Shifts in the baroreflex control of sympathetic nerve activity induced by exercise

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Abstract Exercise causes parallel increases in systemic arterial pressure (AP), heart rate (HR) and renal sympathetic nerve activity (RSNA). This review focused on the potential role of the acute shift in the baroreflex control of RSNA in both increasing and stabilizing AP during exercise, and causing hypotension afterwards. Treadmill exercise shifted the baroreflex curve for RSNA acutely to the right and upward, characterized by a significant increase in the maximum response, about 170%, which could well explain the parallel increases in AP, HR, and RSNA. In contrast, exercise shifted the baroreflex stimulus-response curve for HR upwards in rats, differing from the shift shown for RSNA, suggesting that the dependent variable of baroreflex control has to be specified when shifts in baroreflex stimulus response curves are discussed. During the post-exercise period, the AP-RSNA baroreflex curve was suppressed vertically, with a significant reduction of about 50% shown in the upper plateau without any alteration in the minimum response, which may be the reason for the post exercise hypotension. The loading of cardiopulmonary baroreceptors modulated the baroreflex control of RSNA in a way resembling “Flip-Flop” or “On-Off” type regulation. In part, this may explain the orthostatic intolerance caused by endurance training.

Keywords: arterial baroreflex, sympathetic nerve activity, arterial pressure exercise

Introduction

The onset of exercise causes increases in systemic arterial pressure (AP), heart rate (HR) and sympathetic nerve activity (SNA) in a parallel fashion¹. We measured the responses of AP and central venous pressure, HR, and renal sympathetic nerve activity (RSNA) to treadmill exercise in a rat⁶. The onset of treadmill exercise resulted in an abrupt increase in AP, HR, and RSNA (Fig. 1). Arterial baroreflex plays a dominant role in regulating AP as a feedback control system. However, the same directional changes in AP, HR, and SNA, observed during exercise, cannot be explained by a single feedback control system. The issue of how arterial baroreflex could contribute to the simultaneous increases in AP, HR and SNA, that occur immediately after the onset of exercise, has been controversial³,⁴.

Baroreflex control of HR during exercise has been extensively studied in humans and animals. Several early studies demonstrated that the arterial baroreflex was “switched off” or the sensitivity of the baroreflex reflex had been decreased by exercise⁵,⁶. Melcher & Donald (1981)⁶ constructed full stimulus-response curves of baroreflex control of HR during exercise in dogs, and showed that the baroreflex function curve was reset by exercise without any change in baroreflex sensitivity for HR. Potts et al. (1993)⁷ later confirmed these findings in humans by demonstrating that the carotid baroreflex is reset during leg cycling to operate functionally around an exercise-induced increase in BP. The upward and rightward shift of the stimulus-response curve for HR allows the baroreflex to operate at the prevailing BP during exercise as effectively as at rest⁸,⁹. This view has been widely accepted to explain the same directional changes in AP and HR caused by exercise. However, there is only a very limited amount of data available on the mechanisms involved and how shifts in the baroreflex control of sympathetic nerve activity occur during exercise.

We succeeded in measuring AP, RSNA, and HR during treadmill exercise and daily activity in rats²,¹⁰-¹². We generated the complete stimulus-response curve of the baroreflex control of RSNA during exercise, and found that exercise shifts the AP-RSNA baroreflex curve to the right and upward¹¹. In this review, we focused on a potential role of the acute shift in the baroreflex control of RSNA in increasing and stabilizing AP during exercise.
and causing hypotension after exercise.

**Shifts in the baroreflex control of renal sympathetic nerve activity**

In order to quantify the changes in the baroreflex control of HR/RSNA, the full range of the stimulus response curve for arterial baroreflex has been analyzed by fitting data to a logistic sigmoid function described by

\[
Y = \frac{A_1}{1 + \exp[A_2(X - A_3)]} + A_4,
\]

where \(Y\) is RSNA or HR, \(X\) is AP, \(A_1\) is the response range for \(Y\) (maximum response minus minimum response), \(A_2\) is the gain coefficient, and \(A_3\) is the pressure at the midrange of the curve (centering point). The centering point is the point at which there is an equal depressor and pressor response to a given change in AP. \(A_4\) is the minimum response of \(Y\). The saturation pressure for AP (AP\text{sat}), threshold pressure for AP (AP\text{thr}), operating range for AP, and maximal gain can be estimated by the following equations

\[
\text{Upper plateau} = A_1 + A_4; \\
\text{AP}_\text{thr} = -\frac{2.0}{A_2} + A_3; \quad \text{AP}_\text{sat} = \frac{2.0}{A_2} + A_3; \quad \text{Operating range} = \text{AP}_\text{sat} - \text{AP}_\text{thr}; \\
\text{Gain} = -A_1 A_2 \exp[A_2(X - A_3)] / \{1 + \exp[A_2(X - A_3)]\}^2; \\
\text{Maximal gain} = -A_1 A_2 / 4.
\]

The upper plateau is the maximum response of the curve. AP\text{thr} and AP\text{sat} are the AP at which HR or RSNA is within 5% of its maximum or minimum response, respectively.

