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Symposium Report

Cardiovascular control from cardiac and pulmonary vascular receptors

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New Findings

- **What is the topic of this review?**
  The purpose of this review is to summarize present knowledge of the function of the afferent nerves arising from the heart and the coronary and pulmonary arteries. Although there is abundant evidence that atrial receptor stimulation influences heart rate and urine flow, with little or no effect elsewhere, and that ventricular receptors are strongly excited only by chemical stimuli, there is still the erroneous belief that they act as a homogeneous group causing cardiovascular depression.
- **What advances does it highlight?**
  Coronary receptors deserve to be recognized as a potentially important additional group of baroreceptors. Stimulation of pulmonary arterial baroreceptors at physiological pressures causes reflex vasoconstriction and could have a hitherto unacknowledged important role in cardiovascular control, for example in exercise.

Although there has been a tendency to regard cardiac and pulmonary receptors as a single population of 'cardiopulmonary receptors', this cannot be justified as the various receptor types all induce their own particular pattern of responses. Stimulation of atrial receptors increases activity in sympathetic nerves to the sino-atrial node, causing tachycardia, but there is no effect on activity to the myocardium or to most blood vessels. Renal nerve activity, however, is decreased, and secretion of antidiuretic hormone is inhibited, causing diuresis. Ventricular receptors induce a powerful depressor response, but only in response to abnormal chemical stimulation and possibly to myocardial injury. Coronary arterial receptors function as baroreceptors, but have a lower threshold and a more prolonged effect than other baroreceptors. Pulmonary arterial baroreceptors induce vasoconstriction and respiratory stimulation at physiological pressures and may be of importance in mediating some of the responses to exercise, as well as in hypoxic conditions.

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Atrial receptors

Atrial innervation. The atria are innervated by both myelinated and non-myelinated afferent fibres running in both divisions of the autonomic system. The only receptors described histologically are complex unencapsulated endings and these are concentrated at the vein–atrial junctions (Coleridge *et al.* 1957; Fig. 1). There is also a fine network of nerve fibres throughout the endocardium, the function of which is uncertain. The atrial receptors attached to complex unencapsulated endings have been shown to be sensitive to changes in atrial pressure and volume. Paintal (1953) classified them as type A, which discharge during atrial contraction (*a* wave),

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type B discharging during atrial filling (*v* wave) and intermediate with both A and B activity. The discharge pattern can change in different conditions (Kappagoda *et al.* 1976; Fig. 2). In general, the activity of atrial receptors is related to the degree of atrial filling, which is dependent, among other things, on blood volume; hence, they have sometimes been referred to as volume receptors.

There are many more non-myelinated nerve fibres (C fibres) ending in the atria, the activity of which is also stimulated by increases in atrial pressure and volume (Coleridge *et al.* 1973). However, higher pressures are required, and many are silent at normal pressures, becoming active only at abnormally high pressures.

In addition to vagal nerve endings, there are nerve fibres that run in the sympathetic rami. These afferent sympathetic nerves seem to be stimulated by events similar to those affecting the vagal afferents. One feature of these nerves is that they are frequently attached to more than one terminal, sometimes ending in different cardiac chambers (Maksymowicz & Szulczyk, 1983). Some are stimulated by mechanical events, whereas others are excited only by the application of chemicals.

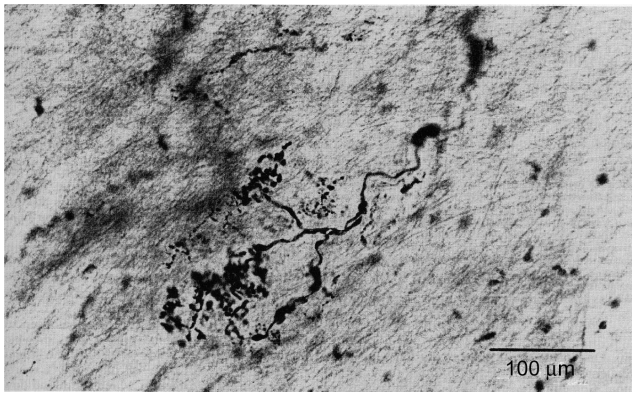

Figure 1. A complex unencapsulated ending of an atrial receptor attached to an afferent nerve

