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Cerebral Hemodynamics during Coronary Artery Bypass Graft surgery: The effect of carotid stenosis Running Head: Carotid stenosis and cerebral regulation

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Abstract

Carotid stenosis is a frequent coexisting condition in patients undergoing coronary artery bypass graft (CABG) surgery. The impact of carotid stenosis on cerebral perfusion is not fully understood. The purpose of this study was to determine the impact of carotid stenosis on cerebral blood flow velocity in patients undergoing CABG. Seventy-three patients undergoing CABG were prospectively recruited and underwent preoperative Duplex carotid ultrasound to evaluate the degree of carotid stenosis. Intraoperatively, transcranial Doppler ultrasound was used to record of the mean flow velocity within the bilateral middle cerebral arteries. Additionally, during the period of cardiopulmonary bypass, regulators of cerebral hemodynamics such as hematocrit, partial pressure of carbon dioxide, and temperature were recorded. The ipsilateral middle cerebral artery mean flow velocity was compared in arteries with and without carotid stenosis using a repeated measures analysis. Seventy-three patients underwent intraoperative monitoring during CABG and 30% (n=22) had carotid stenosis. Overall, MFV rose throughout the duration of CABG including when the patient was on cardiopulmonary bypass. However, there was no significant MFV difference between those arteries with and without stenosis ($F=1.2$, $p=.21$). Further analysis during cardiopulmonary bypass, demonstrated that hemodilution and partial pressure of carbon dioxide may play a role in cerebral

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autoregulation during CABG. Carotid stenosis did not impact mean cerebral blood flow velocity during CABG. The cerebrovascular regulatory process appears to be largely intact during CABG.

Keywords

transcranial Doppler; carotid stenosis; cardiac surgery; cerebral perfusion

Introduction and Literature

Coronary artery bypass graft surgery (CABG) is a common operation, which is associated with significant morbidity and mortality.(Rosamond et al. 2007) While operative techniques, anesthesia, and cardiopulmonary bypass have improved outcomes over the past 10 years, there is inherent neurologic risk associated with CABG. Stroke and postoperative cognitive decline, two major neurological outcomes, may be related to cerebral hypoperfusion during CABG. Given the high incidence of co-existing carotid disease in patients with severe coronary artery disease(Kallikazaros et al. 1999), intuitively, the combined disease may place these patients at a higher risk of cerebral ischemia during CABG.(Borger Fremes 2001; Coyle et al. 1995; Cywinski et al. 2006; Guzman et al. 2008)

Transcranial Doppler (TCD) ultrasound is a useful tool for non-invasive intraoperative monitoring of cerebrovascular hemodynamics. Cerebral blood flow regulation is a fast regulatory mechanism which serves to maintain constant blood flow to the brain by rapidly adjusting cerebrovascular resistance and compensating for fluctuations in cerebral perfusion pressure.(Aaslid et al. 1989; Newell et al. 1994; Paulson et al. 1990) Cerebrovascular resistance is in turn governed by arteriolar diameter. To maintain a constant cerebral blood flow of approximately 50 mL/100 g/min, cerebrovascular resistance increases through arteriolar constriction if perfusion pressures increase, and decreases by arteriolar dilation if perfusion decreases. Studies have shown that larger vessels such as the MCA do not contribute to this process. These studies have repeatedly shown that the diameter of the MCA remains constant under a number of physiological stimuli including changes in pressure as well as pCO₂.(Aaslid et al. 1989; Bishop et al. 1986; Clark et al. 1996; Larsen et al. 1995; Larsen et al. 1994; McIntosh et al. 1985; Sugimori et al. 1995; Ulrich et al. 1995; Vorstrup et al. 1992)

While previous studies have utilized TCD for the assessment of cerebral blood flow velocity during cardiac surgery,(Feldmann et al. 2006; Weyland et al. 1994) few studies have examined intraoperative cerebral hemodynamics during CABG in patients with and without carotid stenosis.(von Reutern et al. 1988) The purpose of this study was to better understand the impact of carotid stenosis on cerebral blood flow velocity and to examine the impact of regulators of vasomotor function on cerebral blood flow velocity during CABG. We posed two aims: 1) to determine the impact of carotid stenosis on cerebral hemodynamics, 2) to identify dynamic changes in cerebral blood flow velocity and to compare the impact of regulators, such as mean arterial pressure, cerebrovascular resistance, hematocrit, partial pressure of carbon dioxide (pCO₂), and others during cardiopulmonary bypass. We hypothesized that preoperative carotid stenosis would not impact ipsilateral cerebral blood flow velocity and that changes in cerebral blood flow velocity during CABG would follow changes in other vasomotor regulators.

