Baroreceptor function during exercise: resetting the record

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This paper briefly reviews the historical evolution of ideas about how baroreflexes operate and continue to regulate arterial blood pressure during exercise. Observations from studies conducted in conscious humans and animals are emphasized and three main questions are asked. First, do baroreflexes contribute to arterial blood pressure regulation during exercise? Second, if baroreflexes contribute to blood pressure regulation during exercise, how do they do it? Third, are there any pathophysiological conditions in which manipulation of baroreflexes or baroreflex ‘dysfunction’ might alter exercise responses? In this context, ideas related to baroreflex resetting during exercise are emphasized, and the potential improvement in exercise tolerance in cardiovascular disease that might be achieved by electrical stimulation of the carotid sinus nerve is highlighted. Additionally, the key contributions of John Shepherd and the late David Donald (along with their colleagues) on related issues are noted.

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The purpose of this paper is to briefly review ideas related to how baroreflexes operate and continue to regulate arterial blood pressure during exercise. In general, information from studies conducted in conscious humans and animals will be emphasized. In this context, there are three main questions. First, do baroreflexes contribute to arterial blood pressure regulation during exercise? Second, if baroreflexes contribute to blood pressure regulation during exercise, how do they do it? Third, are there any pathophysiological conditions in which manipulation of baroreflexes or baroreflex ‘dysfunction’ might alter exercise responses? For all of these questions an effort will be made to discuss them at least superficially in the context of their intellectual evolution. Additionally, the work and ideas of John Shepherd and the late David Donald, who spent much of their careers at the Mayo Foundation (and left me and my colleagues at Mayo a rich intellectual and physical ‘infrastructure’ for our scientific efforts), will be highlighted.

Historical context

One of the earliest, most fundamental, and perhaps obvious observations about the cardiovascular system is that heart rate and blood pressure rise during exercise (Krogh & Lindhard, 1913). Speculation about the ‘causes’ of the rise in heart rate and blood pressure with exercise was clearly underway by the late 1800s, as experimental physiology and medicine emerged. For detailed discussion of the emergence of these ideas there are outstanding recent reviews by Rowell and Tipton (Krogh & Lindhard, 1913; Rowell, 2003; Tipton, 2003). During this time and in the following decades prior to World War II there was marked progress in understanding the basic physiological functions of the sympathetic and parasympathetic nervous systems along with their pharmacology. This era might be described as lasting up to the late 1940s, when U.S. von Euler identified noradrenaline as the neurotransmitter released by the sympathetic nerves.

By this time it was clearly known that there were mechano(bar o)-sensitive regions in the carotid sinus and aortic arch that, when stimulated, could affect heart rate and blood pressure. Perhaps the clearest example of this is the fact that afferents from the aortic arch were termed the ‘aortic depressor nerve’, indicating that when stimulated they evoked a fall in blood pressure and bradycardia. So, by about 1950 it was clearly established that stimulation of vagal efferents to the heart evoked bradycardia, that cutting these vagal efferents caused a rise in heart rate, and that acetylcholine was the key postganglionic neurotransmitter responsible. By 1950 it was also known that stimulation of the sympathetic nerves caused a rise in arterial pressure, that eliminating the tonic activity of these nerves caused...
a fall in arterial pressure, and that noradrenaline was the key postganglionic neurotransmitter. Finally, the idea that there were barosensitive areas in the carotid sinus and aortic arch (in close proximity to chemosensitive areas) had also been established. In summary, by 1950 many (but not all) of the ‘pieces of the puzzle’ needed to understand what happens to blood pressure during exercise were well known and well described, and the brainstem was seen as a key structure in the central nervous system involved in the regulation of autonomic outflow to the periphery (Krogh & Lindhard, 1913; Bevegård & Shepherd, 1966; Bristow et al. 1971; Joyner & Shepherd, 1991; Rowell, 2003; Tipton, 2003).

What ‘makes’ blood pressure rise during exercise?

