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Cognitive dysfunction follows left heart catheterisation but is not related to microembolic count ☆

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ABSTRACT

Background: Left heart catheterisation with coronary angiography (CA) may lead to cognitive dysfunction, as a result of neurological injury. The aim was to assess the incidence of cognitive dysfunction in elderly patients three months after CA and investigate any association between cognitive dysfunction and microembolic count during CA.

Methods: This was a prospective observational study with a control cohort. Cognitive testing was undertaken at baseline and at 3 months using a battery of 8 neuropsychological tests. Subjects comprised 51 CA patients, aged ≥ 50 years, with normal baseline cognition, and 31 community control participants. Microemboli were measured by Transcranial Doppler throughout the procedure. All patients underwent trans-femoral CA with aortography and ventriculography. Cognitive dysfunction was defined in an individual when their reliable change index score was less than -1.96 on 2 or more tests and/or their combined z score was less than -1.96. Microembolic count was assessed by off-line manual counting and automatic software was also used to count and differentiate gaseous from solid microemboli.

Results: Cognitive dysfunction was identified in 15.7% of patients at 3 months. Microemboli were detected in all patients, predominantly during aortography and ventriculography. The median total embolic count was 365 (IQR 192, 574), the majority being gaseous (84%). There was no multivariable association between cognitive dysfunction at 3 months and microembolic count.

Conclusions: This study demonstrated that cognitive dysfunction following CA is not associated with microembolic load. Cognitive dysfunction occurs in 15.7% of patients at 3 months. This is reassuring for the proceduralist and suggests that other perioperative elements are involved.

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1. Introduction

Left heart catheterisation (LHC) for coronary angiography (CA) is commonly used to define coronary artery anatomy and left ventricular function but is associated with several risks including neurological complications. Registry data has confirmed that stroke is a rare but significant complication after LHC, occurring in 0.2% of patients [1]. Stroke is believed to be the consequence of cerebral injury resulting from particulate (solid) micro or macro embolism [2].

Cognitive dysfunction has also been identified after LHC following both interventional and diagnostic procedures. An incidence of 16.7% at 24 h after the procedure and up to 21% after 3 months has been reported [3,4]. Cognitive dysfunction is more subtle than acute stroke and identification requires structured pre and post procedure cognitive testing [5]. Cognitive dysfunction is known to follow major operative procedures [6], especially cardiac surgery using cardiopulmonary bypass (CPB) and, in this context, is termed Postoperative Cognitive Dysfunction (POCD). Microemboli have been hypothesized as a cause of POCD [7]. In the cardiac surgery setting, where microemboli have been measured by Transcranial Doppler (TCD) in the middle cerebral artery, conflicting results have arisen, both in support of and against an embolic mechanism for POCD [8,9].

The identification of microemboli during LHC raises the question of whether these may be associated with cognitive dysfunction following this procedure. Microemboli have been identified during LHC procedures using TCD, where they are temporally associated with catheter

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manipulation in the thoracic aorta and contrast injections in the aortic root and left ventricle. These emboli have been considered as 'benign' because their presence has not been associated with clinical stroke [10,11]. This is not surprising because stroke is believed to result from a larger embolic or thrombotic event. However, even though microemboli may not lead to overt stroke, they may produce smaller cerebral lesions manifesting as cognitive dysfunction.

The aim of this study was to assess the incidence of cognitive dysfunction in elderly patients three months after undergoing elective CA and investigate any association between cognitive dysfunction and microembolic count measured by TCD during CA.

2. Methods

This was a prospective observational study involving a sub-group of patients from the Cardiac Interventions, Surgery and Cognitive Outcome (CISCO) study (ACTRN:12607000051448). Early cognitive outcomes for a subset of the CISCO study patients have been published previously as part of a comparative paper [4]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the St Vincent's Hospital Human Research Ethics Committee (HREC # 172/06). All participants provided written informed consent.

