The role of microembolisation in cerebral injury as defined by functional magnetic resonance imaging

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Abstract

Objective: Cerebral injury, in both overt and subtle forms, is common following cardiac surgery. Current methods of assessment, most commonly neuropsychological testing, have several limitations and do not accurately define the anatomical and functional injury that occurs. We have assessed the degree of cerebral injury following on-pump and off-pump cardiac surgery using functional magnetic resonance imaging and correlated this with the severity of microembolism as measured by transcranial Doppler ultrasound. Methods: Sixteen patients undergoing cardiac surgery (8 off-pump coronary artery bypass grafting (CABG), 4 on-pump CABG and 4 open-heart surgery) underwent functional magnetic resonance imaging of the brain pre-operatively and 4 weeks post-operatively. Each patient had continuous transcranial Doppler monitoring intraoperatively using a recently validated technique (multirange, multifrequency Doppler) that allows rejection of artefacts and separation of gas and solid microemboli. Covariate analysis of pre- and post-operative functional magnetic resonance images was performed to correlate local mean signal intensity change with the extent of gas and solid microembolism. Results: The median number of microemboli was 34 (range 10–176) in the off-pump group, 229 (range 127–314) in the on-pump CABG group, and 1220 (range 874–1261) in the open-heart group (P = 0.05). The proportion of solid microemboli was significantly lower in the off-pump group in comparison to the on-pump CABG and open-heart groups (9 vs. 25 vs. 20%, respectively, P < 0.01). Comparison of pre- and post-operative functional magnetic resonance images demonstrated an overall reduction in task-associated activation in the post-operative period. However, and paradoxically, in certain specific regions of interest there was an increase in the signal intensity which correlated with the total number of microemboli (r = 0.9, P < 0.01). Conclusions: Patients undergoing on-pump surgery have a higher degree of gas and solid microembolism which correlates with post-operative cerebral functional MRI activation. As activation with functional magnetic resonance imaging of the brain is known to be sensitive to a wide range of insults, it may prove to be a useful marker of perioperative cerebral injury that could help in the evaluation of potential cerebroprotective strategies.

Keywords: Functional magnetic resonance imaging; Cognitive impairment; Transcranial Doppler; Cerebral microembolism; Off-pump coronary artery bypass grafting

1. Introduction

Neurological injury remains the most feared complication following cardiac surgery. Improvements in anaesthetic and surgical techniques, as well as in post-operative management, in recent years, have resulted in a significant reduction in mortality. This has not been paralleled by a reduction in cerebral injury as the surgical population has become older and sicker. Cerebral injury occurs in two distinct forms: an overt form which is clinically evident as stroke affecting 2–3% of coronary artery bypass grafting (CABG) patients, and the more subtle injury of cognitive dysfunction that is only evident on detailed neuropsychological testing [1]. The latter can be detected in up to 50% of all patients soon after surgery and persists in a quarter at 6 months post-operatively [2]. More importantly, cognitive impairment early after surgery has been shown to be...
correlated with later decline in cognitive function and impaired quality of life [3,4].

While similar injury may occur after non-cardiac surgery [5], neurocognitive impairment is more common and severe after operations performed with cardiopulmonary bypass (CPB). The aetiology is multifactorial with microembolism, intraoperative hypotension and systemic inflammatory response syndrome (SIRS) being most frequently implicated [2].

Transcranial Doppler (TCD) ultrasonography can be used to detect microemboli intraoperatively. An embolus results in an increase in the reflected ultrasound so that when probes are placed bilaterally on the temple overlying the middle cerebral arteries (MCA) high intensity transient signals (HITS) are detected. These HITS represent microemboli. Until recently, however, it has generally not been possible to reliably distinguish between gaseous and particulate microemboli. The multifrequency TCD system (EmboDop, DWL) can discriminate between gaseous and solid microemboli as well as rejecting artefacts on-line using a multirange, dual frequency technique which has been recently validated [6,7]. This technique utilises two different ultrasound frequencies: 2.0 and 2.5 MHz. Differentiation is then made possible as solid microemboli reflect more ultrasound at higher than at lower frequencies, whereas the opposite occurs in the case of gaseous microemboli. An additional 2.0 MHz insonation reference gate was set extravascularly, 15 mm superficial to the MCA insonation gate. This reference gate serves for the on-line rejection of artefacts as the latter are identified when HITS are detected in both gates (MCA and reference gates) simultaneously, or with a time delay of less than 4 ms. The relative contributions of gaseous and solid microemboli to total count were defined separately to explore their relative abundance and potential pathological significance.