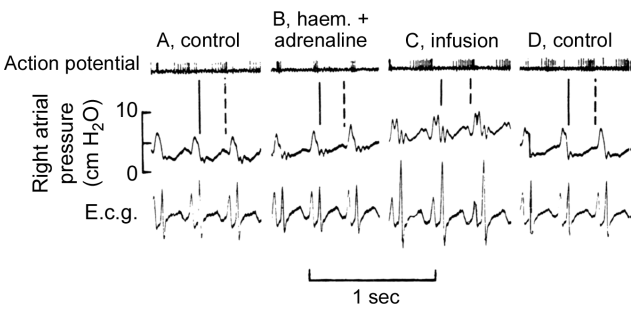

Figure 2. Traces showing changes in discharge pattern of a single unit from an atrial receptor in a cat
Vertical lines relate temporal events in atria and the afferent nerve; continuous line indicates the end of the atrial *a* wave and dashed line indicates the peak of the *v* wave. Control (left), activity is of intermediate type; Haem + Adr, activity has changed to type A pattern after bleeding and administration of adrenaline; Infusion, activity has changed to type B pattern after infusion of dextran; and Control (right), receptor has returned to intermediate pattern. Reproduced with permission from Kappagoda *et al.* (1976).

Reflex responses. Almost 100 years ago, Bainbridge (1915) reported that rapid intravenous infusions resulted in increases in heart rate. The basis for this was established by Ledsome & Linden (1964), who showed that discrete distension of the pulmonary vein–atrial junctions led to a reflex increase in heart rate. Atrial receptor stimulation results in an unusual pattern of responses. There is an increase in activity in cardiac sympathetic nerves, no change in lumbar or splenic activity, and a decrease in renal nerve discharge (Karim *et al.* 1972). The cardiac response seems to be further differentiated, in that there is an increase in heart rate but no apparent effect on cardiac inotropic state (Furnival *et al.* 1971). Carswell *et al.* (1970*a*) found no change in peripheral vascular resistance (Fig. 3), but there was an increase in renal blood flow and consequently, diuresis and natriuresis. Diuresis also occurs in the isolated perfused kidney (Carswell *et al.* 1970*b*) and this is effected through a decrease in the secretion of antidiuretic hormone (Bennett *et al.* 1983). There are decreases also in plasma levels of renin and cortisol (Drinkhill *et al.* 1988; Drinkhill & Mary, 1989).

Physiological role of atrial receptors. As a result of their responses to increases in atrial distension, they are often

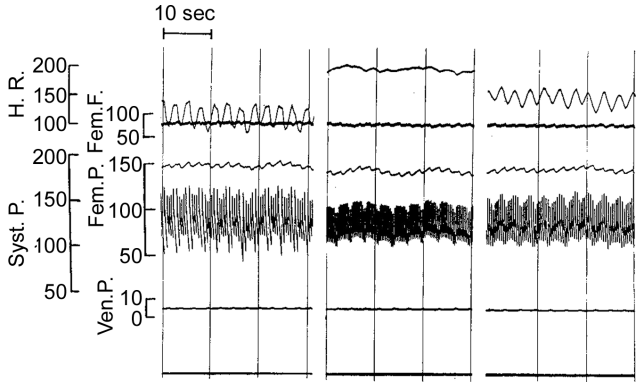

Figure 3. Responses to distension of left pulmonary vein–atrial junctions in an anaesthetized dog
Traces of heart rate, flow to isolated perfused hindlimb (Fem F; in millilitres per minute), femoral arterial perfusion pressure, systemic arterial and venous pressures. Stimulation of atrial receptors caused a large increase in heart rate but no change in hindlimb vascular resistance (perfusion pressure at constant flow was unchanged). Reproduced with permission from Carswell *et al.* (1970*a*).

thought of as volume receptors. The effects on the kidney support this role. The increase in heart rate would have some effect on cardiac output, and it would also decrease heart size, preventing overdistension and possibly ensuring that the heart functions at an optimal level of diastolic filling.

