The Coronary Baroreflex in Humans

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Abstract: Previous studies have identified the presence of coronary baroreceptors in animal models. We set up a study to explore the presence of coronary baroreceptors in humans, which was performed with isolated, graded aortic root perfusion in patients during cardiopulmonary bypass. With ethical approval 12 patients with normal coronary arteries, aged 58–75 (mean 69) years undergoing mitral valve surgery were recruited to the study with informed consent. Those with aortic valve incompetence, coronary, or peripheral artery disease and diabetes mellitus were excluded. They were randomized to have their coronary perfusion pressure set low at 50 mmHg for 90 seconds and then adjusted high to 80 mmHg for 90 seconds (group L–H) or the reverse sequence (group H–L). Average arterial pressure and approximately constant systemic flow over 30-second periods were used to calculate vascular resistance (SVR). The first six experiments followed initiation of cardiopulmonary bypass and aortic clamping but before the delivery of cold blood cardioplegia; the blood temperature for these experiments was kept at 32°C. The remaining six were conducted prior to removal of the aortic cross clamp at 37°C. Coronary sinus blood samples were analyzed to exclude myocardial ischemia. Coronary sinus blood samples showed insignificant variation in oxygen saturation, lactate, and troponin T. Three patients were excluded because of unstable blood pressure. In the (L–H) group SVR reduced in 4 of 4 remaining patients (mean −9.4%, range −3.9 to −19.6%). In the (H–L) group SVR increased in three patients (mean +2.0%, range 1.1 to 3.7%) but decreased in two (−8.9% and −15.8%). These preliminary results, although not statistically different, suggest the presence of coronary baroreceptors in humans. The reflex vascular responses are similar to those previously reported in animal models. Keywords: baroreceptors, coronary artery, blood pressure, coronary pressure, human.

Baroreceptors located in the aortic arch and carotid sinuses play an important part in the regulation of blood pressure. Their action is centrally mediated, results in a rapid vascular response, and quickly is reset when exposed to sustained pressure changes. Increasing evidence exists that baroreceptors also are located in the coronary arteries. Woolard (1) in 1926 described the rich innervation with vagal branches of the adventitia of the left coronary artery in humans and, in 1965, Brown (2) demonstrated afferent vagal activity in response to changes in coronary pressure in cats.

Since 1993, Hainsworth et al. (3–8) have been using an anaesthetized canine model to characterize a range of cardiac and arterial baroreceptors. One model involved independent perfusion of the proximal aortic root, aortic arch, and carotid sinuses at controlled pressures. Pressure in each region was set with blood flow from air pressure regulated reservoirs. Pressure in one region was varied whereas the other two held constant and blood pressure in the remaining systemic circulation at constant flow indicated changes in systemic vascular resistance (SVR).

In 2002, Bennetts et al. (9) reported a sheep model with 2-week survival. A median sternotomy was performed and the left internal mammary artery was grafted to the midportion of the left anterior descending coronary artery (LAD). An angioplasty balloon was inserted retrogradely into the proximal LAD and the LAD ligated at the insertion point. Balloon inflation stretched the LAD without affect on coronary flow, blood pressure, and heart rate changes. This was repeated at intervals over the 2 weeks when the sheep were anaesthetized and conscious.

The relevant observations for this article from the previous two models are that: (1) there are no left ventricular stretch receptors (3,4); (2) there is a prompt decrease in systemic arterial pressure with increased coronary pres-
sure (5,6); (3) there is a delayed increase in systemic arterial pressure with decreased coronary pressure (5,6); (4) the response is to mean rather than pulsatile pressure (7); (5) there is a similar magnitude of response to the carotid effect (7); (6) there is no determinable threshold of action of the coronary effect (7); (7) and no resetting within 40 minutes (8); and (8) there is a similar effect during halothane anesthesia as when awake (9).

Brief Description of our Human Model
During cardiopulmonary bypass the blood cardioplegia system was temporarily modified to perfuse the proximal aortic root with warm blood (Figure 1). With the aortic clamp in place cardioplegia pump flow was adjusted to maintain a target pressure measured with a needle in the aortic root. Patients were randomly allocated to have a high (80 mmHg) target pressure for 90 seconds changed to a low (50 mmHg) target pressure for a further 90 seconds (group H-L) or the reverse sequence (group L-H).