Functional magnetic resonance imaging (fMRI), on the other hand, allows mapping of networks in the brain responsible for sensory, motor or cognitive processing [8]. This technique depends on the fact that the microvascular magnetic resonance signal is strongly influenced by the oxygenation state of the blood. This effect is known as ‘blood oxygenation level dependent’ or ‘BOLD’ effect [9]. Performing a certain task (motor, sensory or cognitive) during the acquisition of fMRI images results in local increases in the metabolic rate in the regions concerned due to neuronal activation. A local increase in regional blood flow to these areas causes a secondary decrease in the relative proportion of deoxygenated haemoglobin. Oxygenated and deoxygenated haemoglobin have different magnetic susceptibilities, i.e. their molecules experience different levels of polarisation when placed in a magnetic field. As deoxygenated haemoglobin is paramagnetic, it has a much larger magnetic susceptibility than oxygenated haemoglobin. A relative reduction in deoxygenated haemoglobin following neuronal activation can therefore be detected as an increase in the local magnetic resonance signal intensity. Comparison of serial brain images before and after initiation of a specific cognitive task allows detection of small signal changes in activation and thus localisation of the responsible areas of the brain. This is now a well-established technique for mapping brain functions involved in many cognitive tasks including verbal working memory. Recent work has demonstrated that cognitive activation can be followed serially in patients to identify even subtle changes [10].

The aim of our study was to explore the ability to assess the degree of cerebral injury following on-pump and off-pump cardiac surgery using fMRI and correlate this measure of injury with the degree of microembolism as measured by TCD ultrasonography.

2. Material and methods

With ethical approval from the Central Oxford Research Ethics Committee (OxREC C01.258) and informed consent, 16 patients undergoing cardiac surgery underwent intra-operative continuous bilateral TCD monitoring. Structural and functional magnetic resonance imaging of the brain were performed pre-operatively and 4 weeks post-operatively (median 28 days, range 15–85). Similar images were acquired in five healthy volunteers on two occasions to ensure the absence of non-specific changes due to repeat testing.

2.1. Cardiopulmonary bypass

Following full anticoagulation with heparin given at a dose of 300 IU/kg to maintain an activated clotting time of 400–600 s, cardiopulmonary bypass (CPB) was instituted using ascending aortic cannulation and a two-stage right atrial venous cannulation. A roller pump (Jostra HL 20) and hollow-fibre membrane oxygenator (Affinity NT, Medtronic Inc.) were used. The extracorporeal circuit was primed with 1000 ml of Hartmann’s solution and 2500 IU heparin. CPB was maintained with non-pulsatile flow with a flow rate of 2.4 l/m² per min at normothermia with temperature allowed to drift to 34 °C. Arterial line filtration was not used. Cardiotomy suction was used. Acid–base was managed with alpha stat control. Myocardial protection was achieved with intermittent antegrade cold crystalloid cardioplegia. On completion of all distal anastomoses, the aortic cross-clamp was removed and the proximal anastomoses performed with partial aortic clamping.

2.2. Off-pump technique

Complete anticoagulation with heparin was achieved as in the CPB group. Regional myocardial immobilisation was achieved with a suction stabilizer (Octopus, Medtronic Inc. or Guidant, Cardiothoracic Systems Inc.). The target coronary vessels were snared proximally with a silastic...
sling. An intracoronary shunt (Guidant Axius™) was only used when there was haemodynamic compromise during construction of the anastomosis (usually the distal right coronary artery). Visualisation was enhanced by using a surgical blower-mister device (Medtronic Clearview®). All the patients had composite arterial grafts with complete avoidance of aortic manipulation.

2.3. Transcranial Doppler monitoring

Continuous intraoperative monitoring was performed using a multifrequency Doppler system (Embodop, DWL). Dual frequency probes (2.0 and 2.5 MHz) were used to simultaneously insonate the middle cerebral arteries (MCA) bilaterally. The probes were fixed to the transtemporal windows using a specifically designed head brace. The MCA insonation depth was set between 45 and 55 mm with a sample volume of 13 mm. An additional 2.0 MHz insonation reference gate was set 15 mm superficial to the MCA insonation gate. This reference gate serves for the on-line rejection of artefacts as the latter are identified when HITS are detected in both gates (MCA and reference gates) simultaneously, or with a time delay of less that 4 ms. This multifrequency system also differentiates between solid and gaseous microemboli as solid microemboli reflect more ultrasound at higher frequencies than at lower frequencies while the opposite occurs in the case of gaseous microemboli. The differentiation occurs on-line during monitoring and the data is recorded on a computer hard drive allowing off-line analysis to be carried out.