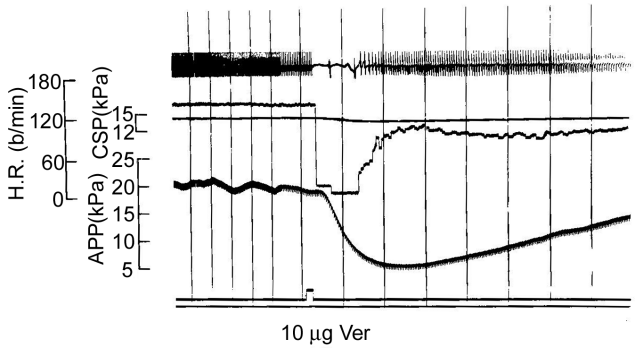

Figure 4. Effects of injection of veratridine into the aortic root of an anaesthetized dog
Responses of ECG, heart rate, carotid sinus pressure and mean systemic arterial perfusion pressure (flow constant). Note the profound bradycardia and vasodilatation (Bezold–Jarisch reflex). Reproduced with permission from McGregor *et al.* (1986).

Ventricular receptors

Ventricular innervation. In contrast to the atria, the ventricles are supplied exclusively by non-myelinated vagal afferents (Thoren, 1977). Some of these nerves respond with a phasic discharge to changes in ventricular pressure, whereas in others the discharge is apparently random and these respond to chemical agents such as bradykin and veratridine (Kaufman *et al.* 1980). Oberg & Thoren (1972) reported that some receptors responded to the combination of reduced ventricular filling and increased inotropic state and suggested that this might form the basis of the vasovagal reaction. However, most receptors are not readily activated by mechanical events and are strongly stimulated only by toxic and irritant chemicals. Some are excited by myocardial ischaemia and infarction (see Hainsworth, 1991).

Reflex responses. Chemical stimulation of ventricular receptors causes profound bradycardia and vasodilatation,