Small adjustments were made to the arterial pump to compensate for changes made to the cardioplegia pump to maintain an approximately constant systemic flow because the input to the cardioplegia pump is effectively from the output of the arterial pump (Figure 1). Mean pressure in the left radial artery, aortic root pressure (patient monitor, Hewlett Packard, Palo Alto, CA) and arterial and cardioplegia pump flow (S3 Heart Lung machine, Sorin, Saluggia) were recorded continuously (bespoke software and Excel spreadsheet, Microsoft, Seattle, WA). A Jostra Heater Cooler Unit (Maquet, Rastatt, Germany) was used with the cardioplegia device to allow rapid reduction of water temperature to 4°C at the end of the study period to deliver cold blood cardioplegia. An Edwards Research Medical retrograde cardioplegia cannula with self-inflating balloon was placed in the coronary sinus. Coronary sinus blood samples (10 mL) were taken immediately before application of the aortic cross-clamp and at the end of the experimental period. These were analyzed for oxygen saturation, lactate and troponin T.

METHOD
Ethical committee approval and written informed patient consent was obtained. Patients with aortic incompetence, coronary, or peripheral artery disease or with diabetes were excluded. Twelve patients were listed for mitral valve replacement and were angiographically free of coronary artery disease.

Anesthesia consisted of premedication with temazepam; induction with alfentanil, etomidate, and pancuronium; and maintenance with propofol and isoflurane. Glyceryl trinitrate and phenylephrine were used as required but not near the period of controlled aortic root perfusion.

Surgery involved sternotomy and aortic root and bicaval cannulation for cardiopulmonary bypass. A pulmonary venous cannula was placed to vent the heart. The

Figure 1. Illustration of heart prepared for isolated aortic root perfusion and heart lung machine with modified cardioplegia system.
heart lung machine included an Avant oxygenator and Vanguard cardioplegia device (both Sorin) with a modified St. Thomas’s cardioplegia solution. Bypass involved prime displacement, resulting in an effective priming volume of approximately 1000 mL of 50/50 Hartmanns solution and Gelofusine, with a non-pulsatile blood flow of 2.4 L/min/m² and systemic cooling to 32°C.

The first six patients (L-H1 to 3, H-L1 to 3) had the retrograde cardioplegia cannula positioned into the coronary sinus. These six patients were established on bypass with the oxygenator and cardioplegia device water temperatures set at 32°C. The study started within 5 minutes of the initiation of bypass and completed in 3 minutes. The coronary sinus blood sample was drawn and at constant systemic flow the aortic clamp was placed. The cardioplegia pump flow was started and adjusted to maintain the target root pressure. The pressure was maintained for 90 seconds to allow systemic blood pressure to stabilize then the alternate target pressure achieved by change in cardioplegia pump flow with compensating change to the arterial pump to maintain constant systemic flow. After a further 90 seconds the second coronary sinus blood sample was drawn and the blood cardioplegia device modifications removed to establish cold blood cardioplegia within 10 seconds. The surgical procedure then continued as normal.

The second group of six patients (H-L4 to 6, L-H4 to 6) had the study period moved to the end of the aortic clamp period, after the valve replacement and at blood temperatures of 37°C. The aortic root was perfused for several minutes with blood at 37°C during closure of the atrium, warming the heart. Aortic root pressure monitoring was positioned and cardioplegia pump flow altered to establish the target pressure. The previously described methodology was then completed. At the end of the study period the aortic clamp was removed and the surgical procedure continued as normal.

RESULTS

The two groups were similar in sex (seven women and three men), age (58–75 years), and weight (51 to 84 Kg). Coronary perfusion pressure was readily maintained within ± 10 mmHg of the target pressures of 50 and 80 mmHg and achieved within 20 seconds, the individual step change in pressure ranged between 25 and 35 mmHg. Coronary artery flow varied considerably from 0.2 to 1.0 L/min. The highest flows were presumably related to leakage through the aortic valve though interruption of the procedure was avoided by the functioning pulmonary venous vent preventing distension of the heart.

In the first six patients, oxygen saturation in the coronary sinus blood samples remained greater than normal (range 58–92%) and lactate and troponin T remained at baseline levels indicating adequate coronary perfusion during the experimental period. Coronary sinus sampling was discontinued for the remaining six patients.