While all this was happening, two main ideas emerged about what might make heart rate and blood pressure rise during exercise. One idea was that a ‘cortical irradiation’ from the motor areas in the central nervous system somehow sends a message to the areas of the brain that control heart rate and blood pressure so that the total level of motor activity is matched by appropriate adjustments in heart rate, blood pressure and respiration. This general line of thinking continues today and is known as ‘central command’ (Krogh & Lindhard, 1913; Rowell, 2003; Tipton, 2003). There were also early ideas and evidence for a so-called ‘muscle heart reflex’, suggesting that feedback from the contracting muscles somehow causes heart rate, blood pressure and respiration to increase. This idea also continues today and today is known as the muscle metaboreflex or the muscle chemoreflex (Alam & Smirk, 1937; Rowell, 2003; Tipton, 2003).

How then do these regulatory mechanisms interact with the autonomic nervous system to cause heart rate and blood pressure to rise during exercise? The main idea for many years was that at the onset of exercise there is a mass sympathetic discharge (Victor et al. 1987; Tipton, 2003). This mass sympathetic discharge causes heart rate and blood pressure to rise, and also evokes vasoconstriction in the periphery. Local metabolic vasodilatation in the active muscles then overcomes this vasoconstriction, and this permits a high fraction of (the increased) cardiac output blood to be directed towards the active muscles (Victor et al. 1987). In this scheme the brain and heart are protected from vasoconstriction because of a relative lack of sympathetic constrictor fibres, along with autoregulation (brain) and metabolic vasodilatation in the coronary circulation as heart rate rises.

So by the 1950s and early 1960s there appeared to be a clear picture about what made heart rate and blood pressure rise during exercise. It could be explained largely by two regulatory mechanisms (cortical irradiation and/or feedback from muscle), and it relied on the general concept of mass sympathetic discharge to make heart rate and blood pressure rise during exercise. While it is easy to look back at this scheme and see its limitations, it should be remembered that it clearly made sense based on what was known at the time, was an extremely plausible explanation for a complex set of phenomena, and provided a platform for subsequent experimental progress. Taken together, these ideas led to an outstanding line of experimental work that continues today.

Key observations

By the early 1960s there was an increasing interest in how blood pressure is regulated. At that time there was also increased attention to the haemodynamic responses to exercise, and newer and better experimental tools, including pharmacologic compounds, were emerging to aid investigation (Bevegård, 1962; Bevegård & Shepherd, 1966; Rowell, 2003; Tipton, 2003). Also, by the middle 1950s and early 1960s it was clear that hypertension was a major medical problem, cardiac catheterization and cardiac surgery were becoming established clinical techniques, and ideas were beginning to emerge that it might be possible to successfully perform cardiac transplantation in humans. This rich intellectual environment was also nurtured by generous funding and improved technology at almost every level (J. T. Shepherd, personal communication). In this context, more subtle ideas emerged about blood pressure regulation in general and blood pressure regulation during exercise in specific.

Question 1: do baroreflexes contribute to arterial blood pressure regulation during exercise?

Several notable experiments were conducted during the 1960s, 1970s and early 1980s in humans and conscious animals to address this topic (Bevegård & Shepherd, 1966; Melcher & Donald, 1981; Walgenbach & Donald, 1983). Since increased mechanical stimulation of barosensitive areas in the carotid sinus and aortic arch evokes reflex changes in heart rate and vascular resistance that tend to cause arterial blood pressure to fall, one idea was that baroreceptor function was ‘turned off’ during exercise and thus heart rate and blood pressure were free to rise. One of the clearest arguments supporting this idea came from Bristow et al. (1971), who used vasoactive drug infusions during exercise (cycle ergometer) to raise arterial pressure in healthy young male subjects. These investigators (Fig. 1) showed that the ability of acute changes in arterial pressure evoked by systemic vasoconstrictor drug infusions to cause elongation of the R–R interval (a decline in heart rate) was blunted during exercise. This observation was interpreted to mean that during exercise baroreflexes were ‘turned off’ and lost their ability to regulate at least heart.
rate and probably arterial pressure. However, based on 30–40 years of constructive hindsight, it is obvious that there are flaws with this analysis. First, systemic blood pressure was changed with drugs, so it was impossible to measure the impact of altered baroreceptor input on arterial blood pressure, the main regulated variable governed by baroreceptors. In other words, a closed loop system had been opened, and changes in R–R interval were used as an incomplete surrogate marker for baroreceptor function. Second, the relationship between R–R interval and its reciprocal, heart rate, is non-linear. Depending on the heart rate, relatively modest changes in R–R interval might lead to dramatic changes in heart rate (Melcher & Donald, 1981; Walgenbach & Donald, 1983; Walgenbach & Shepherd, 1984). This would occur when heart rate is relatively fast. By contrast, large increases in R–R interval are required to evoke comparable increases in heart rate at rest when heart rate is somewhere between 50 and 70 beats min$^{-1}$. However, in spite of these simple numerical observations, this observation and its progeny have led to the idea that arterial baroreflex control of blood pressure is turned off, blunted or eliminated during exercise in humans.