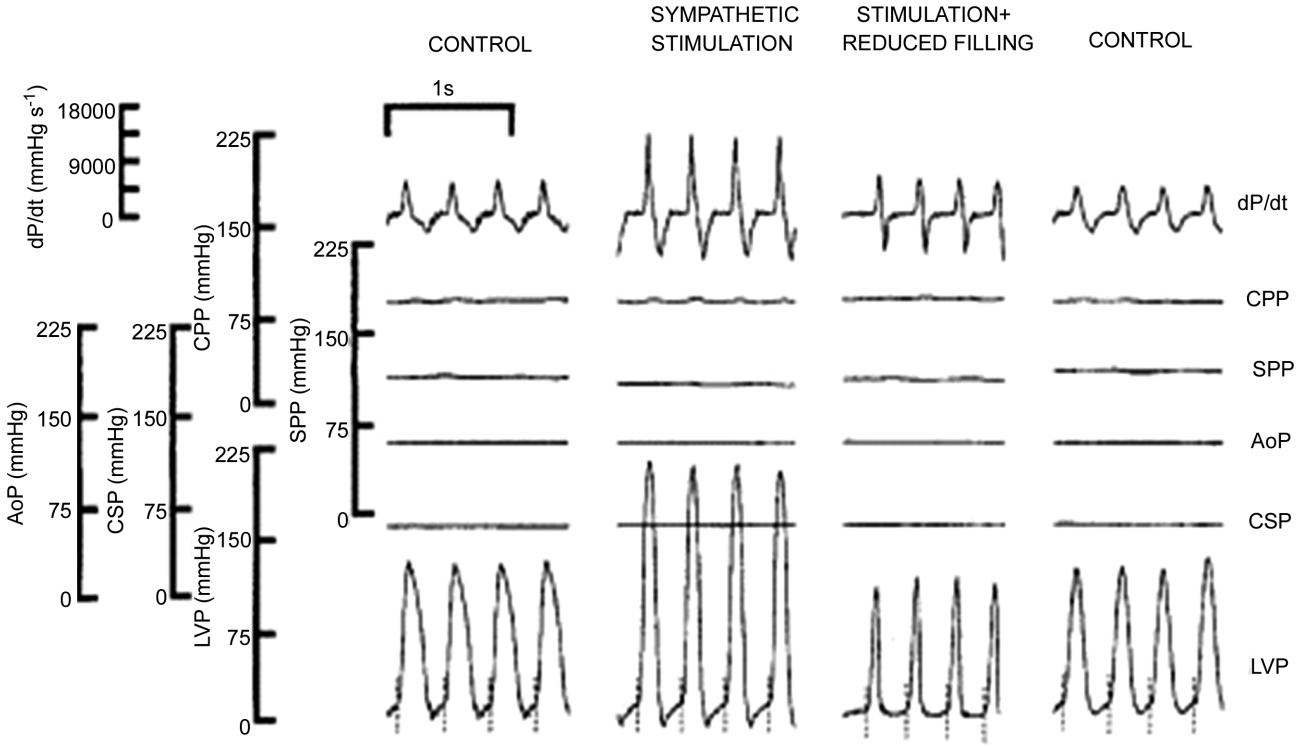

Figure 5. Effects of increased inotropic state (sympathetic stimulation) and stimulation with reduced cardiac filling (bypass) on systemic arterial perfusion pressure (constant flow)
Traces of left ventricular rate of change of pressure (d*P*/d*t*), aortic root (coronary artery) pressure (CPP), systemic arterial perfusion pressure (SPP), aortic arch (baroreceptor) pressure (AoP), carotid sinus pressure (CSP) and left ventricular pressure (LVP). Sympathetic stimulation caused an increase in ventricular systolic pressure and a small vasodilatation (decrease in systemic perfusion pressure); the combination of stimulation and bypass had no apparent effect. Reproduced with permission from Drinkhill *et al.* (2001).

i.e. the Bezold–Jarisch reflex (Jarisch & Zotterman, 1948; Fig. 4). Large increases in ventricular systolic and diastolic pressures cause only a small vasodilatation. An increased inotropic state with or without decreased filling did not induce a response, as had previously been proposed by Oberg & Thoren (1972; Fig. 5; Drinkhill *et al.* 2001).

Physiological role of ventricular receptors. It seems unlikely that ventricular receptors are important in normal circulatory control. It is also unlikely that they are involved in the vasovagal reaction. An increase in activity during injury or ischaemia, which results in decreases in heart rate and blood pressure, suggests that they may have a cardioprotective function.

Coronary arterial baroreceptors

Coronary artery innervation. There are nerves ending in the proximal regions of the coronary arteries that respond to changes in coronary arterial pressure (Fig. 6). Unlike ventricular mechanoreceptors, which are attached to non-myelinated nerves and require high pressures to change their activity, coronary receptors are attached to myelinated nerves and respond to relatively low pressures (Drinkhill *et al.* 1993).

Reflex responses. Increases in the pressure distending the coronary arteries result in reflex dilatation of resistance blood vessels (Fig. 7) and this has also been confirmed in humans (Kincaid *et al.* 2005). Coronary receptors thus act as arterial baroreceptors in that, like those in the aorta and carotid sinuses, they detect changes in arterial blood pressure and bring about responses that buffer the pressure changes (negative feedback). However, unlike carotid and aortic baroreceptors, responses occur when the pressure is changed from below normal up to normal levels (Fig. 8).