**Shifts in the baroreflex curve for RSNA due to exercise**

Treadmill exercise shifted the baroreflex curve for RSNA acutely to the right and upward (Fig. 2), characterized by a significant increase in the minimum response of about 50% (\(A_4\)), a response range of about 120% (\(A_4\)), and a maximum response of about 170% (\(A_1 + A_4\)). The operating range tended to decrease, by about 8 mmHg. The maximal gain, which is dependent on the response and operating ranges, increased significantly by about 150% during exercise, compared with the pre-exercise level. The centering point of the reflex increased by about 15 mmHg.

The major effect of the treadmill exercise on the baroreflex control of RSNA was a marked increase in the maximum response by about 170% (to about 380% from about 210% in the pre-exercise period). This means the treadmill exercise resulted in a twofold increase in the capacity of the sympathetic drive to the peripheral organs. Furthermore, the minimum response of the baroreflex curve for RSNA (lower plateau) also increased significantly by 50%, indicating that the enhanced sympathetic modulation had not been suppressed completely by the maximum inhibitory effects originating from the arterial...
baroreceptors. This suggests that the sympathetic influence on the cardiovascular system was tonically enhanced over the entire operating range of AP during exercise. Exercise may increase the cardiac and visceral sympathetic nerve activities as well, causing an increase in cardiac performance and vasoconstriction of visceral and non-contracting muscles, leading to a rise in AP during exercise.

Moreover, the operating range was reset to the right, accompanied by a relocation of the operating pressure (steady state level before pharmacological manipulation of AP) around the centering point. The relocation of the operating pressure to the centering point, where the gain is maximal, could stabilize AP effectively, because this places the baroreflex curve into a situation such that it can respond to both increases and decreases in AP. In addition, the significant increase in maximal gain would allow the cardiovascular system to buffer the fluctuations in AP more efficiently.

We therefore concluded that the shift of the AP–RSNA baroreflex curve can play a critical role in increasing and stabilizing AP during exercise.

The neural mechanisms underlying the acute shift of the baroreflex during exercise have been extensively studied, but remain unknown. The results of the AP-RSNA baroreflex curve investigation may provide further insights. First of all, the maximum response of RSNA has been considered to reflect the number and/or synchronicity of the bursting population of the sympathetic motoneurones at the lowest baroreceptor afferent activity level. This suggests that exercise could enhance the tonic drive of the sympathetic motoneurones, possibly in the rostral ventrolateral medulla. In turn, leads to the increases in the maximum and minimum responses and the increase in the maximal gain during exercise.

The defense area, including the dorsomedial hypothalamic nucleus (DMH), can be listed as one of the possible candidates in the brain for the area exerting the tonic drive of the sympathetic motoneurones. Dampny et al. showed that the microinjection of bicuculline into the DMH caused a significant shift of the baroreflex control of RSNA, along with increased upper and lower plateaus for these variables. The administration of bicuculline also altered the operating range of the AP, increasing the threshold, midpoint, and saturation levels. Moreover, the maximum gain of the RSNA component of the baroreflex was significantly increased, whereas the maximum gain of the HR component was not significantly changed. These AP-RSNA baroreflex curve findings are very similar to those observed during treadmill exercise. It is therefore likely that the defense area may be one of the regions containing “central command” networks that regulate cardiovascular function through autonomic activity during exercise.

Exercise shifts the baroreflex control for HR, while it occurs in a different manner compared to that for RSNA

Exercise shifts the baroreflex stimulus-response curve for HR upward in rats, but varies from the shift associated
with RSNA\textsuperscript{11}). There was no significant change in the centering point of the reflex or the operating range, but the minimum response increased significantly by about 145 beats/min and the response range decreased significantly by about 60 beats/min, along with an increase in the maximum response by about 85 beats/min, compared with the pre-exercise level. The maximal gain of the baroreflex curve for HR did not change significantly during the treadmill exercise. Obviously, exercise shifts in the baroreflex control for HR occurred in a different manner, compared to that for RSNA in rats.

