with the distribution of regional blood flow to these organs and autopsy studies of fat embolism [102]. Because no intravascular fat was detectable in animals which had not had arthroplasty, this finding also emphasised that systemic fat deposits were related to the orthopaedic procedure. Moreover, Schemitcsh et al. concluded that intravascular fat persists in the lungs, kidneys and brain for 72 hours after canal pressurisation in dogs [100]. The findings from Byrick's study suggest that the composition of embolic material does influence the filtering capacity of the lungs, and that in the presence of pulmonary hypertension transpulmonary passage of deformable fat globules may contribute to post-operative organ dysfunction. Byrick further supported this theory with a recent study of rats where a cranial window was created for orthogonal polarisation spectral imaging videomicroscopy of cerebral blood flow (pial-cortical vessels) [14]. He noted that cerebral lipid microemboli led to a reduction of mean blood pressure requiring resuscitation and that the microemboli changed shape; fragmentation, erosion and transient arteriolar occlusion were also seen. As the blood pressure increased reperfusion of occluded arterioles occurred. Post-mortem revealed brain and lung lipid embolisation with no patent foramen ovale, implying that lipid may pass through the lung during orthopaedic surgery, to the brain.

1.11 Paradoxical embolism

The third theory is **paradoxical embolism.** First described by Cohnheim in 1877 [21], paradoxical embolism (PDE) was defined as venous thrombosis causing systemic embolisation through an intracardiac right-to-left shunt. Multiple autopsy proven cases were described in the French and German literature until 1930 when two patients diagnosed during life were reported [26,112]. Since then well over 170 cases have been reported, [2,9,49,61,68,73,75,77,78,106] with increasing numbers recognised ante-mortem [2,9,29,59,61,73,75,77,106,110,117]. In 1951, Johnson [48] proposed a more systematic definition of PDE consisting of 4 diagnostic criteria:

1. Embolism confirmed by clinical angiographic or pathologic findings without apparent source in the left heart or proximal arteries.
2. Embolic source within the venous system.
3. Abnormal intracardiac or intrapulmonary shunt.
4. A pressure gradient promoting flow through the shunt.

A diagnosis of PDE is presumed if the first 3 criteria are met and is proved conclusively only if embolus is lodged in the intracardiac shunt at autopsy [68,114]; the latter is rarely observed and thus PDE remains a presumptive diagnosis, gaining credibility in the absence of any other reasonable explanations for each individual clinical scenario.

Some authors restrict their definition of PDE to include only emboli due to thrombotic material, [17,58,65,102]whereas others include emboli of any kind [49]. Most reports cite venous thrombi from branches of the inferior vena cava as the major source.

Away from the setting of surgery, intra-cardiac right-to-left shunts have been increasing implicated in the aetiology of stroke, particularly in young patients with no other identifiable cause (cryptogenic stroke). The mechanism is by the passage of venous clots through the shunt into the arterial circulation, enabling cerebral embolism. The paradoxical route for venous embolic material to reach the systemic arterial circulation has been recognised through rare autopsy findings of thrombus straddling a shunt in the setting of fatal stroke [105]. In fact, the most common shunt described is a **patent foramen ovale (PFO).** Paradoxical embolism in the context of a PFO has been documented with

stroke during PE [105], cerebral lesions from gas embolisms in divers [55] and cerebral infarction from fat embolism post orthopaedic trauma [87]. These clinical settings are often associated with increased pressure in the right heart and therefore predispose to PDE. However, right-to-left shunting may occur with normal right heart pressures during normal respiration or be precipitated by the Valsalva manoeuvre (forced expiration against a closed glottis) [58].

As described earlier in this section, endoprosthetic surgery (arthroplasty), particularly of the hip and knee, results in a significant load of embolic material reaching the right heart, as demonstrated by TOE. Therefore, passage of embolic material to the left heart and thus the arterial circulation, is possible through a PFO and has been graphically documented [86]. The cerebral circulation may receive such material during orthopaedic procedures; cerebral embolisation has been documented during a variety of orthopaedic procedures: total hip arthroplasty [22,28,32,83,87] , total knee arthroplasty [80,111,118,126], revision total hip arthroplasty [60,63,96], paediatric scoliosis surgery [97], femoral fracture fixation [74,87] and femoral lengthening[30]. However, only five of the aforementioned authors [22,28,87,97] searched for a PFO as a possible explanation for the paradoxical embolic phenomenon documented.

Documentation of cerebral embolisation during orthopaedic procedures to date has been in the form of case reports or studies with low numbers of patients. Moreover, no study in the English literature to date has examined the effect of cerebral embolisation on a group of homogenous orthopaedic patients and screened for PFO simultaneously. Furthermore, existing case reports seem to only report cerebral embolisation with near fatal or fatal consequences, and the low number studies, which clearly demonstrate cerebral embolisation with non fatal effects, do not investigate thoroughly, effects on cognitive and post-operative outcome in their subjects. In view of these these shortcomings our study was initiated to further assess the role of PFO with cerebral embolisation.

The next two sections will aim to discuss thoroughly PFO, its potential role in cerebral embolisation and current methods of detection.

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Chapter 2

Patent Foramen Ovale

2.1 Historical note

Patent foramen ovale (PFO) is an anatomical inter-atrial communication with potential for right-to-left shunt. PFO has been known since the time of Galen (129 –210 AD). In 1564, Leonardo Botali, an Italian surgeon, was the first to describe the presence of PFO at birth. However the function of foramen ovale in utero was not known at that time. In 1877, Cohnheim [7] described paradoxical embolism (PDE), venous thrombosis causing systemic embolisation through an intracardiac right-to-left shunt, in relation to PFO.

2.2 Anatomy of PFO

PFO permits blood from the inferior vena cava to freely enter the left atrium in utero, thereby bypassing the non-functioning lungs, and facilitating passage of maternal oxygenated blood to the organs of the growing foetus.

Anatomically, a thick muscular ridge, the limbus of the fossa ovalis, borders the foramen ovale. A thin tissue flap on the left atrial side of the septum, which represents an embryological remnant of the septum primum, forms the fossa ovalis.

At birth, the left atrial pressure exceeds the right atrial pressure and forces the valve against the limbus, thus achieving physiological closure. During the first weeks of life, Doppler echocardiographic studies in healthy newborns can often demonstrate incompetence of the valve that allows some degree of left-to-right shunting. Shunting generally resolves by 1 year of age, as the foramen ovale closes.

However, this closure may be incomplete and a residual defect remains in 17-32% of healthy individuals [15,32,36]. The structure of a PFO is much like a flap valve, sealed closed by the higher pressure in the left atrium, thus not causing physiological compromise in normal subjects.

The Mayo Clinic autopsy study[15] revealed that the size of a PFO increases from a mean of 3.4mm in the first decade to 5.8mm in the 10th decade of life, as the valve of fossa ovalis stretches with age. The same study also noted that PFO was less frequent with increasing age.

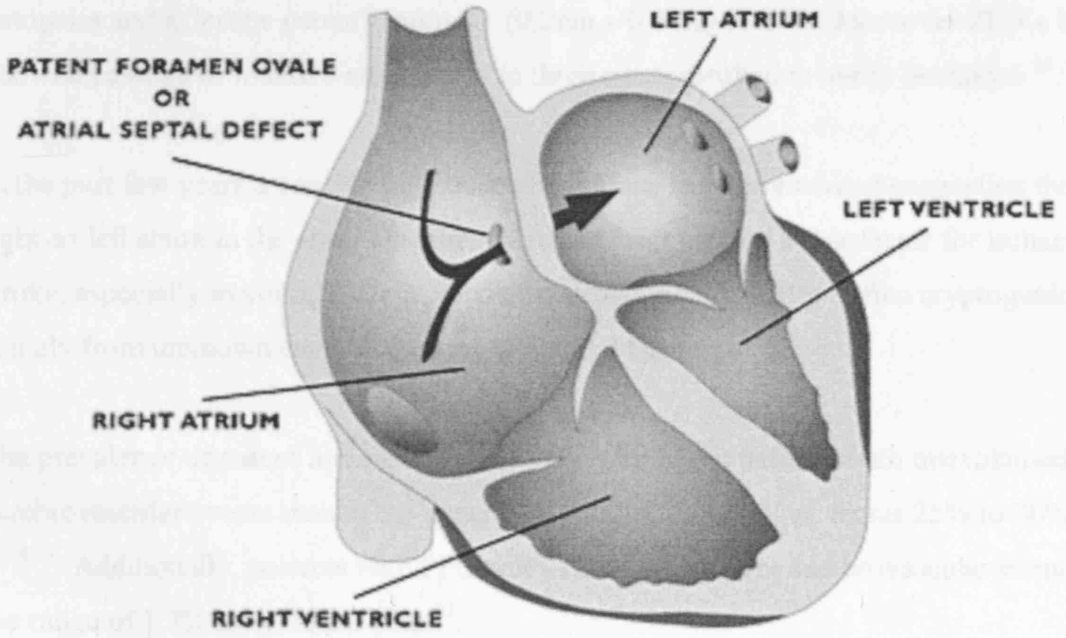
Persistent left atrial enlargement associated with specific cardiac lesions, such as mitral valve stenosis, mitral valve regurgitation, patent ductus arteriosus or ventricular septal defect can dilate the foramen; atrial left-to-right shunting can continue as a result.

2.3 Paradoxical embolism

Most thrombi that cause embolic stroke originate in the heart or arise from athero-thrombotic lesions in the aorta, the carotid artery or the vertebrobasilar system.

The paradoxical route for venous embolic material to reach the systemic circulation has been recognised through rare autopsy findings of thrombus straddling a PFO in the setting of fatal stroke [42]. Elevated right atrial pressures can cause blood to pass from the right atrium to the left atrium and therefore into the systemic circulation.

Figure 2.1 Patent Foramen Ovale



Paradoxical emboli can lodge in the cerebral, peripheral and mesenteric vasculature as well as in the coronary arteries; patients often have embolisation at multiple sites [19,27].

Paradoxical embolism in the context of PFO has been documented with stroke in divers [21], and cerebral infarction from fat embolism post orthopaedic trauma [33]. These clinical settings are often associated with increased pressure in the right heart and therefore predispose to paradoxical embolism. However, right-to left shunting may occur with normal right heart pressures during normal respiration or be precipitated by the Valsalva manoeuvre [24].

Most paradoxical embolisms have been associated with a PFO; among 25 cases diagnosed ante-mortem in whom the interatrial defect was characterised, 18 (72%) had a PFO, 3 had an ASD, 3 had a pulmonary arterio-venous malformation and one had a ventricular septal defect [27]. There has also been a case with Ebstein's anomaly [29] and patent truncus arteriosus [14].

2.4 PFO and cryptogenic stroke

The PFO has been known to be a very common finding since 1930, when Thompson and Evans identified a "pencil patent" defect (0.6cm – 1.0cm in diameter) in 6% of unselected autopsies and a "probe patent" foramen (0.2cm – 0.5cm) in 29%. Moreover PFO's have allowed passage of massive emboli that in three cases resulted in aortic occlusion [25].

In the past few years a considerable bulk of evidence has accumulated suggesting that right-to-left shunt in the atrial chambers across a PFO may be a risk factor for ischaemic stroke, especially in young patients in whom stroke remains all too often cryptogenic, namely from unknown cause according to standard criteria [24,48].

The prevalence of patent foramen ovale (PFO) is higher in patients with unexplained cerebrovascular events than in the general population (up to 75% versus 25% to 30%) [15,24,37]. Additionally, patients with PFO carry risk for recurrent cerebrovascular events in the range of 1.7% to 4.7% per year [31].

The supportive evidence mainly comes from studies performed with transoesophageal echocardiography (TOE) which have shown that PFO is two to three times more frequent in patients with strokes of unknown cause as compared with strokes, where a cause can be identified in age-matched non-diseased controls [5,13,28,34].

A number of recent reports have emphasised the amount of right-to-left shunting as the crucial factor underlying the likelihood of paradoxical brain embolism in stroke patients [10,38,44,46]. However, the evidence collected so far is still mainly the result of TOE studies, where largely arbitrary criteria have been adopted to define large versus small degree of shunt. A more physiological approach is afforded by contrast-enhanced transcranial Doppler (ce-TCD). With ce-TCD, air microbubbles injected in a peripheral vein can be easily detected in the cerebral vessels in the case of right-to-left shunting [2,18]. TCD and PFO detection will be discussed in the next section.

Although PFO is increasingly being incriminated as a risk factor underlying paradoxical cerebral embolism in young stroke patients, its pathogenic role has been disputed on a number of arguments: first, deep vein thrombosis has seldom, if ever, been found more frequently in PFO-associated strokes [26]. Secondly, a Valsalva strain is not commonly reported at the time immediately preceding the onset of symptoms [34]. Thirdly, PFO is present in at least one-fifth of the normal population [15] and thus one would expect a higher prevalence of related cerebrovascular problems than documented. Furthermore, a prevalence of PFO similar to that of cryptogenic stroke has been found in migraine patients [2,12], in transient global amnesia [20] and in conditions unrelated to cerebrovascular disease, such as chronic obstructive pulmonary disease and obstructive sleep apnoea [40,43].

The co-occurrence of PFO with other minor cardiac abnormalities such as atrial septal aneurysm [5,6,16] and Chiari network (a right atrial embryonic remnant consisting of a membrane extending from the region of the ostia of the inferior vena cava and coronary sinus to the atrial septum and tricuspid annulus. It is depicted as a normal variant on echocardiography in less than 5% of subjects) [35], has prompted speculations on the local effects of these associated abnormalities in triggering the coagulation cascade. Moreover, it has been recently reported that subjects with PFO are at increased vulnerability for major dysrhythmia, including atrial fibrillation [4]. These findings suggest that paradoxical embolism may represent just one of multiple pathogenic mechanisms responsible for PFO associated strokes.

Nevertheless, whatever the mechanism, the size of PFO seems to play a crucial role. In the Northern Manhattan study, a PFO larger than 2 mm as measured by TOE was found in 26% of 42 infarcts of unknown aetiology and in 6% of 54 infarcts of determined cause [44]. Stone et al. followed-up 30 patients over a mean period of 21 months, based on the number of microbubbles recorded in the left atrium after intra-venous saline injection [46]. Five of 16 patients (31%) with large shunts (20 bubbles) had subsequent ischaemic neurological events, whereas none of the 18 patients with small shunts (<20 bubbles) had embolic events (P = 0.03). De Castro et al. (2000) defined the co-occurrence of right-to-left shunting at rest and interatrial septum motility exceeding 6.5 mm as 'high risk' PFO and 'low risk' PFO as membrane motility less than 6.5 mm and right-to-left shunting or the combination of membrane motility >6.5 mm with right-to-left shunting only during Valsalva [10]. In 27 'high risk' patients, the cumulative recurrence rate of stroke at 3 years was 12.5% as opposed to 4.3% in 'low risk' patients (P = 0.05). De Castro suggested that increased motility of the fossa ovalis membrane in patients with PFO may play a significant role in permitting paradoxical shunt via a mechanical action in directing blood through the conduit. He used TOE to demonstrate that the preferential orientation of flow from the inferior vena cava is directed towards the foramen ovale through the eustachian valve (a crescentic fold that is attached to the anterior margin of the opening of the inferior vena cava into the right atrium of the heart, also called valvula venae cavae inferioris), and it may be favoured and enhanced by the flap motion of the membrane. These studies had many limitations: rather arbitrary criteria were used to define large versus small shunts, the numbers of patients were small and TOE only was used, which may not be the ideal tool to quantify the impact of right-to-left shunting on cerebral circulation [6]. Nevertheless, the findings, taken together, suggest that the larger the shunt and the greater the membrane motility, the stronger its association with stroke.

2.5 Other causes and associations of paradoxical embolism

Because of its valve like nature, PFO may permit right-to-left shunting as the result of a transient, instantaneous pressure gradient between the right and left atria during the cardiac cycle, even without the need for pathological (i.e. pulmonary hypertension states) or physiological (i.e. Valsalva manoeuvre) augmentation [47]. To clarify this potential risk condition, one may suppose that patients who already have a shunt during quiet breathing

have an increased exposure time for paradoxical embolism, as opposed to those with a shunt induced by provocative manoeuvres only. As shown by clinical practice, the low pathophysiological importance of provocative-only shunts has been documented. In fact, no correlations were found between circumstances able to increase right cardiac chamber pressure (i.e. sporting effort, lifting a heavy weight, coughing, and others considered as equivalents of the Valsalva manoeuvre) immediately preceding stroke onset and the presence of PFO [34].

In the context of cryptogenic stroke, it seems an increase in right heart pressure is not essential for right-to-left shunting across a PFO. However this theory has not been investigated in the setting of surgery with a ventilated patient and nor has it been investigated in orthopaedic surgery, during which, there is good evidence to show that large embolic loads enter the right heart and consequently the pulmonary circulation, thereby increasing right sided pressures and possibly encouraging flow across a PFO; a transient instantaneous pressure gradient between the right and left atria.
In fact, pulmonary embolism is the most common cause of acutely elevated right atrial pressure and right-to-left shunt in patients with PFO or atrial septal defect (ASD), and occurs in at least 60% of PDE [27]. The frequency with which PDE occurs in patients with pulmonary embolism is unknown. Investigations by Sharma and colleagues concluded that in patients without pre-existing pulmonary vascular disease, acute pulmonary embolism may result in PDE if mean pulmonary artery pressure increases to at least 30mmHg and there is 35-40% pulmonary vascular obstruction and an intracardiac defect such as an ASD or PFO [41].
When PDE occurs in the absence of pulmonary embolism, chronic lung disease with pulmonary hypertension has usually been present [30]. The frequency of PDE in this setting is unknown.
Acute elevations of right atrial pressure in a cough or Valsalva manoeuvre have been associated with 15% of PDE cases [27]. In some circumstances, superimposed acute respiratory illness and its treatment may accentuate the potential hazard of PFO: patients with acute respiratory failure who receive positive end expiratory pressure may experience shunting across a PFO [9].

Other causes of elevated right atrial pressure facilitating right-to-left shunt include idiopathic pulmonary hypertension, pulmonary valve stenosis, congestive heart failure, aftermath of a right ventricular infarction, cardiopulmonary bypass, air embolism and platypnea orthodeoxia [39]. The most causal factor of PDE has been suggested to be the co-existence of an atrial septal aneurysm and PFO. However this link is still under investigation; patients with a combination of atrial septal aneurysm (ASA) and PFO have a substantially higher rate of recurrent ischemic events as com pared to PFO alone but in a recent study[49] patients with ASA in addition to PFO do not appear to have an increased risk of right-to-left shunting as measured by contrast TCD as compared to PFO alone.

Paradoxical embolism clearly requires not just a PFO acting as a conduit route, but also the presence of embolic material passing through the right heart. Past definitions of PDE required the demonstration of such a substrate in the deep venous system [30]. The search for an association between DVT and paradoxical embolus has been hampered by four problems. Firstly, peripheral DVT are frequently clinically silent. Second, the sensitivity of standard ultrasound and venography has been poor, particularly for pelvic sources of DVT [8]. Third, stroke itself is a risk factor for DVT, which develops secondarily in as many as 30% of those with severe paresis not treated with anticoagulants [23]. Fourthly, objective evidence of DVT potentially resolves over time in patients receiving full anticoagulation for their stroke [45]. As a consequence of these factors, studies of patients with cryptogenic stroke and documented PFO have reported incidences of DVT varying between 0 and 57% [11,23,26,34,45]. Thus the relationship remains unclear.

2.6 PFO and Orthopaedic Surgery

What is clear, however, in relation to this study, is that DVT is common during or as a consequence of orthopaedic surgery (joint arthroplasty) [1,17] and therefore providing substrate in the deep venous system; right heart pressures do increase during certain phases of orthopaedic surgeries providing the transient pressure gradient from right to left chambers to promote paradoxical flow of right heart material; fatal pulmonary embolism and cerebral embolism has been reported time and again in the setting of joint replacement even in patients receiving thromboprophylactic treatments and measures; and most importantly, the intramedullary surgery itself precipitates thrombogenesis providing the source of the substrate for consequent embolisation.

Koch et al. examined the incidence of cerebral microemboli using TCD in 42 patients with isolated femoral fractures treated surgically [22]. They found microembolic signals in all patients during hospitalisation; neurological symptoms developed in 17%, all of whom had a PFO. The mean microembolic count was higher for those patients with a RLS and even higher in those with RLS and neurological symptoms. They concluded that PFO influenced neurological sequelae associated with orthopaedic surgery.

Potentially, therefore, PFO has a pivotal role to play in the setting of joint replacement, but from the evidence discussed above, is not solely responsible for embolic material reaching the arterial circulation. Rather a co-occurrence of several factors seems to be important, all of which may yet not be known, but some of which this study aims to uncover.

In addition, paradoxical embolism and in particular associations such as cryptogenic stroke, describe cerebral sequelae as a result of macroscopic embolic material lodging in a PFO itself (as in numerous post-mortem reports), or in the larger vessels of the cerebral circulation manifesting in the neurology seen in stroke. However, in this study, it is the effect of microscopic embolic material reaching the cerebral circulation as a direct consequence of arthroplasty surgery that is of interest.

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Chapter 3

Transcranial Doppler and Patent Foramen Ovale detection

3.1 Introduction

Cardiac right to left shunts (RLS) can be identified by transoesophageal echocardiography (TOE), and more recently, by transcranial Doppler (TCD) with the use of different contrast agents and different provocation procedures.

TOE enhanced by echo-contrast agents is considered the "gold standard" for detection of cardiac RLS[5, 9,52,57,65].

The Valsalva manoeuvre (VM) increases right atrial pressure, thus facilitating or demasking intermittent right to left shunting of contrast medium via an atrial septal defect (ASD) or a patent foramen ovale (PFO)[9,46,53]. Normally the foramen ovale is closed by the left atrial pressure-right atrial pressure gradient[30], although this is controversial[68]. This may account for the fact that paradoxical embolism occurs in a minority of patients with venous thromboembolic disease who also have a PFO.

PFO prevalence has been reported as between 17% and 32% of healthy individuals[30,56,61]. It is the anatomic means by which paradoxical embolic stroke is generally believed to develop[15,32,51], and saline contrast TOE with provocative manoeuvres is considered the method of choice in detecting it during life[19,33].

First described by Cohnheim[13] in 1877, paradoxical embolism (PDE) was defined as a venous thrombosis causing systemic embolisation through a RLS. The medical literature now contains descriptions of more than 170 instances of this phenomenon[38,73].

Four elements must be present for PDE: 1) systemic embolism confirmed by clinical, angiographic or pathologic findings without an apparent source in the left area of the heart or proximal arterial tree; 2) an embolic source within the venous system (in the case of this study, generation of intramedullary emboli from arthroplasty surgery); 3) an abnormal intracardiac or intrapulmonary communication between right and left circulations; and 4) a pressure gradient that promotes right to left shunting at some point in the cardiac cycle. Pulmonary embolism is the most common cause of acutely elevated right atrial pressure and RLS in patients with PFO or ASD, and occurs in at least 60 % of PDE[45]. When PDE occurs in the absence of PE, chronic lung disease with pulmonary

hypertension has usually been present[49]. Other causes of elevated right atrial pressure facilitating RLS include idiopathic pulmonary hypertension, pulmonary valve stenosis, congestive heart failure, aftermath of a right ventricular infarction, cardiopulmonary bypass, air embolism and platypnea orthodeoxia[64].

The term PDE is reserved for clinical conditions where neurological changes complicate cardiovascular events, DVT or PE, or when any unexplained arterial occlusion occurs, particularly in the young or post-operative patient. PDE via a cardiac RLS is a well recognised cause of cryptogenic stroke/cerebral ischaemia, especially in younger patients[18,43,74].

In a report by Loscalzo[45] seven of thirty patients who had a PDE had had a recent operation. Given the prevalence of thromboembolic events after major orthopaedic operations, recognition of the potential for PDE is important. Cases of intra-operative cerebral infarction have been reported during arthroplasty surgery, both in the presence and absence of pulmonary embolism or DVT[16,73] and after long bone fracture[24,58]. Giachino et al[28] reported cerebral infarctions in association with 0.5% of 4271 total joint arthroplasties. These reports further enhance the suggestion that patients who have a known history of unexplained systemic embolisation, should undergo routine preoperative screening for a defect in the atrial septum that could lead to paradoxical embolisation [16], as short term follow up of patients who had a PDE showed a 1.9% to 3.4% annual rate of recurrence of stroke or transient ischaemic attack. Mas et al[48] investigating adult patients with PFO and a prior cerebrovascular ischaemic event, detected a 6.7% risk rate for stroke or TIA at 2 years. De Castro et al[15] demonstrated a similar risk rate (7.2%) at 3 years in an similar group of patients. However, when high-risk and low-risk patients are analysed separately, a significant difference in risk of cerebrovascular ischaemia recurrence is noted (12.5% vs 4.3% at 3 years follow up, p=0.05). Various therapeutic options are available to this group of patients but it is still unclear, which is the best strategy to adopt. However the importance of this area of investigation translates to PFO patients undergoing orthopaedic surgery as thromboembolic complications in this field are not rare and could further help to stratify risk of adverse events associated with these procedures.

With regard to this study, in the context of RLS, which primarily aims to quantify cerebral microemboli load during arthroplasty surgery and correlate these findings with neuropsychological outcome, the detection of PFO in these individuals, as a potential communication between venous and arterial circulations, may prove to be a positive finding; that is those patients who test positive for PFO also demonstrate higher microemboli load and worse neuropsychological outcome when compared to those who test negative for PFO. Therefore the technique used in detecting PFO must be sensitive, specific and reproducible.

3.2 Arguments on detection technique

3.2.1 Transoesophageal Echocardiography and Transthoracic Echocardiography

Before the availability of TOE, transthoracic echocardiography (TTE) or even TCD, many approaches were used to demonstrate RLS. Following the use of oximetry to document a drop in oxygen saturation during the VM in the study by Lee and Gilmette[44], various indicators were injected into the right side of the circulation with their early systemic appearance signifying a RLS[4,10,49,71]. Accurate ante-mortem diagnosis has been facilitated greatly by contrast echocardiography[72].

Contrast TTE is more sensitive than oximetry and dye curves, but its sensitivity is only 64%[42]. Technical limitations relate to spontaneous variations in RLS during normal breathing, the quality of the VM, uneven distribution of contrast solution and missing the sampling site of the M-mode beam. Contrast shunting is apparent immediately in patients with cyanotic heart defects but is often subtle in patients with uncomplicated ASD. The TTE also frequently demonstrates echo dropouts because the ultrasonic beams do not generally hit the interatrial septum with a perpendicular orientation and may result in false positive appearances of ASD's. TTE cannot also reliably differentiate ASD from PFO, since the degree of contrast shunt is independent of defect size[42]. By contrast, TOE is unrestricted by lung tissue or thoracic malformations, providing superior imaging of the atrial septum and a clear view of the foramen ovale.

As aforementioned, contrast TOE is currently viewed as the gold standard in the detection of right to left communications. In the first report validated by catheterisation or

operative results. Chen et al.[9] documented PFO's with contrast TTE and TOE in 32 patients. A RLS was seen by TOE in 14 in normal breathing subjects and 20 with the VM and by TTE in 8 with normal breathing and 12 with the VM. All PFO's seen by TTE were also seen by TOE and all but one (case of right atrial myxoma causing the highest right atrial pressure of the group, accentuating the RLS by communications "other than PFO") of the PFO's seen by TOE were confirmed by catheterisation or surgery. The diagnostic sensitivity was 100 vs 63% and accuracy 97 vs 78% of TOE vs TTE. However TOE has disadvantages of semi-invasiveness, higher cost, limited availability and limitations in elderly patients with acute strokes although overall, they are relatively infrequent[55,66,78]. In addition, a VM which is frequently necessary to elicit a RLS may not be feasible during contrast TOE examinations because patients often require sedation[25,66].