In contrast to this explanation, slightly earlier observations in humans and later studies in chronically instrumented conscious dogs made at the Mayo Clinic in the 1960s and onwards into the 1970s and 1980s offered an alternative explanation for baroreceptor function during exercise. Figure 2 shows the work of Bevegård and Shepherd, who were early users of neck suction and pressure to alter the transmural forces in the carotid sinus and selectively alter input from the carotid receptors in humans. This figure shows that application of suction (i.e. increasing transmural pressure and baroreceptor stimulation) clearly evokes reflex bradycardia and a fall in blood pressure during supine exercise in humans. By contrast, neck pressure (which reduces stimulation of the baroreceptor afferents) continues to evoke tachycardia and vasoconstriction as evidenced by a pressor response during supine exercise. Importantly, the changes in heart rate evoked by neck suction or pressure are similar at rest and during exercise.

Along similar lines to the experiments of Bevegård and Shepherd were those conducted by their colleague, the late David Donald (Professor Donald died in the autumn of 2004 at the age of 83). Donald was originally educated as a veterinarian in Scotland and came to the Mayo Clinic in the early 1950s for scientific training under the direction of Earl Wood and colleagues. His early time at the Mayo Clinic was spent in collaboration with Dr Wood and the surgeon John Kirkland, as they perfected the techniques required to safely use mechanical cardiopulmonary bypass to facilitate open heart surgery in humans (J. T. Shepherd, personal communication). After successful development and application of these techniques in clinical medicine, Donald received the degree of PhD from the University of Minnesota and returned to the Mayo Clinic. During the 1960s and 1970s and into the early 1980s he conducted

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**Figure 1.** Relationship of pulse (R–R) interval (○, left axis) and heart rate (●, right axis) versus systolic pressure on (x axis)

This figure demonstrates that changes in R–R interval in response to systemic infusions of the blood pressure-raising drug phenylephrine are blunted during exercise in comparison to resting conditions. The right axis shows similar data plotted for heart rate. However, it is interesting to note that the heart rate scale on the right axis is not linear. Figures such as this led to the widespread conclusion that baroreceptor control of blood pressure was largely ‘turned off’ during exercise. (Reproduced with permission from Bristow et al. (1971) (http://www.com).)
Figure 2. Baroreflex function during exercise
A, individual responses in one subject to neck suction applied during supine exercise. Neck suction increases the transmural pressure in the carotid arteries, thus leading to increased activation of baroreceptor afferents. The left panel shows responses at rest. The middle and right panels show responses during mild and moderate exercise.
a number of landmark studies on cardiovascular reflexes in dogs (Walgenbach & Shepherd, 1984). During the early 1960s he showed that the exercise capacity of the racing greyhound remained remarkably well preserved after cardiac denervation. Later he began to work on the problem of blood pressure regulation during exercise in his canine model (Melcher & Donald, 1981; Walgenbach & Donald, 1983; Walgenbach & Shepherd, 1984).