The efferent limb of the vascular response is the same as that for the aortic and carotid baroreceptors and relies on withdrawal of efferent sympathetic nerve activity to the vascular beds, seen as reductions in lumbar and renal nerve activities (Drinkhill *et al.* 1996). However,

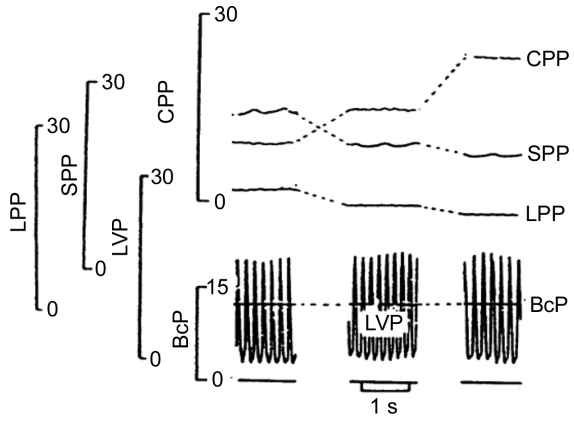

Figure 7. Responses of systemic perfusion pressure (SPP) and hindlimb perfusion pressure (LPP) to increases in coronary arterial (aortic root) pressure (CPP) at constant left ventricular pressure (LVP) and constant brachiocephalic pressure (BcP)
Pressures are in kilopascals (1 kPa = 7.5 mmHg). Increases in coronary pressure from 8 kPa (60 mmHg) induced vasodilatation. Reproduced with permission from Al-Timman *et al.* (1993).

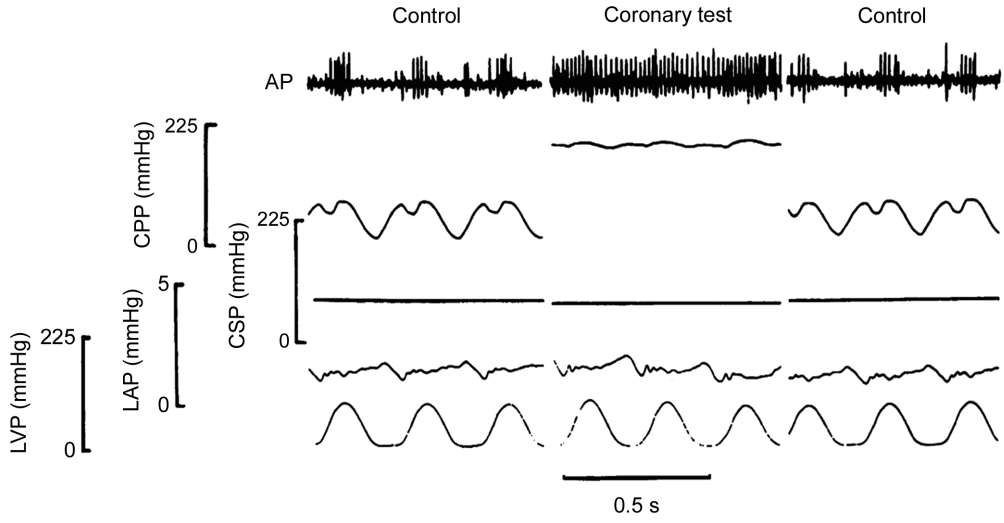

Figure 6. Afferent discharges from a coronary arterial mechanoreceptor in a slip of vagus nerve
Traces of action potentials, coronary artery (aortic root) pressure (CPP), left atrial pressure (LAP) and left ventricular pressure (LVP). An increase in coronary pressure resulted in an increase in afferent nervous activity. Reproduced with permission from Drinkhill *et al.* (1993).