3.2.2 Transcranial Doppler Ultrasound

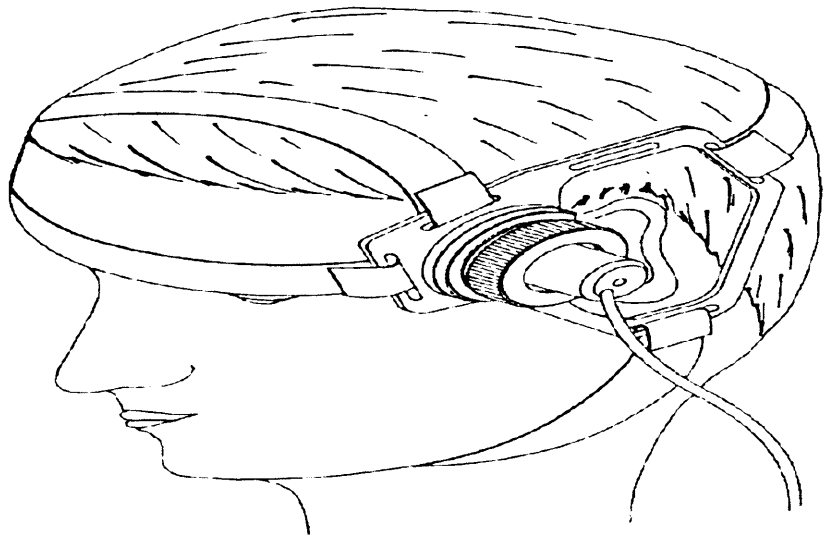
The study of brain embolism has been greatly advanced with the advent of transcranial Doppler with embolism monitoring. Transient increases in the Doppler signal are termed microembolic signals (MES) and are presumed to be caused by an embolus moving through the Doppler sample volume[47]. TCD is capable of detecting microembolic material, both gaseous and solid within the intracranial arteries. Due to increased scattering and reflection of ultrasound from the embolus, compared with the surrounding red blood cells, an embolus appears as a short duration high intensity signal within the Doppler flow spectrum. It has been appreciated since the 1960's that gas bubbles can be detected using ultrasound[3]. However, it was only in 1990 that it was appreciated that solid emboli, composed of thrombus or platelet aggregates, could also be detected.

The middle cerebral artery (MCA) is insonated for convincing reasons. Firstly, work carried out by Wijman et al[76] investigating the characteristics of in vivo cerebral microembolism detected by TCD in the territories of the anterior cerebral artery (ACA) and the MCA, demonstrated that microembolic signals (MES) were more frequent in the MCA than in the ACA in 85.7% of studies. Of the total 979 MES, 689 (70.4%) were detected in the MCA and 290 (29.6%) in the ACA ($p<0.01$). Previous studies have suggested that the anatomical arrangement of the two arteries and the volume of blood supply to each may contribute to this difference[6,7,27,29,50]. Secondly the MCA projects laterally from the circle of Willis. As a result it approaches the temporal surface more

closely than any of the other Willisian branches and is the only artery producing a signal at depths of 35 to 50 mm from the temporal window and it carries nearly 80% of the flow to the hemisphere[70]. In the region of the skin above the zygomatic arch and anterior to the ear lies the thinnest section of the squamous portion of the temporal bone, an acoustic window that allows passage of ultrasound in most adults (figure 3.1).

It has become the standard technique for monitoring emboli during coronary artery bypass surgery[8,12,55,59]. The method has been widely used, but results of tests vary considerably, depending on methodological factors such as type of contrast agent, injection mode, volume of contrast agent, body position, timing of the injection with respect to the VM and diagnostic time windows. Recommendations on a standardised approach for cardiac RLS detection using TCD according to the data available and consensus in the case of lacking data have been published[37,60]. Arguments for the technique of PFO detection using TCD in this study are outlined below.

Figure 3.1 Diagram of Transcranial Doppler ultrasound probe mounted in headpiece



A number of studies[1,21,22,41,62] have recently shown that contrast enhanced TCD examination of the middle cerebral artery is highly sensitive and specific compared with contrast TOE to detect RLS. Contrast TCD is a non-invasive and safe technique that does not cause the patient discomfort[1]. Most recently, Arquizan et al.[2] report a sensitivity of 90.5% and a specificity of 82.9% using contrast TCD with contrast TOE as the gold standard. Some studies report sensitivities of 100%[52,62,69] and others, a specificity of 100%[1,19,31,36,39]. However, only two studies[11,17] reported 100% sensitivity and specificity. Moreover, they employed different contrast agents, the selection of which remains a contentious issue. Other confounding factors between the studies were different gold standard techniques, timing of injection and diagnostic time windows.

Droste et al[20,21] advocated the use of Echovist instead of the widely used and cost-effective agitated saline contrast; this finding was accounted for on the basis of a higher amount of bubbles and greater bubble durability seen with Echovist contrast solution. In addition, Echovist is a suspension of galactose microparticles in an aqueous 20% galactose solution with adherent tiny microbubbles smaller than human erythrocytes; it is

thought to be a non-transpulmonary ultrasonic contrast and hence it cannot be detected in intracranial arteries by TCD unless a RLS is present[62]. However, sensitivities of 100% have been achieved by using both Echovist[36] and saline solution[17] and specificities of 100% for agitated saline[1] and one of 93.8% for Echovist[36] were reported. Moreover, results from the study directly comparing saline/air mixture and Echovist[20,21] demonstrated no superiority of any contrast agent concerning sensitivity, only that more microbubbles were detected using Echovist which may be an advantage when quantifying an RLS, an issue this study is not concerned with. At the dose recommended by the consensus committee, there are currently no reports on side effects after air/saline administration and since its availability is not restricted, it was the contrast agent of choice in this study.

The volume of contrast medium used has also been investigated[62]; their findings were, that with decreasing doses of contrast medium the total MES count declined and the latency (period after injection of contrast to when the first MES was detected) increased. With smaller contrast medium doses, it may take >2 heartbeats to propel a sufficient amount of contrast into the arterial branch of the vasculature so that detectable amounts reach the intracranial arteries, accounting for the "delay" of the first MES detected, since the more contrast will pass through a PFO, the more is available in the right atrium. The same author recommended that 10mls of contrast (1ml air and 9ml saline) be injected – a method which is now widely used with good consistency.

The timing of the contrast solution injection in relation to the VM is also still a matter of debate. Indeed, which provocative manoeuvre is preferable (VM or cough), still varies from study to study although the consensus committee recommend the use of VM. Stoddard et al.[67] reported that the cough test is superior to VM in diagnosing a PFO during contrast TOE, although this observation has not been confirmed by TCD. Most authors use the VM, while both were only used in one study which did not mention any difference between the manoeuvres. Results from the study by Zanette et al.[79] showed that cough detected a slightly lower number of positive patients.

The physiology of VM explains why substantial haemodynamic changes caused by the manoeuvre enhance detection of PFO in contrast TOE/TCD. The strain phase of the VM

amplifies the physiological interatrial left-to-right pressure gradient, counteracting potential right to left shunting. During the release phase, however, the pressure gradient reverses because of a sudden surge in venous return and a concomitant increase in right atrial pressure, while the left atrial pressure decreases temporarily, thereby facilitating R/L shunting[53]. Therefore the strain phase of the VM prevents the contrast agent from passing through the PFO, causing a "delay" of the intracranial appearance of the contrast. This explains the increased latency observed by Schwarze et al.[62] of the first MES detected when the VM was performed 5 seconds after injection. On the other hand, the decreased venous return during the strain phase may have an accumulating effect on the contrast agent, increasing the bolus dynamics of the injection, which may be responsible for the greater MES count for VM 5 seconds after injection compared with VM performed simultaneously with the start of the injection. In the same study, when patients did not perform a VM, 42% of the patients who tested positive under the VM after 5 seconds condition did not have evidence for a RLS. This underscores the importance of a VM in the detection of RLS, which has been reported by others[9,19,37,79]. Consensus committee[14] recommendations are that the VM should start 5 seconds after the beginning of the injection and be maintained for at least 5 seconds.

All patients in this study were anaesthetised for surgery (see later for anaesthetic protocol), and therefore simulation of the VM in these intubated patients was effected by increasing and holding the end inspiratory pressure for 5 seconds, with subsequent release.

Droste et al.[22] investigated the duration of the diagnostic time window for the appearance of contrast bubbles in the TCD recording after injection of the contrast agent. MES were noted up to 40 seconds after injection and first appearances of MES up to 30 seconds after injection of contrast agent in one case. It is a well known phenomenon that more patients are identified as having an RLS when investigated by contrast TCD than with TOE. In these cases the lungs are the most likely location of venous-atrial shunts, allowing the contrast material to bypass the pulmonary capillaries and to slip into cerebral arteries; or these shunts may correspond to very small intracardiac shunts unnoticed during TOE. Some authors believe that those MES that occur late after contrast injection may have passed these pulmonary shunts[41,37,77]. However Horner et al.[35] reported that in

pulmonary shunts, the transit time is in a range comparable to that in cardiac shunts and that this parameter does not allow reliable discrimination between the two conditions. Similar to intracardiac shunts, pulmonary shunts can allow early transit of contrast bubbles. Droste et al.[22] recommend a 20-25 sec window after injection, to achieve a higher specificity of the TCD investigation. Time windows less than 20 seconds decrease sensitivity and should not be used.

Body position has also been scrutinised, comparing sitting with supine positions. Schwarze et al.[62] noted that the median MES declined from 20 with the patient supine to 9 in a sitting position. They also noted that the latency increased from 14.2 seconds in a supine position to 14.8 seconds sitting but this was not significant. For the purposes of this study, the supine position was utilised for all patients undergoing knee arthroplasty; hip arthroplasty necessitates the patient to be in a lateral decubitus position either on the patients left or right side depending on which hip is being replaced. Therefore, the side from which the TCD records from corresponds to the side of the hip being operated on, as this is the side uppermost. Interestingly, the left lateral decubitus position was the position adopted in the validation study for TCD when comparing it to TOE; in our centre where TOE is carried out this is the universal position for all patients. Moreover, direct comparison of MES numbers will be made between those patients supine and those in the lateral decubitus position (i.e. between knee and hip arthroplasty groups) and between those patients in the right lateral decubitus position and those who were operated on in the left lateral decubitus position. A hypothesis suggesting that patients lying on their left side will have enhanced interatrial flow from right to left because of the effect of gravity and therefore greater MES numbers, will be tested. Thus it follows that this group of patients may display a higher incidence of PFO than those lying on their right side as more contrast agent will flow from right to left through an intracardiac defect, if present and hence more microbubbles will trespass into the intracranial circulation.

Khan et al.[40] recommended the use of an 18-guage needle as opposed to a 20-guage needle in the right forearm, to increase the sensitivity of TCD in detecting PFO. Some examiners use single testing without VM and a second test with VM if the first proves to be negative, while others use repeated testing with VM (usually three times in total)[63,77]. As already discussed, since VM after the injection allows a significantly higher number

of microbubbles through the MCA[79], it seems reasonable to choose the procedure with the highest yield of contrast signals to quantatively evaluate the contrast TCD examination; therefore we employed the use of VM repeatedly, and if 2 negative tests were noted, then a third test was attempted. Three negative tests implied the patient did not have a detectable PFO. If the first test demonstrated intracranial contrast agent then no further testing occurred. The detection of one or more MES within 25 seconds after the injection of contrast agent, constituted a positive test.

The number of MES required to constitute a positive result has also varied between authors. As aforementioned, the number of MES is affected by several methodological variations, including position of the patient and dosage of contrast agent as well as inter-individual differences in haemodynamics. Some[26,37] recommended positive tests if one MES was detected whilst others used 5 MES detected as the parameter[2,62] for a RLS to be present using TCD. Again, results were comparable and either lower limit seems valid.

At present, the various manufacturers and investigators use greatly different parameters and criteria for identifying short-lasting ultrasound event as microembolic in nature. Particularly, greatly different decibel thresholds ranging from 3dB to 9dB have been recommended for discriminating MES from the general background noise and from spontaneous speck-like intensity fluctuations of the physiological Doppler flow signals[47].

Discrimination of true embolic signals from artefacts e.g. signals produced by probe displacement, is of crucial importance. Bidirectional signals, i.e. signals above and below the baseline, are frequently artefacts.

With these results, discussion points and conclusions in mind, the methods chosen and utilised in this study for TCD microembolus detection and PFO detection are outlined in the Materials and Methods section of this thesis.

During hip replacement surgery Herndon and colleagues[34] used Doppler ultrasound to monitor the common femoral vein of the leg that was being operated on. Emboli were consistently detected, and specific surgical stages were associated with high embolic

loads. Edmonds et al.[23] detected cerebral emboli by TCD during total hip replacement in 40% of their patients.

However, correlation to the presence of a PFO or neuropsychological outcome was not studied and in part, this is what this study intends to investigate. Conclusions about the possible routes for emboli passage and their significance, can then perhaps, be drawn.

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Chapter 4

Primary Total Hip Arthroplasty

4.1 Historical note

First performed in 1962, total hip replacement surgery is one of the most important surgical advances of last century. Since then, improvements in joint replacement surgical techniques and technology have greatly increased the effectiveness of this surgery. Today, more than 200,000 total hip replacements are performed each year in the United States and nearly 50 000 in the UK. Similar surgical procedures are performed on other joints, including the knee, shoulder, and elbow.

Severe pain and disability usually with accompanying radiological changes at the hip are generally thought to be the indications of the operation, in patients where non-operative treatment has failed or is futile[1]. Where co-morbidities exist, risk-benefit considerations may rule out the operation in an individual patient. The relief of pain and the restoration of functional activities are the main outcomes of primary total hip replacement for the treatment of arthritis.

The discipline of total hip arthroplasty has undergone an exciting evolution over the past decade. Much work has been done with regard to improvements in surgical techniques, implant designs, recognition and treatment of complications, outcome measurement, long term clinical follow-up, cost containment, epidemiology, biomedical engineering and new biomaterials.

As a consequence, orthopaedic surgeons have a large number of hip devices and techniques from which to choose. Many factors determine surgeon preference for an individual implant including purchasing authorities, Trust or Directorate policy and budget limitation.

As part of THA, the surgeon must choose an acetabular (cup) component, a femoral (stem) component and an articulating beraing surface to comprise total hip arthroplasty. The fixation of each of these can be achieved with or without cement. Furthermore, either the stem or the cup may be fixed with cement or without cement; if one component is fixed with cement and the other without, this is known as a hybrid THA; a common combination seen in our regular practice is an uncemented cup and cemented stem. Neither component may be fixed with cement (fully uncemented), which may be preferred for the younger patient. Many factors influence the decision to use cement in the primary arthroplasty setting including age, bone quality, activity level, co-morbidity, implant design and surgeon familiarity, manufacturer service quality and published peer reviewed evidence including ongoing surveillance. It is the utilisation of cement during

total hip arthroplasty that bears most relevance to this study for reasons already discussed in previous chapters. Our hypothesis regarding cement use in total hip arthroplasty thus follows that, greater microembolic loads in the cerebral circulation are seen when cement is used to fix the components of the hip replacement.

The patients recruited for this study were assessed, examined and followed up as set out in guidelines issued by the British Orthopaedic Association[2]. Implants and the decision of cement use, was made by the consultant surgeon caring for the patient and using the criteria aforementioned. Choices of implant and fixation were not randomised as this would have seriously jeopardised outcome and would not have been in the patients' best interests.

The evidence behind the rationale for fixation is outlined below in brief summary of published evidence.

4.2 Femoral component

4.2.1 Fixation with cement

Cement has remained the most popular mode of femoral stem fixation for primary hip arthroplasty in the United States and United Kingdom. The durability of cemented stem fixation has been well documented. Berry et al.[3] recently reported the results of the longest follow-up study of cemented total hip arthroplasty in the USA; nearly 2000 Charnley total hip arthroplasties were followed up for as long as twenty-five years, and even with the use of early-generation cementing techniques the survival rate was 86.5% at twenty-five years with revision of either component for aseptic failure as the end point. The study also found that age at the time of index procedure also had an important impact on the survival rate, with the younger age associated with a higher risk of failure; 68.7% survival rate at twenty-five years for patients less than forty-nine years old at the time of procedure compared with 100% for those who were at least eighty years old. The same author recently reported the thirty year follow-up results for 333 Charnley arthroplasties. Only thirty-seven patients were still alive. The thirty-year survival rate was 90% for stems with aseptic loosening as the end point. Several other studies have reported similar data at similar follow-up intervals [7,21,34].

Controversies persist with regard to the impact of stem surface texture on cement fixation. The principle mechanism of stem loosening is cracks in the pores within the

cement mantle and subsequent debonding. Studies suggest that increased surface roughness causes voids in the cement-implant interface leading to stress concentration, fracture of the cement mantle and loss of fixation[29]. However, other authors have reported good clinical results with pre-coated, rough stems[22,33,39] up to fifteen years after procedure and likewise for smooth, polished stems up to thirty years after insertion[14,43]. Unlike stem fixation without cement, there is good **long-term** (thirty years) data supporting the use of cement for femoral component fixation and hence it is regarded as the gold standard method.

4.2.2 Fixation without cement

Cementless fixation of the femoral stem has undergone a period of evolution over the last two decades. More data is being presented with regard to their medium and long-term clinical performance and durability at ten to fifteen years[12,20,23,25,28,35]. Surface finish is an integral factor influencing the success of cementless fixation of the stem. Two main types of surfaces have been used over the last two decades: porous and hydroxyapatite. Evolution of clinical efficacy of the many stem designs over this time period has been complicated by the variables of stem geometry (straight, curved, tapered or modular), the extent of surface treatment (proximal or extensive), and biomaterials (titanium alloy or cobalt chromium alloy).

Survival rates up to fifteen years have been reported in large number studies and are encouraging[20,35] and equivocal to that of cemented fixation. Longer term data is not yet available.

Presently, concerns over cementless fixation of the stem include, proximal femoral osteolysis (bone loss), subsidence of the stem, high prevalence of thigh pain and whether early weight-bearing after insertion of a cementless stem results in greater micromotion between the stem and the host bone which is detrimental in terms of subsidence and rehabilitation. However, the majority of these concerns are radiographically based and thankfully do not reflect in clinical failure or high revision rates of these stems to date. Much work is being carried out to solve these problems as the evolution of the cementless stem continues.

There are several advantages of cementless fixation. Firstly, reduced operating time and associated benefits. Secondly, the reduction of interfaces of fixation and therefore potential reduction in production of wear particles over time, thereby supposedly

enhancing longevity of the stem. Thirdly, popular consensus suggests that cementless stems may be easier to revise i.e. removal without destroying host bone in the process, a particularly hazardous task when revising a cemented stem. This may make cementless implants favourable in younger patients (under fifty-five years old) who will outlive their initial replacement and require revision surgery, as the evidence suggests. Fourthly and relevant to this study, cementless fixation should confer a lower intramedullary pressure in the femoral canal[19,36] and therefore generate less thromboembolism through the mechanisms described in earlier chapters. This is not only an advantage for the brain, but all end organs especially the lungs and kidneys. Methlymethacrylate particles in particular are thrombogenic[42] and thus the ongoing cascade effect that may ensue in the vasculature and end organs is lessened.

4.3 Acetabular component

4.3.1 Fixation with cement

In 1958 Sir John Charnley addressed the eroded arthritic socket by replacing it with a Teflon implant. He hoped this would allow for a smooth joint surface to articulate with the metal ball component. When the Teflon did not achieve this goal, he went on to try polyethylene. This worked wonderfully well. In order to obtain fixation of this polyethylene socket as well as the femoral implant to the bone, Charnley borrowed polymethylmethacrylate from the dentists. This substance, known as bone cement, was mixed during the operation then used as a strong grouting agent to firmly secure the artificial joint to the bone.

Although for many years cemented fixation of the acetabular component was the only option available, with the advent of cementless technology and techniques, the use of cemented cups is declining.

However, contrary to femoral stems, the bulk of the evidence shows that cement in the acetabulum does very well for about ten years. Then, increasingly, there is more loosening and a higher revision rate. It is the process of osteolysis (bone resorption), which is macrophage driven which causes the loosening. The macrophages are stimulated by small foreign particles which can be cobalt chrome, titanium, methylmethacrylate, polyethylene or hydroxyapatite. It is particles of a certain size that activate the macrophage which scavenge the material but cannot break them down leading to a

cascade reaction involving cytokines and enzymes which ultimately activate the osteoclast to resorb bone. Particles of this size are a feature of wear occurring at the interfaces and articulating surfaces of the hip replacement as they undergo repetitive cyclical loading. This process seems to be more prevalent and florid around the acetabular component particularly of cemented cups. The drive to eradicate cement and thus lower particle formation and subsequent loosening, led to cementless cup fixation. Concurrent research into bearing surfaces and better wear rates is ongoing with numerous options available (see below). Wear of course is influenced by numerous factors including age, weight and activity of the patient but most importantly by the biomaterials used for the bearing surfaces of the replacement joint. Clear relationships have been established with regard to cemented cup fixation and increased wear and loosening in young, active patients, but in the older patient (over eighty years old) cementing an acetabular component is still advocated by some authors[31,32].

Fixation without cement

Cementless fixation has evolved into the preferred method for acetabular reconstruction as a result of the excellent clinical results that have been documented in numerous reports over the past decade. The clinical success of porous coated hemispherical cups or more accurately shells, into which liners (polyethylene, ceramic or metal) are inserted, is well documented in the literature. Medium to long-term results have been reported in all age groups.

Epinette et al.[13] reported 99.4% survivorship of cementless hydroxyapatite coated cups at ten years. Valle et al.[40] reported recently a 98% survival at seven year follow up of cementless cups with 99% showing no or little radiographic osteolysis and very low wear rates. However, Lewallen et al.[24] at the Mayo clinic reviewed over five thousand primary cementless cups which at ten years showed survival rates of the shell as 88.4% and 82.2% for the liner with a significant fall off in the second decade, highlighting concern for the long-term. Dunkley et al.[11] reported the results of cementless cups in patients less than fifty years of age at seven years. No cup was revised because of loosening but six liners were changed due to wear. Also radiolucency on X-ray was noted in 29% of patients but no migration, also of concern but perhaps expected due to the young age of the cohort. More encouragingly, Bojescul et al.[5] recently reported the fifteen year results of 120 total hip arthroplasties of which seventy-two were still living at fifteen years, reflecting the

younger age of patients who generally receive cementless implants particularly on the femoral side. No cup was revised for loosening and osteolysis was seen in 6.9% of patients but wear, radiographically assessed, was marginally higher than that found in Dunkley's study.

Several similar studies have echoed the findings of those summarised above. Concerns remain over long-term survival of cementless cups but established failure of cemented cups at similar intervals has been well documented. Furthermore, even though pelvic osteolysis and evidence of wear are common findings in patients with cementless acetabular components, the cups (shells) themselves seem well fixed and the problem seems to lie with the liner (bearing surface) rather than the outer shell. Much of this data is of patients of a younger age and may reflect other physiological and environmental factors.

Cementless fixation of the cup is an increasingly appealing surgical technique. This has been further advocated by advances in bearing surface materials showing better wear characteristics (tribology).

4.4 Bearing surfaces

Alternative bearing surfaces in total hip arthroplasty have been area of intense investigation over the last eight years. Bearing surfaces include hard-on-soft (metal-on-polyethylene and ceramic-on-polyethylene) and hard-on-hard (ceramic-on-ceramic and metal-on-metal) combinations. Improvements in the manufacturing, machining, sterilization and storage of these materials have made these options increasingly attractive. Furthermore, other factors influence wear as well as the biomaterials used. Activity level (and age), sex, joint kinematics, component orientation, thickness of the component and femoral head size contribute significantly to the tribology of the articulations used. However controversies remain as to which combination is the most effective clinically.

4.4.1 Polyethylene

Metal-on-polyethylene is the most widely used bearing surface combination. Improvement in the wear characteristics of polyethylene has been a major focus of research and development. Emphasis has been on controlling the amount of free radicals.

The vast majority of polyethylene implants (cemented and liners for uncemented shells) inserted over the last three decades were sterilised with gamma irradiation in air. Gamma irradiation produces free radicals, which then, when combined with air lead to oxidative changes in the polyethylene, resulting in inferior wear characteristics. At the same time gamma irradiation produces cross-linking of the polyethylene, resulting in improved tribology. Moreover, longer durations of shelf storage of the implant result in more oxidative changes in the polyethylene when oxygen diffuses into the implant and reacts with residual free radicals in the material.

Recently several polyethylene products have been introduced to increase cross-linking and to reduce oxidative degradation. The wear characteristics of highly cross-linked polyethylene continue to be documented to be superior to those of conventional polyethylene[9,17,18], even in the setting of third body debris within the joint space. Bragdon et al.[9] conducted a simulator test in which cobalt-chromium femoral head articulated against cross-linked or conventional polyethylene in the presence of aluminium oxide (severe third body wear) or cement (mild third body wear) particles. There was a significant difference in the wear rate between the two types of polyethylene under the two wear conditions. Cross-linked polyethylene showed higher wear resistance than conventional polyethylene in both conditions.

Therefore highly cross-linked polyethylene appears to be the material of choice if polyethylene components wish to be used for the acetabular reconstruction.

4.4.2 Ceramic

Ceramic remains an attractive bearing surface. It can be used for the cup as well as the femoral head. It can be cemented or used as a liner in an uncemented shell. Studies have shown better wear rates of ceramic-on-polyethylene compared with metal-on-polyethylene[8] but other authors report similar wear rates for the combinations[26]. The studies which have shown ceramic-on-polyethylene to be superior have been simulator-testing and nit in-vivo studies. Urban et al.[36] examined sixty-four hips that had been treated with ceramic-on-polyethylene coupling and cement fixation followed up at a mean of 18.2 years. The twenty-year survival rate was 79% but the wear rate was dramatically lower than in comparable metal-on-polyethylene series that had only been followed up for ten years.

Ceramic-on-ceramic articulations have been the subject of similar studies. Bierbaum et al.[4] in a multi-centre, randomised trial compared ceramic-on-ceramic with metal-on-polyethylene and concluded that after five-year initial follow-up, the ceramic-on-ceramic group are clinically as good as the metal-on-polyethylene group.

One of the proposed benefits of ceramic-on-ceramic articulations is decreased generation of wear debris Mochida et al.[26] compared tissue samples retrieved from site of failed hip arthroplasties involving both ceramic-on-ceramic couplings and ceramic-on-polyethylene couplings. All the acetabular shells and femoral stems were made of titanium alloy. The total particle quantity was threefold higher in the ceramic-on-polyethylene group.

All the above evidence should make ceramic bearing surfaces an ideal choice for all types of hip arthroplasty patient particularly the younger patient as it seems more resistant to wear and allows the surgeon to use larger femoral head sizes to increase range of motion and reduce dislocation rate. But ceramic is not without its' problems.

Fracture of the component, be it a liner, cup or head is infrequent but nevertheless disastrous. Hannouche et al.[16] reported thirteen fractures recorded retrospectively in over five and a half thousand hip arthroplasties. Hard-on-hard surfaces demonstrate less linear wear in most cases but are more sensitive to failure due to surgical technique (e.g. component positioning, third body debris, etc). Transition forces between prosthesis and bone may be elevated in hard-on-hard couples, as there is no dampening effect of a soft material. Finally, micro-separation, a newly discussed concept where the ball and socket separate slightly during the swing phase of gait, may change the expected wear profile of hard-on-hard surfaces.

4.4.3 Metal

Although metal-on-metal couples were originally introduced in the 1960s, a poor understanding of optimal design characteristics and limitations of the manufacturing process caused poor results. Second-generation metal-on-metal products were developed to address problems such as loosening of the hip replacement, high frictional torques and seizing of the articulation. Important design characteristics appear to be use of a hard, high-carbon wrought alloy; the goals of polar contact, optimal clearance, and maximal sphericity and extremely low surface roughness. One potential concern in this type of hip replacement is the metal-metal acetabular connection, where the cobalt-chromium /

titanium junction may be difficult to disassociate or where fretting corrosion could occur. Despite a lower volume of wear associated with metal-on-metal implants, the particles that are produced are very small, possibly resulting in a larger number of particles compared with metal-on-polyethylene couples. This may be of some concern because the full biological response to metal particles or ions is currently unknown. A major negative issue with contemporary metal-on-metal couples is a question of metal toxicity and carcinogenesis. Elevated urine and blood levels of the metals that make up the prosthesis have been measured, and ongoing research will confirm the safety of this combination. This issue seems to be most important in patients with poorly functioning kidneys, as the metal ions can build up in the blood. Although "seizing" of the implant has been reported, this is uncommon.

Low volumetric wear rates have been reported by Dorr et al.[10] who found no osteolysis after fifty-six total hip arthroplasties that were followed up at a mean of 5.2 years. Wagner et al.[40] reported similar results. Although reported complications are rare (Dorr) dislocation, disassociation and metallosis appear to be the most common.