One of Donald’s great contributions (gifts might be a better description) to physiology was his ability to develop a variety of techniques which permitted selective and reversible denervation of sensory input from the aorta, the carotid receptors and cardiopulmonary afferents (Walgenbach & Shepherd, 1984). In experiments using these approaches Donald demonstrated that acute barodenervation during exercise caused a marked increase in blood pressure (Walgenbach & Donald, 1983; Walgenbach & Shepherd, 1984; Fig. 3). This suggested that the baroreceptors continued to function to regulate arterial pressure during exercise.

Along these lines, Vatner et al. (1970) demonstrated that electrical stimulation of the carotid sinus nerve in both resting conditions and during exercise in dogs caused bradycardia and peripheral vasodilatation. This observation (Fig. 4), like Donald’s in dogs and Bevegård and Shepherd’s in humans, also suggested that baroreflexes continue to regulate arterial blood pressure during exercise.

**Question 2: if baroreflexes contribute to blood pressure regulation during exercise, how do they do it?**

Again, the work of Donald and colleagues provided fundamental insight into this question. Donald developed a way to selectively manipulate pressure in the carotid sinus of chronically instrumented dogs. When the carotid sinus was isolated on one side and coupled with selective denervation of the contralateral carotid sinus and aortic arch, it was possible to study how changes in pressure in an ‘isolated’ carotid sinus affected systemic arterial blood pressure and heart rate when competing counter-regulatory feedback from the other carotid sinus and aortic receptors was absent (Walgenbach & Donald, 1983; Walgenbach & Shepherd, 1984). Studies using this preparation showed that there was a sigmoidal relationship between changes in pressure in the isolated carotid sinus and systemic arterial pressure so that when pressure was lowered in the sinus it evoked reflex increases in systemic arterial pressure and heart rate, with the opposite occurring when pressure in the sinus was raised.

When this strategy was applied to exercising animals there was the expected exercise-induced increase in blood pressure and heart rate but changes in carotid sinus pressure continued to evoke changes in arterial pressure and heart rate that were remarkably similar to those seen at rest (Fig. 5). So the ‘operating point’ for blood pressure was raised during exercise but there was little change in the relative stimulus response characteristics from this increased operating point (i.e. no change in gain). Additionally, depending on whether heart rate or R–R interval was analysed, there were differing conclusions about baroreceptor control of the heart during exercise. When R–R interval was used it appeared as if exercise did indeed ‘turn off’ or blunt baroreceptor control of the heart. By contrast, when heart rate was used in the analysis it was clear that baroreceptor control of heart rate was maintained around an exercise-induced increase in heart rate (Bevegård & Shepherd, 1966; Melcher & Donald, 1981; Walgenbach & Donald, 1983; Walgenbach & Shepherd, 1984). Therefore the data from Donald and his coworkers demonstrated that baroreflexes continue to regulate arterial pressure and heart rate during exercise but that they are reset to regulate blood pressure around an exercise-induced increase. Interestingly, limited data from humans who have no carotid baroreflex, either as a result of bilateral glomectomy for glomus tumours or because of neck irradiation, suggests that blood pressure is more variable after carotid denervation in humans (Smit et al. 2002; Timmers et al. 2003). Additionally, these limited observations suggest that during periods of physical and mental stress, including exercise, the rise in arterial pressure is larger than normal. However, owing to the rare nature of these patients, comprehensive studies in humans on this topic are lacking.

While the question about whether or not the situation is the same or different in humans compared to dogs is of interest, resetting clearly occurs in humans (Ogoh et al. 2002). While this topic will be covered in greater detail in the companion paper in this series (Raven et al. 2006), there is one observation that deserves a mention. At rest, heart rate is controlled predominantly by parasympathetic nerves travelling in the vagus, and there is high baseline vagal tone. Under these circumstances baroreflex-mediated changes in heart rate are almost exclusively...
brought about by changes in vagal nerve traffic (Rowell, 2003; Tipton, 2003; Victor et al. 1987). During exercise in humans, heart rate increases initially by withdrawal of vagal tone, and as heart rate reaches about 100 beats min\(^{-1}\) there is increasing activation of cardiac sympathetic accelerator fibres. As noted earlier, some of the controversy concerning baroreflex control of heart rate during exercise is probably caused by different analysis of techniques, such as R–R interval or heart rate is used in the analysis. However, during very high heart rates there is likely to be almost total suppression of vagal outflow, and while it appears as if carotid baroreceptors continue to regulate arterial pressure, their influence on heart rate might in fact wane.