Mean blood pressure for each patient during the study period is represented in Figure 2. Three patients were excluded from interpretation, patient L-H1 required a 1-L/min flow to reach the target pressure resulting in a significantly reduced systemic flow, patients L-H5 and H-L5 had inexplicable blood pressure instability at the end of the stabilization period.

Manual adjustments of the two pumps caused systemic flow to change slightly during the course of the study resulting in the systemic arterial pressure not accurately after changes in SVR. Systemic flow was calculated by subtracting the cardioplegia pump flow from arterial pump flow. Systemic arterial pressure and systemic flow were averaged over the course of 30-second intervals and SVR calculated by assuming venous pressure on bypass to be zero and dividing pressure by flow. SVR during the 30 second period at the end of the stabilization period was taken as baseline and subsequent changes in SVR during the three following 30-second intervals reported as a percentage change from this baseline (Table 1).

Systemic arterial pressure in the first six studies at the beginning of bypass lacked stability (L-H1 to 3, L-H1 to 3; Figure 2) perhaps as the result of some of the known effects of initiating cardiopulmonary bypass. To avoid this early instability the study period was then changed to the end of the aortic clamp period, despite the resulting uncertain degree of myocardial reperfusion and rewarming. Systemic arterial pressure stability was not markedly improved.

The entire L-H group showed a fall in SVR (mean –9.4%, SD 7.2) during the time period 30 to 60 seconds after the change in root pressure, which was consistent with the rapid onset and magnitude found by Hainsworth et al.

The H-L group had three of five patients with slightly increased or unchanged SVR (mean + 2.0%, range 1.1% to 3.7%) at the end of the study period, which was consistent with the later onset of change found by Hainsworth et al. The remaining two patients showed large falls in SVR (–8.9% and –15.8%) with a mean for the whole group of –3.7%, SD 8.3 during the 60- to 90-second period. The differences between the two groups are not significantly different returning a probability of difference of 0.25 with a two-tailed Student t test.

Study Limitations

The study was designed to minimize the variation from normal operative procedure in magnitude and time. The relatively small aortic root pressure step was selected to remain within our normally acceptable perfusion pressure range of 50 to 80 mmHg. The duration of each step was selected to be 90 seconds because, in the model of
Hainsworth et al., the response to increased pressure had peaked before 90 seconds and had just started in response to a fall in pressure. Each patient was exposed to one pressure change, again to minimize the study period to 3 minutes.

Aortic baroreceptors are primarily located along the aortic inner arch (10); therefore, the placement of the aortic clamp will mostly separate aortic and any coronary baroreceptors. There was no control of aortic or carotid baroreceptors and it is unknown how much they would buffer blood pressure, although the model of Bennetts et al. (10) suggested a positive response would still be obtained. We considered it impractical to control for aorto-carotid baroreceptors manually, by changing systemic blood flow to maintain a constant systemic arterial pressure. Systemic flow was maintained approximately constant to reduce any variation in metabolic affect on vascular resistance.

The effect of our anesthetic regime on the baroreceptor response at the time of the study period is unknown, only propofol was used during the study period but any of the drugs or even surgical stimulation could have a residual effect on baroreceptor response. Propofol has a marked vasodilating effect but it might reasonably be considered constant during the study period. The use of a cloralose allowed a response in dogs (3-8) and in sheep pentathol induction and halothane had a similar effect on SVR as when awake (9) as an illustration to the range of drugs that may allow a response.

Our study group had an age range of 58 to 75 years, and some as a result may have had age related changed baroreceptor responses. Blood pressure was typically low during the study period and there may have been limited reserve for further vasodilation, similarly the low coronary pressure may have been below a “trigger” level with no additional baroreceptor effect.

CONCLUSION

Seven of nine patients responded in a way consistent...
with coronary baroreceptors as described in animal studies. There was a consistent reduction in SVR in response to increased coronary pressure but an inconsistent response to reduced coronary pressure. The changes in SVR between the two groups did not reach a statistically significant level. Blood pressure was surprisingly variable during the study period and further studies will probably need a longer study period to exclude artifact and allow development of a response.

REFERENCES