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Cerebral fat emboli: A trigger of post-operative delirium☆

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ABSTRACT

Accumulating evidence implicates cerebral fat embolism (CFE) as a causative agent in post-operative confusion (POC). CFE occurs following orthopaedic procedures including, intra-medullary (IM) nailing and total joint arthroplasty (TJA). The incidence of CFE is high (59–100% TJA) and the resulting POC is associated with higher overall complication rates. Cognitive dysfunction improves in many patients but can persist – with potentially disastrous outcomes. The pathomechanics of CFE implicate circulating lipid micro-emboli (LME) that are forced from IM depots by instrumentation/nailing. Passage to the left side of the heart is possible through intra-cardiac or arteriovenous shunts in the lung. LME are propelled to the brain where they cause disruption via ischemia or by alterations in the blood-brain-barrier – causing cerebral oedema. Prevention of CFE follows established practices for preventing FES and consideration of additional techniques to remove resident fat and reduce IM pressures. When CFE occurs supportive treatment should be established.

Introduction

Post-operative confusion is common following orthopaedic operations with a recent systemic review finding post-operative delirium levels of 3.6–28.3% following elective procedures and 4–53.3% following hip fracture surgery.[1] Confusion may be secondary to systemic dysfunction, as can occur in hypoxia and hypotension, or be due to neurological pathology.[2] One neurological cause of post-operative confusion that has been highlighted in recent medical literature is cerebral fat embolism (CFE).[3–8]

CFE occurs when lipid micro-emboli (LME) are propelled, via the blood stream, to lodge in the brain. It was first noted as part of the fat embolism syndrome (FES)[9] but has since been shown to arise in circumstances where the full-blown syndrome is not evident. It should be noted that although FES syndrome is relatively rare, fat emboli (FE) are common following fracture.[10,11] In addition to this many orthopaedic procedures have been implicated in producing FE and causing CFE including, IM nailing of femoral fractures[3], hip fracture surgery[4], total knee replacement (TKR)[5], and cemented/uncemented total hip replacement (THR).[6,7,12] The incidence of this problem is high with 59% to 100% of patients during total joint arthroplasty (TJA) having evidence of cerebral emboli. In these studies 41% to 75% had a measurable decrease in their cognitive state in the first post-operative week or at discharge.[5,13] This condition was seen to persist in 18 to 45% of patients at 3 months.[5,14]

In the acute setting this reduction in cognitive ability makes additional impacts on overall patient morbidity and demands on nursing care.[15] Many patients improve after the immediate post-operative period[8] but prolonged neurological compromise can occur.[16,17] Persistent cognitive changes are now known to be associated with higher three month and first year mortality rates than those of unaffected patients.[2] Post-operative confusion is also associated with poorer outcomes, higher complication rates and longer bed occupancy in patients undergoing lower limb TJA.[5,8] It is noted that the elderly have an increased incidence, and decreased ability to recover from this effect.[2]

Exact costing of this complication is beyond the scope of this paper, however, a recent study found average costs per day among "non-orthopaedic" patients with delirium exceeded 2½ times the costs among patients without.[18] The increased length of admission, complication rates and levels of nursing care make a significant impact on the resources of the healthcare provider.

It is thus clear that post-operative cognitive changes of patients should be of great interest to the treating orthopaedic surgeon as it may be the harbinger of a disastrous outcome. The roles of pathomechanics, prevention and treatment of CFE in orthopaedic patients are incompletely understood and form the subject of this study.

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The pathomechanics of CFE

The sources of embolic fat have traditionally had two longstanding contending hypotheses when described as part of FES – one mechanical[19] and one biochemical.[20] The mechanical theory explains the observed incidence of fat embolism (FE) following pelvic and long bone fractures[21–23] and during processes that increase intra-medullary (IM) pressures, including the reaming/nailing of long bones.[24–26] The biochemical theory, with mediation via lipases releasing free fatty acids[27], accounts for the incidence following non-fracture pathology including soft tissue trauma[28,29], burns[30] and pancreatitis.[31]

Fat passes into the venous system and thus into the right side of the heart where it is propelled to the lung capillary bed.[9,21–23] This embolization of pulmonary vasculature causes ventilation/perfusion mismatching.[32,33] This, with the possible complication of adult respiratory distress syndrome (ARDS)[34] accounts for the respiratory compromise that is seen in FES.