Ogoh et al. (2003) have tried to understand the relative contributions of changes in heart rate (and also cardiac output) and vascular resistance to baroreflex control of blood pressure during exercise. They studied subjects during light, medium and heavy exercise, and selected workloads on the basis of heart rate. This meant that subjects were studied at heart rates of approximately 90, 120 and 150 beats min\(^{-1}\). Based on this innovative experimental design and their technical expertise, they demonstrated that at rest roughly one-third of the changes in arterial pressure during baroreflex stimulation were due to changes in heart rate/cardiac output and two-thirds were dependent on alterations in vascular resistance. With increasing exercise intensity, the contribution of vascular resistance to changes in pressure increased and those of heart rate/cardiac output declined. The key points in this observation are: first, that baroreflex control of blood pressure does in fact remain robust during exercise; second, that varying combinations of cardiac output and vascular resistance can be ‘used’ to maintain this high level of baroreflex control; and third, that questions concerning baroreflex control of heart rate, especially during heavy exercise, remain open.

**Question 3: are there any pathophysiological conditions in which manipulation of baroreflexes might alter exercise responses in humans?**

As discussed above, baroreflex control of blood pressure is ‘reset’ with little change in gain during exercise in humans. There are also a variety of conditions (most...
notably hypertension) in which there is chronic resetting of arterial baroreceptors so that the increase in pressure is seen as ‘normal’ and changes in pressure are regulated around this increased baseline or set point. There is also evidence to demonstrate that exercise (as a therapeutic treatment for hypertension) can lower arterial pressure and restore or partially restore baroreflex control of heart rate and blood pressure to more normal values (Timmers et al. 2003, 2004). However, relatively less is known about the acute effects of exercise on baroreflex control of blood pressure in conditions like hypertension and congestive heart failure.

Along the lines discussed above, an interesting argument advanced by Clausen in the 1970s was that trained subjects frequently have a lower arterial blood pressure at a given level of exercise, and that highly trained subjects seem to be able to tolerate both lower diastolic blood pressures and mean arterial pressures during heavy exercise (Clausen, 1977). By contrast, subjects with cardiovascular disease appear to have a limited capacity to vasodilate during exercise and perhaps ‘defend’ a higher arterial pressure under these circumstances. Clearly, changes in the brain-stem cardiovascular centres and baroreceptor function, local adaptations in trained versus untrained skeletal...
muscle, the so-called pump function of the heart, and changes in sympathetic vasoconstriction in active and inactive tissues could all play a role in the altered circulatory and blood pressure responses to exercise in patients with cardiovascular disease, untrained subjects, trained subjects and highly trained (and genetically gifted) athletes. (For a recent discussion of the ‘low’ mean arterial pressure that can be tolerated by athletes, please see Calbet et al. 2004). However, in a global context baroreflexes can play a central role in regulating all of these factors. These concepts raise the possibility of altered baroreflex function during exercise in populations with cardiovascular disease. They also raise the possibility that endurance exercise training and exercise rehabilitation programmes might improve exercise tolerance in patients with conditions such as hypertension and congestive heart failure by altering baroreflex function in a way that limits sympathetic outflow to contracting skeletal muscles, permits a relative increase in skeletal muscle blood flow, and allows subjects to tolerate somewhat lower arterial pressures during large muscle mass dynamic exercise.

With the above comments as a background, one tantalizing piece of information suggesting this might be possible comes from studies done in the late 1960s (Epstein et al. 1969). At that time there were limited therapeutic options for angina pectoris (ischaemic chest pain) and coronary ischaemia during exercise. Invasive procedures to improve coronary blood flow had not been developed, coronary artery bypass surgery was in its infancy, and key pharmacological treatments for coronary disease, such as $\beta$-blockade, were also in their infancy. Based on this absence of options and on evidence that had emerged in the 1950s and 1960s about baroreflex control of the circulation, Epstein et al. (1969) implanted electrical stimulators in the carotid sinus nerves of 17 patients with severe, intractable and untreatable angina during exercise. These subjects developed predictable patterns of exercise-induced chest pain that occurred at a given heart rate and blood pressure. These symptoms probably occurred as a chronic condition owing to high-grade fixed lesions of the coronary arteries.