Urban et al.[38] reported dissemination of wear debris to the para-aortic lymph nodes in 68% of twenty-eight patients and 38% rate of metallic debris and 14% rate of polyethylene debris in the liver and spleen. Lymphatic transport was the major mechanism of dissemination. Clinical effects were undetectable. Metal hypersensitivity has also been the subject of debate. Hallab et al.[15] suggest that is more prevalent in patients with a prosthetic joint.

Nevertheless, the recent massive increase in popularity of hip resurfacing implants, which is a metal-no-metal articulation, seems to have thrown caution to the wind with regard to the potential harmful side-effects discussed, in favour of a bone conserving, less bone invasive hip replacement procedure which is well suited to the young patient.

4.5 Summary

Many other factors contribute significantly to the success of a total hip arthroplasty other than those discussed above. The decision making process for the surgeon has to take into account a multitude of issues in addition to method of fixation, bearing surface and implant choice.

Timing of the procedure, rehabilitation, follow-up protocol and pain management are all integral to successful outcome both in the short and long term.

Reduction of complications such as infection, dislocation and thromboembolism are paramount to successful outcome.

There is no substitute for good, consistent surgical technique, regardless of implant and experience of the surgeon.

For this study, the method of fixation was chosen as the most appropriate for the patient and decided by the consultant surgeon caring for the patient. The majority of arthroplasties were hybrid, although a smaller number of fully uncemented and fully cemented arthroplasties were carried. The exact implants are described in the Materials and Methods section of this thesis as are peri-operative preparation and protocol.

The bearing surface in all patients was ultra high molecular polyethylene and cobalt chrome articulation.

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Chapter 5

Primary Total Knee Arthroplasty

5.1 Historical note

In the 1860's Fergusson reported performing a resection arthroplasty of the knee for arthritis and Verneuil is thought to have performed the first interposition arthroplasty using joint capsule.

The first artificial implants were tried in the 1940s as moulds fitted to the femoral condyles following similar designs in the hip. In the next decade tibial replacement also was attempted but both designs had problems with loosening and persistent pain.

Combined femoral and tibial articular surface replacements appeared in the 1950s as simple hinges. These implants failed to account for the complexities of knee motion and consequently had high failure rates.

In 1971 Gunston[8] importantly recognized that the knee does not rotate on a single axis like a hinge but rather the femoral condyles roll and glide on the tibia with multiple instant centres of rotation. His polycentric knee replacement had early success with its improved kinematics over hinged implants but failed because of inadequate fixation of the prosthesis to bone. However, with the development of polymethylmethacrylate cement, this problem was addressed.

The Total Condylar prosthesis was designed by Insall at the Hospital for Special Surgery in 1973. This prosthesis concentrated on mechanics and did not try and reproduce normal knee motion. Ranawat et al.[22] reported a survivorship of 94% at 15-year follow-up which is the most impressive reported to date. By 1974, replacing the patellofemoral joint and either preserving or sacrificing the cruciate ligaments had become standard practice.

At the same time prostheses with more natural kinematics were developed at the Hospital for Special Surgery relying on the retained cruciate ligaments to provide knee motion. The argument as to whether knee ligaments should be preserved or sacrificed goes on to this day. Long term follow up studies do not show any significant differences.

The concept of replacing the tibio-femoral condylar surfaces with cemented fixation has been developed and refined since. Subsequently, condylar knee designs were improved to include modularity and non-cemented fixation, with use of universal instrumentation.

Today, over 19 companies in the United States distribute total knee implants of three different types: cruciate-preserving, cruciate-substituting, and revision implants.

Future developments, such as navigation-guided surgery, enhanced kinematics, and wear-resistant bearing surfaces with better fixation, promise a consistent evolution for the total knee replacement.

Approximately 350,000 knee replacements are performed every year in the United States[13]. Osteoarthritic destruction of the knee is the commonest reason for total knee replacement. Other causes of cartilage destruction include rheumatoid arthritis, haemophilia, the seronegative arthritides, crystal deposition diseases, pigmented villonodular synovitis, avascular necrosis and the rare bone dysplasias.

The surgeon must choose an implant design and a fixation method, whether the posterior cruciate ligament will be sacrificed and whether the patella will be resurfaced; although uncemented TKA exists, its popularity is overshadowed by cemented prostheses thus far. The relevance of cement use to this study through similar mechanisms as those described for THA, is clear.

The patients recruited for this study were assessed, examined, treated and followed up as set out in guidelines issued by the British Orthopaedic Association[1].

Many factors contribute to the success of TKA and its longevity. Surgical technique is a crucial factor, with errors in soft tissue balancing and component alignment relatively common. A brief discussion on TKA and its vagaries follows.

5.2 Component alignment

Rotational alignment has been the topic of several reports. Novotny et al.[19] demonstrated that potential errors in femoral component alignment can occur in association with the use of intramedullary instrumentation. Katz et al.[12] compared the use of the trans-epicondylar axis, the antero-posterior axis, the posterior condylar line and the balanced flexion gap technique for determining alignment and found the antero-posterior axis and the balanced flexion gap technique to be more accurate for defining the flexion-extension axis of the knee. Vaidya et al.[28] found that performing the posterior condylar cut parallel to a previously performed tibial cut was more reliable (as determined by post-operative CT scanning) and was associated with better functional scores compared with the method of using the often ill-defined trans-epicondylar axis. Sodha et al.[27] evaluated the need for lateral retinacular release as a function of femoral component rotation and found that the need for release significantly decreased with the method of performing equal posterior condylar resections. While there remains some controversy with regard to the most accurate technique, relying on one landmark for femoral rotation alignment may be inadequate. Similarly for the tibia, Matsuda et al.[17] compared three different techniques for tibial preparation in a study of thirty TKA's and found that the use of an original

template connecting the centre of the cut surface of the tibial plateau to the centre of the talar dome was more accurate than the use of the tibial shaft as the alignment guide, although the latter technique still predominates.

5.3 Soft tissue balancing

Soft tissue balancing is of paramount importance in the achievement of a successful result after TKA. Many techniques have been described to achieve good reproducible outcomes and continue to be the subject of some scrutiny. The goal is to achieve equal flexion and extension gaps after making the bone cuts, taking into account the pre-operative deformity. This is aided by release of soft tissue structures around the knee and much focus has been on the lateral structures of late [11,15,20,21]. The medial structures are always released to an extent but a cadaveric study by Saeki demonstrated that the posterior cruciate ligament provides medial stability to the knee following medial collateral ligament release, especially in flexion, thereby strengthening the case for cruciate retaining prostheses[25].

5.4 Fixation techniques

Fixation techniques remain controversial. In one of the largest meta-analyses to date, Rand et al.[23] performed survivorship analysis of 11,606 primary total knee replacements. The implant survival was better for patients who had cement fixation compared with patients who had cementless fixation (92% cf. 61% $p<0.005$). Goldberg et al.[7] evaluated the results of 124 consecutive cementless TKA's after a minimum duration of follow up of fourteen years and noted only one case of tibial revision but a 21% rate of tibial osteolysis. Mikulak et al.[18] evaluated the results of 183 TKA's including hybrid fixation and found that osteolysis was more pronounced in knees with cementlesss femoral components, but did not affect survival at eleven to thirteen years follow up.
Furthermore, studies exist which examine whether cementation of the tibial tray alone or in combination with cementation of the tibial stem is beneficial. Maloney et al.[16] found an aseptic loosening rate of 14.4% in components that had cementation of the cut surface alone and concluded that this technique should not be used.
The evidence remains heavily in favour of fixation with cement, but prosthesis survival is dependent on many other factors of which fixation is just one.

5.5 Patellar resurfacing

Controversy continues regarding patellar resurfacing during primary TKA [31]. When the original total knee prostheses were designed, the patello-femoral articulation was not taken into consideration as a potential source of pain, and results were complicated by patello-femoral symptoms despite an otherwise well performed knee arthroplasty. Subsequent designs incorporated a femoral flange for the patello-femoral articulation and provided the option for patellar resurfacing.

Numerous clinical trials have been done to help clarify the indications for resurfacing the patella, but unfortunately there is little consensus and surgeon preference remains the primary variable. There are three basic strategies: always resurface, never resurface or selectively resurface.

Patient satisfaction, anterior knee pain, incidence of mal-tracking (clunking syndrome) and rate of re-operation to resurface are determining factors of success. Scott and Kim indicated that, regardless of the management of the patella, surgeons can expect approximately 10% of patients to have anterior knee pain after TKA[26].

The largest registry study (Swedish)[24] reported on 27 372 knees operated on between 1981 and 1995 and revealed that those who had not had the patella resurfaced were generally not as satisfied as those who had had the patella resurfaced. However, satisfaction lessened with time in the latter group.

Studies exist which examine patients that have had one patellar resurfacing in one knee and the patella left unresurfaced in the other. Barrack et al.[3] found no significant difference in function, pain or patient satisfaction between the two knees.

Waters and Bentley[29] studied 514 TKA's at mean follow up of 5.3 years and found a prevalence of anterior knee pain of 25% in the non resurfaced group and 5% in the resurfaced group. Eleven of the non resurfaced patellae required resurfacing with a 97% success rate. Burnett et al.[4] presented similar findings at 10 years minimum follow up but using outcome measures found no significant difference between the groups.

Implant design, obesity, gender, stair-climbing and type of arthritis are factors that have been shown to have an influence on outcome, both patient-based and surgeon assessed. An algorithmic approach to selective resurfacing may include such factors as patient age, patello-femoral symptoms and signs, radiographic assessment of the patello-femoral joint and intra-operative assessment of the patella and the femoral trochlea. Few studies exist

testing this system, but development of joint registries will allow surgeons to draw conclusions on the basis of larger numbers of patients in the future.

5.6 Deep Venous Thrombosis following TKA

The most appropriate form of prophylaxis against thrombo-embolic disease following TKA remains controversial. The subject is vast and countless studies have been performed comparing mechanical and chemical methods. The relevance to this study seems obvious but most prophylactic treatment is commenced post-operatively except the use of thrombo-embolic disease stockings (TEDS) which are often worn pre-operatively but removed from the limb of surgery pre-operatively. On table mechanical prophylaxis such as foot or calf pumps is popular but was not used in this study.

There is general agreement that prophylaxis against deep vein thrombosis is necessary after total joint arthroplasty, but the ideal prophylactic regimen has not been identified. The selection of a prophylactic regimen involves a balance between efficacy and safety. Surgeons are particularly concerned about bleeding because it can lead to haematoma formation, infection, a re-operation, and a prolonged hospital stay. The selection of a prophylactic agent is also influenced by the more frequent use of regional anaesthesia; the recent development of peri-operative pain protocols involving the use of anti-inflammatory medications, which can also increase the risk of bleeding complications; and the continued decrease in the duration of hospital stays.

DVT is a common complication following TKA with significant morbidity, but thankfully less frequent mortality. Without either mechanical or pharmacologic prophylaxis, asymptomatic deep venous thrombosis will develop after 40% to 60% of total hip and knee arthroplasties[5]. Proximal deep vein thrombosis will develop after 15% to 25%, and a fatal pulmonary embolism will develop after 0.5% to 2%[2,9,10,14,30].

An ideal prophylactic regimen has not been identified, and the selection of an appropriate agent is usually a balance between efficacy and the risk of bleeding. The most effective prophylactic agents for these patients include low-molecular-weight heparin, warfarin, and fondaparinux. Aspirin reduces the risk of deep venous thrombosis compared with that associated with a placebo, but it does not appear to be as effective as warfarin or the low-molecular-weight heparins[6]. Mechanical devices appear to provide effective prophylaxis after total knee arthroplasty, but they have not been studied as extensively as the chemoprophylactic regimens, and new studies are necessary to evaluate their efficacy in

light of the reduction of hospital stays. The selection of a prophylactic regimen is influenced by the experience of the surgeon and individual patient factors. The ideal duration of prophylaxis after total joint arthroplasty has not been established, but a minimum of ten to fourteen days is safe and effective[6]. The goal in the future is to stratify patients according to risk as determined with genetic screening to select the most appropriate agent and duration of prophylaxis.

5.7 Summary

Similar to THA, many factors are to be taken into consideration for a successful outcome of TKA surgery.

Developing implant design and materials, exploration of new surgical techniques including computer assisted surgery appear to be minimising alignment issues and increasing longevity of prostheses.

However, patient selection and patient factors remain variables that surgeons must acknowledge with regard to selection for surgery, selection of implant, surgical technique, minimising complications and optimising outcome after TKA.

For this study all components were cemented and were the same implant design. Intramedullary alignment rod (fluted) technique was used in all cases for femoral component orientation. All patellae were resurfaced. Anti-thrombotic prophylaxis was standardised as outlined later as was the anaesthetic.

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Chapter 6

Mechanisms of cerebral injury during Orthopaedic surgery

6.1 Introduction

There is good evidence to suggest that intra-operative cerebral embolisation occurs during total joint arthroplasty [17,21,52]. During total joint arthroplasty, showers of bony spicules, marrow fat, clot and other particulate matter are carried by venous blood to the lungs[14]and studies have shown the possibility of the embolic material passing to the cerebral circulation via a patent foramen ovale[19,43,55] or across the pulmonary circulation[12].

The pathophysiology of cerebral injury secondary to orthopaedic surgery and more specifically arthroplasty is incompletely understood. A large body of work exists examining this consequence in response to cardiac surgery. The evidence thus far relating to orthopaedic surgery is minimal but some interest has been shown. Predominantly, many case reports exist of cerebral embolisation during arthroplasty and long bone fracture fixation [1,18-20,29,33,34,41,42,47,55,56]; the incidence of fat embolism syndrome is well documented and has been recognised for some time[24] but there is a paucity of evidence regarding aetiological factors, mechanisms of injury and the complex relationships between patient and operative factors that may help us understand the pathophysiology in greater detail. As the next chapter will address, there are even fewer studies which attempt to examine the relationship between cerebral embolisation and post-operative neuropsychological outcome in orthopaedic surgery, the clinical significance of which remains speculative.

The two main aetiological factors that will be discussed in this chapter are cerebral blood flow and microembolism. It is likely that these factors are inter-related as an increase in blood flow may lead to an increased microemboli load.

6.2 Cerebral Blood Flow

As cerebral blood flow may be a factor, attempts are made to keep it constant in this study (see Materials and Methods). Cerebral blood flow (CBF) is auto regulated across a range of blood pressure; the principle regulating mechanism is the arterial partial pressure of carbon dioxide and acidity although there is a response to the arterial partial pressure of oxygen. Cerebral blood flow is normally 40-60mls/g/min and Astrup[3] has shown that CBF must fall to below 20mls/g/min before ischaemic cell death occurs; this rarely

happens intra-operatively and is unlikely to be the main cause of cerebral damage. Relying on a study performed in cardiac surgery, Tufo et al.[53] found that in patients having coronary artery bypass grafting the incidence of post-operative neurological signs was higher in those with a mean perfusion pressure of 40mmHg compared to 60mmHg. Therefore, hypoperfusion may be a significant factor in to ischaemic cerebral injury in the setting of cardiac surgery. Many orthopaedic surgeons favour hypotensive anaesthesia for arthroplasty surgery particularly when cement is utilised and thus the findings by Tufo may influence surgeons to be wary of prolonged periods of low blood pressure intra-operatively.

Studies by Caplan[15] suggest that CBF may have a significant effect upon neuropsychological outcome via effects on microemboli. He hypothesised that the effect of emboli is worse when the perfusion pressure to the brain is less because there is less "washout" of emboli. However, there is no direct evidence to support this. Conversely a higher CBF (not necessarily resulting in a higher perfusion pressure) could theoretically result in more microemboli being delivered to the brain.

Hypoxia must not be forgotten as common complication of almost any surgery post-operatively. Browne et al.[11] showed hypoxia to be a weak but significant predictor of neuropsychiatric outcome at 5 days, again in a cohort of cardiac patients.

6.3 Microembolism

This section will define microemboli, discuss their consistency, examine the evidence supporting their aetiological role in the production on neuropsychological deficits in orthopaedic surgery, and outline theories as to how they produce cerebral injury. Other postulated theories of peri-operative cerebral injury will also be discussed briefly.

Microemboli have begun to receive more attention as possible mediators of cerebral injury in orthopaedic surgery as a consequence of their established role in cardiac surgery[5,39,45]. The belief that brain embolisation has clinical importance because of the suspicion that it may underlie post-operative delirium (or confusional states and/or cognitive dysfunction) is growing. This condition is common in the elderly, occurring in

10-15% of general surgical patients and in as many as 44-55% of particular subgroups of orthopaedic surgery patients[23,32].

Patients undergoing cardiopulmonary bypass surgery (CPB) may develop systemic inflammatory response syndrome (SIRS) and will probably suffer from post-surgical cognitive deficits (transient 61%, permanent 23%)[50]. The traditional belief in cardiac surgery was that the damage perpetrated by an embolus was caused by the occlusion of an arterial branch, resulting in an ischaemic event and subsequent infarction. However, ongoing research has demonstrated that the mere passage of a deformable embolus (air, lipid, or semi-solid clot) will disrupt the endothelium as it is extruded through the vessel. A cascade of events follows endothelial irritation. In the closed environment of the brain, a disruption of the blood-brain barrier has been demonstrated after the passage of lipid microemboli. A significant breakdown of the blood-brain barrier causes marked brain swelling, increased intracranial hypertension, and a possible increase in the size of the lesions associated with larger occlusive emboli. Gaseous microemboli are also a well-documented endothelial irritant and can cause significant brain dysfunction. It is important to avoid delivering emboli of any size or composition to the cerebral vasculature in order to reduce the impact of cardiac surgery on the brain[51]. A similar model for orthopaedic surgery has not yet been identified, a deficiency this study aims to begin to address.

The mechanisms by which arthroplasty surgery is emboligenic have been discussed at length in Chapter 2. The possible fate of these emboli and their significance remains uncovered although a similar mechanism of injury to that described by Stump is likely.

A microembolus has been arbitrarily defined as an embolus which measures no more than 200μm in diameter[7]. A larger embolus is said to be a macroembolus. Microemboli may be gaseous, lipid or particulate with further subdivisions into organic or inorganic. Detection criteria using TCD have been outlined in Chapter 4.

Gaseous emboli may enter via cannulae or as trapped air within tubing. This is uncommon. Anaesthetic gases have also been implicated in the production of gaseous microemboli[7]. Gaseous microemboli are more common during cardiac surgery especially

bypass surgery due to cannulation of the aorta and the right heart or during valve replacement procedures. Bypass equipment and bubble oxygenators are also a common source of gaseous emboli during CPB. During orthopaedic procedures air may be forced out of the intramedullary canal during pressurisation when cementing or out of poorly mixed cement but is otherwise uncommon. Gaseous emboli pertinent to this study are the microemboli detected during PFO detection formed by bubbles within agitated saline. There is a long list of potential particulate microemboli relevant to orthopaedic surgery. Thrombin, fibrin, platelets, leucocytes, fat globules, atheroma, calcium, bone, cement and even denatured proteins may form organic particles. Studies have concentrated on the fate of lipid emboli above other particulate emboli to date, in the field of cardiac and orthopaedic surgery.

The most interesting study thus far was conducted by Byrick et al [12]. They recognised that massive pulmonary fat embolism is a clinically important complication during joint arthroplasty, especially with the use of cement. Intra-operative haemodynamic instability and hypoxaemia have been attributed to right ventricular dysfunction secondary to pulmonary fat embolism and acute hypertension (the source of the embolic material being the marrow cavity). It has been proposed that small fat globules may pass through the lung vasculature and enter the systemic circulation causing peri-operative microembolism[22,48]. This theory suggests that, because of the fluidity and deformability of the fat globule, pulmonary vascular occlusion is transient and variable over time[14,49]. The timing of transpulmonary passage of fat emboli would be important if peri-operative cardiac or cerebral dysfunction is attributable to systemic fat embolism. Byrick reported a series of experiments in which bilateral cemented arthroplasty was performed in anaesthetised dogs. Tissue samples showed intravascular fat in the brain, heart and kidney within 3 hours of cemented arthroplasty. Their data indicated that transpulmonary passage of fat into the systemic circulation occurred within minutes to hours of bilateral cemented arthroplasty in the presence of pulmonary hypertension. No PFO was detected in any animal at post-mortem. An alternative hypothesis is that fat forms from intravascular chemical reactions[4,44].

Byrick also noted that the mean diameter of vessel occluded decreased within 5 minutes of arthroplasty, consistent with the hypothesis that deformable fat globules are

progressively forced into the more distal pulmonary vascular bed and that a particle diameter of 15μm or less appeared to be the threshold for the size of particle able to traverse the lung in large numbers.

Except for the aforementioned dog study, little is known about the histopathological characteristics of brain emboli found in patients after arthroplasty. Autopsy studies following cardiopulmonary bypass surgery have shown multiple focal dilatations or microaneurysms[36]. The walls of the affected arterioles or capillaries were apparently stretched, and their appearance suggested the effect of microembolic occlusion with subsequent disappearance of the embolus. These microvascular lesions have been called Small Capillary and Arteriolar Dilatations (SCADs)[10] and they are strong evidence of widespread microembolism to the brain during bypass surgery. Colonna reported a case of acute brain fat embolisation occurring after total hip arthroplasty in the absence of PFO where histopathological examination revealed similar SCADs of the cerebral vasculature but in greater numbers[17]. It is though that SCADs are the "footprint" left behind by mainly lipid microemboli when the solvent used to prepare specimens has removed the actual embolic material. However, although SCADs are not exclusive to cardiac surgical patients, their actual cause remains unknown.

Visualisation of lipid microemboli (LME) passing through the cerebral circulation would give a more dynamic impression of what happens rather than the single "snapshot" obtained at post-mortem as described above. A further observational study by Byrick et al.[13] described visualising cerebral LME using videomicroscopy in a rat model. They observed LME passing through the pial-cortical vessels confirming that human marrow fat, after injection into the superior vena cava, passes through the lung and can be detected in the brain in rats. However, LME were only seen after injection of adrenaline and crystalloid to treat systemic hypotension. This suggests transpulmonary passage of fat may have been enhanced and may be attributable to increased pulmonary blood flow, opening of pulmonary vessels, increased pulmonary artery pressure or a direct effect of adrenaline. No patent foramen ovale was present in any of the rats suggesting that transpulmonary passage of fat occurred. The findings also revealed that LME are not static but rather move at variable speeds through the arteriolar and capillary vessels, appearing to be dependent on perfusion pressure, although other factors may be

implicated such as arterial partial pressure of carbon dioxide. The pial-cortical vessels were not exclusive to LME as large numbers of LME were noted throughout the brain at post-mortem. However, a flaw of this study was species difference (although human marrow fat was used). Moreover, similarity of the findings to other human case reports and other animal models are striking[12,17]. This suggests that SCADs are LME lodged in the microcirculation during transit through the cerebral circulation[9,17]. They concluded that the dynamic characteristics of LME (streaming, fragmentation and erosion) that were observed are actually mechanisms by which the LME are broken up into fine lipid droplets that traverse the microcirculation. Under normal circumstances, these processes may occur over in the brain and the lung over time. This would account for the rarity of major neurocognitive dysfunction in patients despite the fact that more than 90% have echogenic evidence of emboli[16]. Despite the efforts of these studies, the ultimate fate of LME in the brain remains unresolved.

6.4 Other postulated mechanisms of cerebral injury

The evidence relating microemboli to potential post-operative neuropsychological deficits exists and the mechanism by which this may occur has been postulated. However, other explanations should be mentioned which are principally based on observations and studies in cardiac surgery.

A number of investigators maintain that atheroma of patients is the most significant of microembolic sources and that the atheromatous microemboli are detrimental to neuropsychological outcome[6,38]. The fact that microemboli are detected in children[40] having surgery to correct congenital cardiac defects suggests that non-atheromatous sources are important in the production of emboli.

Techniques that decrease cerebral blood flow during CPB would be expected to decrease embolic burden and to consistently improve neurological outcome. They do not. Even avoiding CPB altogether, which should virtually eliminate both gas and lipid emboli, does not significantly decrease chronic cognitive dysfunction when compared to a CPB-based technique[54]. Hindman[28]suggests that there must be something in addition to emboli that contributes to post-operative dysfunction. Furthermore, Heyer et al.[27] and Murkin et al.[37] both observed that cardiac patients had greater rates of neurocognitive abnormalities

than non-cardiac patients in the first week after surgery. However, when one or two months later, cardiac and non-cardiac patients observed had equivalent rates of cognitive dysfunction. Thus, they postulate that there is some element of the surgery and/or anaesthesia itself that results in, contributes to, acute and chronic post-operative cognitive dysfunction – an element not unique to cardiac surgery.

One possibility may relate to central nervous system (CNS) responses to peripheral tissue injury and/or inflammation. Many systemic inflammatory mediators increase with cardiac and non-cardiac surgery (e.g. IL-6, IL-8, IL-1, TNFα, complement acvtivation)[25,26] and appear to be a significant determinant of post-operative recovery, as demonstrated after total hip arthroplasty[25]. In animals, systemic inflammatory mediators trigger extensive changes in CNS inflammatory gene expression, neurochemistry, neuroendocrine status, thermoregulation, behaviour and cognition [8,31]. Notably, the glial response to injury increases with age, resulting in increased brain expression of all inflammatory genes[30], which in turn increases blood-brain barrier permeability[35], cortisol secretion and the induction of fever[46]. Hence, CNS responses to systemic inflammatory mediators rapidly alter gene expression and functional status, and, by their nature, are likely to augment CNS injury from any co-existing peri-operative neurological insult[2]. Therefore, other interventions that decrease systemic and /or CNS inflammatory responses have the potential to decrease the incidence and severity of post-operative neurocognitive dysfunction, which carries some significance as systemic inflammatory mediators are increased during and after most types of surgery.

The mechanism of injury arising from microemboli is unclear but unlikely to be merely a mechanical plugging effect. The SCADs that have been found in autopsy specimens suggest that microemboli may have a local destructive effect. Microemboli may induce a local inflammatory reaction as well as plugging capillaries.

In summary, the role of microemboli causing deterioration in neuropsychiatric outcome after cardiac surgery is not resolved and even less is known in relation to orthopaedic surgery. Microemboli seem to be the most likely candidates for such a causative role but it would appear that the inflammatory response and any interaction between inflammation and microemboli require further investigation.

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Chapter 7

The assessment of neuropsychological function after Orthopaedic surgery

7.1 Introduction

Anaesthetists and surgeons have suspected for many years that some elderly patients may suffer a decline in cognitive or neuropsychological (NP) function after an operation, so called post-operative cognitive dysfunction. Changes in anxiety levels, personality and memory impairment may occur and contribute to morbidity[3].

Over the past 40 years many studies have been performed to assess the relationship of these features to anaesthesia and surgery. The incidence reported has varied. Despite radical changes in anaesthetic practice with the development of new drugs and monitoring techniques which should have improved safety, the proportion of patients affected remains similar to earliest reports[5].

Although the incidence appears unchanged, the number of elderly patients has been increasing with larger numbers undergoing arthroplasty surgery. As arthroplasty is a relatively safe procedure and long term survival is not related to surgery, proportionately more procedures will be performed in older subjects and increasing expectations of the elderly could extend the demand into higher age groups. This possible growth in surgical demand makes it important to establish features, incidence and causes of post-operative neuropsychological decline.

This section will describe the role of anaesthesia and NP outcome, examine methodological issues in NP testing, summarise the main findings relating to orthopaedic surgery and discuss more complex issues such as analysis of the tests used.

7.2 Role of anaesthesia

In 1955 Bedford reported dementia in old people after operations under general anaesthesia[2]. He concluded that minor degrees of dementia were common and described 18 extreme examples. No controls were available and anaesthetic records were incomplete but effects were attributed to the anaesthetic drugs. This prompted Simpson et al.[28] to prospectively survey physical and mental changes occurring after anaesthesia and elective surgery in elderly patients. A total of 741 patients were studied and none showed

gross dementia. Lesser degrees of deterioration occurred in some patients but all survivors showed good reasons for decline unrelated to organic cerebral damage or anaesthesia. They concluded that anaesthesia had no effect on physical activity, mental ability or personality. There were unfortunately testing flaws and at least one of the patients described has clear post-operative cognitive deficit[8].

Blundell measured psychological changes with daily ratings before and after operation in 86 elderly patients using more rigorous tests[5]. The surgical group showed marked deterioration in the arithmetic and memory tests both immediately and long term and this decline was believed to be a result of the effects of the anaesthetic agents on the cerebral cortex which was aggravated in some cases by additional complications such as fever, or the drugs given to combat it. Little was noted, unfortunately, on type of surgery or anaesthetic.