2.4. Magnetic resonance imaging (MRI) and working memory paradigm

Structural T1-weighted (3D Turbo FLASH sequence; TR 15 s; TE 6.9 ms) and T2-weighted MRI (spin echo sequence, time to repeat [TR] 5 s; echo time [TE] 65 ms) images were obtained in all patients. 3T (Varian Innova) echo-planar images (EPI) (24 slices; TR 3 s; TE 30 ms; field of view [FOV] 192 × 256 mm; matrix 64 × 64) were acquired during performance of an n-back verbal working memory paradigm [11] presented on a back-projection screen visible from the subjects’ feet. The n-back task included 0-back and 1-back conditions.

2.5. Statistical analysis and presentation of data

The number of microemboli is presented as median. As the data is not normally distributed, the non-parametric Kruskal–Wallis test was used to compare the difference in microembolisation between the 3 groups. The Mann–Whitney U-test was used to compare the difference in microembolisation between each pair of groups. Differences in proportions of gaseous and solid microemboli were compared using χ²-test.

fMRI images were analysed with software in the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). Group contrasts were generated using a mixed-effects model, which includes contributions from individual measurement variance and variance between individuals within the groups. Region-of-interest (ROI) analysis measured mean signal intensity change.

3. Results

3.1. Patients

Sixteen patients were included in the study. Eight patients underwent OPCABG, four had on-pump CABG (ONCABG) and four had open-heart procedures (aortic valve replacements). The mean age of the patients was 55 years (range 31–75).

No patient showed clinical or MRI evidence of stroke. There was no significant difference in accuracy of the 0- or 1-back task performance between the pre- and post-operative periods.

3.2. Microembolism

The median (range) number of microemboli was 34 (10–176) in the OPCABG group, 229 (127–314) in the ONCABG group and 1220 (874–1261) in the open-heart group (9%) relative to both the ONCABG (24%) and open-heart groups (20%) (P < 0.01). Most emboli were gaseous. The proportion of solid microemboli was, however, significantly lower in the OPCABG group (9%) relative to both the ONCABG (24%) and open-heart groups (20%) (P < 0.01).

3.3. Functional magnetic resonance imaging

Contrast of pre- and post-operative images demonstrated a significant overall reduction in task-associated fMRI activation in the post-operative period. In contrast to the overall reduction in activity, certain specific regions of interest showed an increased activation which correlated with the total number of ME. Activation change across the group in a region of interest in the left superior and middle frontal gyri (coordinates in standard space x = −24, y = −12, z = 66) confirmed that intensity change was correlated with the total number of gas and solid microemboli (r = 0.9, P < 0.01) (Fig. 1).

4. Discussion

Recent years have seen an increasing interest in off-pump coronary artery bypass surgery [12]. The latter has proven to be a safe and efficacious procedure with its major benefits realised in higher risk patients. Here we demonstrate that...
patients undergoing surgery without CPB have a significantly lower number of intraoperative gas and solid microemboli. This benefit is maximised with avoidance of aortic manipulation, i.e. avoiding aortic side-clamping by performing composite arterial grafts in addition to avoidance of cross-clamping by eliminating cardiopulmonary bypass [2].

fMRI is a sensitive method of detecting subtle changes in cerebral activation patterns to specific tasks following a wide range of insults. The aetiology of neurocognitive dysfunction following cardiac surgery is thought to be related to the use of cardiopulmonary bypass and to result from the effects of microembolism, intraoperative hypotension and the systemic inflammatory response syndrome [2]. The neuropathological nature of this dysfunction remains largely unknown. The fact that two-thirds of patients recover within 6 months post-operatively means that either the injury is reversible, or that compensatory mechanisms of adaptive change occur within the brain that allow for this functional recovery. One-third of patients, however, make no recovery and longitudinal follow-up for 5 years post-operatively demonstrate a significant degree of late decline that correlates with the degree of initial insult [3]. Moreover, this late decline is paralleled by impairment in quality of life measures [4].