Fat is then able to pass into the left side of the heart where it is embolized to the end organs, including the brain[35,36], skin[36] and kidneys.[35,36] The mechanism for this occurrence is controversial, with many studies citing a patent foramen ovale (PFO) as the cause, allowing right to left cardiac shunt.[37,38] CFE has however been found in patients[5,13,39–42] and animal models[43] without this abnormality. An explanation for this is the existence of arteriovenous (AV) anastomoses in the lung.[44] Several studies have suggested AV recruitment in exercise[45–48] and hypoxia[49], with a corresponding reduction in shunting in the hyperoxic state.[50] In addition to this, transpulmonary passage of molecules exceeding diameter of pulmonary capillaries (7–10 μm)[51,52] has been shown, in healthy humans at exercise (radio-labelled, macroaggregated albumin (45 μm))[53] and in cadaveric lungs (microspheres 25 and 50 μm) at physiological pressures.[54] Furthermore, it should be noted that LME are able to deform in shape, allowing access to available vascular apertures, as is shown at section[41] and by video microscopy (http://www.anesthesia-analgesia.org/cgi/content/full/97/6/1789/DC1).[43] This phenomenon explains the findings of one study, in dogs, 3-hours post-bilateral hip replacement, where fat had penetrated the brain, heart and kidney of every canine specimen but no 15 μm spheres had accessed the arterial circulation.[55]

Embolization of the brain causes LME to become lodged in the capillary bed – with this abnormality sometimes referred to as small capillary arteriolar dilatations (SCADS), which are seen at histological sectioning.[56–59] This blockage to blood flow may cause local ischaemia, as is seen with other embolic types of stroke[60] and is one possible mechanism for cerebral compromise. Another proposed mechanism, which has been suggested by animal models, is that LME alter the permeability of the blood brain barrier (BBB) causing post-operative cerebral oedema.[61,62] An overview of the pathomechanics of CFE can be seen in Fig. 1.

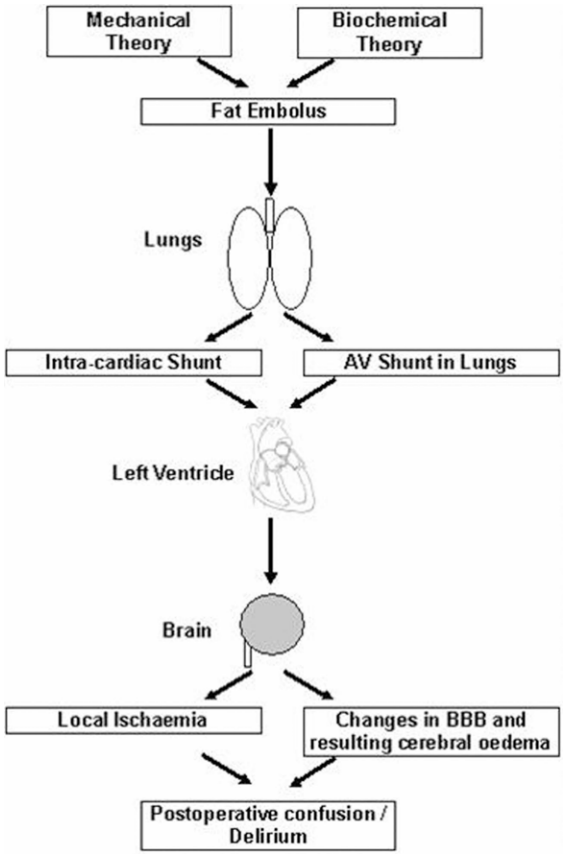

Fig. 1. An overview of the pathomechanics of Cerebral Fat Embolism (CFE).