Others from the 1970's onwards, studied the hypothesis that post-operative cognitive changes were caused by psychological effects of the anaesthetic, such as hyperventilation, hypotension or hypoxia alone or in combination.
Observational studies continued into the 1980's when many studies were performed comparing the difference in post-operative neuropsychological function in patients receiving general anaesthesia with those receiving regional anaesthesia. Discussion of those studies assessing patients undergoing orthopaedic procedures follows (Table 7.1).
Hole et al.[11] studied 60 patients who were randomly given regional anaesthesia (RA) or general anaesthesia (GA) for THA. Marked cognitive decline was noted overall and a difference between the two groups was also seen. Significantly low arterial partial pressures of oxygen was recorded in the GA group on the first post-operative day, and significantly lower than the baseline values in the GA group on the first and third post-operative days. This may have contributed to the cognitive decline noted and they concluded that elderly patients do better after THA with less deterioration of cerebral and pulmonary functions when given RA than when surgery is performed under GA.
Rasmussen et al.[26] studied patients over 60 years old undergoing major non-cardiac surgery randomly allocated GA or RA. The incidence of post-operative cognitive dysfunction after 1 week was significantly greater after GA; no significant difference was found 3 months after surgery suggesting no causative relationship between GA and long

term cognitive dysfunction. However they concluded that RA may decrease the incidence of cognitive dysfunction early after surgery.

Table 7.1 Studies of orthopaedic procedures comparing general anaesthesia with regional anesthesia and congnitive dysfucntion

Study	n	Op	Age (yr) (mean)	Time P=pre-op d=days m=months	Deteriorat ion occurs	Long term change
Hole 1980[11]	60	THR	56-84 (71)	P,1,3,7,12 d	Yes	Slight both grps
Riis 1983[27]	30	THR	>60	P,2,4,7 d 3m	Yes	No
Bigler 1985[4]	40	Acute Hip	>60 (78.9)	P,7d,3m	No	No
Hughes 1988[12]	30	THR	50-80	P,1,2,7 d	Yes	Not tested
Jones 1990[13]	146	THR/ TKR	>60	P,3m	No	No
Nielsen 1990[22]	60	TKR	60-86 (70)	P,3m	No	No
Williams-Russo 1996[36]	262	TKR	>40 (69)	P, 7d, 6m	Yes	Yes
Rasmussen 2003[26]	364	THR/ TKR	>60	P,7d, 3m	Yes	No

Six other studies exist: Riis et al.[27] examined the post-operative course of cognitive performance during the first week and after 3 months in patients undergoing THA, randomly allocated into 3 groups, GA alone, RA alone and GA in combination with RA. An equal degree of post-operative mental impairment in performance of 3-4 days duration was found in all groups. Three months after surgery cognitive function had improved slightly and to the same extent in all groups. Bigler et al.[4] assessed 40 patients undergoing surgery for acute proximal femoral fractures and were randomly given GA or RA. Cognitive function was studied pre-operatively, 1 week and 3 months post-operatively. Although time to ambulation was shorter in the RA group, no persistent

impairment of mental function was found in either group. Hughes et al.[12] studied patients scheduled for THA, again using either GA or RA. Only recall and recognition tests were employed and little overall change of memory was seen although there was an inexplicable but significant decrease in the ability to recognise words after RA.
Jones et al.[13] conducted a prospective study of patients randomly allocated to receive GA or RA. However, the group was heterogeneous in that patients underwent THA or TKA. Overall, cognitive and functional competence in elderly patients was not detectably impaired after GA or RA when attention was paid to the known peri-operative influences on mental function. Nielson et al.[22] studied the psychosocial effects of TKA in patient over 60 years of age receiving GA or RA. Psychometric tests were used and conducted pre-operatively and 3 months post-operatively. In their patient population GA posed no more of a risk to long term mental function rather than epidural analgesia.
Finally Williams-Russo et al.[36] studied 262 patients undergoing TKA. Neuropsychological assessment was performed pre-operatively, 1 week and 6 months post-operatively. Patients were randomly allocated GA or RA as the anaesthetic method for surgery. The NP tests used were thorough and the technique will be discussed later in this chapter. There were no significant differences between GA and RA groups in within-subject change from baseline (see later) on any of the test results at 1 week and 6 months post-operatively. Overall, 5% of patients showed a long term clinically significant deterioration in cognitive function. The study represented 99% power to detect a clinically significant difference on any of the neuropsychological tests and none were found.

Inconsistency between these studies is wide ranging, even though seemingly, similar patients were studied. The variety of assessment tools used, ranging from unstructured interviews, to postal questionnaires to more formal NP testing is the most obvious inconsistency. The tests employed were often traditional intelligence tests or screening tests such as the Mini Mental State Examination. These global batteries tend to be reliable but are relatively insensitive to change following surgery[20].

Cardiac surgery has once again been the model for the majority of work carried out in this subject as the documented frequency of NP decline post-operatively is common. Much inference will be made in the rest of this chapter to studies pertaining to cardiac

surgery, particularly as the methodology of NP testing as been fine tuned within this sphere of surgery. Numerous patient factors that may affect NP outcome have been elucidated as a consequence and will be discussed briefly at the end of the chapter as not all are pertinent to orthopaedic surgery. In addition test variables, study design and data analysis factors will be discussed as these could affect NP results.

7.3 Methods of testing

Neuropsychological testing is able to detect slight impairment in cognitive function by assessing various aspects of intellectual function[16] using appropriate objective tests. These are frequently administered by a specialised individual and can be paper and pencil or computer based tests which can be undertaken by the patients themselves. Different aspects of brain function can be assessed by using these tests such as problem solving, speed of information processing, flexibility and short term memory. Psychomotor function may be assessed by reaction time measurements.
Some NP tests are variable with respect to either the subjects or their examiners. Variability in performance from one session to another is also recogniosed[14].

Test conditions should be identical at each session with the same tester administering the material in the same room at the same time of day if possible, to minimise test variability. External distraction must be avoided and this may be a problem when testing is carried out on a ward and if the battery is long and arduous. In the early post-operative phase, pain, sleep deprivation and residual effects of analgesics or hypnotics and physical limitations can also affect performance[7]. This is particularly relevant to this study as many of these factors are apparent post-operatively after arthroplasty surgery which requires significant analgesia for up to 1 week and physical limitation for several months in some cases.

In a clinical setting a psychologist would conduct the standard clinical NP assessment of an individual patient over one or two test periods totalling between two and five hours. The patient can be administered a comprehensive battery of up to 25 standardised tests with the aim of identifying and localising a brain lesion, assessing the degree of cognitive disturbance in patients with known brain lesions or in order to distinguish between neurological and psychiatric symptoms[16].

7.4 Test variables

In the context of orthopaedic surgery, assessments should be made both prior to and then following surgery, thus enabling comparisons to be made between the patients baseline score pre-operatively to post-operative performance. The purpose is to measure change in performance over time. The post-operative interval can be varied to include various time points. As a result, one may assess long term effects and examine whether short term changes noted, persist or resolve.

Time constraints around surgery restrict the testing to an hour each for each of the pre-operative and post-operative tests. Therefore, in order to perform as many tests as possible and so be as comprehensive as possible in testing different cognitive domains, relatively short tests must be selected. Previous investigators have used between 1 and 14 tests. The fact that the test will be repeated shortly afterwards demands that the test should have minimal learning effect. Parallel forms of the same test may reduce learning effects. If tests were too easily learnt this would decrease the sensitivity of post-operative testing. Some degree of learning is inevitable with most tests and it is expected that the majority of patients without impairment will show an improvement in NP test performance post-operatively. As learning is inevitable, one way it can be taken into account is to use Z change scores (see later). It can be seen therefore that the battery of tests one uses to assess patients before and after orthopaedic surgery is a compromise between wishing to be as comprehensive as possible while completing testing in about one hour.

The model of NP assessment following orthopaedic surgery is based broadly on a model used at our institution for cardiac surgery[17,19].

7.5 Patient variables

There are a number of patient variables that could influence NP outcome and may be the reason for the differences seen in incidence in cardiac and orthopaedic surgery of neuropsychological decline thus far.

In the seven studies comparing methods of anaesthesia in orthopaedic surgery and NP outcome the age of the patients studied is generally similar except in the study by Williams-Russo et al.[36]. They studied patients as young as 40 years of age whereas the other authors used 60 years of age as the cut off. Average or median ages for the study populations were all over 75 years of age. This is probably a fair representation of the age group of the general population undergoing arthroplasty surgery and in these studies there was no evidence found to support the theory that age affects NP outcome.

The evidence in cardiac surgery indicates that old age is associated with worse NP outcome[20,23,29,34]. Theories of increased microemboli loads[30] and impaired cerebral blood flow have been put forward to account for this[20]. The average age of patients undergoing arthroplasty has risen over the last ten years but younger patients are also more readily considered for arthroplasty and thus the study population age should reflect this.

Gender of patients has been an issue in cardiac surgery where the preponderance for CABG surgery is male but recent study indicating that women were more likely to suffer from a peri-operative neurological event [10]. No such evidence exists for orthopaedic surgery but arthroplasty surgery is commoner in the female as there is a predisposition to the female gender for osteoarthritis.

7.6 Study design

Moving on, there is a possibility that selective recruitment of patients may lead to the study population being unrepresentative of the general population undergoing arthroplasty surgery. Even if one aims to be as inclusive as possible, a proportion of patients will inevitably decline consent to be studied leading to a possible sampling bias. Potential differences in outcome, between the studied and non-studied populations, are possible. Researchers may deliberately select healthier individuals for their trial. This may increase the risk of NP deficit, but better represents the general arthroplasty population.

Selective attrition at follow up may also alter the reported incidence of NP deterioration after surgery. Patients who suffer a severe deterioration may be unable or unwilling to

attend follow up assessment and so lead to an underestimate of the incidence of deterioration. However, follow up data in cardiac surgery does not support this[32]. In most studies of this nature, some patients cannot complete the study for reasons such as lack of interest or time for testing on return for follow up. Some patients refuse or give up on individual tests in the battery. Missing test scores can be handled in several ways although some recommend that tests with missing data are not used at all for evaluation because such data cannot be substituted in any reasonable way[25].

The timing of NP assessment both pre- and post-operatively may have a considerable affect on NP performance. In cardiac surgery it has been shown that assessment of cognitive function carried out in the first week post-operatively is influenced by the residual effects of the surgical procedure and anaesthesia[19].

Anxiety is frequent in patients tested the night before surgery. Although there is little evidence that anxiety depresses performance, it has become conventional to assess anxiety and depression contemporaneously to the NP assessment. A recent study has found that patients are less anxious the day before surgery than they are a week before surgery but that this difference in anxiety did not alter NP performance[31].

After surgery, pain, analgesia, tiredness and decreasing effects of anaesthetic drugs are likely to hinder performance in NP tests. A recent consensus decided that the ideal timing of post-operative assessment should be three months, when any deficit detected would be a true, permanent deficit[17]. However, particularly in orthopaedic arthroplasty surgery, many surgeons see their patients 6-8 weeks post-operatively and many psychologists assess the patients then to coincide with a return to hospital. With specific regard to arthroplasty of the knee and hip, pain and mobility should be significantly better at this juncture and testing for an hour should be less distressing. Customarily, orthopaedic surgeons review joint arthroplasty at 6 months when the "bedding in" process of the implant and recovery of the muscles should be nearing completion or complete.

7.7 Putative mechanism - Microemboli

A large body of evidence suggests that microemboli may influence NP outcome in cardiac surgery. Although it is a consistent finding that there is a greater number of

detectable microemboli during valve surgery than CABG surgery[6,18], there is no clear consensus as to whether this leads to poorer NP outcome. Only two reliable human studies have detected cerebral microemboli during arthroplasty surgery[10,33] but neither reliably tested NP outcome. Consequently this relationship is still unclear in orthopaedic surgery, an issue this study aims to address.

7.8 Methods of analysis

The statistical analysis of NP data may have a significant influence on the incidence of neuropsychological deficit found. Methods of analysis have evolved in an effort to be more sensitive but there is no universally accepted method. Are statistically significant differences between groups also clinically relevant? A difference of just a few seconds in the performance of NP tests may be statistically significant due to the large study group but is clearly of little clinical importance. Investigators who have used as many methods as possible to analyse their results and then presented the methods which yields the most significant results have been criticised. Definition of the type of analysis to be used when designing a trial is important; moreover, the analysis should be adhered to.

Again, a large body of work exists in this domain in cardiac surgery. Orthopaedic patients, in the past, have not been subject to this type of NP testing and analysis. We hope to bridge this gap between the surgical specialities with regard to NP outcome and perhaps adjust test variables, study design and methods of analysis accordingly. Traditional analysis of a single group of cardiac patients, examining change before and after surgery, has been group comparison or individual comparison. Group comparison consists of pooling data and determining whether the group as a whole has altered its performance. In order to detect a deficit the mean of the group has to drop significantly. This makes the assumption that most patients will experience a deficit, but in fact only a minority are likely to. Also it takes no account of the potential learning effect of the tests. The patients who improve through learning may mask those who deteriorate. This type of analysis has flaws. Individual comparisons are probably superior for single group studies which examine individual changes, with each patient acting as his own control. The problem then arises as to how to define what extent of NP deterioration constitutes a deficit. Most researchers accept that deterioration on at least two tests is required as a

poor performance; on only one test may reflect a lapse in performance. (Although it may also mean that only one cognitive domain has been affected).

A deficit has usually been defined as a drop in one or more standard deviations (SDs) from the pre-operative to post-operative levels. The SD may be a population SD when standardised tests are used or it may be calculated from the pre-operative performance in an attempt to establish a notional standard score for the group examined. However this method may become insensitive because it applies a fixed amount of deterioration to all individuals regardless of their absolute levels. A similar approach may be to take a proportional drop in performance to constitute a deficit.
When interventional studies are analysed, there are again a number of approaches. In these studies two or more groups are having surgery with or without a particular intervention. There are several methods of analysis applicable in this situation. The use of group means is best avoided. The individual incidence approach, used by Pugsley and described by Newman[24] enables a comparison to be made between groups in terms of the number of individuals showing a deficit. All patients' pre-operative scores are used to calculate a SD unit. A change in score is calculated for each patient for each test. A deficit in a test occurs when the patient's individual score in test decreases by more than one SD from their pre-operative score. A significant deficit is said to occur if this occurs in 2 or more tests. The incidence of deficits between groups can then be compared.

However, some drawbacks became apparent recently. In addition to the problem of arbitrarily defining a deficit, as explained above, it also has become less sensitive. The method classifies a patient in a binary fashion as having a deficit or not with no intervening scale. Sensitivity is therefore reduced when analysing by the incidence of deficits. Another criticism of this method is the phenomenon of "regression towards the mean" which is the statistical observation of a biological phenomenon whereby extreme baseline scores tend to become less extreme on repeated testing. It can be argued, therefore, that those with higher pre-operative scores are more likely to regress towards the mean and show apparent, although not real, deterioration. This can be refuted, however, by the facts observed in cardiac surgery where those patients with better pre-operative scores tend to deteriorate less.

More recently Arrowsmith et al.[1] have introduced "Z" or "change" scores and these are now becoming an additional accepted way of analysing NP data with greater sensitivity. To calculate a Z score each patients' test score on each occasion is converted into a standardised score by dividing by the SD of the pre-operative group performance of all the patients in a study. A change score is then calculated for each patient by subtracting the post-operative standardised score from the pre-operative standardised score. One can then calculate a mean of the change scores for each group. This method is more sensitive because it is a continuous change score without absolute cut offs. It also allows group comparisons which tale into account potential learning effects.

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Chapter 8

Materials and Methods

8.1 Design

This study was a prospective controlled clinical trial. This single centre study was collaboration between University College London Unit of Health Psychology and University College London Hospitals Trust Department of Trauma and Orthopaedic Surgery.

8.2 Ethical Approval

Approval was obtained from the University College London Hospitals Trust committee (see appendix 1).

8.3 Statistical Planning

A review from the last four years data suggested that approximately 125 total hip arthroplasties and 125 total knee arthroplasties are carried out by the Department of Orthopaedics at our institution every year. To achieve equal groups for our study, we aim to recruit 50% of each arthroplasty type. Approximately 40% of these will have an underlying inflammatory arthropathy. It was therefore estimated that 100 patients in total will be recruited over 24 months. It is further estimated that 40% (40/100) will demonstrate microemboli and of these we expect 25% to show deficits at 6 months. Assuming 5% will show deficits in those showing no microemboli, a χ^2 analysis will show significance at 11.7 (OR 5.32; CI 2.04- 13.86). Estimating a 20% withdrawal rate, we aimed to include a total of 150 patients in the study.

8.4 Study Population

Patients scheduled for primary total hip arthroplasty or primary total knee arthroplasty at the Middlesex Hospital (University College London Hospitals Trust) were invited by the author to participate. The patients from the waiting list of two consultant orthopaedic surgeons were recruited. The waiting list of one surgeon would not have allowed sufficient recruitment. More waiting lists were not used for two main reasons. Firstly, using fewer surgeons minimises any differences in surgical technique. Secondly, patients from additional waiting lists would have been operated on in additional theatre lists, attendance at which for intra-operative data collection, would not have logistically allowed sufficient time for further recruitment and follow up of patients in the out patient setting.

8.5 Recruitment and Consent of patients

Exclusions:-

Patients unable to speak and read English. This was essential for conduction of NP testing and outcome measurement.

Patients with a history of Transient Ischaemic Attack or stroke or previous history of cerebral injury or other ongoing cerebral disease e.g. tumour, could also confound results.

Patients with auditory or visual impairment. This was again essential for NP testing and outcome measurement.

Patients with a history of or ongoing alcoholism. Depression of cerebral function as a result of excess alcohol consumption would confound results.

Patients with carotid artery stenosis. (Patients were screened with auscultation of the neck. If a bruit was audible the patient was excluded and carotid duplex scanning was arranged).

Patients fulfilling the criteria were then invited to participate. In accordance with ethics guidance, fully informed consent was obtained from all patients. The trial was explained verbally to patients who were then given a written information sheet to read (see appendix 2). Patients were requested to sign a consent form if they agreed to participate (see appendix 2).

8.6 Types of prosthesis

For all patients undergoing primary total knee arthroplasty, one type of prosthesis was used. This was the Press Fit Condylar (PFC) Sigma – Depuy Johnson & Johnson Leeds, UK. This comprises of a cobalt chrome femoral component which was cemented, a cobalt-chrome tibial tray which was cemented and a polyethylene insert which clip fits into the tibial tray. Posterior cruciate ligaments were sacrificed in all cases.

For patients undergoing total hip arthroplasty, the type of prosthesis was initially pre-determined using clinical and radiographic evidence, as outlined in chapter 4. Three main choices of fixation for each component existed: fully cemented, fully uncemented and hybrid (acetabular component uncemented, femoral component cemented). Once fixation method was chosen the prosthesis type was as follows:

Fully cemented: - Stanmore (Biomet, Swindon, UK) polyethylene acetabular component and Spectron (Smith & Nephew Orthopaedics, UK) femoral component.

Fully uncemented: - Reflection (Smith & Nephew Orthopaedics, UK) acetabular component and Synergy (Smith & Nephew Orthopaedics, UK) femoral component.

Hybrid: - Trilogy (Zimmer Ltd, UK) acetabular component and Spectron (Smith & Nephew Orthopaedics, UK) femoral component.

Unless there was clear evidence intra-operatively that the fixation and the prosthesis choice was unsuitable, as deemed by the consultant surgeon, the combinations of components were adhered to as above. If a change was decided upon to a prosthesis not listed above or a different procedure, that patient was excluded from the study.

8.7 Theatre protocol

All operations were carried out in the same laminar air flow theatre at the Middlesex Hospital.

8.8 Anaesthesia

No pre-medication was used. Supplemental oxygen was administered via a face mask at a rate of 4l/minute prior to induction of anaesthesia. A 14 gauge cannula was inserted in the antecubital fossa dedicated for patent foramen ovale detection. A 10 cm extension tube was attached. Separate cannulae were inserted elsewhere for administration of drugs or anaesthetic agents. Induction was carried out using propofol (3-5mg/kg). The trachea was intubated with a cuffed oral endotracheal tube. Intermittent positive pressure mechanical

ventilation was used and titrated to maintain an end tidal CO_2 of 4.2 – 4.5 kPa. Maintenance was with a mixture of O_2, air and desflurane.
Although propofol (and etomidate and thiopentane) have potential neuroprotective effects, they are unproven, particularly in humans [17,19,26,28].

8.9 Surgical technique

Patients of two consultant orthopaedic surgeons, Mr Fares Haddad and Mr Ali Fazal, were used. All procedures were carried out by only those two consultants.

For total knee arthroplasty, a tourniquet was used for all cases. A midline incision with a medial parapatellar approach performed. Appropriate soft tissue releases were carried out to correct deformity. The extra-medullary jig device was utilised to perform the tibial osteotomy and intra-medullary femoral guide rod (fluted) was inserted to aid with alignment of the distal femoral osteotomy. Patella resurfacing was carried out in all cases. The tourniquet was only released after skin closure and application of dressing and compression bandage.

For total hip arthroplasty, the patient was placed in the lateral decubitus position, with the side to be operated on uppermost. A lateral incision was employed for all cases. A posterior approach was used by one surgeon (FH) and an anterolateral (Hardinge) approach by the other surgeon (AF). There is no evidence to suggest that the difference in approach has any effect on microemboli genesis and distribution. The acetabulum was prepared first followed by the femur in all cases. In the cases where cement was used third generation cement mixing techniques were employed as the literature supports improved outcomes with these techniques[4,29].

For both total hip and total knee arthroplasty, the cement used was Palacos R cement (Biomet, Swindon, UK) which is impregnated with the antibiotic gentamicin. It is radio-opaque and widely used.

8.10 Transcranial Doppler

Intra-operative transcranial Doppler (TCD) was used to measure cerebral microemboli load. It therefore functioned as a measure of a potential end point variable and a mediating variable.

Monitoring was continuous, commencing before the operation started i.e. before the skin incision and ending after the tourniquet was released but continuing until no microembolus had been detected for 2 minutes in the case of total knee replacement and ending after the dressing was applied and the patient had to be returned to the supine position after total hip replacement.

The two procedures were further subdivided into phases. This enabled relationships between specific surgical activity and microemboli load to the brain to be assessed. The duration of each phase was also noted.

The phases for TKA were: -

- Pre tourniquet inflation (>2 mins for all pts)
- Tibial cut
- Femoral guide rod insertion
- Femoral cuts
- Patella cut
- Component insertion
- Cement setting
- Tourniquet deflation

The phases for THA were: -

- Femoral osteotomy
- Acetabular reaming
- Acetabular component impaction
- Femoral canal reaming
- Femoral component insertion
- Joint relocation

The Doppler machine used was a Nicolet EME Pioneer 2020 Transcranial Doppler system. The middle cerebral artery was insonated using a 2 MHz pulsed wave transducer and the probe was secured to the skull using an elasticated headset, which allowed for prolonged monitoring. The side was dependent on the type of surgery. Equal numbers of left and right middle cerebral arteries were insonated in the cases of knee arthroplasty. Microembolic events were recorded onto videotape for subsequent playback and analysis. The microemboli were counted manually "off line" (i.e. after the operation) using their unique auditory and visual characteristics. International consensus criteria were used for defining microemboli[35]. The author performed the microemboli counting first, noting during which surgical phase of the procedure microemboli were detected. A second investigator reviewed 10% of the tapes to assess inter-observer reliability.

8.11 Patent foramen ovale detection

All patients were prepared with an 18-guage intravenous catheter into an ante-cubital / large forearm vein and a connecting short flexible tube.

Microcavitation saline contrast was generated by mixing 9ml of normal saline and 1ml of air between two 20ml syringes connected to a three-way stopcock. The contents of the syringes were exchanged energetically and rapidly between each other at least ten times. After preparation, the contrast was injected as a bolus immediately with a two minute interval between each test.
A Valsalva manoeuvre was created by increasing and holding end inspiratory pressure. This was facilitated in the intubated patient by positive pressure ventilation for 5 seconds after the start of the injection and released after 5 seconds had elapsed.

The diagnostic time window for a microemboli signal to appear was 25 seconds after injection. One or more microembolic signals in the diagnostic time window was deemed a positive result. If a positive test occurred, no further tests were carried out. A total of three such tests were performed.
All testing was performed before surgery commenced.

8.12 Neuropsychological tests

A trained psychologist administered these tests to all patients. Two psychologists carried out all tests and as much as was practically possible, the same psychologist saw the same patients at the follow up intervals. All patients were brought from the ward to the same room where the tests were carried out under relaxed conditions pre-operatively, and from the out-patients setting after their consultation with the surgeon (author).

A battery of nine neuropsychological tests was administered on each occasion. The tests selected are widely used in the literature on coronary artery bypass grafting surgery and have been shown to be sensitive to change following cardiac surgery[31], and can be performed in the limited time available. Where available, parallel forms were administered to limit the effects of learning between assessments. The battery consisted of: -

8.12.1 New Adult Reading Test [30] was administered pre-operatively to obtain an estimation of pre-morbid IQ.

8.12.2 Rey Auditory Verbal Learning Test[34]. This widely used test involves free recall following the repeated verbal presentation of a 15-word list. The same list is repeated 5 times with free recall after each presentation. This sequence is followed by a presentation of a second (distracter) list followed by free recall. Immediately following this, the participant is required to recall as many as they can from the first list without a further presentation (delayed recall). The total number correctly recalled over the first 5 trials (verbal learning) and the change between trials 5 and 7 (delayed recall) was recorded.

8.12.3 Non-Verbal Recognition Memory Test[31]. This is a computerised timed recognition memory test in which one chequer-board design is presented on a computer screen for 10 seconds and is followed by 3 designs. The task is to identify which of the three designs is the same as the previous one as quickly as possible. The task consists of 20 presentations and total response time is recorded.

8.12.4 Trailmaking A. This and the following test originally formed part of the Army Individual Test Battery[1] and assesses motor speed and attentions. Test A involves the participant in drawing lines, as quickly as possible through consecutively numbered circles. Time to completion was recorded.

8.12.5 Trailmaking B. This is a parallel task to trailmaking A but more difficult, as it involves alternating between ascending numbers and letters. This test measures not only motor speed and attention but also mental flexibility.

8.12.6 Letter Cancellation Test [41]. This paper and pencil task consists of cancelling a random target letter from rows of letters. Performance was scored on time to completion.

8.12.7 Symbol Digit Replacement Test [31]. This is a computer driven task adapted from the paper and pencil version devised by Smith[37]. This requires the participant to pair 45 pre-coded digits with symbols. The score was time to completion.

8.12.8 Choice Reaction Time Test [31]. This is a computerised task in which participants are required to discriminate and respond as quickly as possible to two letters (A&B) which are displayed randomly on a computer screen. Mean response time was recorded.

8.12.9 Grooved Pegboard – Dominant and Non-dominant [25]. This timed test of manual dexterity and complex fine-motor co-ordination discriminates differences in right and left hemispheric performance. It consists of a small board containing a 5 x 5 set of slotted holes angled in different directions. Each peg has a ridge along one side requiring it to be rotated into position for correct insertion. The score was time to completion.

8.12.10 Mood State

In order to examine the impact of anxiety and depression on neuropsychological performance, it has become increasingly common for mood state to be assessed at each time of testing.

8.12.11 ***Depressed Mood: Centre for Epidemiologic Studies Depression Scale***[33]. This is a 20 item self-report measure for use in the general population studies to assess the presence and severity of depressive symptomatology.

8.12.12 ***Anxiety: Spielberger State and Trait Anxiety Inventory*** [40]. This questionnaire consists of 20 items for measuring trait anxiety and 20 items for measuring state anxiety. The trait measure (administered pre-operatively only) provides an index of personality based anxiety level whereas the state anxiety level provides a measure of anxiety in the current situation.

All tests were performed pre-operatively, usually the day preceding surgery, 6-8 weeks and 6 months post-operatively. The post-operative tests were performed on the day the patient returned for routine follow up clinic.

8.13 Demographic data

Age, sex and race were recorded. A general physical examination was performed to detect any exclusion criteria.

8.14 Pre-operative Quality of life and Orthopaedic outcome measures

8.14.1 EuroQol

EQ-5D (as the descriptive measure is known)[32] is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. EQ-5D was originally designed to complement other instruments but is now increasingly used as a "stand alone" measure. EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The EuroQol visual analogue scale (EQ-VAS) was not used as part of the outcome measure, as at the time of the study it was thought to be an optional component of the measure. The EQ-5D descriptive system (appendix 4) comprises 5 dimensions of health (mobility, self-care, usual activities,

pain/discomfort, anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions and a score is obtained by comparing with a value set for the local population[12](UK value set used). Scores range from -0.594 (poor) to 1.000 (best outcome) using the UK value set.
It has been used extensively and validated in orthopaedic use against other existing quality of life measures[12,13,20,32].