Patients scheduled for elective first-time CA were eligible if they were: ≥50 years; resided within proximity to the hospital to enable home visits for cognitive assessment; no history of neurovascular disease (e.g. prior stroke); and adequate English to enable cognitive testing. Exclusion criteria were: severe impairment of cognition at baseline (evidenced by either a Mini Mental State Examination (MMSE) ≤ 26 or a Clinical Dementia Rating score ≥ 1.0); physical limitations that would limit cognitive testing (e.g. significant visual or hearing impairment), significant medical comorbidities (e.g. severe cardiac failure); and daily long-term medication use that may confound cognitive testing (e.g. benzodiazepines).

Eligible patients were contacted by telephone to explain the study and gain verbal agreement to visit them at home. Home visits were within 7 days prior to the procedure to gain written informed consent, perform final screening (medical history and MMSE) and should the patient be then eligible, administer baseline cognitive testing. The majority of this testing was done at the patient's home to provide a more relaxed and stress-free environment. Noisy and unfamiliar testing environments, such as hospitals, have been shown to negatively affect test results [5]. Cognitive tests included a battery of 8 standard neuropsychological tests comprising: Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Auditory Verbal Learning Test (CERAD-WLT), Trail making test part A (TMTA); Trail Making test part B (TMTB); Digit Symbol Substitution test (DSST); Controlled oral word association test (COWAT); Consortium to Establish a Registry for Alzheimer's Disease verbal fluency – animals (CERAD fluency) and the Grooved pegboard for dominant (GPBd) and non-dominant hands (GPBnd). In addition, depression and anxiety scores were obtained using a Visual Analog Scale[12], and the National Adult Reading Test (NART) was used to infer baseline IQ[13]. These tests have been detailed elsewhere [14].

Cognitive dysfunction after CA was assessed using the same test procedures and analyses employed for assessing POCD after both cardiac and non-cardiac surgery[14,15]. As LHC with CA is not generally described as an operation, we define the term Post Procedural Cognitive Dysfunction (PPCD) to encompass cognitive dysfunction in this context. PPCD was determined using the reliable change index (RCI) [16] as previously described for POCD[4]. For each cognitive test, the individual baseline test score was subtracted from the test score at 3 months. From this, the mean change occurring in the control group over the same time was subtracted, removing any practice effect. This score was then divided by the standard deviation for the change in test results of the control group which adjusted for population variability. These scores were then used to create a combined test score using the sum of z scores for each test divided by the standard deviation of this total in the control group. PPCD was defined in an individual when their RCI score was less than −1.96 on 2 or more tests and/or their combined z score was less than −1.96. This provides a robust classification of PPCD based on either a substantial failure on 2 or more individual tests, or a more pervasive subtle decline across the cognitive test battery.

TCD was performed using a Doppler Box™ digital analyser (Compumedics, GmbH, Singen, Germany) and QL software (Version 2.8, Compumedics GmbH, Singen, Germany) which continuously recorded the data. This system incorporated a dual-frequency ultrasound probe (2.0/2.5Mhz) to provide software based discrimination between solid and gaseous microembolism, as recommended by recent reviews [17]. Prior to LHC, an intravenous cannula was inserted and the TCD probe was applied to the patient's right temple to determine if a trace of sufficient quality could be obtained by aligning the probe with the patient's right middle cerebral artery using the temporal window. Although emboli arising from LHC can spread throughout all the cerebral arteries, the right middle cerebral artery was targeted because it reflects a significant proportion of the cerebral inflow and is a reliable TCD target. The depth of the insonation was adjusted to provide optimal signal flow amplitude. TCD settings were depth 40–50 mm; scale settings −100 to 100 cm/s; detection threshold 9 dB; sample volume 12 mm; Fast Fourier transformation points used 256; and High-pass filter settings 150 Hz.

Once the patient was settled on the procedure table, the TCD probe was adjusted to re-establish a stable TCD signal and TCD recording continued throughout the procedure.

Both automated and manual analysis of TCD data was performed offline. For manual detection, microemboli (particulate and gaseous) were identified as high intensity transient signals (HITS) based on consensus committee recommendations using acoustic (characteristic brief 'chirp') and amplitude criteria (>3 dB above background intensity)[18] and matching the event with the colour Doppler M-mode profile to determine direction[19]. It is technically difficult to resolve more than 10 HITS per second so showers of emboli (e.g. during ventriculography) were allocated 10 emboli per second of shower duration. Automated emboli counting with discrimination between solid and particulate emboli was attempted for all patients[20], with a threshold of 9 dB set for artefact rejection. We used the manual count as the primary measure because automated counting lacks sensitivity and specificity[18] and because the automatic count failed to work due to technical difficulties in some patients and furthermore, failed to differentiate solid from gaseous microemboli in other patients.