Materials and Methods

Patients

We prospectively recruited 80 patients undergoing CABG at a tertiary VA medical center in Boston, MA. Subjects with inadequate TCD windows (n=6) and those who underwent cardiac

surgical procedures other than CABG (n=1) were excluded. All patients provided written informed consent and the study was approved by the human subjects committee.

Duplex Carotid Ultrasound

All subjects underwent a preoperative Duplex carotid ultrasound using a HDI 5000 Duplex Ultrasound (ATL, Inc. Bothell, WA). The Duplex ultrasound maximal flow was determined and interpreted by an attending radiologist, independent of study aims using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria for determining the degree of carotid stenosis based on mean peak flow of three readings. (NASCET Investigators 1991)

TCD recording

All patients underwent bilateral TCD monitoring of the bilateral middle cerebral arteries (MCA) during the operation using a Pioneer 8080 transcranial Doppler instrument (Nicolette Vascular, Madison, WI) using 2 MHz probes by an experienced TCD technician. Initial depth was set to 55mm and was adjusted to optimize MCA signal. We analyzed TCD readings at 9 stages of the CABG procedure. These stages were chosen because each is a necessary step during the CABG procedure which occur sequentially and thus provided consistent analytic timepoints. Surgical stages were defined as follows: 1) Baseline: recorded following anesthesia but prior to any surgical incision; 2) Surgery start: recorded upon the first incision; 3) Insertion of the aortic cannula of the cardiopulmonary bypass pump; 4) Cardiopulmonary bypass initiation; 5) Application of the aortic cross clamp; 6) Removal of the aortic cross clamp; 7) Cessation of cardiopulmonary bypass; 8) Removal of the aortic cannula; and 9) End of case: recorded in the minute following the closure of the pericardial cavity. During periods of aortic cross clamp application and removal, cardiopulmonary bypass flow was reduced by protocol. TCD readings in these periods were recorded after the patient had returned to a steady state.

The TCD records for the 5 seconds prior to and for 1 minute following the initiation of the surgical stages were saved and analyzed after the case. The 5 seconds prior to initiation was necessary to capture the initial event. Over the 1 minute of interest after initiation, the mean cerebral blood flow velocity (MFV) in each MCA was averaged from the envelope feature of the TCD instrument. Prior to including the waveform, we ensured that the envelope fit the waveform. Mean arterial pressure (MAP) was recorded from the arterial line. Cerebrovascular resistance (CVR) was calculated as the ratio of MAP to MFV. To compare MFV, MAP, and CVR on a similar scale, the percent change from baseline was calculated for each timepoint $((t_i - t_0)/t_0 * 100)$. For the analysis of vasoregulatory factors, the percent change was calculated using the initiation of cardiopulmonary bypass timepoint as the referent value.

Operative procedure

All patients underwent standard general anesthesia including induction, paralysis, and intubation. The operative procedure was performed by an attending surgeon who made intraoperative clinical decisions necessary for the patient. The perfusion strategy featured the following components: 1) systemic normothermia ($>35^{\circ}\text{C}$); 2) low-dose heparin protocol including heparin-coated circuits (Medtronic Inc., Minneapolis, MN); 3) closed system with elimination when possible of the blood-gas interface; and 4) reduction of hemodilution elements. A double-stage venous cannula, directional arterial cannula, and a collapsible, soft-shell, venous reservoir (Medtronic Inc., Minneapolis, MN) were used to minimize air to blood interface and avoid stagnation of stored blood. To minimize hemodilution, the perfusion lines were kept short and the crystalloid prime was replaced by retrograde filling of the circuit with the patient's blood resulting in a prime volume of ≤ 800 ml whenever clinically possible.

During cardiopulmonary bypass, a CDI 500 continuous in-line arterial blood gas monitor (Terumo Cardiovascular Systems, Inc, Ann Arbor, MI) was used and values for temperature, partial pressure of oxygen, partial pressure of carbon dioxide, and hematocrit were recorded during the surgical stages. Activated clotting time was monitored every 15 minutes and maintained near a goal of 250 seconds. At the end of bypass, the HEPCON Heparin Management System (HMS) (Medtronic, Inc.) heparin-protamine titration assay was used to assess the circulating heparin level and to determine the precise dose of protamine necessary for heparin reversal. Aminocaproic acid (Amicar®, Xanodyne Pharmaceuticals, Inc., Florence, KY) at a dose of 10 gm was given at the same time of the initial heparin dose with another 10 gm dose given immediately after protamine administration.