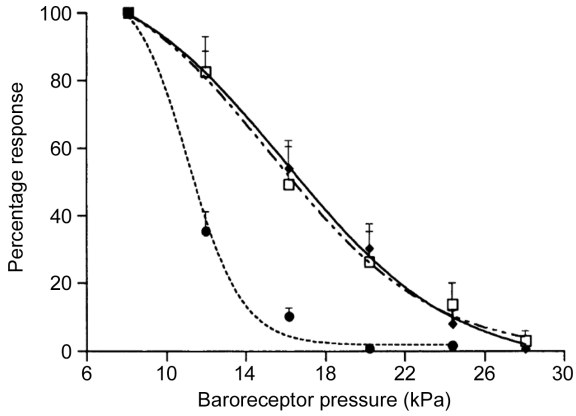

Figure 8. Vascular responses in perfused hindlimbs of anaesthetized dogs to changes in pressure to coronary (filled circles), aortic arch (open squares) and carotid sinus baroreceptors (filled diamonds)
Pressures are in kilopascals (1 kPa = 7.5 mmHg). Each curve is normalized so that the values of vascular resistance at the lowest perfusion pressures are 100%. Note the lower operating range of the coronary baroreceptors. From McMahon *et al.* (1996).

they differ from the other baroreceptors in that, at least in the dog, they do not result in changes in heart rate. They also have a number of other characteristics marking them as distinct. They have a much lower threshold for activation and saturate at lower pressures (McMahon *et al.* 1996). Also, unlike other baroreceptors, they do not show signs of resetting over the short term (McMahon *et al.* 1998), and stimulation of the coronary baroreceptors results in a much more prolonged central inhibition of efferent sympathetic nerve activity (Drinkhill *et al.* 1996; Fig. 9).

Physiological role of coronary baroreceptors. It is now apparent that blood pressure is controlled not only by receptors in the carotid arteries and aortic arch but also by receptors in the coronary arteries and probably also in other still-undiscovered regions. However, relatively little work has been done to establish their exact role. They are likely to be involved in blood pressure control, but protecting against hypotension rather than hypertension. The slow nature of the reflex and the absence of resetting,