Investigating LME & CFE

Much of our knowledge of LME follows investigation of patients who have experienced cardiopulmonary bypass (CPB). CPB has been shown to be associated with high levels of post-operative confusion with this effect thought to be secondary to microemboli to the brain.[60,63,64] These microemboli may be of lipid origin from scavenged "shed blood"[35,65–67], or non-lipid from atheromatous aortic plaques or gaseous bubbles from the CPB machine.[68]

Real-time measurement of emboli has been established using transcranial Doppler (TCD) looking for high-intensity transient signals (HITS). HITS have been shown to positively correlate CFE[64,69] and are the chosen method of investigation of many papers.[5,14,65,69] The appearance of CFE can also be seen using magnetic resonance imaging (MRI)[70,71] and high-resolution computer topography (CT) scanning[72] – with MRI being the recommended imaging modality showing the "starfield pattern" of multiple punctate hyperintensities on diffusion-weighted (DWI) and T2-weighted imaging.[71,73]

Preventing & treating CFE

Prevention

Attempts to reduce the production of FE have been attempted ever since recognition of its presence and potential sequelae. Movement of fracture ends has been shown to release showers of fat emboli[74] and this has led to the principle of early stabilization of long bone fractures – with timing of definitive surgery being determined by the physiological status of the patient.[75] Techniques have been adapted to try and prevent raised IM pressures during IM nailing of fractures, including the slow insertion of hollow nails.[76] Whether reaming prior to nail insertion increases LME is controversial with a recent review suggesting the evidence is inconclusive.[25] Techniques to try and prevent raised IM pressures have been attempted including; distal venting, which may reduce IM pressures by 50–90%[77] and changes in reamer design, including narrower reamers allowing debris to "flow by".[78] Innovative modifications in hardware have culminated in the reamer irrigator aspirator (RIA) – which in addition to reducing IM pressures also removes resident fat and as such may be of particular use.[79–85]

Although these methods have been developed for the trauma patient they have been adapted in elective orthopaedics where IM instrumentation is necessary. The incidence of HITS is reduced in cemented THR when a cannula attached to a vacuum has been placed distal to the femoral prosthesis during cementing.[86] A similar reduction is seen in TKR using computer-assisted surgery (without IM jig)[87] or by using RIA prior to standard IM jig placement.[88]

Attempts to reduce LME have not rested with surgical techniques as it has been shown that a reduction of embolic load can be achieved when scavenged "shed blood" is passed through a "cell-saver" prior to infusing the patient.[65–67,89] Patients transfused with processed blood from which micro lipid particles were removed showed a significant difference ($P < 0.038$) in cognitive dysfunction at 6 weeks when compared to those patients that did not receive cleansed blood.[89] An additional study found the relative number of fat globules circulating in the cerebral vasculature correlated to a reduction in prefrontal activation assessed by MRI.[90] The use of a mechanical filter in the venous system has been suggested to reduce the load of emboli during IM nailing in a canine model[91] but is unproven in the clinical setting.

Treatment

The management of FES has traditionally concentrated on prevention and support for the respiratory compromise.[92] Attempts to modify the effect of FES at the lung have included steroids[93,94], anticoagulants[95,96], ethanol and dextrose[97] all of which have dubious effectiveness. Of the experimental techniques, including anticytokines[98], antibodies to adhesion proteins[99] and blockade of tissue factors[100] only activated protein C (APC) has been approved for use in humans.[101] APC does increase the risk of haemorrhage and as such may be of limited use in trauma/orthopaedic surgery.[101] The effect of these interventions on CFE has not been established. What has been established is that all patients with cerebral pathology should have adequate perfusion, oxygenation and access to appropriate nursing. This supportive treatment with an emphasis on prevention should be the focus of management.

Conclusions

CFE is of significance to the orthopaedic surgeon given its frequency and the increase in overall patient morbidity/mortality associated with its presence.[102–112] Accumulating evidence implicates circulating LME, forced from IM depots, as an agent of neurological injury. The movement of LME to the left side of the heart is possible through an intra-cardiac shunt, e.g. a PFO, or via AV shunts in the lung. Disruption of normal brain activity may be due in part to ischemia and in part to alterations in the BBB and resulting cerebral oedema. Preventing CFE follows traditional guidelines for preventing FES but with consideration of additional techniques – to remove resident fat or reduce IM pressures before LME are displaced systemically, causing harm. When CFE occurs supportive treatment should be established, with keen follow-up to search for associated complications. CFE, like FES remains a case where prevention is better than cure.

Conflict of interest

The authors declare that there is no conflict of interest

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