8.14.2 WOMAC

The most widely used condition-specific instrument for the assessment of hip or knee osteoarthritis is the Western Ontario and McMaster Universities osteoarthritis index (WOMAC)[5-8]. The index is self-administered and assesses the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions. Validity and responsiveness are the most important criteria when deciding which particular instrument to use in a clinical trial and extensive data exists on these criteria for the WOMAC score[5,9,36,38].
This index has gained growing acceptance in osteoarthritis assessment since its introduction in 1986. The pain dimension or scale includes five items asked about pain at activity or rest. The stiffness dimension includes two questions. The function dimension asks about the degree of difficulty in 17 activities. All 24 WOMAC items are rated on a numerical rating, zero to four (none, mild, moderate, severe, extreme) as the modified Likert scale. The minimum score is therefore zero (no disability) and maximum score is 96 (severe disability).

8.14.3 Harris Hip Score (HHS)

Developed by William Harris in 1969[22], the HHS is the most frequently used measure to assess the outcome of total hip arthroplasty. Assessment is through five modalities: pain (none, slight, mild, moderate, disabled), daily activity (stairs, transportation, sitting, shoes and socks), gait (limp, support and distance), absence of deformity and range of motion. The maximum score is 100 (no disability) and minimum score is zero. Outcome is traditionally grouped into four categories by score: excellent (100-90), good (89-80), fair (79-70) and poor (less than 70). The HHS is an objective outcome measure, completed by

the surgeon. It has been validated in numerous studies and some involving large population groups[2,3,39].

8.14.4 Oxford Hip Score (OHS)

In contrast to the HHS the OHS is completed by the patient. Introduced by Dawson et al.[15] in 1996 it has rapidly gained popularity. It is a 12 point questionnaire assessing the hip over the last four weeks before completion. Its validity and reliability has been assessed in comparison to the SF-36, AIMS, and Charnley hip scores with excellent results[14,15,16,27]. The validity of doctor derived data is questionable because of potential inter-observer error, reporting bias and differences between perceptions of doctors and patients. Also the use of doctor derived data necessitates the use of out-patient services. Consequently there are likely benefits associated with the use of patient derived clinical evaluation data. Meghee et al.[26] focused on whether data obtained from the patient and doctor differed concluding that on the whole patient and doctor perceptions of symptoms and outcome was relatively similar. Pain was the commonest symptom "under-recognised" by the doctor. Age, type of assessor and the presence of co-morbidity (joint or health) significantly affected the extent of inter-rater agreement. However, in uncomplicated cases, overall agreement was good and the use of patient-completed questionnaires was advocated. Therefore, to balance the use of the HHS in this study, the OHS was also used.

8.14.5 Hospital for Special Surgery Knee score (HSS)

Developed at the Hospital for Special Surgery in 1976[23], this knee scale was one of the first to widely acknowledged as the gold standard knee score for assessing outcome after total knee arthroplasty. The modalities assessed are pain, function, range of movement, muscle strength, fixed deformity and instability. Maximum score is 90. The minimum score is zero (poor outcome). It is widely used and validated[10,21].

8.14.6 The Knee Society Score (KSS)

Developed later than the HSS[18,23], this outcome measure separates function and attributes a separate score to it. Pain, range of movement and stability comprise subtotal A. Subtotal B is derived from flexion contracture, extension lag and alignment. A "Knee" score (C) is then calculated by subtracting subtotal B from subtotal A. The "Function" score (F) is

derived by subtracting subtotal E (walking aids) from subtotal D (walking and stairs). The "Knee" and "Function" scores are quoted separately. Each maximum is 100 (the best outcome). As for the HSS, the KSS is objective and completed by the surgeon.

As well as the specific tests and outcome measures detailed above, other descriptive data were prospectively collected for each patient as follows: -

8.15 Intra-operative data

ASA grade, operation time, tourniquet pressure and time and presence of a patent foramen ovale (as outlined above) were recorded for each patient.

8.16 Post-operative data

Any complications and days to discharge were noted. At the six week follow up interval, neuropsychological tests, WOMAC and EuroQol were re-assessed. At the six month interval, neuropsychological tests, WOMAC, EuroQol, HHS, OHS, HSS and KSS were re-assessed. All orthopaedic outcome measures were carried out by the author except the OHS which is self-administered.

8.17 Neuropsychological and other Test Statistical Analysis

Data was assessed for parametric or non parametric conformity. The appropriate statistical test in each case was then used.

The primary outcome measure of the study was the standardised change (Z) score. Z scores were calculated for individual tests and to give a total Z score for each group using the standard deviation of the pre-operative group performance. Z score was calculated as $z = (X_2 - X_1) / \mu SD_1$, where X_1 is the pre-operative score and μSD_1 is the standard deviation of the pre-operative group scores. A higher post-operative score gives a positive Z score and a lower post-operative score gives a negative Z score. However, some of the tests are timed tests and a better performance is reflected in a lower time score. Therefore X_2 and X_1 are swapped for timed tests to ensure that positive Z scores consistently indicate improved performance. The t test was used for significant differences in Z score between groups. The previous conventional definition of a neuropsychological deficit is that a patient's post-operative score has dropped by one standard deviation or greater from their pre-operative score in two or more tests. As a secondary neuropsychological

outcome the incidence of deficits in each group using this definition measure were calculated. Comparison of the proportion of patients with deficit in each group was performed using χ^2 test. Comparison of the performance of the groups on any one test was determined using the Mann Whitney U test.

Difference in microemboli counts between groups were analysed using the Mann Whitney and χ^2 tests.

Pearson and Spearman correlation coefficients were used for the analysis of pre-operative and six week WOMAC scores.

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Chapter 9

Results

9.1 Recruitment

One hundred and sixty-six patients initially consented to take part in the study over 24 months between January 2002 and December 2003.

Seven patients received hip resurfacing. They were initially recruited as the possibility of receiving total hip arthroplasty (THA) existed pre-operatively; an intra-operative decision was made that resurfacing would be suitable and in the best interests of the patients. These patients were then excluded from the study.

Seventy-four patients underwent THA and 85 underwent total knee replacement (TKA). Ninety-five of these patients received pre-operative neuropsychological testing; forty-five patients underwent THA and 50 patients underwent TKA.

Table 9.1 Summary of groups and tests completed (total number of patients)

Tests completed	NP Group (95)	Non-NP Group (64)
NP Testing	Y	N
Quality Of Life measures	Y	Y
Orthopaedic Outcome	Y	Y

These 95 patients constitute the neuropsychology (**NP**) group. The remaining 64 patients (**non-NP group**) contributed to the data to by completing orthopaedic outcome and Quality of Life measures, but did not attempt the neuropsychological tests (see appendix 3 for summary of whole results (NP + Non-NP) and comparison of relevant data between the groups).

For this thesis only the results from the NP group will be presented.

9.2 Removal from study before or during surgery or adverse outcome

Two patients were withdrawn from the study (NP group) at the time of the first neuropsychological assessment due to inability to complete the tests, such that a meaningful score could not be obtained and 11 patients did not attend either of the follow-up neuropsychology assessments. However all but one of these patients continued to be followed-up for outcome data, successfully. One patient was medically unfit to be retested at the first post-operative interval and 3 patients died post-operatively. Therefore,

meaningful neuropsychology and outcome data was collected from 78 patients in the NP group.

From the remaining patients (non-NP group) one patient died. The baseline pre-operative and intra-operative data for the 4 patients who died and the one medically unfit patient remains in the data set, as the causes of death were unrelated to the variables analysed in this study and do not have direct effect or influence the data in any way.

Table 9.2 Summary of reasons for not returning for follow up neuropsychological assessment

Reason for not returning for follow-up	No of Patients
Death	3
Medically unfit to return for NP testing	1
Unwilling to return for NP testing	11
Withdrawn from NP testing	2

9.3 Patient Characteristics

There were no differences in the demographic and clinical characteristics between the THA and TKA groups.

Table 9.3 Demographic data for all patients and separate groups

	ALL (95)	THA (45)	TKA (50)	P value
Age (years)	71.1 (8.5)	69.9 (9.6)	72.2 (7.3)	0.20
Sex (% m:f)	37:63	31:69	42:58	0.27
Race(%cauc:black:asian)	95:2:3	100:0:0	90:4:6	0.09
Arthritis (% OA:RA)	97:3	100:0	94:6	0.10

Numeric data are expressed as means with standard deviation in brackets. There were no statistical differences found between groups using the χ^2 tests for categorical data and independent t test for continuous data.

The average age of the patients, the predominance of female patients and osteoarthritis are all typical of the UK population undergoing arthroplasty surgery (The National Joint Registry for England & Wales. 1st Annual report September 2004).

9.4 Pre –operative Neuropsychological Tests

All ninety-five patients attempted baseline pre-operative neuropsychological testing. Table 9.4 details the results (including the number of patients that were able to give meaningful results for each test).

Table 9.4 Mean (SD) pre-operative neuropsychological test scores (raw) for all patients and each group

	ALL	THA	TKA	P value
Choice Reaction Time Test (secs)*	0.61 (0.19)	0.63 (0.22)	0.59 (0.16)	0.39
Grooved Peg Board Test D (secs)#	89.23 (25.60)	86.39 (25.48)	91.83(25.73)	0.32
Grooved Peg Board Test ND (secs)#	95.76 (29.48)	92.84 (24.51)	98.50 (33.51)	0.36
Letter Cancellation Test (secs)#	86.67 (20.84)	85.18 (21.61)	88.11 (20.21)	0.50
Non-verbal Memory Test (secs)ɜ	79.39 (21.81)	80.22 (19.19)	78.59 (24.24)	0.72
Rey Auditory Verbal Learning Test 1-5α	39.41 (9.94)	40.56 (10.59)	38.26 (9.23)	0.14
Rey Auditory Verbal Learning Test 7-5¶	-1.80 (2.24)	-1.44 (2.35)	-2.16 (2.08)	0.29
Symbol Digit Replacement Test (secs)#	207.74 (80.10)	208.35 (97.51)	207.15 (60.02)	0.94
Trail Making Test A (secs)#	43.58 (12.48)	42.47 (13.66)	44.67 (11.24)	0.40
Trail Making Test B (secs)#	99.78 (38.71)	97.07 (42.60)	102.56 (34.56)	0.51
New Adult Reading Test μ	31.51 (11.60)	33.40 (11.43)	29.42 (11.58)	0.13
Speilberger Anxiety State μ	9.98 (3.95)	10.47 (4.42)	9.49 (3.39)	0.24
Speilberger Anxiety Trait μ	34.64 (8.77)	35.75 (8.60)	33.52 (8.89)	0.24
CSED Depression score μ	11.80 (8.98)	13.38 (9.10)	10.18 (8.66)	0.09

*mean response time #time to completion ɜtotal answer time α total number of words recalled in 5 trials (max 75) ¶change in total number of words recalled between trial 5 and 7 μ score on measure D dominant ND non-dominant

There were no significant differences using the independent t test in pre-operative neuropsychological scores between the THA and TKA groups. The two groups were therefore well matched in terms of pre-operative neuropsychological performance.

9.5 Pre-operative Orthopaedic and Quality of Life Scores

The pre-operative scores for all patients and for each group are shown in the tables below. The EuroQol and WOMAC scores are shown in a separate table as these measures are not operation dependent. Thus the whole group may be analysed with regard to these scores and meaningful conclusions may be drawn. The rationale for using the scores is discussed in the previous chapter.

Table 9.5 Mean (SD) pre-operative EuroQol and WOMAC scores for all patients and each group

SCORE (min-max)	ALL	THA	TKA	P value
EuroQol (0-10)	0.469 (0.268)	0.450 (0.290)	0.486 (0.248)	0.54
WOMAC (0-96)	46.9 (12.6)	48.4 (13.4)	46.9 (11.9)	0.66

No significant difference was found between the THA and TKA groups at baseline regarding Quality of Life and Osteoarthritis indices, using a two-tailed independent t test.
NB: For the WOMAC score, "0" is the best score, reflecting low disability and pain.
For the EuroQol score, 1.000 is the best result.

Table 9.6 Mean (SD) pre-operative hip scores for all patients in the THA group

SCORE (min-max)	THA (45)
Harris Hip Score (0-100)	52.2 (12.6)
Oxford Hip Score (12-60)	39.2 (6.7)

NB: For the Oxford Hip Score, "12" is the best score i.e. the disability caused by the hip is low.
The Harris Hip Score results can be stratified as excellent (90-100), good (80-89), fair (70-79) and poor (less than 70).
64.4% of patients were Trendelenburg positive, 26.7% level and 4.4% negative.

Table 9.7 Mean (SD) pre-operative knee scores for all patient in the TKA group

SCORE (min-max)	TKA (50)
Knee Society Score – Function (-50-100)	54.7 (13.4)
Knee Society Score – Knee (-20-100)	54.3 (14.2)
Hospital for Special Surgery Score (0-100)	60.8 (10.2)

For all scores, low disability is reflected by a high score.

All scores, for both groups, adequately reflect disability, pain, function and quality of life for patients about to undergo arthroplasty surgery. For those scores where a lower score indicates lower disability (WOMAC and Oxford Hip Score) the score for each patient will be reversed for statistical analysis.

9.6 Intra-operative data

Variables that can be analysed as a whole group (ie NP group) and can be compared between the THA and TKA groups are ASA and incidence of patent foramen ovale (PFO); no significant difference was found between the two groups.

Total emboli, operation time, operative side, discharge day and prostheses are analysed independently as they are operation type dependent (tables 9.8 & 9.9). Variables such as tourniquet time and tourniquet pressure are unique to TKA, but all are shown in the same table (table 9.12).

Table 9.8 ASA and PFO data for all patients and separate groups

	ALL (95)	THA (45)	TKA (50)	P value
ASA (%1:2:3)	10:70:20	16:67:17	6:72:22	0.31
PFO (%yes:no)	29:71	37:63	22:78	0.11

All figures are expressed as percentages. No statistical significance was found using the χ^2 test for both variables.

An overall prevalence of 29% for PFO was found. A larger number of patients were tested for PFO incidence, the results of which are discussed later in this chapter. ASA grade 2 was most prevalent in the study population. A greater number of patients had this data recorded also, which will be demonstrated later.

Table 9.9 Side of operation for both groups

	THA (45)	TKA (50)
Right	26	19
Left	19	31

Table 9.10 Types of prosthesis used for THA

	Number	Percentage
Hybrid (Spectron / Trilogy)	35	78
Fully cemented (Stanmore/ Stanmore)	4	9
Uncemented (Synergy / Reflection)	6	13

Table 9.11 Types of prosthesis used for TKA

	Number	Percentage
PFC	46	92
AMP	2	4
Genesis II	2	4

All TKA components are fully cemented.

The issues surrounding selection of prosthesis type and fixation method has been discussed extensively in previous sections.

It is pertinent at this point to mention a particular patient (H23) in the THA group who demonstrated significantly larger number of total microemboli than other patients in either group. She underwent a hybrid total hip arthroplasty. Because of this apparent anomalous result, data which might have an influence on, or be influenced by the total microemboli count, will be analysed including and excluding the patient from the THA group. The total emboli count for the outlier was 438 (figure 9.1). The total microemboli range for the THA group is 0 – 483 including the outlier and 0 – 81 excluding the outlier (cf. TKA 0-57). This alters the mean microemboli count from 13.2 including the outlier, to 2.8 excluding the outlier. **However as the table 9.12 below shows, there is no statistical significance between the THA and TKA groups in terms of microemboli whether the outlier is included or not.**

Fugure 9.2 shows the distribution of total microemboli counts in the THA group excluding H23, graphically representing the aforementioned range.

Figure 9.1 Scatter plot showing total microemboli for each patient in THA group

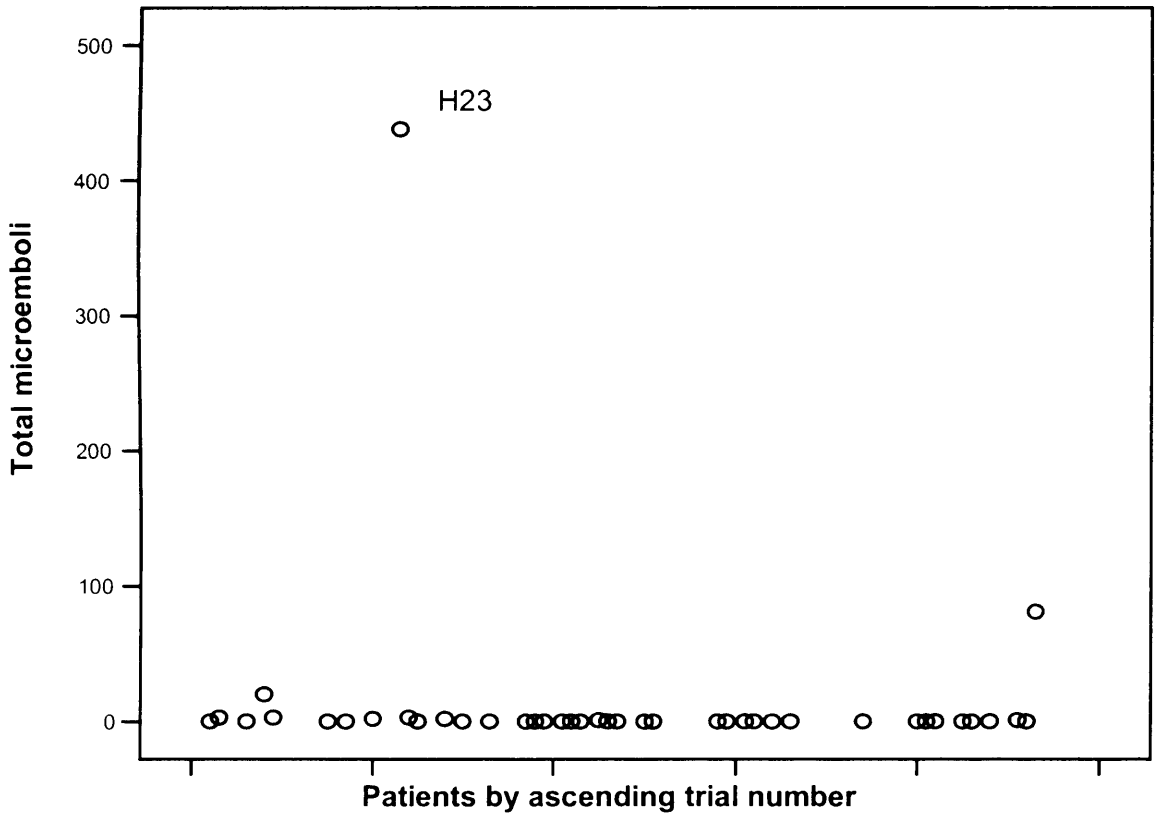


Figure 9.2 Scatter plot showing total microemboli for each patient in THA group excluding H23

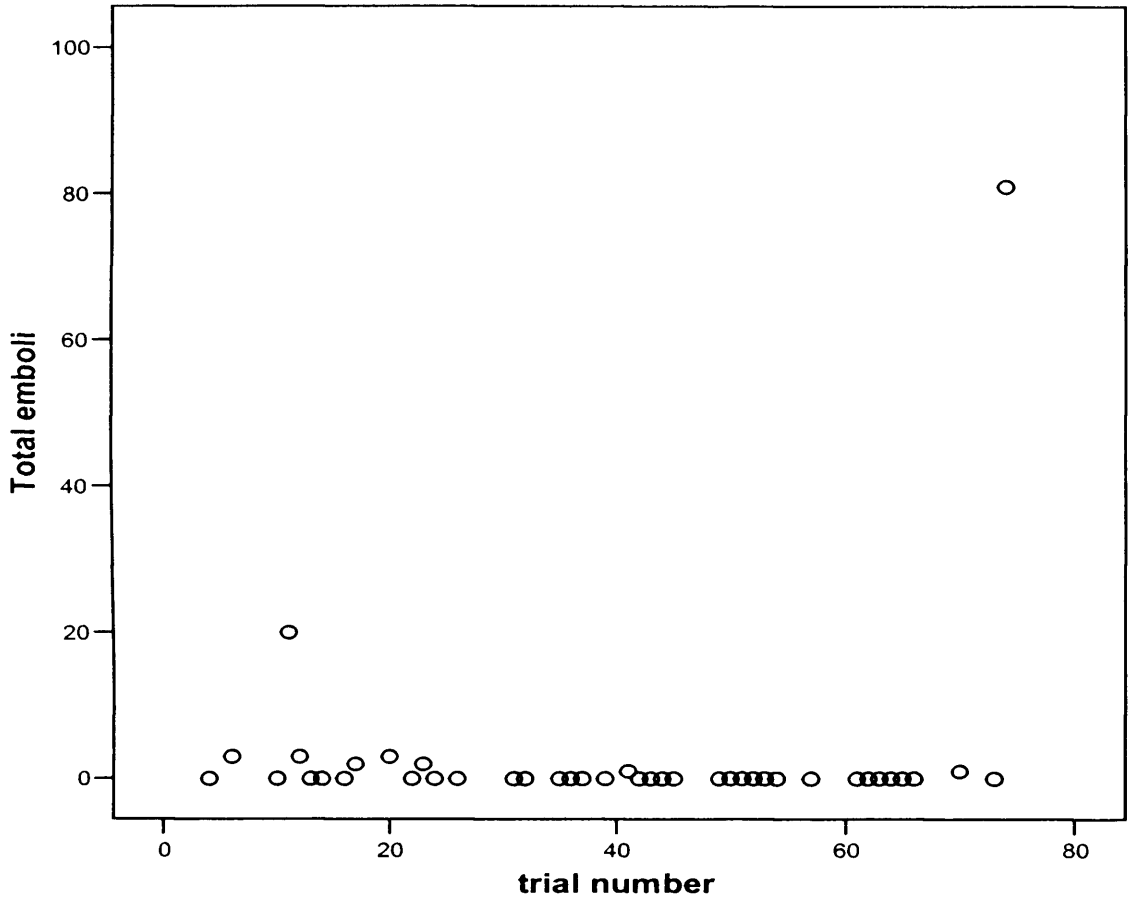


Table 9.12 Mean (SD) intra-operative variables for patients in each group including discharge day

	THA (45)	TKA (50)	p value	p value excl. outlier
Op Time (min)	102.2 (17.0)	93.4 (15.3)	**0.01**	**0.01**
Microemboli	13.2 (68.3)	3.76 (9.8)	0.39	0.70
Tourniquet Time (min)		78.5 (19.4)		
Tourniquet Pressure (mmHg)		269 (17.6)		
Discharge Day	9.6 (4.2)	9.6 (6.4)	0.98	0.93

Significant results are shown in bold.
Operative time was significantly different between the groups using a two-tailed independent t test; this is not an unusual finding as THA is a longer operation than TKA. The two-tailed independent t test was used to compare the other variables between groups also.

9.7 Days to Discharge

The median day to discharge was day 8 for both groups; range = 5-29 for the THA group; range = 3-31 for the TKA group.

The independent t test was performed to test for a significant difference in days to discharge between THA and TKA groups: p=0.98; therefore there was no significant difference in day to discharge.

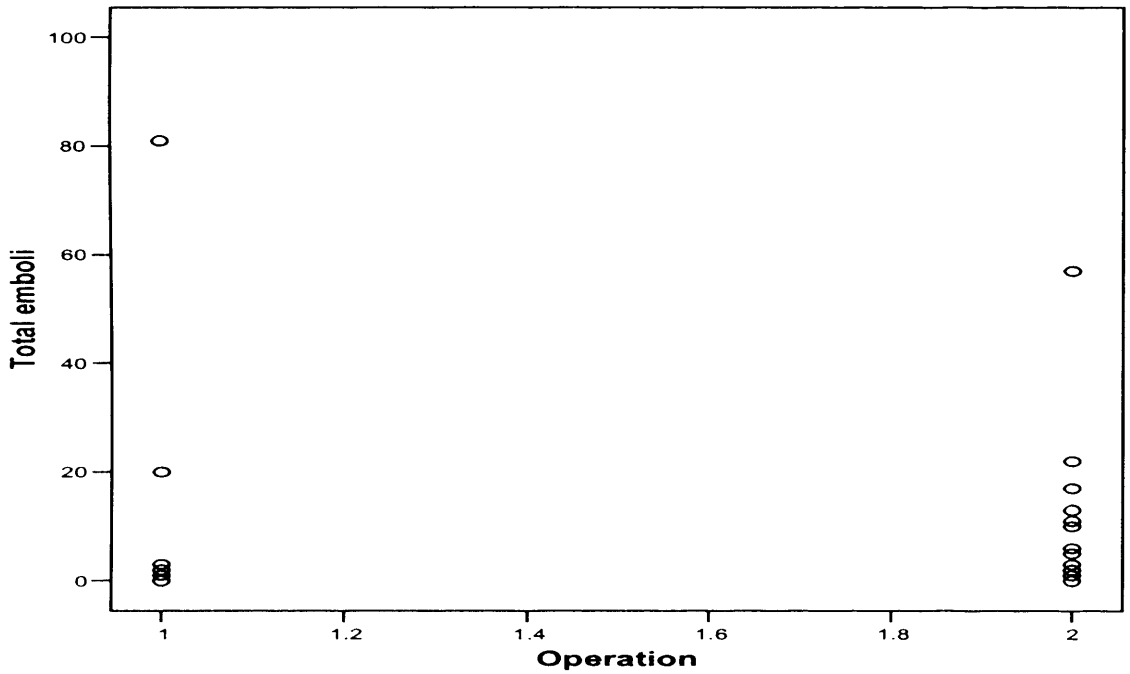
9.8 Transcranial Doppler and Microemboli Data

Eighty-four out of 95 patients (forty-two in each group) received successful intra-operative TCD monitoring and video recording. In the case of TKA, twenty-one patients had the right cerebral artery monitored and twenty-one patients the left. This was deliberately even. In the case of THA, the side of cerebral artery monitoring was dependent on the side being operated on. The patient was placed in a lateral decubitus position and consequently both sides of the skull cannot be accessed. Hence if a right total hip replacement was performed, the right cerebral artery was monitored. Thus, twenty-five right and sixteen left sides were used for obtaining a TCD trace during THA. Data from the eleven unsuccessful patients was not obtained either due to inability to find a suitable transcranial window (four), malfunction of the TCD machine (two) and video recorder (one) or the probe was irretrievably dislodged (four).

Eighty-four video tapes were then reviewed off-line. Microembolic events were counted and surgical steps were recorded as time periods, as described in Materials and Methods.

The data will be presented separately wherever appropriate as there is no surgical relationship between THA and TKA.

Figure 9.3 Scatter gram showing range of total microemboli for each operation. 1 = THA, 2 = TKA. Outlier H23 excluded.



9.8.1 THA

Table 9.13 details the mean time for each surgical step and the mean number of emboli generated by that surgical activity. It is clear that femoral component insertion (and the cement setting time, if used) generated the most emboli on average. The period termed "other time" constitutes time between surgical stages and time from joint relocation to skin closure. It is evident that a significant proportion of microemboli were detected during this collective period. However, no obvious pattern was elicited when analysing the TCD recordings for these microembolic signals; that is to say clusters of microemboli were not noticed between the same surgical steps.