Patients were admitted to the Cardiac Investigation Unit on the morning of their CA. They were given an oral premedication of temazepam (10 mg) and promethazine (25 mg) 1–2 hours prior to the procedure. Patients were then transferred to the cardiac catheter laboratory and underwent continuous EKG, blood pressure and oxygen saturation monitoring during the procedure. No further sedation was required for any of the patients. All LHC was undertaken using a femoral arterial approach and all patients underwent selective CA. In addition, left ventriculography was routinely performed, using a high-pressure contrast injection (typically 30 mL of contrast at 15 mL/s). Time-points for key events are detailed in Fig. 1. Procedure duration and contrast volumes were recorded.

A control group is required to calculate PPCD. These participants were volunteers recruited from the community following advertisements as part of the concurrent Anesthesia Cognition Evaluation study in orthopedic surgery (ACTRN: 012607000049471). The control participants were aged between 55–73 years, had large joint osteoarthritis, and had no surgery planned for the next 12 months. Otherwise, they met the inclusion and exclusion criteria cited above for the study patients. The control participants underwent neuropsychological testing with the same battery of tests, and at the same time intervals, as the study patients. Control participants and study patients who underwent surgery between baseline testing and 3 months were excluded.

2.1. Statistical methods

The number of patients required for this study was based on the distribution of microembolic signals per patient associated with LHC measured by Bladin et al. [21]. Assuming cognitive decline at 3 months occurs in 15% of patients undergoing LHC [4] and that the majority of these have the highest microembolic count, then the mean count for patients suffering cognitive decline would be 95.4 (SD 68.6) (the mean of an upper 15% from Bladin et al. [21]). The mean count in the remainder of this group (i.e. those likely to be without cognitive decline) would be 40.4 (SD 23.1). Sample size calculations show that we would require 52 patients to verify this hypothesis with an $\alpha < 0.01$ and a power of 0.9. In order to allow for patient withdrawal, non-compliance and procedural difficulties we chose to recruit 70 patients.

Univariable analysis was performed using Student's t-test for continuous data, and Chi-square or Fisher's Exact test (two-tailed) for non-parametric data. Multivariable analysis for the primary outcome was applied using logistic regression with entry set at a univariable p-value of 0.2 or less. IQ and age are known associates of POCD and were included in the multivariable analysis. Data distribution is reported as mean and standard deviation (SD) or median and interquartile range (IQR). Odds ratios are expressed with 95% confidence intervals (CI). Analysis was performed using STATA (Version 12.1; Stata Corp., College Station, TX). A probability value of less than 0.05 was taken to indicate statistical significance.
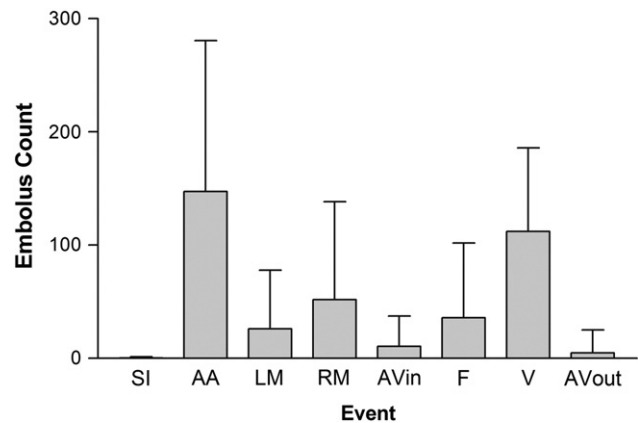

Fig. 1. Mean embolic count per angiography event. Error bars represent standard deviation. Events: SI, sheath insertion; AA, aortic arch – root; LM, LMCA injection; RM, RMCA injection; AVin, crossing AV into LV; F, flush in LV; V, ventriculogram; AVout, crossing AV out of LV.