The idea behind this therapeutic trial of carotid sinus nerve stimulation was that increased nerve traffic from the carotid sinus would send messages to the brainstem cardiovascular centres that would be interpreted as a rise in arterial pressure. This neural signal would then evoke a reflex reduction in heart rate and blood pressure. The reduction in heart rate and blood pressure would reduce myocardial oxygen demand and thereby reduce or relieve the angina.

The results from this remarkable study (Fig. 6) showed that activation of the carotid sinus stimulator before or during exercise caused small (3–5 beats min$^{-1}$) reductions in heart rate and large (15–20 mmHg) reductions in mean arterial pressure. It also reduced ST-segment changes, suggesting less cardiac ischaemia in many of the patients, and it improved exercise tolerance. It is also interesting to note in retrospect that several of the subjects died in the immediate perioperative period. This probably reflects the fact that anaesthesia and surgery on patients with advanced coronary artery disease was relatively primitive and very risky in the 1960s. It is of note that surgery can now generally be conducted safely in patients with coronary artery disease.

From a physiological perspective, these observations suggest that in patients with coronary artery disease, hypertension and/or cardiac dysfunction, blood pressure might be ‘inappropriately’ high during exercise as a result of disease-related changes in blood pressure regulation.
during exercise. Clearly, this is an area that might benefit from additional attention and renewed study. Since circulating noradrenaline is inversely related to exercise tolerance and congestive heart failure, maybe these therapeutic concepts can be revisited to improve exercise tolerance in selective patients with cardiovascular disease. If this strategy reduced the exercise-limiting sympathetic activation of heart failure, it might improve exercise tolerance in these patients (Cohn et al. 1984). If this strategy were effective it might have the added benefit of permitting relatively debilitated individuals to participate in more comprehensive exercise rehabilitation programmes and improve their functional independence and ability to participate in a variety of normal everyday activities.

Summary

In summary, in this paper some key observations suggesting that baroreceptor-mediated control of blood pressure is maintained but reset during exercise have been presented. Questions remain about baroreflex control of heart rate during heavy exercise in humans, but the data on blood pressure regulation, at least in normal subjects, appear very strong. By contrast, less information is available in pathophysiological conditions associated with baroreceptor dysfunction at rest. Does the normal resetting occur in these conditions? Does exercise training or other therapeutic strategies that improve exercise capacity alter baroreflex control of blood pressure during exercise in selected patient groups? Can therapeutic

Figure 6. Effects of electrical stimulation of the carotid sinus nerve on heart rate and blood pressure during exercise in patients with stable angina

Carotid sinus nerve stimulation would send signals to the brainstem cardiovascular centre, suggesting that there had been an acute rise in arterial pressure. These signals would then evoke reflex reductions in heart rate and blood pressure. Since chest pain (angina) during exercise is dependent on a mismatch between the supply and demand of oxygen to the contracting heart, reductions in heart rate and blood pressure would reduce demand and potentially relieve the chest pain. In these patients when the stimulator was activated (Prophyl CSN stim) during chest pain (left panel) there were modest reductions (3–5 beats min\(^{-1}\)) in heart rate and marked reductions in arterial blood pressure (right panel). This was accompanied by reductions in chest pain, less evidence of myocardial ischaemia on electrocardiogram and improved exercise tolerance. (Reproduced with permission from Epstein et al. (1969).)
strategies that improve or normalize baroreflex control of the circulation during exercise also improve exercise tolerance or contribute to an improvement in exercise tolerance in patients with cardiovascular disease? Is it time to revisit ideas from 1960s about therapeutic use of carotid stimulation to improve exercise responses in patients with cardiovascular disease?

References


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