Table 9.13 Mean (SD) time for each surgical stage and mean emboli load generated during each stage

	Time (mins/secs)	Microemboli	Microemboli excl. outlier
Femoral Osteotomy	0.48 (0.59)	0 (0)	0 (0)
Acetabular reaming	6.49 (3.46)	0.1 (0.7)	0.03 (0.2)
Acetabular component impaction	4.01 (5.53)	0.5 (2.5)	0.13 (0.8)
Femoral canal reaming	10.22 (9.00)	0.9 (5.3)	0.03 (0.2)
Femoral component impaction	6.09 (1.14)	6.6 (39.5)	0.31 (1.2)
Joint relocation	0.52 (1.57)	0.2 (0.9)	0.11 (0.5)
Other time	72.24 (14.41)	5.8 (24.1)	2.5 (11.9)

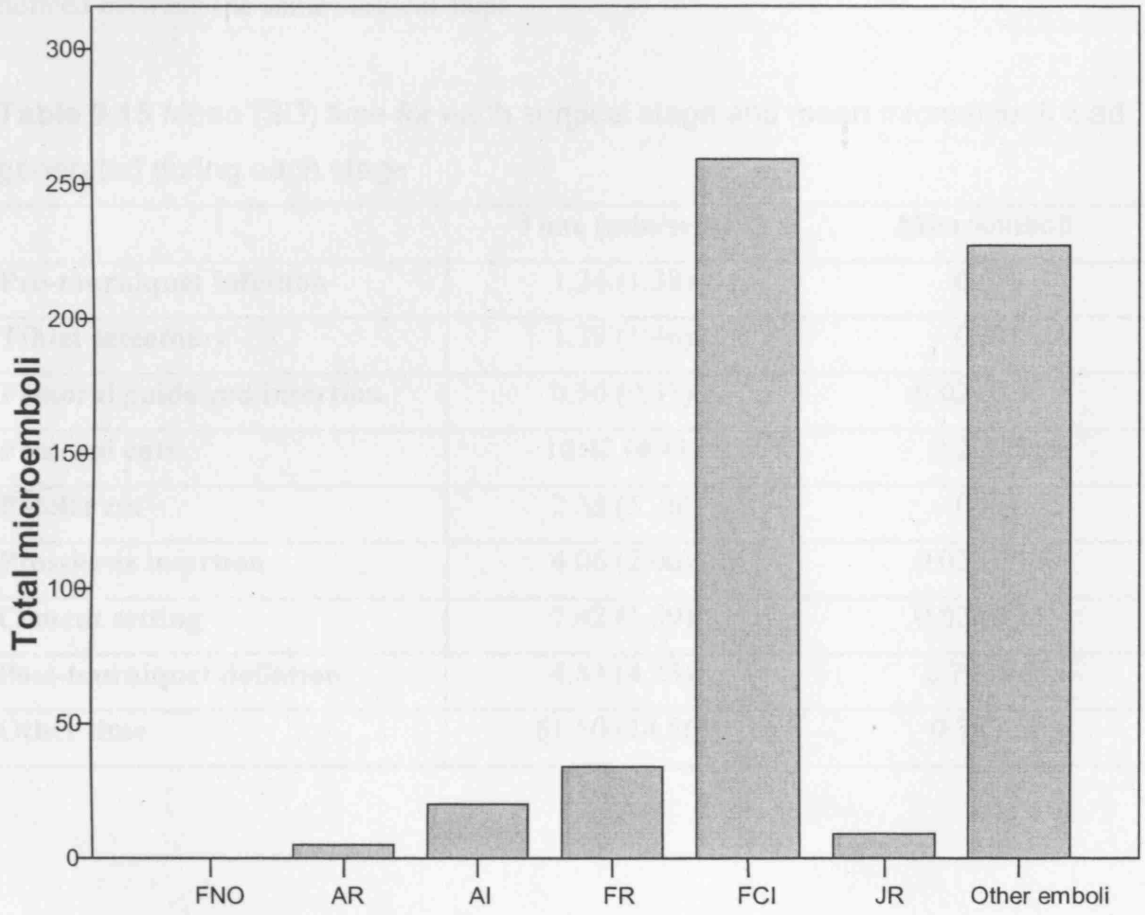
Mean time for each surgical stage is very similar when excluding the outlier, hence not shown.

Table 9.14 Total microemboli generated during each surgical stage

	Total Microemboli	Total Microemboli excl. outlier
Femoral Osteotomy	0	0
Acetabular reaming	5	1
Acetabular component impaction	20	5
Femoral canal reaming	34	1
Femoral component impaction	259	12
Joint relocation	9	4
Other time	227	93

The table 9.14 shows the total number of microemboli detected during each surgical step for all patients in the THA group. The numbers are very low for all steps except during femoral component impaction and other time i.e. time between stages and time after last surgical step to closure (figure 9.4).

Figure 9.4 Total microemboli load for each surgical stage during THA



FNO = femoral neck osteotomy, AR = acetabular reaming, AI = acetabular component impaction, FR = femoral reaming, FCI = femoral component insertion, JR = joint relocation

9.8.2 TKA

Table 9.15 details the mean time for each surgical step and the mean number of emboli generated by that surgical activity. It is clear that the time after the tourniquet was deflated generated the most emboli on average. The period termed "other time" constitutes time between surgical stages and time from joint relocation to skin closure. Again, it is evident that a significant proportion of microemboli were detected during this collective period. However, no obvious pattern was elicited when analysing the TCD recordings for these microembolic signals; that is to say clusters of microemboli were not noticed between the same surgical steps.

Table 9.15 Mean (SD) time for each surgical stage and mean microemboli load generated during each stage

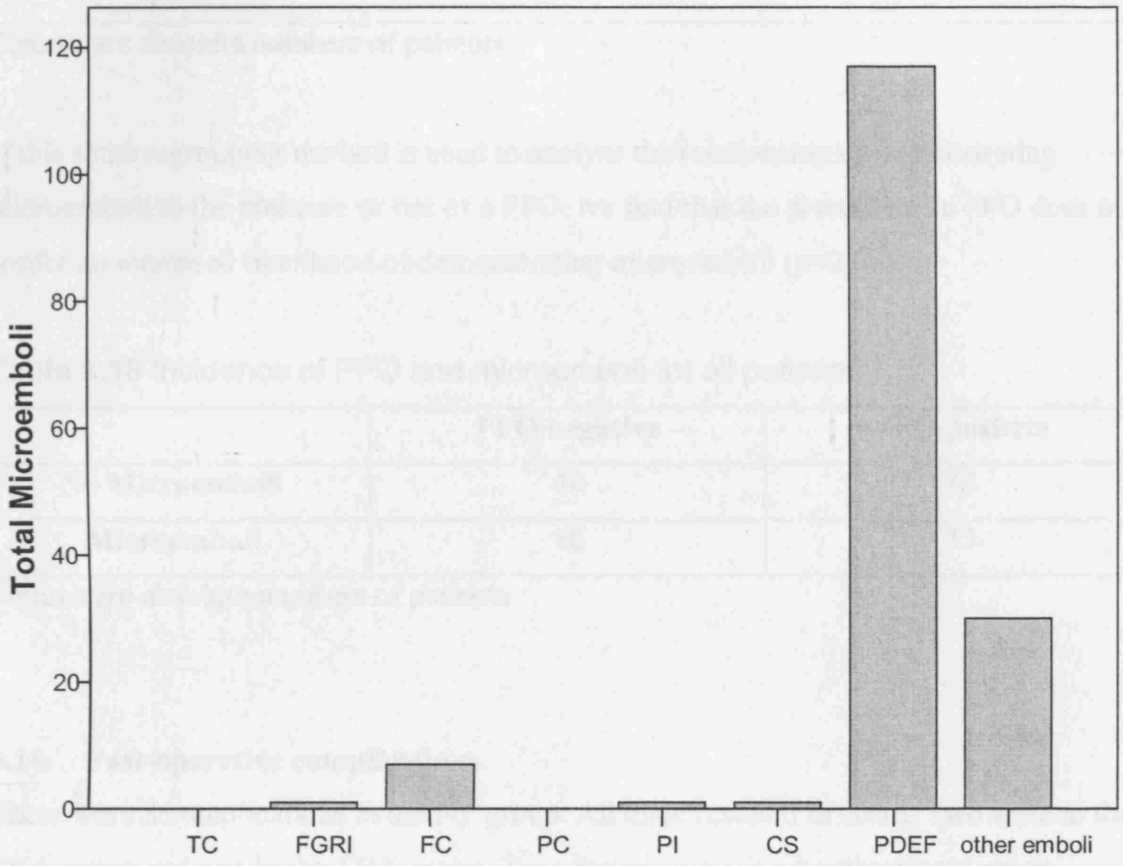
	Time (min/secs)	Microemboli
Pre-tourniquet inflation	1.24 (1.38)	0 (0)
Tibial osteotomy	1.39 (1.46)	0 (0)
Femoral guide rod insertion	0.56 (0.37)	0.02 (0.15)
Femoral cuts	10.42 (4.41)	0.2 (0.7)
Patella cut	2.33 (5.26)	0 (0)
Prosthesis insertion	4.06 (2.00)	0.02 (0.15)
Cement setting	7.42 (1.59)	0.02 (0.15)
Post-tourniquet deflation	4.83 (4.23)	2.79 (9.2)
Other time	61.50 (14.56)	0.7 (2.5)

Table 9.16 Total microemboli generated during each surgical stage

	Total Microemboli
Pre-tourniquet inflation	0
Tibial osteotomy	0
Femoral guide rod insertion	1
Femoral cuts	7
Patella cut	0
Prosthesis insertion	1
Cement setting	1
Post-tourniquet deflation	117
Other time	30

The table 9.16 above clearly shows most microemboli were detected after the tourniquet was deflated. Note the low number of emboli associated with femoral guide rod insertion. The total number of microemboli detected for all the patients in the TKA group during the other surgical steps was low in comparison.

Figure 9.5 Total microemboli load for each surgical stage during TKA



TC = tibial cut, FGRI = femoral guide rod insertion, FC, femoral cuts, PC = patella cut, PI = prosthseses insertion, CS = cement setting, PDEF = post tourniquet deflation

9.9 Incidence of microemboli

The median microemboli count overall is zero. Thus, if the population is regrouped into those with no microemboli (total microemboli= zero) and those with microemboli (total microemboli > 0), then further analysis by Chi Squared tests reveals that in our study population, patients were more likely **not** to demonstrate microemboli during THA compared to TKA. This was a significant result (p=0.046). However, this result must be treated with caution as the numbers for analysis are low.

Table 9.17 Incidence of microemboli in for THA and TKA

	No Microemboli	Microemboli
THA	32	10
TKA	23	19

Figures are absolute numbers of patients

If this same regrouping method is used to analyse the relationship of demonstrating microemboli to the presence or not of a PFO, we find that the presence of a PFO does not confer an increased likelihood of demonstrating microemboli (p=0.06).

Table 9.18 Incidence of PFO and microemboli for all patients

	PFO negative	PFO positive
No Microemboli	40	13
Microemboli	16	13

Figures are absolute numbers of patients

9.10 Post-operative complications

There were 3 complications in the NP group. All three resulted in death. Two were in the TKA group and one in the THA group. Two deaths, one in each arthroplasty group, occurred more than 12 weeks post-operatively, due to unrelated causes. The remaining death occurred on the 12th post-operative day due to septicaemic shock assumed to be secondary to necrotising fascitis noted on the 7th post-operative day.

9.11 Post-operative Orthopaedic and Quality of Life Scores

The 6 week mean post-operative Quality of Life scores for all patients and for each group are shown in table 9.19 below. Orthopaedic scores were not collected at this stage as explained in the methods section.

Table 9.19 6 week mean (SD) post-operative EuroQol and WOMAC scores for all patients and each group

SCORE (min-max)	ALL	THA	TKA	P value
EuroQol (0-10)	0.738 (0.249)	0.710 (0.236)	0.764 (0.261)	0.15
WOMAC (0-96)	27.3 (14.8)	29.0 (14.5)	25.7 (15.2)	0.30

No significant difference was found between the THA and TKA groups at 6 weeks post-operative regarding Quality of Life and Osteoarthritis indices, using a two-tailed independent t test.
NB: For the WOMAC score, "0" is the best score, reflecting low disability and pain. For the EuroQol score, 1.000 is the best result.

The 6 month mean post-operative Quality of Life and Orthopaedic scores for all patients and for each group are shown in tables 9.20, 9.21 and 9.22 below.

Table 9.20 6 month mean (SD) post-operative EuroQol and WOMAC scores for all patients and each group

SCORE (min-max)	ALL	THA	TKA	P value
EuroQol (0-10)	0.914 (0.184)	0.900 (0.171)	0.927 (0.196)	0.74
WOMAC (0-96)	15.6 (13.1)	14.9 (12.8)	16.2 (13.5)	0.63

No significant difference was found between the THA and TKA groups at 6 month post-operative regarding Quality of Life and Osteoarthritis indices, using a two-tailed independent t test.
NB: For the WOMAC score, "0" is the best score, reflecting low disability and pain. For the EuroQol score, 1.000 is the best result.

Table 9.21 6 month mean (SD) post-operative Hip scores for all patients in the THA group

SCORE (min-max)	THA (45)
Harris Hip Score (0-100)	81.8 (12.6)
Oxford Hip Score (12-60)	23.4 (8.9)

NB: For the Oxford Hip Score, "12" is the best score i.e. the disability caused by the hip is low.
The Harris Hip Score results can be stratified as excellent (90-100), good (80-89), fair (70-79) and poor (less than 70).
6.7% of patients were Trendelenburg positive, 46.7% level and 37.8% negative.

Table 9.22 6 month mean (SD) post-operative Knee scores for all patients in the TKA group

SCORE (min-max)	TKA (50)
Knee Society Score – Function (-50-100)	69.3 (14.5)
Knee Society Score – Knee (-20-100)	87.2 (10.7)
Hospital for Special Surgery Score (0-100)	80.6 (9.1)

For all scores, low disability is reflected by a high score.

All scores reflect a good orthopaedic and Quality of Life outcome at 6 weeks and 6 months. Pain and function is markedly improved, even at the six week interval, evidenced by the WOMAC scores. At six months, the orthopaedic outcome can be realistically interpreted as most surgeons agree that the benefits of arthroplasty surgery are not realised until this interval and for some individuals, even later. The orthopaedic scores for both TKA and THA represent a good outcome overall. Moreover, all scores show improvement between intervals.

9.12 Post-operative neuropsychological tests

Table 9.23 Six week mean (SD) post-operative neuropsychological test scores (raw) for all patients and each group

	ALL	THA	TKA
Choice Reaction Time Test (secs)*	0.59 (0.16)	0.57 (0.15)	0.60 (0.16)
Grooved Peg Board Test D (secs)#	87.21 (23.50)	84.26 (18.75)	90.08 (27.30)
Grooved Peg Board Test ND (secs)#	98.76 (27.61)	97.94 (28.70)	99.60 (26.84)
Letter Cancellation Test (secs)#	88.94 (21.70)	86.40 (22.54)	91.35 (20.88)
Non-verbal Memory Test (secs)ɜ	79.97 (22.29)	82.35 (23.13)	77.66 (21.50)
Rey Auditory Verbal Learning Test 1-5α	41.68 (10.19)	43.31 (10.52)	39.93 (9.69)
Rey Auditory Verbal Learning Test 7-5¶	-2.27 (1.78)	-2.14 (1.77)	-2.41 (1.81)
Symbol Digit Replacement Test (secs)#	184.24 (52.72)	172.31 (44.70)	195.85 (57.77)
Trail Making Test A (secs)#	36.68 (12.28)	36.36 (11.18)	40.95 (13.01)
Trail Making Test B (secs)#	83.71 (28.93)	77.13 (27.04)	90.09 (29.68)
New Adult Reading Test μ			
Speilberger Anxiety State μ	8.43 (3.23)	8.86 (2.90)	8.00 (3.52)
CSED Depression score μ	10.46(9.21)	11.80 (9.95)	9.17 (8.37)

*mean response time #time to completion ɜtotal answer time α total number of words recalled in 5 trials (max 75) ¶change in total number of words recalled between trial 5 and 7 μ score on measure D dominant ND non-dominant

Table 9.24 Six week post-operative mean Z scores for all patients and each group

	ALL	THA	TKA	P value
Choice reaction Time test	0.05	0.14	-0.03	0.38
Grooved Pegboard Test D	0.08	0.02	0.13	0.55
Grooved Pegboard Test ND	-0.09	-0.22	0.03	0.17
Letter Cancellation Test	-0.11	-0.11	-0.10	0.98
Non-verbal Memory Test	-0.03	-0.11	0.53	0.33
Rey Auditory Verbal Learning Test 7-5	-0.19	-0.28	-0.09	0.79
Rey Auditory Verbal Learning Test 1-5	0.15	0.17	0.13	0.46
Symbol Digit Replacement Test	0.16	0.19	0.13	0.53
Trail Making Test A	0.38	0.37	0.39	0.92
Trail Making Test B	0.17	0.12	0.22	0.44
Total Z score	**0.52**	**0.27**	**0.78**	**0.41**

There was no significant difference in the total Z change scores at six weeks post-operatively between the THA group and the TKA group ($p = 0.41$).

The difference between the two groups was analysed using the independent 2 tailed t test.

Figure 9.6 Mean Z change scores for all neuropsychological tests at six weeks post surgery in both groups.

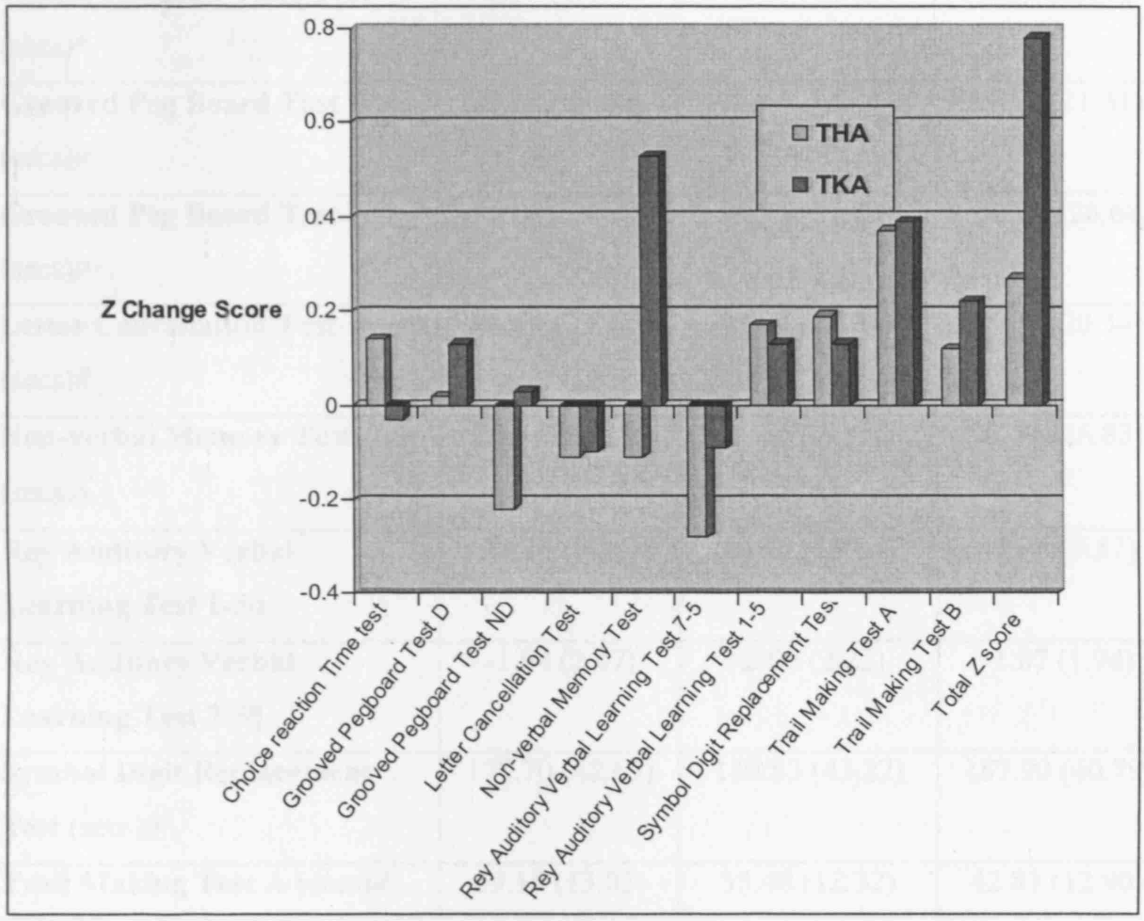


Figure 9.6 illustrates there was an overall trend towards improvement in both groups on most of the neuropsychological tests. The Z scores for both groups were negative (worse performance than baseline) at six weeks in the letter cancellation test and the Rey auditory verbal learning test 7-5. The non-verbal memory test showed the largest disparity of Z score between the groups, but this was not statistically significant ($p = 0.33$).

Table 9.25 Six month mean (SD) post-operative neuropsychological test scores (raw) for all patients and each group

	ALL	THA	TKA
Choice Reaction Time Test (secs)*	0.59 (0.17)	0.61 (0.22)	0.55 (0.07)
Grooved Peg Board Test D (secs)#	83.62 (19.02)	77.65 (14.48)	89.58 (21.31)
Grooved Peg Board Test ND (secs)#	94.08 (24.81)	88.33 (21.83)	100.04 (26.68)
Letter Cancellation Test (secs)#	94.19 (21.71)	92.30 (23.23)	96.07 (20.34)
Non-verbal Memory Test (secs)ɜ	80.01 (24.27)	81.24 (21.87)	78.79 (26.83)
Rey Auditory Verbal Learning Test 1-5α	43.38 (9.30)	44.69 (10.64)	41.96 (7.57)
Rey Auditory Verbal Learning Test 7-5¶	-1.94 (2.07)	-2.00 (2.22)	-1.87 (1.94)
Symbol Digit Replacement Test (secs)#	178.70 (42.63)	169.83 (43.22)	187.90 (40.79)
Trail Making Test A (secs)#	39.15 (13.03)	35.48 (12.32)	42.81 (12.90)
Trail Making Test B (secs)#	87.90 (32.16)	78.08 (26.04)	97.32 (35.06)
New Adult Reading Test μ			
Speilberger Anxiety State μ	8.57 (2.69)	8.74 (2.74)	8.38 (2.67)
CSED Depression score μ	9.49 (7.80)	9.52 (7.07)	9.46 (8.63)

*mean response time #time to completion ɜtotal answer time α total number of words recalled in 5 trials (max 75) ¶change in total number of words recalled between trial 5 and 7 μ score on measure D dominant ND non-dominant

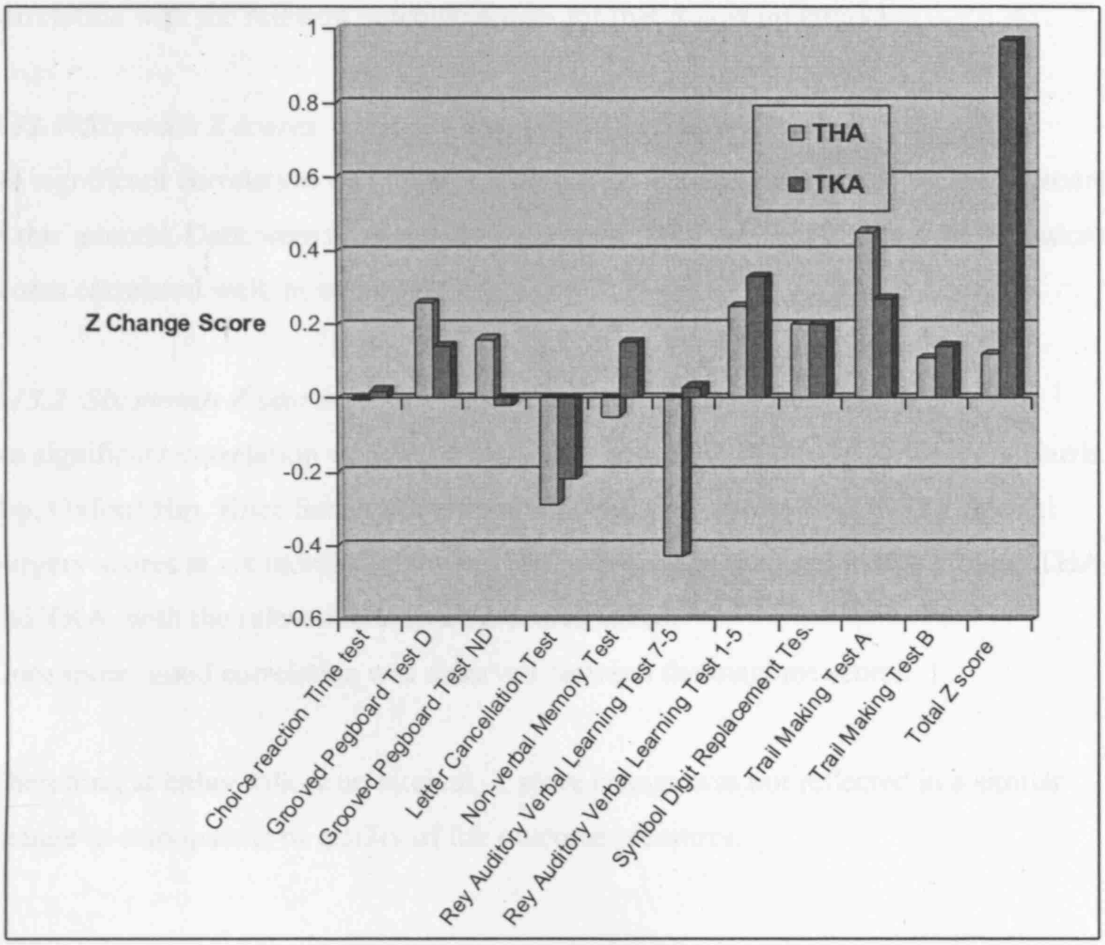
Table 9.26 Six month post-operative mean Z scores for all patients and each group

	ALL	THA	TKA	P value
Choice reaction Time test	0.01	-0.004	0.02	0.92
Grooved Pegboard Test D	0.20	0.26	0.14	0.43
Grooved Pegboard Test ND	0.07	0.16	-0.02	0.20
Letter Cancellation Test	-0.26	-0.29	-0.22	0.73
Non-verbal Memory Test	0.50	-0.05	0.15	0.47
Rey Auditory Verbal Learning Test 7-5	-0.21	-0.43	0.03	0.71
Rey Auditory Verbal Learning Test 1-5	0.29	0.25	0.33	0.24
Symbol Digit Replacement Test	0.20	0.20	0.20	0.99
Trail Making Test A	0.36	0.45	0.27	0.47
Trail Making Test B	0.12	0.11	0.14	0.85
Total Z score	**0.53**	**0.12**	**0.97**	**0.36**

There was no significant difference in the total Z change scores at six months post-operatively between the THA group and the TKA group ($p = 0.36$).

The difference between the two groups was analysed using the independent 2 tailed t test.

Figure 9.7 Mean Z change scores for all neuropsychological tests at six months post surgery in both groups.



At six months post surgery, the trend is still towards improvement in Z scores for most of the individual tests and overall (figure 9.7). Although the improvement overall in Z score seems vastly greater in the TKA group, this is not statistically significant as described above.

9.13 Correlation of Orthopaedic and Quality of Life outcome with Z scores

The Z scores at six weeks follow up and six month follow up were analysed for correlation with the relevant outcome scores for that follow up interval.

9.13.1 Six week Z scores

No significant correlation was found between Z scores and EuroQol or WOMAC scores at this interval. Data were analysed in two groups, THA and TKA. However the outcome scores correlated well, as one might expect.

9.13.2 Six month Z scores

No significant correlation was found between Z scores and EuroQol, WOMAC, Harris Hip, Oxford Hip, Knee Society (knee and function scores) and Hospital for Special Surgery scores at six months follow up. Data were again analysed in two groups, THA and TKA, with the relevant orthopaedic scores tested.
Once more, good correlation was observed between the outcome scores.

Therefore, at either follow up interval, Z score change was not reflected in a similar change in orthopaedic or quality of life outcome measures.

9.14 Deficit Scores

The Z change scores presented above represent the performance of each group collectively. Within each group, some patients will have shown a deficit on their NP tests at either of the two follow up intervals or at both. A deficit is defined as a decline by more than one standard deviation in two or more tests. The performance of these individuals is masked by the overall trend of the group.

9.14.1 Six week deficit scores

The incidence of deficit in the THA group was 7/45 (15.6%) and in the TKA group 5/50 (10%). It must be taken into account that there were patients that did not attend the six follow up NP tests in each group: six (13.3%) in the THA group and 15 (30%) in the TKA group. It is unknown whether these patients would have shown a deficit or not and thus weakens the statistical significance of the incidence of deficits.

Table 9.27 Incidence of deficits in THA and TKA groups at six weeks.

Deficit at 6 weeks	THA	TKA
Yes	7	5
No	32	30
Did not attend	6	15

Figures are absolute numbers of patients

The difference between the two groups did not reach statistical significance using the Chi Squared test. (p=0.13).

9.14.2 Six month deficit scores

The incidence of deficit in the THA group at six months was 3/45 (6.7%) and in the TKA group 4/50 (8%).

Table 9.28 Incidence of deficits in THA and TKA groups at six months.