Field suction and blood remaining in the CPB circuit was directed to a cell saving device (Haemonetics Corp, Braintree, MA), processed into washed red cells suspended in saline (hematocrit 50–55%), and transfused to the patient upon cessation of CPB. Allogeneic blood was transfused intraoperatively when the hematocrit fell below 25 %. The hematocrit, drawn prior to surgery, was used as the baseline. Cerebral oximetry (Somanetics Inc, Troy, MI) was performed on all patients and the cerebral saturation readings were recorded during the operative stages. Partial pressure of carbon dioxide (pCO₂) was altered as needed to maintain cerebral oxygen saturation at $\geq 65\%$.

Statistical Analysis

We compared the baseline characteristics of those with and without carotid stenosis using a Student's t-test for continuous variables and a Chi square test for dichotomous variables. For each of the nine operative stages, the ipsilateral carotid artery stenosis and MFV were paired for analysis. Comparison between those with and without carotid stenosis was performed using a Student's t-test at each stage. To determine if there were ipsilateral MFV differences with carotid stenosis during the course of the operation and difference with degrees of carotid stenosis, we performed a linear model repeated measures analysis.

The qualitative analysis of vasoregulatory factors on MFV presents the percent change from baseline for MFV, MAP, CVR, and hematocrit. Beginning with the initiation of CPB, we were able to examine the percent change in partial pressure of carbon dioxide, partial pressure of oxygen, temperature, hematocrit, and cerebral oximetry at the four stages of CPB. All statistical analyses were performed with SPSS version 11.5 (SPSS, Inc. Chicago, IL).

Results

After exclusion of those with no TCD windows (n=6) and those who underwent additional cardiac surgery procedures (n=1), data for seventy-three patients were analyzed. The mean age was of 71.6 ± 7.2 years and 30% (n=22) had carotid stenosis. Eight patients had bilateral carotid stenosis. The degree of carotid artery stenosis was 50–70% (n=21), 70–90% (n=6), and occlusion (n=3). Table 1 compares the patients with and without carotid stenosis. The group with carotid stenosis was slightly older (73.7 ± 7.4 vs. 69.3 ± 8.3 years, $p=.04$). Otherwise, the groups were well matched for historical and physiologic variables which can affect CBF such as cardiac comorbidities, prior stroke, diabetes, hematocrit, and systolic blood pressure. Surgical time was not statistically different between the groups (265 ± 53 min. vs. 255 ± 63 min., $p=.51$). The baseline MFV and MAP were not different between the two groups.

The comparison of MFV in patients with and without carotid stenosis is displayed in Figure 1. In the repeated measures analysis, there was no significant MFV difference between those arteries with and without stenosis ($F=1.2$, $p=.21$). MFV in patients with 70–89% carotid stenosis and occlusion did not differ significantly from those with 50% carotid stenosis or those with no stenosis ($F=0.615$, $p=.56$). The number of subjects with 70–90% and occlusion limited

the interpretation of these findings. In post hoc analysis, there was a small, but significant decline in MFV with carotid stenosis at the removal of the aortic cross clamp (MFV with stenosis 36 ± 11 cm/sec vs. MFV without stenosis 48 ± 22 , $p < .05$) compared to arteries without carotid stenosis. No other points were significantly different. A review of the tracings showed the decline of MFV upon the aortic cross-clamp was removed was < 10 seconds in most cases and was of less than one minute duration in all cases.

Figure 2 displays the percent change from baseline in MFV, CVR, MAP, and hematocrit during the 9 stages of the operation for the entire population. There is a substantial increase in MFV (90% increase from baseline) and a concomitant decrease in CVR (60% decline from baseline) and MAP (40% decline from baseline) during the 9 operative stages. Due to hemodilution from intraoperative intravenous fluids and CPB crystalloid prime, hematocrit fell to $28 \pm 4\%$ (an approximately 25% decline from baseline). Figure 3 examines the changes during cardiopulmonary bypass in each of the vasoregulator variables measured in our protocol. During CPB, MFV (panel a) continues to rise in accordance with a decline in CVR (panel c). There is also a simultaneous increase in pCO_2 (panel e) which is also contributing to the rise in MFV. Oxygen levels (pO_2) remained supertherapeutic throughout the case (> 100 torr). During CPB, hematocrit (panel d), temperature (panel g), and cerebral oximetry (panel h) did not change substantially. MAP declined and the decrease was greatest during CPB stages (30–40% from baseline). Comparatively, cerebral oximetry and pCO_2 remained closer to the baseline levels and fluctuated less.