In contrast, in humans, exercise results in an upward and rightward shift in the baroreflex control of HR, with relocation of the operating point away from the centering point, and a reduction in the response range as the intensity of the exercise increases\textsuperscript{4}. Interestingly, for the carotid baroreflex-AP baroreflex curve, the operating pressure does not relocate away from the centering point and the response range remains the same as at rest in humans.

These findings indicate that shifts in the baroreflex control of HR do not represent the changes in the whole baroreflex function during exercise. In other words, the shifts in the baroreflex control of HR may not occur in the same manner as those associated with SNA. However, the results of changes in the baroreflex control of HR have been extrapolated to that of SNA without providing evidence for sympathetic nerve activity. It is therefore necessary to specify the dependent variable of baroreflex control when shifts in baroreflex stimulus response curves are discussed. This view is consistent with the review article by Sagawa, which concluded that arterial baroreflex consists of a multi-input, multi-output, and multilevel control system\textsuperscript{26}.

**Shift in the AP-RSNA baroreflex curve after exercise**

Post-exercise hypotension associated with an inhibition of SNA has been observed in humans and animals with hypertension\textsuperscript{27-29}. The AP-RSNA baroreflex curve is suppressed vertically, with a significant reduction of the upper plateau by about 50% without any alteration in the minimum response. This leads to a situation where the RSNA becomes lower at all levels of AP, compared with the pre-exercise level. In contrast, the AP–HR baroreflex curve obtained during the post-exercise period was identical to that obtained in the pre-exercise period. These findings suggest that post-exercise hypotension may be caused mainly by suppression of SNA in the peripheral vasculature, and that it may not be caused by a reduction in cardiac performance.

It should be noted that the AP–RSNA baroreflex curve is different from that of AP–HR during the post-exercise period. This confirms the view that the physiological relevance of baroreflex sensitivity or a gain in the RSNA is different from that of HR.

Orthostatic intolerance has been observed in athletes\textsuperscript{30}. Chronic exercise training causes an increase in plasma volume, which may be one of the factors causing the orthostatic intolerance, due to the following reasons. It has been consistently reported that cardiopulmonary baroreceptors modulate the baroreflex control of SNA and AP\textsuperscript{31}. The loading of cardiopulmonary baroreceptors induced by head-down tilt and plasma volume expansion modulates the baroreflex control of SNA\textsuperscript{32,33}. We have reported that water immersion (WI), which causes an increase in central blood volume, shifts the AP-RSNA baroreflex curve to the left with significant decreases in AP\textsubscript{sat} and the operating range by half, along with increases in a gain coefficient and maximal gain in dogs\textsuperscript{30}. Moreover, WI relocated the operating pressure to near the AP\textsubscript{sat} (Fig. 3). These observations suggest that cardiopulmonary baroreceptor loading moves the baroreflex feedback system into an unstable state. WI relocated the operating pressure to near the AP\textsubscript{sat}, where baroreflex sympathetic gain is low around AP\textsubscript{sat}. Furthermore, the operating range decreased by half during WI. This would be disadvantageous for maintaining a stable AP when arterial pressure decreases rapidly, because AP would be out of the operating range before the onset of the compensatory increase in SNA occurs. In other words, the baroreflex feedback control system may be modulated in a manner resembling a “Flip-Flop” or “On-Off” type regulation, which would fail to drive linear compensatory feedback mechanisms when arterial pressure changed rapidly, and then fail to maintain a stable systemic arterial pressure. Accordingly, the chronic loading of cardiopulmonary baroreceptors induced by the increase in plasma volume can explain, at least in part, the orthostatic intolerance caused by endurance training.

In summary, the AP-RSNA baroreflex curve is shifted...
during and after exercise. During exercise, the AP-RSNA baroreflex curve is shifted to the right and upward, with a marked increase in the maximum response and maximal gain, which plays a critical role in increasing and stabilizing AP during exercise. After exercise, the AP-RSNA baroreflex curve is suppressed vertically, with a significant reduction of the upper plateau by about 50% without any alteration in the minimum response, which may be related to the post-exercise hypotension. Plasma volume expansion, which is caused by chronic endurance training, modulates the baroreflex control of RSNA to an "On-Off" type unstable control system, which can explain, in part, the orthostatic intolerance observed in athletes. Exercise shifts the AP-HR baroreflex curve in a different manner, compared to that for RSNA, suggesting that the results for the baroreflex control of HR cannot be extrapolated to that of SNA.

References