Deficit at six months	THA	TKA
Yes	3	4
No	24	20
Did not attend	18	26

Figures are absolute numbers of patients

The difference between the two groups did not reach statistical significance using the Chi Squared test. (p=0.43).

9.15 Comparison of characteristics of patients who showed deficit and no deficit

Table 9.29 compares the characteristics of patients, who at either interval showed a deficit, with those that did not show a deficit. No distinction is made between THA and TKA and respective orthopaedic outcome scores are not considered as the numbers in these groups are small.

Table 9.29 Peri-operative comparison of characteristics of patients with and without deficit at six weeks and six month follow up.

	SIX WEEKS			SIX MONTHS		
	Deficit	No Deficit	P value	Deficit	No Deficit	P value
Age	74.3(8.2)	69.6(8.5)	0.08	73.3(5.4)	70.2(8.4)	0.4
Microemboli *	1.4(3.4)	11.8(59.5)	0.2	1.9(3.8)	12.8(69.1)	0.7
Days to Discharge	10.4(6.3)	9.7(5.5)	0.7	9.0(2.2)	10.7(6.8)	0.5
WOMAC	26.6(15.4)	25.9(14.3)	0.8	9.6(6.6)	16.1(15.9)	0.3
EuroQol	0.78(0.26)	0.75(0.23)	0.7	0.98(0.04)	0.89(0.24)	0.3

All figures are mean values (SD)
All p values are calculated using the independent t test.
* If microemboli counts are compared excluding H23 no significant difference is found again.

No significant differences were found between groups at either follow up interval.

Two further characteristics were analysed using Chi Squared tests – **ASA grade and PFO**.

Again no significant differences were found between patients who showed deficit and those patients without deficit, at either follow up interval.

Therefore, those who suffered deficits at six weeks or six months did not have significantly different peri-operative characteristics when compared with those who did not show any deficit at that follow up interval.

To analyse the deficits further, because patients were followed up over two intervals, it is possible to determine whether deficits, if they manifested at six weeks, persisted or improved. It is also possible to ascertain whether deficits were detected only at six months.

In the THA group, 2 patients showed deficits at six weeks which persisted at six months. One patient who showed deficit at six weeks, showed no deficit at six months. One patient did not show deficit at six weeks but did show deficit at six months.

In the TKA group, 2 patients showed deficits at six weeks which persisted at six months. One patient who showed deficit at six weeks did not show deficit at six months. Two patients did not show deficits at six weeks but did show deficits at six months.

A further 6 patients attended the six week follow up and showed deficits but did not attend the six month follow up (4 patients in the THA group and 2 patients in the TKA group).

9.16 Relationship of Microemboli to NP outcome

9.16.1 Six Weeks

A total of 61 patients received intra-operative TCD and then completed NP follow up at six weeks.

Thirty-one patients were in the THA group and 30 in the TKA group.

No Spearman's correlation was found between the total microemboli count during either procedure and the overall Z scores at six weeks. This held true even when H23 was excluded from the calculations (Table 9.30)

Table 9.30 Spearman's correlation for total microemboli count and six week total Z scores.

	R	P
ALL	0.09	0.50
THA	0.14	0.46
THA excl. H23	0.02	0.93
TKA	-0.06	0.74

9.16.2 Six Months

A total of 42 patients received intra-operative TCD and then completed NP follow up at six months.

Twenty-two patients were in the THA group and 20 in the TKA group.

Again, no Spearman's correlation was found between the total microemboli count during both types of arthroplasty and the overall Z scores at six months. H23 was excluded from the calculations as this patient did attend the six month follow up, but similar to the findings at six weeks post surgery, no correlation was determined (Table 9.31).

Table 9.31 Spearman's correlation for total microemboli count and six month total Z scores.

	R	P
ALL	0.07	0.68
THA	-0.12	0.60
THA excl H23	-0.14	0.51
TKA	0.21	0.37

9.17 Relationship of Microemboli to Patent Foramen Ovale

A total of 82 patients had a result from PFO testing and microemboli data available for analysis.

There were 41 patients in each of the arthroplasty groups.

No relationship was established between the presence of a PFO and a higher total microemboli count using an independent t test on each occasion (all patients p=0.18, THA p=0.23, TKA p=0.26)

Again exclusion of the outlier H23 did not alter the significance of the result overall (p=0.10) or for the THA (p=0.21) group.

9.18 Relationship of Microemboli to Age, Operation time and Days to Discharge

Table 9.32 Pearson's correlation for total microemboli and Age, Operation time and Days to Discharge for all patients, THA patients and TKA patients

	ALL		THA		TKA	
	R	**P**	**R**	**P**	**R**	**P**
Age	0.05	0.7	0.09	0.6	-0.12	0.5
Op Time	0.05	0.6	0.03	0.8	0.06	0.7
Day to Discharge	0.06	0.6	0.22	0.2	-0.13	0.4

No significant correlation was determined between total microemboli and the variables above.

9.19 Relationship of Microemboli to ASA grade

This correlation was determined using the Kruskal-Wallis statistical test. No significant correlation was found for all patients (χ^2= 0.37, p=0.8) or for THA (χ^2= 1.10, p=0.6) or TKA (χ^2= 0.23, p=0.9) patients alone.

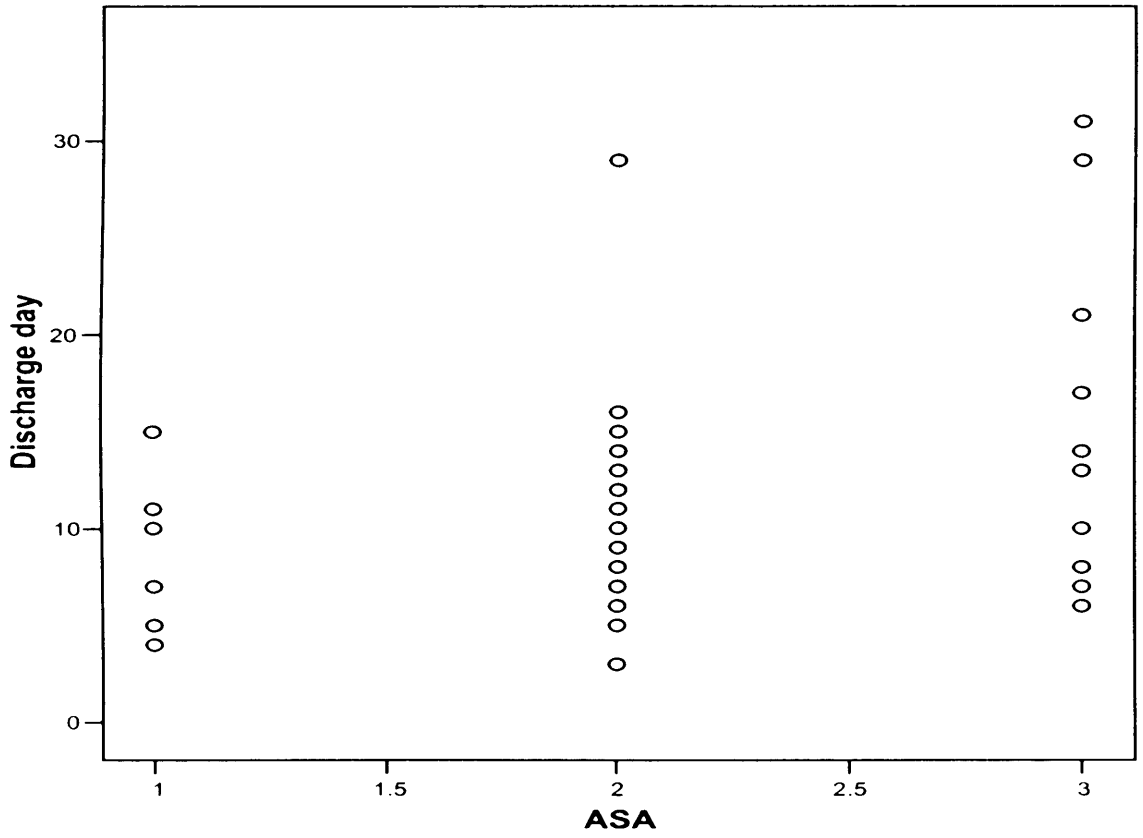
9.20 Relationship of Day to Discharge and Age

A significant correlation was found when analysing day to discharge and the age of the patient. It appears from our data that the older the patient the longer that patient stayed in hospital (R= 0.3, **P= 0.004**). This correlation was not apparent for the THA patients when analysed separately (R= 0.2, P= 0.1), but there was a significant correlation for the TKA patients (R=0.4, **P= 0.008**).

It follows that older patients stay in hospital longer after total joint arthroplasty; the reason may be a multi-factorial one. Increasing co-morbidity with age, slower recovery time and poorer pre-operative mobility may be some of the factors responsible.

These factors may manifest in ASA grading of the patient but the scatter gram below, figure 9.7, and statistical analysis shows no correlation exists (p=0.1).

Figure 9.8 Scatter gram showing the range of days to discharge for the three ASA grade groups.

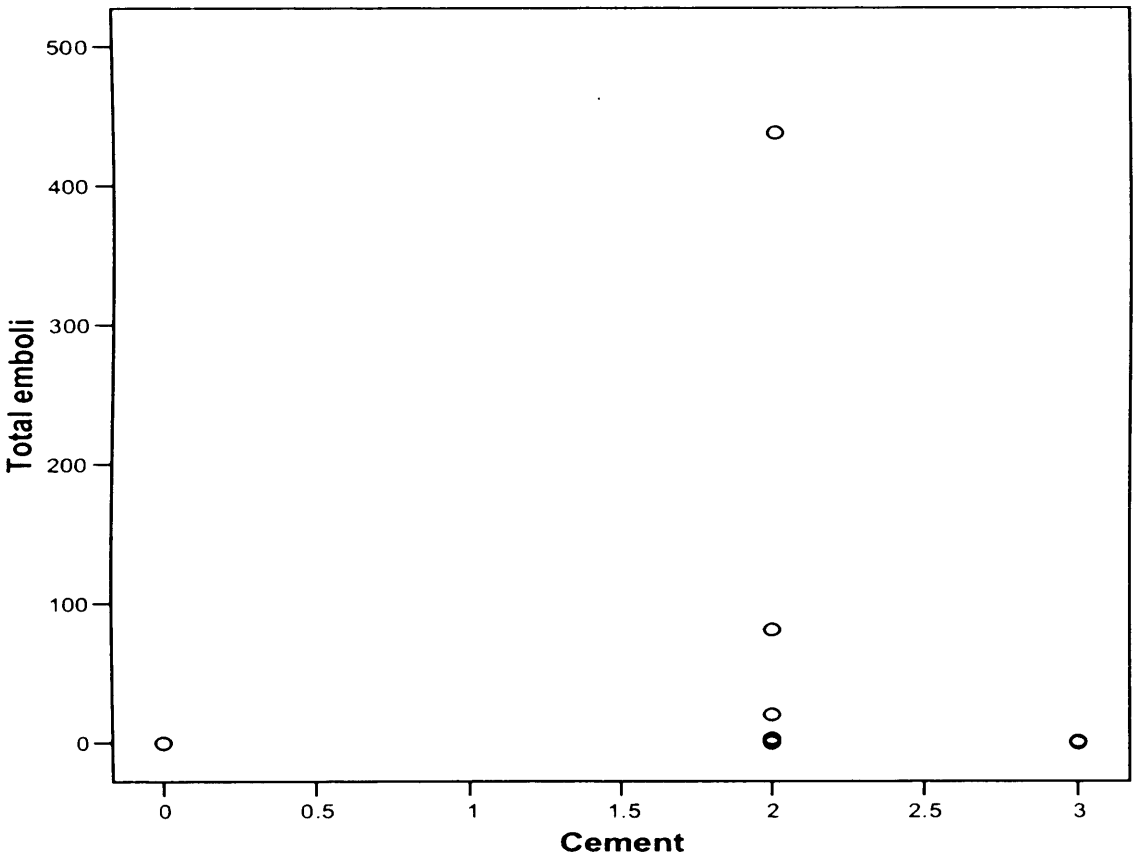


9.21 Relationship of the use of cement to microemboli in THA

Patients undergoing THA received prostheses using methods of fixations falling into three groups: uncemented, fully cemented and hybrid. Following evidence suggesting that polymethylmethacrylate may be responsible for a larger thrombogenic response and hence microembolic load, it is pertinent to analyse the THA patients in this study to assess whether a relationship exists between the use of cement and microemboli load.

The outlier H23 has been deliberately included in this analysis. Kruskal-Wallis analysis reveals that no significant correlation exists (p=0.3). Figure 9.8 depicts this in a scatter gram format.

Figure 9.9 Scatter gram showing relationship of the use of cement during THA and microemboli counts. 0=uncemented, 2= hybrid, 3= fully cemented.



Chapter 10

Discussion

10.1 Neuropsychological Outcome

The neuropsychological data in this study has been analysed in two distinct ways: Z change score analysis was the primary NP outcome and the conventional analysis of the incidence of deficit as the secondary outcome. Deficit was defined as greater than 1 standard deviation deterioration in 2 or more tests.

The most important finding of this study is that neuropsychological performance does not worsen as a consequence of arthroplasty surgery. Z change score analysis shows a trend towards improvement in most tests for both THA and TKA patients and no statistical significant difference in Z change scores between the two groups was detected. Analysis of deficits reveals a very low number of patients (4 patients, 2 in THA group and 2 in TKA group) demonstrated persisting deficit at 6 month follow up. A further 6 patients who showed deficit at 6 week follow up did not attend the 6 month assessment and therefore this number may be higher. However, no differences in patient characteristics or differences in relevant variables were found when these patients were compared to those who did not show deficit and thus little significance can be attributed to this finding.

Deficit analysis is arbitrary and has a binary cut off and is therefore less sensitive analysis than Z change score [3,39]. Hence, Z change score analysis is now an accepted method of analysis, particularly after cardiac surgery [3,5,18,33,34,35,37] used by researchers in both Europe and the United States. By using both methods, the difference in sensitivity between the two methods can be assessed; no study of this type exists in the field of orthopaedic surgery, but the use of both methods should enable comparison with future studies.

Mean Z change scores for each test showed improvement in both groups of patients at 6 weeks and 6 months follow up. Out of the battery of ten tests, at six weeks follow up, 7 tests for the THA group and 8 tests for the TKA group showed improvement of scores. This remained as 7 tests for the THA group and increased to 9 tests for the TKA group at six months follow up. Because this trend is almost across all tests in the battery, this suggests that this a real effect rather than a chance finding. The learning effect seems to

be demonstrated well as there is evidence that most patients improve between repeat assessments.

The incidence of deficits was low in this study and there could be several reasons to explain this. However, as no comparable study exists, this may be assumed as an expected result for arthroplasty surgery. Chapter 8 outlines potential factors that may play a role in influencing NP outcome and some aspects of study design may be a factor also (surgical technique, anaesthesia, analysis methods). This chapter also discusses conclusions drawn from several studies examining NP outcome in patients receiving either general or epidural anaesthesia during orthopaedic surgery. Nearly all these studies employed less rigorous NP testing and thus results from these studies must be treated with caution when comparing findings. Only one study by Hole et al.[15] made a significant finding: patients receiving general anaesthesia showed poorer NP outcome when compared to those receiving epidural anaesthesia for THA but the NP testing in this study was not robust. Only the study by Williams-Russo et al.[42] used good NP testing and no significant differences were seen when comparing the two methods of anaesthesia for TKA patients. Overall, 5% of patients showed a long term clinically significant deterioration in cognitive function, and although methods of anaesthesia were different, this may be the closest comparative result available. Although the null hypotheses for these studies were very different from this study, they are the closest in design to this study to date, and it is clear that further work is indicated using thorough NP testing.

The incidence of NP deficits found post-operatively may be influenced by the follow up rate. It has previously been found that those patients who perform less well on the pre-operative tests are less likely to attend for post-operative follow up [4]. Therefore unless 100% NP follow up is achieved there remains the possibility that selective attrition leads to an underestimate of the deficit rate in the study sample. Meaningful NP data was collected from 82% of the patients in this study. Many reasons apart from poor performance at the first visit could be responsible for not attending follow up including travel and the time taken for testing (one hour approximately), which may have been uncomfortable for a patient suffering from an arthritic joint or recovering from an arthroplasty.

More importantly, the powering of this study was based upon incidence of deficits found in the only existing model of this type of study. It certainly seems that the incidence of deficits is lower in orthopaedic surgery than in cardiac surgery [20,24,37,44] from the results of this study. This study is by definition underpowered but our view is that it is unlikely that a significant difference would be seen if numbers were higher.

In summary, using the two methods of analysis discussed, this study has found a low incidence of NP deficits. However, no similar studies are available for comparison. The loss to NP follow up may through selective attrition have led to an underestimation of the true incidence of deficits. The Z change score analysis shows an overall trend towards improvement post-operatively (continued improvement up to six months) but no significant difference between the two types of arthroplasty. Low patient numbers may be responsible for the low incidence of deficits.

10.2 Transcranial Doppler Data – Microemboli and Patent Foramen Ovale

This study has shown that intra-operative cerebral microembolisation recorded by transcranial Doppler does occur during primary total hip and knee arthroplasty, complementing findings in the small number of previous studies [12,31,36]. Many case reports exist suggesting brain embolisation as the cause of collapse, infarction or death following arthroplasty procedures, but these reports do not prove intra-operative embolisation; transcranial Doppler was not employed and in most cases MRI scans of the brain or post-mortem examinations suggested that fat emboli related changes seen were responsible for the outcomes reported [2,8,9,10,11,16,19,25,27,29,38,43]

Moreover, fewer implicate paradoxical embolism (patent foramen ovale) as a possible conduit for embolic material to reach the systemic circulation [8,10,11,29,38,43] but no study attempted to identify the presence of PFO in vivo using validated techniques. Again post mortem examination revealed the presence or absence of PFO in these studies. Of course, following the findings of Byrick's study in mongrel dogs hypothesising that transpulmonary passage of fat emboli was possible, PFO may not be the only route available for passage of microemboli into the systemic circulation [6]. However, this study did not find any correlation between the presence of PFO and increased incidence or higher load of cerebral microemboli using the independent t test. Patients who were PFO positive and negative demonstrated cerebral microembolisation irrespective of the type of arthroplasty performed. Furthermore, incidence of NP deficits was not related to the presence or absence of PFO using the Chi-squared test.

The overall prevalence of PFO in the study population was 29%, similar to the general population [14] with a slight non-significant preponderance in the THA group. This solidifies further the findings discussed above and suggests that PFO may not play a significant role in cerebral microembolisation during primary total hip and knee arthroplasty but once more, due to low patient numbers, results must be treated with caution. In addition, although no significant difference was found in the incidence of PFO between those who showed NP deficit and those who didn't, because 100% follow up was not achieved, the true NP deficit was not elicited in this study and thus the relationship of PFO and NP deficit is not clearly defined. To reiterate, it is possible that

those who did not return for follow up performed less well on the baseline NP testing, or six week tests and therefore this may mask the true relationship of NP outcome and PFO.

Returning to microemboli, the mean microemboli counts for each group were low when compared to those for cardiac surgery. The outlier in the THA group demonstrated significantly greater microemboli than any other patient (438) but this did not alter the significance between the groups. There are no patient characteristics, intra-operative events or other predisposing factors relating to this patient which may have influenced this result. The patients' individual NP performance showed improvement between the intervals (patient did not attend six month follow up) and this suggests that the relationship between microemboli and neuropsychological outcome is complex, as established by numerous studies in cardiac surgery: most pertinently, a study by Whitaker et al. investigating the effect of a leucocyte depleting filters on cerebral microemboli and NP outcome in CABG surgery [40]. They found a reduction in microemboli but no significant improvement in NP outcome; NP outcome showed a strong trend towards improvement but it was not statistically significant. They postulated that such filters may be neuroprotective but other mechanisms may play a role in cerebral injury during CABG surgery.

Microemboli counts showed no significant correlation with NP deficit in this study. When the outlier was excluded, the mean microemboli count was not significantly greater for those displaying deficits than for those patients that did not show deficits. Because of low numbers, this was not analysed for each type of arthroplasty. No correlation was found between total microemboli counts during each procedure and Z scores for patients in the THA and TKA groups. The analysis was performed including and excluding the outlier. This was true for the six week and six month follow up intervals. This further emphasises the complexity of the relationship between NP outcome and microemboli and that microemboli may not always be the most significant determinant of NP outcome. However, the incidence and load of cerebral microemboli was low and therefore any relationship between microemboli and NP outcome may have been masked by low patient numbers.

In relation to specific surgical steps for each type of arthroplasty and microemboli load recorded, one step for each procedure seemed to be associated with greater microembolic load to the brain.

During THA, impaction of the femoral component (with or without cement) was associated with the greatest mean microembolic load and during TKA, immediately after the tourniquet was deflated. In the THA group the total number of microemboli was high for this stage (259), but this was contributed to in the large part by the outlier; removing the contribution from the outlier, the total dropped to twelve, still greater than any other surgical step. This result correlates well with the mechanisms described in Chapter 1.8; impaction of the femoral component results in a dramatic increase in intramedullary pressure thereby forcing tissue thromboplastin into the veins with subsequent activation of clotting, cytokine and kinin cascades, progressing to emboli generation local and remote to the site of surgery. The decisive pathogenic factor is the increase in intramedullary pressure.

The total number of microemboli recorded after tourniquet deflation in the TKA group was 117. Again, this correlates well to mechanisms described in Chapter 2 and noted by other authors. Embolic showers have frequently been observed after tourniquet release, suggesting that pulmonary embolism and thromboembolism to other end organs may also occur at that time [7,21,26,28] and the findings from this study are no different. However, microemboli were also noticed during other stages and in between stages ("Other time") and this corroborates well with mechanisms postulated by Kato et al.[17] and Parmet et al. [28] that embolic material can flow proximal to the knee (i.e. to the heart) even when the tourniquet is inflated. However, the numbers noted in this study in relation to surgical activity while the tourniquet was inflated were lower than when it was deflated and in addition, the total number of microemboli recorded in between stages was lower, suggesting that the most cerebral microemboli occur immediately after the tourniquet is deflated.

As a tourniquet was used in all TKA cases we are unsure of the effect of duration of tourniquet inflation on emboli generation or load. A threshold of tourniquet duration may exist after which microembolic signals are seen more frequently. Moreover, it is possible that less emboli would have been recorded if no tourniquet had been used at all.

It is interesting to note the low numbers of microemboli associated with insertion of the femoral guide rod, which was fluted to aid in the egress of marrow elements in order to reduce further the intramedullary pressure and the likelihood of pulmonary shunting, as suggested occurs in other studies. [13,32]

With the surgical activity findings in mind, it may be pertinent to suggest that surgical techniques to reduce the increase of intramedullary pressure in the case of THA (such as the bone vacuum venting technique described by Pitto et al.[30]) and judicious use of the tourniquet, for example only when cementing the components during TKA, may minimise microemboli generation and subsequent passage into the circulation, thereby minimising complications and sequelae of microemboli in the end organs and optimising outcome.

Statistical analysis shows that patients in this study were less likely to experience cerebral microemboli if undergoing THA when compared to TKA, using the Chi-squared test. This result was calculated with very low patient numbers for any real clinical significance to be applied to the finding.

The use of cement during arthroplasty surgery and the consequent effect on cerebral microembolisation was analysed. Because all total knee arthroplasties were carried out with cement, this group could not be used in the analysis. The THA group contained three subgroups of cement use, fully cemented, hybrid and fully uncemented. Unfortunately the numbers in the fully cemented and fully uncemented groups were low but nevertheless, analysis revealed no significant correlation between fixation method and microemboli generation using the Kruskal-Wallis analysis.
The use of cement has been implicated in the aetiology of post-operative deep venous thrombosis and fat embolism syndrome in numerous studies (Chapter 1.7). The pathophysiology of systemic polymethylmethacrylate and its thrombogenic properties is complex and not fully understood; some authors believe that cement is not responsible for activation of clotting pathways whereas others do. This study suggests that the use of cement does not significantly influence cerebral microembolisation. It must be noted that it is the increase in intramedullary pressure which is responsible for embolisation to occur

which may be irrespective of cement use. However cement may trigger clotting and other physiological cascades which in turn may heighten this response.

Total microemboli count were analysed for relationship to various other patient and peri-operative variables, namely age, operation time, day to discharge and ASA grade. No correlation with these variables was uncovered, even when analysed for each type of arthroplasty.

In truth it is virtually impossible to compare microemboli counts between different studies in a meaningful way because of the various techniques used to measure them. The probe frequency of Doppler used varies and is not always reported. It is rarer still for more precise settings of the Doppler probe to be reported. Although there are consensus criteria for defining a microembolus on the Doppler trace there may be inter-observer variability in identifying microemboli between studies. The fact that inter-rater reliability was checked adds validity to the microemboli data in this study.

Although TCD is the best current method for assessing intra-operative microemboli it also has a number of limitations. Only about 90% of people have an adequate window in the temporal bone through which to insonate the middle cerebral artery. This anatomical fact and technical problems with the trace recording meant that not all (84/95 = 88%) patients in our study received TCD monitoring. The middle cerebral artery (left or right) is one of only six arteries supplying the circle of Willis leading to the question of whether unilateral or bilateral cerebral artery detection should be used. In the case of THA, bilateral monitoring would not have been possible due to the lateral decubitus position of the patient. In TKA, bilateral monitoring would have been possible. Some investigators argue that a combined bilateral count is more accurate as it is closer to the total number of microemboli. However even this is likely to be a proportionate estimate unless all the arteries supplying the brain are monitored. Moser et al.[22] examined unilateral and bilateral monitoring in 29 patients and found only 4% error between sides. This suggests it does not matter whether the right or left middle cerebral artery is used for monitoring. Mullges et al.[23] on the other hand found a significant difference in microemboli counts between sides with either right or left having more microemboli varying for each individual patient. Wijman et al.[41] have shown that cerebral microembolisation occurs

more frequently in the middle as compared to the anterior cerebral artery when TCD is used to detect microemboli. Another limitation of TCD is its current inability to distinguish between gaseous and particulate microemboli, let alone the many potential types of particulate microemboli. Additionally the size of each microembolus is not known. Size and substance of microemboli are likely to have a considerable impact on their pathological effect and so a simple "microemboli count" as is currently available must be accepted as a fairly crude measure. New technology offers the possibility of identifying size and nature of microemboli and a future study should be able to determine which factors carry pathological influence.

Given the limitations of microemboli detection it is unsurprising that this study uncovered little association between NP outcome and microemboli. The true microemboli load to the brain may not have been uncovered and furthermore, inability to determine size and substance and therefore the pathological effect of microemboli in this study may account for the poor relationship found between microemboli and NP outcome and indeed other variables.

10.3 Orthopaedic and Quality of Life Outcome

A wide variety of outcome measures were used in this study, all of which have been used extensively in joint disease research. All the scores used have been validated thoroughly and thus provide this study with robust outcome data.
The reasons behind choosing the individual outcome measures are discussed in the "Materials and Methods" chapter.

A six month interval following surgery is widely considered to be an adequate amount of time to recover and rehabilitate from arthroplasty procedures, especially for the knee and hip. Thus the most genuine outcome data in this study was uncovered at the six month follow up interval. However measures were undertaken at six weeks, primarily to assess NP outcome early after surgery, but orthopaedic and quality of life data was also assessed so meaningful relationships could be sought with NP outcome; no relationship was found between early poor NP outcome (deficit) and orthopaedic or quality of life outcome at six weeks. Furthermore, no relationship was elicited between those patients who showed deficits early and orthopaedic or quality of life outcome at six months.

No relationship with the other major outcome variable for this study, microemboli, was found when analysing the orthopaedic and quality of life outcome data.

Thus neither NP outcome nor microemboli were predictors of poor orthopaedic or quality of life outcome, at either follow up interval.

Considering Quality of Life outcome first, the EuroQol health measure showed that patients' quality of life had improved as compared to pre-operatively, at six months follow up. An improvement overall was also seen at six weeks, as might be expected. The scores at six months reflect a good/excellent quality of life outcome for all patients.

A similar pattern was seen for the WOMAC osteoarthritis index and the joint specific scores: improvements overall were seen at six weeks and continued improvement was noted up to six months post-operatively. If the joint specific scores are stratified, THA

patients showed a good outcome overall as did TKA patients. This is consistent with the reported success of total joint arthroplasty, as documented over the last 30 years.