Discussion

The findings of this study suggest that significant systemic and cerebral hemodynamic changes occur during the course of CABG surgery. The overall decline in MAP during the procedure was associated with cerebral vasodilation (decrease in CVR) and increase in MFV to maintain cerebral perfusion, as would be expected with intact autoregulation. Carotid stenosis did not alter cerebrovascular autoregulatory responses. However, autoregulation of cerebral blood flow is a dynamic process which can be affected by many other factors besides MAP. Two such vasomotor regulators which were altered during CPB include hematocrit and pCO_2 .

In response to loss of pulsatile flow, changes in CPB flow rate, and decreased peripheral vascular resistance, there is a decline in MAP during CABG. The resulting decrease in cerebral perfusion leads to cerebral vasodilation in the resistance vessels (arterioles) distal to the MCA, corresponding to an increase in cerebral blood flow velocity through the insonated MCA. This autoregulatory response remains intact during the course of the operation (Figure 2). However, at the same time, pCO_2 and hematocrit are both altered. pCO_2 , which is a potent cerebral vasodilator, is regulated by the perfusionist to maintain cerebral oxygen saturation during the course of the operation. Figure 3 (panel C) shows that pCO_2 levels follow the shape of the MFV curve (panel A). Additionally, hemodilution, resulting from the crystalloid prime occurs during the cardiopulmonary bypass procedure and has been shown to increase cerebral flow velocity. (Brass et al. 1988; Bruder et al. 1998) Given that a decline in hematocrit and an increase in pCO_2 are both associated with an increase in MFV, it is very likely that the overall response of the MFV to the pressure drop may have been lower if pCO_2 and hematocrit had remained stable.

While these results increase our understanding of cerebral hemodynamics during CABG, there are many remaining questions which require further studies. We are unable to describe how the cerebral blood flow response would have reacted had the perfusionist not altered the pCO_2 to maintain cerebral oxygen saturation or if hemodilution was not such a prominent component in the procedure. However, it is important to note that the combined effect of such tight regulation of cerebral vasoregulators is associated with enhanced cerebral perfusion even in

the presence of carotid stenosis. Therefore, given the higher risk of perioperative complications with combined CABG and carotid revascularization (Coyle et al. 1995; Cywinski et al. 2006; Guzman et al. 2008) the data from this study do not support the practice of combined procedures to improve cerebral blood flow prior to CABG.

In post hoc analysis, we found a statistically significant difference in MFV between patients with and without carotid stenosis during the removal of the aortic cross-clamp. This reaction was of short duration in all patients, and we suspect it is not clinically significant. Additionally, there are statistical limitations to the implications of this point and the most interesting aspect is that those with carotid stenosis reacted differently at this stage, compared to other stages. von Reutern and colleagues examined cerebral blood flow velocity in patients with severe carotid stenosis (>80%) and patients without stenosis and did not find reduced cerebral perfusion related to carotid stenosis.(von Reutern et al. 1988) Our findings are in agreement, but extend upon their work by including lower degrees of carotid stenosis (>50%) and collection of other vasomotor regulators, such as pCO₂ and hematocrit.

A major limitation of this work is that we did not assess the intracranial vasculature of our patients, and have no data regarding the intracranial stenosis, vasomotor reactivity and collateral pathways of these patients. In a study of patients with unilateral carotid artery occlusion, Vernieri and colleagues found that increased collateral vessels decreased the risk of ipsilateral stroke.(Vernieri et al. 2001) Collateral vessels may explain why carotid stenosis did not significantly impact MFV during CABG. Additionally, measures of cerebrovascular reactivity have been reported to be impaired in patients with symptomatic carotid artery stenosis(Reinhard et al. 2003; Soenne et al. 2003; Telman et al. 2006). However, our population was substantially different in that those with symptomatic carotid stenosis were unlikely to undergo CABG and very few patients had occlusion. Moreover, our study is unable to identify the impact of longer operative procedure and anesthesia duration on cerebrovascular reactivity and MFV. Future studies with measurement of preoperative vasomotor reactivity and collateral vessels may provide additional insights into our understanding of cerebral hemodynamic regulation during CABG.