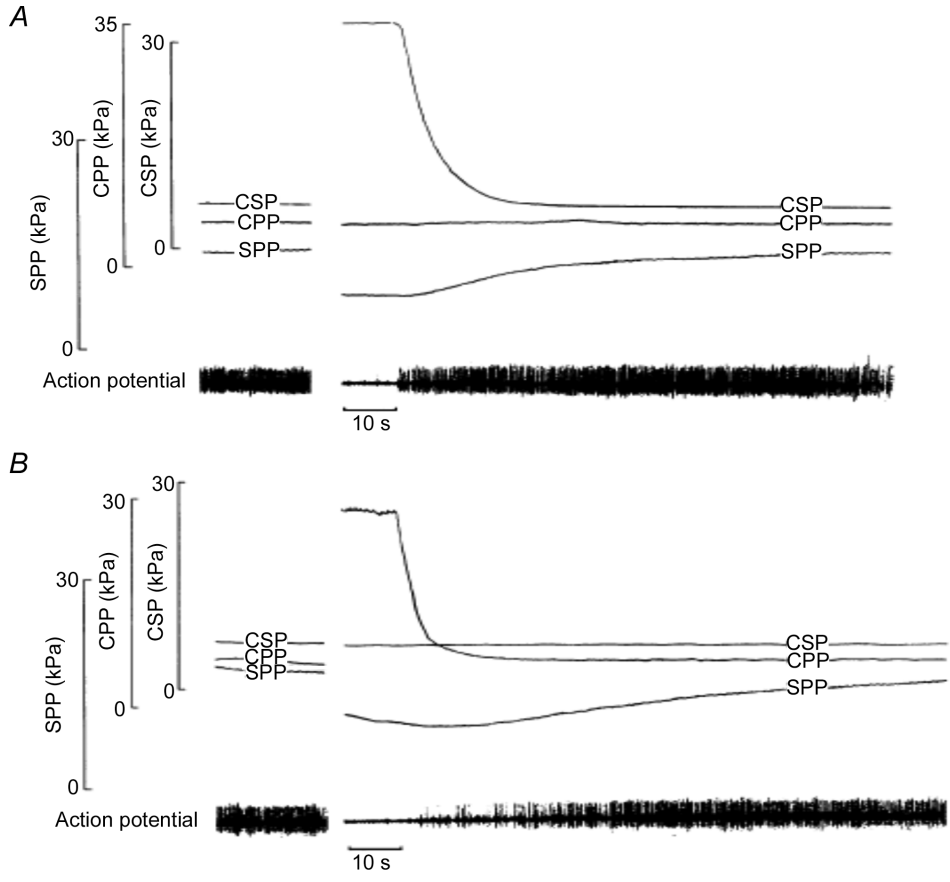

Figure 9. Responses to step decrease in carotid sinus pressure (CSP; *A*) and coronary arterial pressure (CPP; *B*)
Both resulted in increases in systemic arterial perfusion pressure (SPP) and in efferent activity in the renal nerve. Responses to the coronary pressure decrease, however, were slower. Reproduced with permission from Drinkhill *et al.* (1996).

at least in the short term, make it possible to speculate that, unlike the other baroreceptors, they may have a role in the long-term control of blood pressure.

Pulmonary arterial receptors

Pulmonary arterial innervation. The pulmonary trunk and proximal parts of the pulmonary arteries are innervated by myelinated afferents running in the vagus nerves (Coleridge *et al.* 1961). The activity in these nerves is affected by interventions such as venous infusions and vena caval occlusion. Moore et *al.* (2004*a*) re-examined the characteristics of these receptors using a preparation in anaesthetized dogs, in which they vascularly isolated a pouch of pulmonary trunk and main arteries. They found that the range of pressures required to stimulate these receptors was lower after closing the chest and lower still when applying phasic negative intrathoracic pressures (Fig. 10).

Reflex responses. Earlier studies had provided conflicting results and had indicated that unphysiologically high pressures were required to induce any responses (Coleridge & Kidd, 1960; Ledsome & Kan, 1977; McMahon *et al.* 2000). Moore *et al.* (2004*b*), however, showed that, when pulsatile pressures were used to distend the pulmonary arteries, with the chest closed, and phasic negative intrathoracic pressures were applied to simulate respiration, reflex responses were obtained at pressures well within the physiological range. Threshold and inflexion pressures were reduced

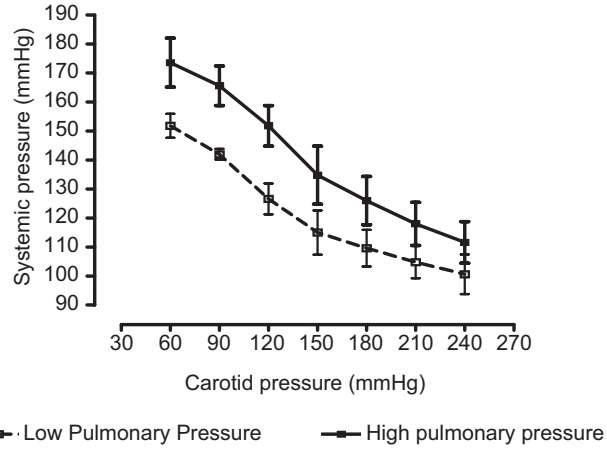

Figure 11. Carotid sinus stimulus–response curves
Changes in systemic arterial perfusion pressures at various carotid pressures plotted at low (5 mmHg) and high pulmonary arterial pressures (33 mmHg). Increasing pulmonary arterial pressure caused a rightward shift of the carotid stimulus–response curve. Reproduced with permission from Moore *et al.* (2004*a*).