Before drawing some conclusions it is worth commenting on the strengths and weaknesses of this study and discussing how this should limit interpretation. This was not a randomised trial, but was prospective. To randomise patients in the case of THA to receive one of three types of prosthesis fixation is unethical as each case is treated individually and fixation chosen as appropriate. Every attempt was made however to standardise the operative procedures for THA and TKA, but some events are inevitably beyond the investigators control. For example, several anaesthetists were used and although a standard protocol for anaesthesia was established, some choices of anaesthetic drug are left to the anaesthetist's discretion. Likewise, two orthopaedic surgeons were used; it would have been ideal to have one surgeon and one anaesthetist performing all the necessary procedures but this was not practical or an efficient use of theatre and investigator time. Also there are limitations to the extent one can impose protocols on clinicians however willing they are to participate in trials. In this study we believed it important to avoid the uncontrolled use of Propofol, which is a popular intravenous anaesthetic agent, because it may have neuroprotective effect. It was impossible to incorporate this restriction into the trial protocol and achieve compliance from those anaesthetists who would have ordinarily used Propofol. Moreover, it is not clear how anaesthesia affects NP outcome and the only way the effect of surgery could be distinguished from the effect of anaesthesia would be to perform anaesthesia without surgery and surgery without anaesthesia, both of which would be unrealistic and unethical.

Power calculations showed that 150 patients should be included in this study. This was based upon the incidence of microemboli reported from previous studies [12,31,36] and the expected incidence of deficits in those showing no microemboli, extrapolated from a cardiac surgery model. It may be that the incidence of deficits is lower in orthopaedic surgery and greater numbers are required. Nevertheless, in order to recruit that number within a realistic time period, it was necessary to recruit widely, hence the use of two surgeons. More surgeons could have been used but available time for follow up (including NP testing) was a limiting factor. Differences in operative procedure between the two surgeons was minimal; the approach for THA differed, with one surgeon employing the posterior approach and the other an anterolateral approach, a difference with negligible influence on the main outcome parameters. In the case of TKA both

surgeons deflated the tourniquet after the skin closure and dressings and compressive bandaging had been applied.
Follow up rates were not 100% for either interval and this may have been partly due to the length of NP assessment (one hour) and the discomfort experienced by some patients whilst being assessed. However, as discussed previously, some patients may not have returned on account of a previous poor performance and the fear of performing badly again. In this light, it may be considered for future studies that two post-operative follow up intervals are not necessary and one will suffice. This may increase follow up rates.

Exclusion of patients with previous cerebral injury or disease and history of TIA was thought to reduce confounding variables for the study. It may be argued that although we were attempting to reduce variables outside our control, we were excluding the very patients who could potentially derive more benefit from neuroprotection. The strict selection criteria may also mean that the present study is not representative of the whole arthroplasty population and thus limit the ability to generalise from its results.

This study did achieve similar variability between the two groups of arthroplasty patients at baseline. The age and sex ratio, indications for surgery and ASA grade ratio was representative of the UK population reported in the National Joint Registry for England & Wales 2nd Annual report 2005 [1]. PFO incidence also matched that reported by previous large number studies[14] suggesting that bias in the study population was not responsible for the lack of correlation between PFO and microembolisation.

10.4 Conclusions and suggestions for further research

Using both incidence of deficit and standardised Z change scores, this prospective clinical trial of 95 patients, has not found conclusive evidence that total hip or knee arthroplasty negatively affects neuropsychological outcome. In the majority of the battery of tests, there was a non-significant trend towards improved neuropsychological outcome. The incidence of neuropsychological deficits was lower than a similar study in a cardiac model and thus this study may have been underpowered despite adequate statistical planning.

This study found the incidence of cerebral microembolisation to be 24% for THA and 45% for TKA, lending weight to previously reported incidences. A significant proportion of microemboli were recorded after femoral component insertion during THA and after tourniquet deflation during TKA. In the case of THA, the use of cement did not influence microemboli incidence or load. However, the numbers of patients were low for each subdivision of the THA group based on use of cement. These findings may influence modification of surgical technique during arthroplasty. Further investigation is necessary to fully explore microemboli seen in between surgical steps, as this study demonstrated a significant number of cerebral microemboli during this collective period.

This study found an overall incidence of patent foramen ovale of 29%, similar to reported incidences in large study populations. No relationship was found between the presence of patent foramen ovale and cerebral microemboli incidence or load for either procedure. No relationship was found between the presence of patent foramen ovale and neuropsychological outcome.

Further work is needed to explore the relationship of surgical activity and cerebral microembolisation, perhaps with the inclusion of modifications to surgical technique. Newer Doppler techniques may be able to determine whether there is a tendency for gaseous or particulate microemboli to reach the cerebral circulation or whether they are noted in the same proportion.

The low incidence of neuropsychological deficits in this study suggests that future studies will need to either have less strict inclusion criteria or have greater numbers of participants. This is the first study to examine neuropsychological outcome after total joint arthroplasty using "gold standard" neuropsychological testing. However, refinement of the existing battery of tests may be necessary to make them more sensitive.

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Appendices

Appendix 1 – Ethical Approval

Appendix 2 – Patient Information Sheet & Consent form

Cognition and quality of life following hip/knee surgery

PATIENT INFORMATION SHEET

Thank you for agreeing to take part in this study. We hope the information below will answer any questions you have about the study process.

During some operations, especially those involving large blood vessels (e.g. cardiac surgery) or orthopaedic surgery, very small blood clots of blood or other particles are sometimes created within blood vessels and carried around the body's circulation in the bloodstream. These microscopic clots or emboli can therefore be delivered to other organs such as the brain, where they may block off the tiny blood vessels and cause transient or permanent injury. The changes to brain function are often very subtle and difficult to notice by the patient or relatives / friends but commonly involve changes in attention, memory and mood (cognitive function). They may not occur at all.

Studies in patients undergoing cardiac surgery show that these changes may be linked to the numbers of emboli reaching the brain and methods to reduce the amount of embolic material are regularly used. It is known that joint replacement surgery is associated with emboli production and methods to prevent clots in the limbs i.e. DVT are common practice. However little is known about the effects of these emboli on cognitive function or even if significant numbers of emboli even reach the cerebral circulation.

Thus, this study intends to investgate how many emboli reach the cerebral circulation during joint replacement surgery and what effect they have on cognitive function. To detect these subtle changes we need to examine cognitive function before and after the operation. A trained psychologist will perform these tests today and then 6 weeks AND 6 months after your surgery. These purposefully coincide with the regular follow up appointments for joint replacement surgery. The tests take approximately 1 hour and can actually be quite fun; they involve tests of your memory, concentration and mood as well as quality of life measures. In addition some orthopaedic measures of function and pain will be recorded and repeated after your operation at the same intervals. These are questionnaire based.

To measure the amount of emboli reaching the cerebral circulation during your operation a special device called transcranial Doppler ultrasound (TCD) will be used. As the name suggests, it is an ultrasound device (no radiation or X-rays) which is non-invasive. It will be placed on your temple whilst you are under anaesthesia and removed before you wake up. It is not harmful in any way.

We would like to reiterate that taking part in this study is optional and in no way changes the surgery itself.

If there is anything you do not understand or are unclear about please do not hesitate to ask any of the research team.

Once again thank you for your time and cooperation.

Mr Rahul Patel (Research Fellow in Orthopaedic Surgery)

Cognition and quality of life following hip/knee surgery

PATIENT CONSENT FORM

Have you read the Patient Information Sheet? Yes/No

Have you had an opportunity to ask questions and discuss this study? Yes/No

Have you received satisfactory answers to your questions? Yes/No

Have you received enough information about the study? Yes/No

Who have you spoken to? _____

Do you understand that you are free to withdraw from the study:-

* At any time?

* Without having to give a reason for withdrawing?

*Without affecting your medical care? Yes/No

Do you agree to take part in this study? Yes/No

Signed ..... Date .....

Name (BLOCK LETTERS) .....

Appendix 3 – Results for all patients (NP and non-NP groups)

The results presented in brief format below represent data collected from all patients successfully recruited. No neuropsychology data will be presented here as this is shown in Chapter 9 (NP group).

Total numbers of patients for each variable measured may vary due to the collection of incomplete data from some patients. However, the results presented below, merely attempt to provide further statistical robustness to the results for corresponding variables shown in Chapter 9.

Patient Characteristics

There were no differences in the demographic and clinical characteristics between the THA and TKA groups.

Demographic data for all patients and separate groups

	ALL (159)	**THA (74)**	**TKA (85)**
Age (years)	69.8 (11.6)	67.3 (14.0)	72.1 (8.5)
Sex (% m:f)	37:63	32:68	40:60
Race(%cauc:black:asian)	94:3:3	96:3:1	93:2:5
Arthritis (% OA:RA)	94:6	99:1	91:9

Numeric data are expressed as means with standard deviation in brackets. There were no statistical differences found between groups using the χ^2 tests for categorical data and independent t test for continuous data.

Pre-operative Orthopaedic and Quality of Life Scores

Mean (SD) pre-operative EuroQol and WOMAC scores for all patients and each group

SCORE (min-max)	ALL	THA	TKA
EuroQol (0-10)	0.465 (0.318)	0.450 (0.310)	0.491 (0.253)
WOMAC (0-96)	56.4 (20.7)	56.0 (20.0)	56.7 (21.4)

Total number of patients for EuroQol is 139 (65 for THA, 74 for TKA). Total number of patients for WOMAC is 159.

No significant difference was found between the THA and TKA groups at baseline regarding Quality of Life and Osteoarthritis indices, using a two-tailed independent t test.
NB: For the WOMAC score, "0" is the best score, reflecting low disability and pain.
For the EuroQol score, 1.000 is the best result.

Mean (SD) pre-operative hip scores for all patients in the THA group

SCORE (min-max)	THA (74)
Harris Hip Score (0-100)	47.4 (20.4)
Oxford Hip Score (12-60)	45.4 (19.8)

NB: For the Oxford Hip Score, "12" is the best score i.e. the disability caused by the hip is low.
The Harris Hip Score results can be stratified as excellent (90-100), good (80-89), fair (70-79) and poor (less than 70).
67.6% of patients were Trendelenburg positive, 18.9% level and 2.7% negative. Eight patients' data was not collected for this test.

Mean (SD) pre-operative knee scores for all patient in the TKA group

SCORE (min-max)	TKA (85)
Knee Society Score – Function (-50-100)	46.9 (20.2)
Knee Society Score – Knee (-20-100)	47.1 (20.5)
Hospital for Special Surgery Score (0-100)	53.2 (19.1)

For all scores, low disability is reflected by a high score.

Intra-operative data

ASA and PFO data for all patients and separate groups

	ALL	THA	TKA
ASA (%1:2:3)	10:69:21	18:65:17	4:72:24
PFO (%yes:no)	28:72	34:66	21:79

All figures are expressed as percentages. No statistical significance was found using the χ^2 test for both variables.
Total number of patients for ASA is 159. Total number of patients for PFO is 131 (64 in the THA and 67 in the TKA group)

The overall and group prevalences of PFO are very similar to that of the NP group and to incidences quoted in the literature, thus adding robustness to the reproducibility and method of our PFO detection technique.

ASA ratios were also very comparable to the NP group.

Side of operation for both groups

	THA (74)	TKA (85)
Right	46	55
Left	28	30

Mean (SD) intra-operative variables for patients in each group including discharge day

	THA	TKA	p value	p value excl. outlier
Op Time (min)	99.3 (20.6)	95.6 (16.2)	0.21	0.19
Microemboli	10.56 (56.7)	4.07 (10.4)	0.36	0.85
Tourniquet Time (min)		82.0 (20.7)		
Tourniquet Pressure (mmHg)		267 (34.6)		
Discharge Day	9.8 (4.9)	10.4 (6.6)	0.51	0.49

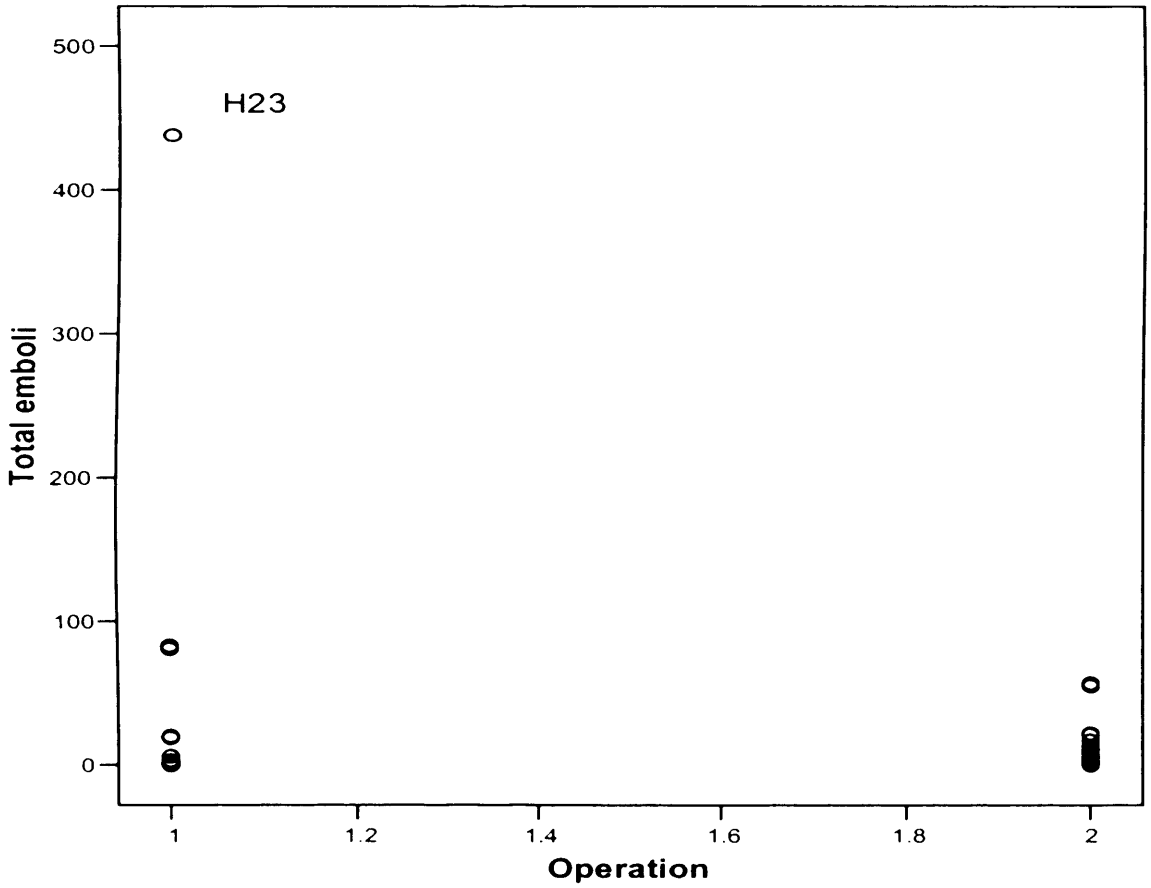
Total number of THA patients from whom microemboli counts were obtained is 63; sixty-seven for the TKA group. Otherwise there is no missing data for these variables. Operative time was not significantly different between the groups using a two-tailed independent t test.

Mean microemboli for the THA group was 3.66 excluding the outlier H23.

The two-tailed independent t test was used to compare the other variables between groups also.

These results are again comparable to the NP group.

Scatter gram showing range of total microemboli for each operation. 1 = THA, 2 = TKA. Outlier H23 included.



Mean (SD) time for each surgical stage and mean emboli load generated during each stage

	Time (mins/secs)	Microemboli	Microemboli excl. outlier
Femoral Osteotomy	0.44 (0.51)	0 (0)	0 (0)
Acetabular reaming	6.38 (3.37)	0.09 (0.5)	0.02 (0.1)
Acetabular component impaction	3.34 (5.24)	0.3 (2.1)	0.1 (0.7)
Femoral canal reaming	9.26 (8.09)	0.7 (4.3)	0.1 (0.5)
Femoral component impaction	5.46 (3.23)	4.9 (32.4)	0.7 (2.3)
Joint relocation	0.49 (1.47)	0.2 (0.8)	0.07 (0.4)
Other time	56.13 (32.21)	5.5 (22.0)	3.2 (13.5)

Mean time for each surgical stage is very similar when excluding the outlier, hence not shown.

Total microemboli generated during each surgical stage

	Total Microemboli	Total Microemboli excl. outlier
Femoral Osteotomy	0	0
Acetabular reaming	5	1
Acetabular component impaction	20	5
Femoral canal reaming	39	6
Femoral component impaction	285	38
Joint relocation	9	4
Other time	307	173

It is clear that the same pattern of microemboli generation in relation to surgical activity persists for THA as seen for the NP group.

Mean (SD) time for each surgical stage and mean microemboli load generated during each stage

	Time (min/secs)	Microemboli
Pre-tourniquet inflation	0.58 (1.20)	0 (0)
Tibial osteotomy	1.15 (1.15)	0.02 (0.1)
Femoral guide rod insertion	0.34 (0.22)	0.02 (0.12)
Femoral cuts	11.07 (4.30)	0.12 (0.6)
Patella cut	2.00 (4.25)	0 (0)
Prosthesis insertion	3.43 (1.44)	0.02 (0.13)
Cement setting	7..01 (1.47)	0.05 (0.28)
Post-tourniquet deflation	6.26 (4.10)	3.2 (10.2)
Other time	49.42 (24.47)	0.7 (2.2)

Total microemboli generated during each surgical stage

	Total Microemboli
Pre-tourniquet inflation	3
Tibial osteotomy	1
Femoral guide rod insertion	1
Femoral cuts	7
Patella cut	0
Prosthesis insertion	1
Cement setting	3
Post-tourniquet deflation	207
Other time	45

It is clear that the same pattern of microemboli generation in relation to surgical activity persists for TKA as seen for the NP group.

Incidence of microemboli in for THA and TKA

	No Microemboli	Microemboli
THA	48	15
TKA	37	28

Figures are absolute numbers of patients

Further analysis by Chi Squared tests reveals that in our larger study population, patients were more likely **not** to demonstrate microemboli during THA compared to TKA. This was a significant result ($p=0.032$) and therefore adds weight to the findings for the NP group. However, as before, this result must be treated with caution as the numbers for analysis are still low.

Incidence of PFO and microemboli for all patients

	PFO negative	PFO positive
No Microemboli	69	18
Microemboli	26	16

Figures are absolute numbers of patients

Analysis of the relationship between microemboli and the presence or not of a PFO, reveals that the presence of a PFO does not confer an increased likelihood of demonstrating microemboli ($p=0.1$).

Post-operative complications

SYSTEM	COMPLICATION	OUTCOME
GI	Cholecystitis	Cholecystectomy
CVS	MI	Treated successfully
	Arrythmia	Treated successfully
	Pulmonary Embolism	Anticoagulated
ORTH	Superficial wound infection	Resolved on antibiotics
	Superficial wound infection	Resolved on antibiotics
	Superficial wound infection	Resolved on antibiotics
	Instability at 3 months post TKA	Spacer change at 6 months
	DVT	Anticoagulated
RESP	Chest Infection	Resolved on antibiotics
GU	Urinary Tract Infection	Resolved on antibiotics

Post-operative Orthopaedic and Quality of Life Scores

6 week mean (SD) post-operative EuroQol and WOMAC scores for all patients and each group

SCORE (min-max)	ALL	THA	TKA
EuroQol (0-10)	0.710 (0.236)	0.738 (0.261)	0.764 (0.210)
WOMAC (0-96)	29.3 (15.8)	29.7 (14.4)	29.0 (17.2)

No significant difference was found between the THA and TKA groups at 6 weeks post-operative regarding Quality of Life and Osteoarthritis indices, using a two-tailed independent t test.
NB: For the WOMAC score, "0" is the best score, reflecting low disability and pain.
For the EuroQol score, 1.000 is the best result.

Sixty-three THA patients and 70 TKA patients provided data for this outcome measure.

6 month mean (SD) post-operative EuroQol and WOMAC scores for all patients and each group

SCORE (min-max)	ALL	THA	TKA
EuroQol (0-10)	0.954 (0.171)	0.927 (0.196)	0.936 (0.145)
WOMAC (0-96)	16.9 (13.9)	15.6 (14.2)	18.1 (13.6)

No significant difference was found between the THA and TKA groups at 6 month post-operative regarding Quality of Life and Osteoarthritis indices, using a two-tailed independent t test.
NB: For the WOMAC score, "0" is the best score, reflecting low disability and pain.
For the EuroQol score, 1.000 is the best result.

6 month mean (SD) post-operative Hip scores for all patients in the THA group

SCORE (min-max)	THA (63)
Harris Hip Score (0-100)	81.7 (13.0)
Oxford Hip Score (12-60)	23.6 (9.2)

NB: For the Oxford Hip Score, "12" is the best score i.e. the disability caused by the hip is low.
The Harris Hip Score results can be stratified as excellent (90-100), good (80-89), fair (70-79) and poor (less than 70).
5.4% of patients were Trendelenburg positive, 36.5% level and 12.2% negative. Missing data accounts for the shortfall in percentage terms.

6 month mean (SD) post-operative Knee scores for all patients in the TKA group

SCORE (min-max)	TKA (50)
Knee Society Score – Function (-50-100)	67.0 (16.2)
Knee Society Score – Knee (-20-100)	85.9 (14.3)
Hospital for Special Surgery Score (0-100)	79.0 (13.0)

For all scores, low disability is reflected by a high score.

All scores reflect a good orthopaedic and Quality of Life outcome at 6 weeks and 6 months. Pain and function is markedly improved, even at the six week interval, evidenced by the WOMAC scores. Moreover, all scores show improvement between intervals and a similar pattern to the NP group.

Relationship of Microemboli to Patent Foramen Ovale

A total of 129 patients had a result from PFO testing and microemboli data available for analysis.

There were 66 patients in the TKA group and 63 in the THA group.

No relationship was established between the presence of a PFO and a higher total microemboli count using an independent t test on each occasion (all patients p=0.20, THA p=0.27, TKA p=0.20)

Again exclusion of the outlier H23 did not alter the significance of the result overall (p=0.19) or for the THA (p=0.49) group.

Relationship of Microemboli to Age, Operation time and Days to Discharge

Pearson's correlation for total microemboli and Age, Operation time and Days to Discharge for all patients, THA patients and TKA patients

	ALL		THA		TKA	
	R	**P**	**R**	**P**	**R**	**P**
Age	-0.07	0.4	-0.03	0.8	-0.2	0.2
Op Time	0.04	0.6	0.1	0.3	-0.02	0.9
Day to Discharge	-0.05	0.5	-0.08	0.5	-0.04	0.8

No significant correlation was determined between total microemboli and the variables above.

Relationship of Microemboli to ASA grade

This correlation was determined using the Kruskal-Wallis statistical test. No significant correlation was found for all patients (χ^2= 0.8, p=0.7) or for THA (χ^2= 1.05, p=0.6) or TKA (χ^2= 0.38, p=0.8) patients alone.

Relationship of Day to Discharge and Age

A significant correlation was found when analysing day to discharge and the age of the patient, but only for the THA group. It appears from our data that the older the patient the longer that patient stayed in hospital (R= 0.3, **P= 0.005**). This correlation was not apparent for the TKA patients when analysed separately.

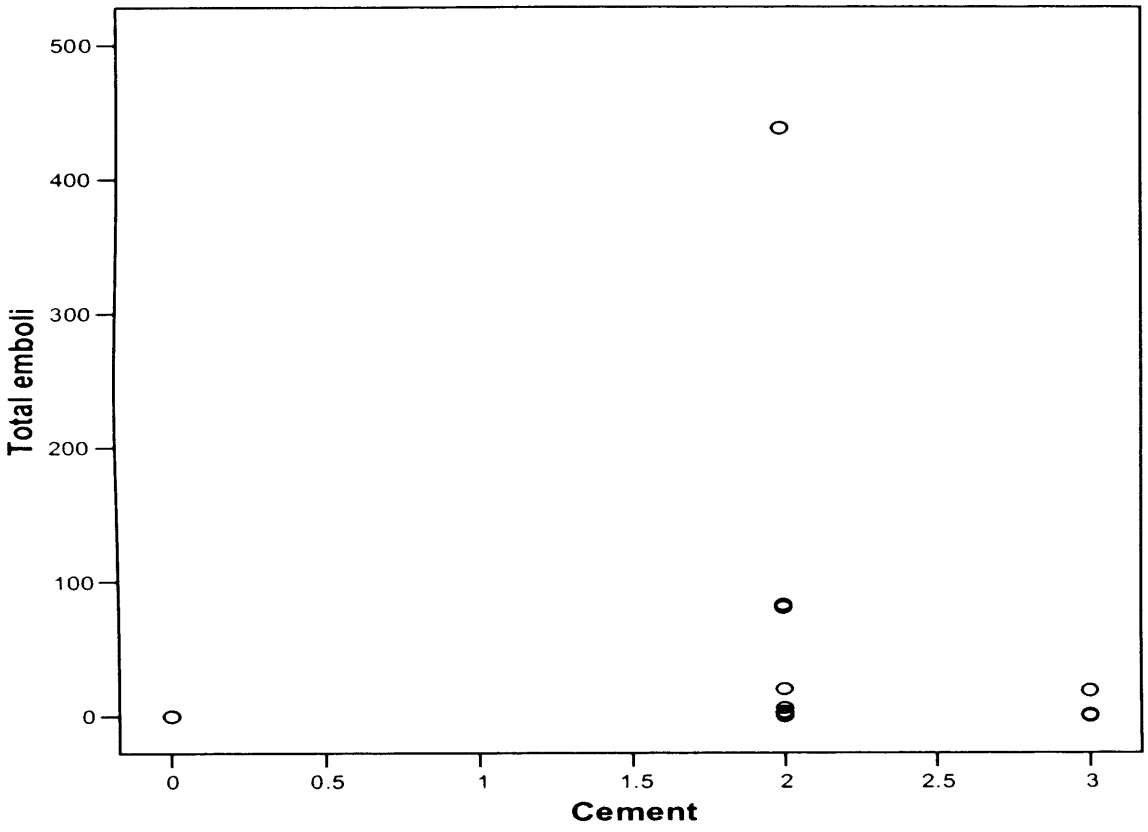
This is different to the findings for the NP group, where a significant correlation was found when analysing all the patients and the TKA patients separately. Due to the disparity between findings for the NP group and those above, it is very difficult to comment on the relationship between Day to Discharge and Age in this study.

Relationship of the use of cement to microemboli in THA

Patients undergoing THA received prostheses using methods of fixations falling into three groups: uncemented, fully cemented and hybrid. Following evidence suggesting that polymethylmethacrylate may be responsible for a larger thrombogenic response and hence microembolic load, it is pertinent to analyse the THA patients in this study to assess whether a relationship exists between the use of cement and microemboli load.

The outlier H23 has been deliberately included in this analysis. Kruskal-Wallis analysis reveals that no significant correlation exists (p=0.3), as was the case for the NP group THA patients. The figure below depicts this in a scattergram format.

Scatter gram showing relationship of the use of cement during THA and microemboli counts. 0=uncemented, 2= hybrid, 3= fully cemented.



Comparison of relevant data between NP group and Non-NP group

Table Comparison of demographic, pre-operative and post-operative variables, Quality of Life scores and Orthopaedic outcome between NP and NON-NP groups.

	NP GROUP (95)	NON-NP GROUP (64)	P VALUE
Age (years)*	71.1	68.0	0.13 ¶
Sex (% m:f)	37:63	36:64	0.91 #
Race (%cauc:black:asian)	95:2:3	94:3:3	0.92 #
Arthritis (% OA:RA)	97:3	91:9	0.10 #
Pre-op EuroQol*	0.450	0.516	0.26 ¶
6 wk EuroQol*	0.710	0.764	0.23 ¶
6 month EuroQol*	0.927	0.944	0.12 ¶
Pre-op WOMAC*	47.6	55.9	0.15 ¶
6 wk WOMAC*	27.6	33.0	0.07 ¶
6 month WOMAC*	15.4	14.2	0.07 ¶
ASA (% 1:2:3)	11:69:20	9:67:24	0.87 #
PFO (% yes:no)	33:67	17:83	0.05 #
Total Emboli*	8.5	5.0	0.34 ¶
Discharge Day*	9.6	11	0.21 ¶

* Values expressed as means.
¶ Independent t test used.
# Chi-Squared test used.

No significant differences were detected between the NP and Non-NP groups. This suggests that the NP group data, which forms the mainstay of the results section of this thesis, does not display selection bias.
As certain variables are operation specific, they are not included in the analysis above.