Results about increasing degree of carotid stenosis should be interpreted with caution because the reduced number of subjects with severe stenosis. Additionally, it is important to note that patients with more than 90% stenosis, those presumably at highest risk of stroke, were not included, as the clinical practice at our medical center is to perform combined carotid endarterectomy and CABG operations in these cases. Findings from our study now justify future studies with this higher risk group to determine if combined revascularizations are warranted. We also we did not obtain preoperative and postoperative imaging studies of the brain to monitor for silent strokes, nor did we obtain perform neurological examinations. For these reasons, the clinical significance of our findings remains unknown. Thus our findings present only a limited view of a complex surgical procedure. Our findings should be viewed mostly as a gross snapshot of cerebrovascular physiology during CABG. Despite the limitations of our measurement abilities, we do present important information related to cerebral hemodynamics during CABG; notably that autoregulation is intact and cerebral perfusion can be maintained with tight adjustment of cerebral vasoregulators.

Summary

In summary, we show that carotid stenosis did not affect MFV during CABG and that there was a relative cerebral vasodilation to maintain cerebral perfusion during the course of the operation in response to a decrease in MAP and hematocrit and an increase in pCO₂. There are many factors which may influence the MFV during cardiopulmonary bypass including

pCO₂, pO₂, and hematocrit. While we explored these factors, further correlation with clinical outcomes is necessary.

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Figure 1.

The impact of ipsilateral carotid stenosis on mean cerebral blood flow velocity. The ipsilateral MFV with carotid stenosis (dotted line) was not significantly different than the MFV without carotid stenosis. In post-hoc tests, there was a difference upon removal of the aortic cross clamp (*). AXC- aortic cross clamp, CPB – cardiopulmonary bypass, Op.- operation

Figure 2. Cerebral Hemodynamics during CABG. The rise in mean flow velocity nearly doubles during the course of the operation while mean arterial pressure and cerebrovascular resistance decline. AXC- aortic cross clamp, CPB – cardiopulmonary bypass, Op.- operation

Figure 3.

Physiological measurements during cardiopulmonary bypass. The eight panels depict the percentage change from initiation of cardiopulmonary bypass. Each measurement is represented in a separate panel: (a) mean flow velocity (MFV), (b) mean arterial pressure (MAP), (c) cerebrovascular resistance (CVR), (d) hematocrit, (e) partial pressure of carbon dioxide (pCO₂), (f) partial pressure of oxygen (pO₂), (g) temperature, and (h) cerebral oximetry. AXC- aortic cross clamp, CPB – cardiopulmonary bypass

Table 1

	Without Stenosis (n=51)	With Stenosis (n=22)	p-value
Age, yrs	69.3 (8.3)	73.7 (7.4)	.04
Sex, Male	51 (100%)	21 (96%)	.94
Blood Pressure, mmHg			
Systolic	112 (19)	119 (24)	.28
Diastolic	55 (7)	55 (15)	.98
Mean	74 (10)	76 (16)	.60
Blood Flow Velocity, cm/s			
Systolic	51.2 (16.4)	49.6 (12.4)	.88
Mean	26.1 (9.5)	26.5 (7.3)	.72
Baseline Hematocrit (%)	39.4 (6.2)	37.4 (5.4)	.21
History of Diabetes	24 (47%)	12 (54%)	.62
History of Hypertension	39 (76%)	20 (87%)	.52
History of Dyslipidemia	36 (71%)	19 (86%)	.24
History of stroke/TIA	7 (14%)	4 (18%)	.72

Table 2

Mean values for physiological measurement upon initiation of cardiopulmonary bypass

Physiological Variable	Mean (SEM)
Mean Flow Velocity (cm/sec)	40.8 (1.8)
Mean Arterial Pressure (mmHg)	46.8 (1.7)
Cerebrovascular Resistance (mmHg)	1.4 (0.1)
Hematocrit (%)	27.8 (0.4)
pCO ₂ (mmHg)	47.6 (0.8)
pO ₂ (mmHg)	288 (8)
Temperature (°C)	35.2 (0.2)
Cerebral Oximetry (%)	57.6 (0.8)