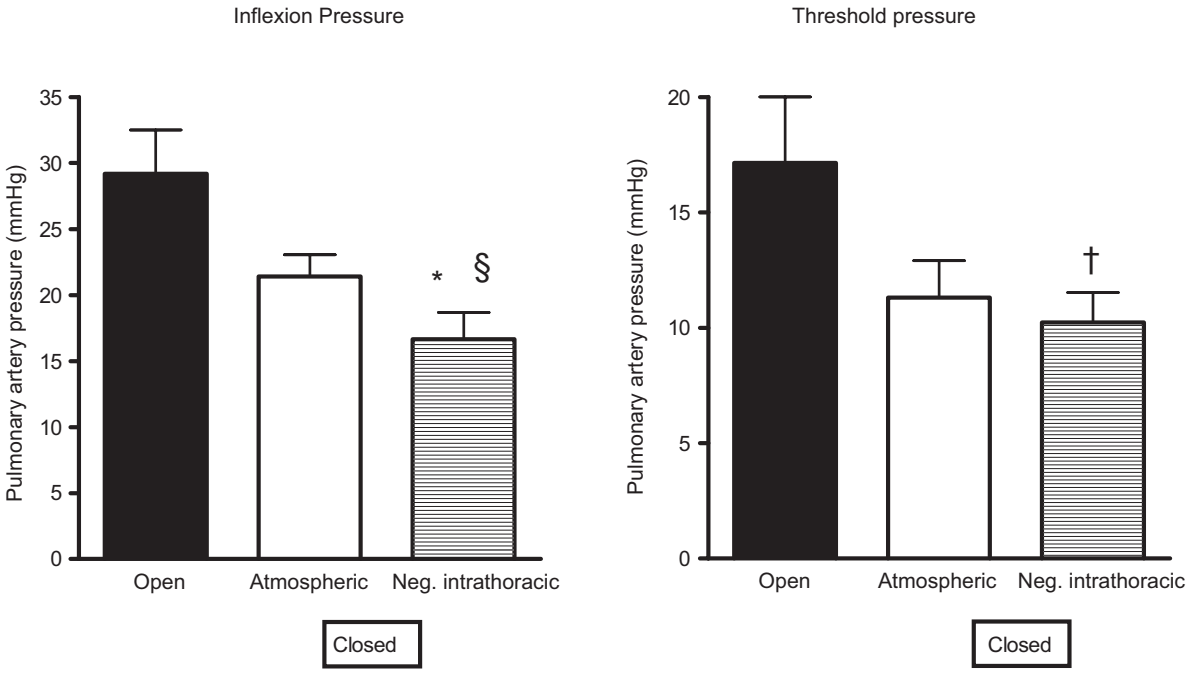

Figure 10. Mean values of pulmonary arterial pressure at inflexion and threshold from plots relating afferent impulse activity in slips of vagus nerve and pulsatile pulmonary arterial pressure with chest open, closed and during phasic negative pressure
* and § significantly different from open. † significantly different from open ($P < 0.05$). Reproduced with permission from Moore *et al.* (2004*a*).

from 28 and 38 mmHg, respectively, with the chest open to 19 and 27 mmHg with the chest closed and phasic negative intrathoracic pressures. The responses were vasoconstriction and an increase in respiratory activity.

Physiological significance of pulmonary baroreceptors. The responses, increases in blood pressure and respiratory activity, are opposite to those from stimulation of systemic baroreceptors. One situation in which they could be of importance is during exercise. The increase in venous return would increase stimulation, and this would be further enhanced by the increased respiratory efforts (a feedforward mechanism). The reflex vasoconstriction could contribute to the hypertension of exercise, and this would be enhanced even more by the rightward shift in the carotid baroreceptor stimulus–response curve that has been shown to occur with pulmonary artery distension (Moore *et al.* 2011; Fig. 11).

Other situations in which pulmonary artery baroreceptors may be important are those associated with hypoxia, such as exposure to high altitudes and respiratory and cardiac diseases, in which pulmonary hypertension could contribute to a generalized increase in sympathetic activity.

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Additional Information

Competing interests

None declared.

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