This study offers new insights into cerebral dysfunction after cardiac surgery by demonstrating, for the first time, a link between intraoperative microembolisation and impairment of verbal memory processing as quantified by fMRI. These functional changes occur in the absence of any obvious structural changes. While our results suggest an overall reduction in post-operative cerebral activation associated with a working memory task, they also show that impaired function in primary processing regions are associated with increased brain activation in other regions. The intensity of activation in the left superior and middle frontal gyri correlated positively with increasing numbers of intraoperative microemboli. As previous studies have demonstrated a relationship between microemboli and cognitive deficits after cardiac surgery, and microemboli are unlikely to improve memory functions, we interpret the increased brain activation in the left superior frontal and middle gyri as evidence for recruitment of additional brain regions during task performance by the patients. This may represent a potential compensatory mechanism or adaptive change that contributes to functional recovery after cerebral injury.

While we have confirmed previous findings that patients undergoing off-pump surgery have fewer microemboli [13], we also report, for the first time, a qualitative difference in microembolisation between on-pump and off-pump surgery. Using dual-frequency ultrasound to distinguish between solid and gaseous microemboli, we found a significantly lower proportion of solid microemboli in the off-pump
group. Cholesterol microemboli probably arise from the atherosclerotic aorta during manipulation, whereas use of the cardiotomy suction as well as platelet aggregation may result in solid microembolisation during CPB. All the open-heart cases were aortic valve replacements which involve manipulation of the ascending aorta especially the intima. This may be the cause of the higher number of solid microemboli in this group.

It has previously been demonstrated that intraoperative manoeuvres which reduce the number of microemboli, reduce the risk of neurocognitive impairment in on-pump CABG [14]. There are, therefore, persuasive theoretical reasons why elimination of microemboli in off-pump CABG should reduce the risk of cognitive dysfunction. Our findings are consistent with two randomised clinical trials which demonstrated a reduction in cognitive impairment [15] and better preservation of learning capacity [16] with off-pump CABG.

The use of fMRI may prove to be a powerful tool to investigate pathophysiological mechanisms in subtle cerebral injury and in the evaluation of potential cerebroprotective strategies. Neuropsychological testing is currently regarded as the ‘gold standard’ in the investigation of post-operative cognitive impairment [17]. However, it has many limitations. It is time-consuming and laborious for the patient and examiner alike. It identifies the deficit but not the underlying pathology. In addition, there are limitations related to learning effects with repeated testing and the effect of regression toward the mean [18]. It follows that neuropsychological testing may have too much ‘noise’ to be able to detect subtle changes in cognitive function, particularly in lower risk groups, with adequate sensitivity.

In summary, cerebral microembolisation of both solid and gaseous matter can be minimised with avoidance of cardiopulmonary bypass. The use of fMRI as a neurobiologically rational surrogate marker in the investigation of post-operative cerebral injury may provide enhanced sensitivity in the evaluation of potential cerebroprotective strategies.

Acknowledgement

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References


Appendix A. Conference discussion

Dr B. Walpoth (Geneva, Switzerland): In your functional MRI study you included other tests such as neurocognitive testing. How did your patients perform and is there a correlation with your functional MRI data?
this has been validated in the past. So patients that were recruited all scored over 70% in these tests.

**Dr R. Poston (Baltimore, MD, USA):** How did you manage cardiopulmonary bypass? Were patients cold, tepid (30 degrees), or warm? Did you maintain MAPs in the 70 s or 80 s, which has been shown to improve neurocognitive outcome or at least reduce strokes after bypass?

Was the pump sucker used a lot?

These kinds of cardiopulmonary bypass variables might influence your results and affect the external validity of your study.

**Dr Abu-Omar:** The pump sucker was used in the on-pump group.

In terms of cooling, the temperature was allowed to drift in patients having cardiopulmonary bypass.

**Dr F. Mohr (Leipzig, Germany):** Dr Deigler, you may know the study, has also looked into this subject and published in the EACTS Journal. He has shown that there is a close correlation in the approach to the aorta, meaning if you clamp side-biting, or whatever you do to the aorta, or cross-clamp the aorta even in off-pump cases, it is a clear moment where you detect microemboli.

And it is not really clear from your data given, what you do. Did you connect to the aorta in the off-pump cases at all, I mean, no-touch aorta or proximate anastomosis to the aorta? And how was it in comparison to the on-pump cases?

Again, the question, how did you perform the proximal anastomosis? Just to answer the question whether there is some differences in terms of the surgical technique for the aorta.

**Dr Abu-Omar:** It is our practice in off-pump surgery to perform total arterial revascularization using composite arterial graft with complete avoidance of aortic manipulation. All the cases that were included in this study had complete avoidance of aortic manipulation, and this is generally the technique that we use. Clearly, in the on-pump group, aortic manipulation would have been performed with the use of cross-clamp and cardioplegia.