Baroreflex-autonomic control of regional coronary blood flow conductance in awake sheep

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We have previously shown in the awake dog that integrated baroreflex control of autonomic nerves investing the coronary vessels varies between coronary territories during acute, then steady-state changes in arterial pressure (Quail *et al.*, 1996). It is not known how such mechanisms vary in other species. Confirmation of like mechanisms would offer understanding of reflex coronary autonomic function in other mammals including man. Reflex coronary mechanisms in man are unknown. An awake sheep model was developed for this investigation (Hamut *et al.*, 2006). Merino ewes (n = 5) were prepared under general anaesthesia, *i.e.*, i.v. propofol 5mg/kg, followed by inhaled 2.5-3.5% isoflurane in oxygen. Pulsed Doppler flow probes were implanted on the right, circumflex, and anterior descending coronary arteries. Pacemaker leads were attached to the left atrial appendage and right ventricle. An external vascular occluder was placed around the descending thoracic aorta to control changes in aortic pressure (AoP), and central aortic and venous catheters were positioned in superficial cervical artery and vein to measure pressures (Bishop *et al.*, 2003). The sheep recovered for at least one week. Data were collected under conditions of rest and raised AoP at a constant pacing rate of 150/min, with and without combined cholinoceptor, β1- and β2-adrenoceptor, and α1- and α2-adrenoceptor control (''Total autonomic block'', (TAB)). This was achieved using combined i.v. methscopolamine bromide 270 microgram/kg, propranolol 1 mg/kg, and phentolamine 0.4 mg/kg statum, 1mg/min continuous infusion.

On raising aortic pressure serving all 3 coronary beds in the autonomic intact state, AoP rose by 14, 28 and 32 mmHg at 4s, 8s (immediate reflex period) and 25s (steady-state reflex period), respectively. Changes in coronary conductance varied between time intervals in each bed, and also between beds at specific times. In the circumflex bed at 4 and 8s, conductance rose significantly to 109% ($p < 0.001$) and 104% ($p < 0.05$) of resting control, respectively, but was not changed at 25s. By contrast, while at 4s conductance rose in anterior descending bed to 104% ($p < 0.01$), it did not change in the right coronary bed. In the right bed at 8 and 25s, coronary conductance fell substantially to 87% ($p < 0.01$) and 72% ($p < 0.001$), respectively. In the anterior descending bed at 8 and 25s, conductance fell to 92% ($p < 0.001$) and 91% ($p < 0.001$), respectively. In TAB, the responses in the circumflex bed were strongly modified at 4 and 8s, but not in the steady-state. At 4s, the rise in circumflex conductance was halved, and at 8s reversed, to a significant vasoconstriction to 92% ($p < 0.001$). During TAB, there were minor changes in the response of the anterior descending and right coronary beds.

Therefore, reflex neural vasodilator events dominate myogenic and metabolic local responses mainly in the circumflex bed during the immediate rise in AoP, but do not in the steady-state of maintained AoP. The data suggests neural controls facilitate circumflex coronary flow as an immediate response to rapid left ventricular loading. The effect on circumflex flow is to raise flow to a level (136% of resting) above that observed in the absence of neural control (124%). These effects resemble those in the awake dog. However, in the dog immediate baroreflex dilator effects in the right coronary circulation exist at elevated ventricular rates (White, 1998), and these are absent in sheep. The difference in the right coronary circulation may reflect in sheep a more substantial right coronary vascular bed serving the septal and more distal myocardium relative to the base of the heart, where, *e.g.*, vagal innervation, is less extensive. The response of the anterior descending bed appears similar between the species, and is largely without reflex vasodilator effects.

It is concluded that baroreflex-autonomic control of coronary conductance in the awake sheep varies regionally as it does in the awake dog. The vasodilator events in the circumflex and vasoconstrictor events in the anterior descending beds resemble those in the dog, but in the sheep they are vasoconstrictor in the right coronary circulation.

Quail AW, Cottee DBF, White SW, Porges WL & Hennessy EJ. (1996) *Clinical and Experimental Pharmacology and Physiology*, **23:** 866-73.

Hamut M, Quail A, Cottee D, Seah P, Blake R, White S, McLeod D & Bishop R. (2006) *FASEB Journal*, **20:** A1398.

Bishop R, McLeod D, McIlveen S, Blake R, Gunther R, Davis J, Talken L, Cottee D, Quail A, Parsons G & White S. (2003) *Archives of Physiology and Biochemistry*, **111:** 313-4.

White SW. (1998) *Cardiologia*, **43:** 559-70.

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