Neuromechanical Features of the Cardiac Baroreflex After Exercise

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Abstract—A single bout of exercise is associated with postexercise hypotension, transient decreases in autonomic function, and changes in baroreflex sensitivity. The baroreflex is less sensitive to falling blood pressure than to rising blood pressure; we characterized the cardiac baroreflex in terms of hysteresis and its mechanical and neural components. We hypothesized that hysteresis would be exacerbated postexercise because of a greater relative decrease in falling blood pressure. In 10 healthy young humans (5 men), we used bolus injections of sodium nitroprusside and phenylephrine hydrochloride to drive transient decreases and increases in blood pressure, respectively, to quantify cardiac baroreflex sensitivity to falling and rising blood pressure. This was completed before and at 10, 30, and 60 minutes after 40 minutes of cycling at 60% estimated maximal oxygen consumption. Analyses of beat-to-beat blood pressure, R-R intervals and heart rate, and carotid artery diameter were used to determine the integrated cardiac baroreflex response; this was further quantified into a mechanical component (systolic blood pressure versus carotid diameter) and a neural component (carotid diameter versus R-R interval). There were 2 principle findings: after aerobic exercise baroreflex sensitivity is reduced and hysteresis manifests, and the reduction in sensitivity to falling blood pressure is mediated by decreased mechanical and neural gains, whereas the decreased baroreflex sensitivity to rising blood pressure is mediated by a reduced mechanical gain only. We suggest that impaired neural transduction of the cardiac baroreflex, and its influence on hysteresis, plays an important role in transient autonomic dysfunction after exercise. (Hypertension. 2011;57:927-933.)

Key Words: baroreflex sensitivity ■ cardiac ■ exercise ■ postexercise hypotension ■ autonomic

A single bout of moderate-to-high-intensity exercise is associated with postexercise alterations in cardiac baroreflex sensitivity (BRS) and often a period of postexercise hypotension. It has been reported that 10 to 30 minutes after exercise, in both hypertensive patients and young healthy subjects, BRS is initially reduced or unchanged as assessed using nonpharmacological or pharmacological techniques. Some studies have demonstrated recovery or augmentation of BRS >20 minutes postexercise cessation whereas others indicated a maintained BRS attenuation. On cessation of exercise, postexercise hypotension is common, with the magnitude of change dependant on resting blood pressure (BP) and the intensity and duration of exercise; hypertension and greater intensity exercise both elicit a larger postexercise BP drop. During this postexercise period there is altered regulation of sympathetic vascular tone or increases in vasodilator substances, or both, such that systemic vascular resistance is not restored until hours later. Likely because of these alterations to autonomic and vascular function, there is a high incidence of syncope after exercise. Changes in sympathetic vascular regulation and local and systemic release of vasoactive substances, such as NO and histamine, have been examined in detail; however, the role of changes in baroreceptor-mediated autonomic function after exercise is not well understood.

The arterial baroreflex consists of nerve endings in the vessel walls of the aortic arch and carotid sinus, mechanical deformation of which stimulates afferent nerve activity by way of the carotid sinus and aortic nerves to the nucleus tractus solitarius. Subsequent central processing gives rise to vagally mediated adjustments in the cardiac period (R-R interval; RRI) and sympathetically mediated adjustments in vascular resistance to buffer changes in BP, termed the cardiac and sympathetic vascular baroreflexes, respectively. Thus, the integrated cardiac BRS can be quantified as the RRI or heart rate (HR) response to changes in BP. Moreover, this response is composed of a mechanical component represented as carotid diameter for a given systolic BP and a neural component quantified by the relationship between carotid diameter and HR or RRI. Although studies have docu-
mented postexercise changes in BRS, to date, only integrated BRS values have been reported. The baroreflex is also more sensitive to rising than to falling changes in BP, and a property termed “baroreflex hysteresis.” This hysteresis is attributed to both the mechanical properties of the carotid artery and neural characteristics of the baroreflex. Hysteresis, to our knowledge, has not been examined after exercise.

The objectives of this study were to evaluate the relative contribution of the mechanical and neural components of the cardiac baroreflex to postexercise changes in baroreflex function and to explore the influence of exercise on baroreflex hysteresis. This was achieved by pharmacologically perturbing BP across a wide range with concurrent recordings of cardiac period intervals (modified Oxford method) and beat-to-beat carotid artery diameter at rest, before, and at 10, 30, and 60 minutes after moderate-intensity exercise. Because vascular properties change after exercise, and the neural component of the baroreflex has been shown to possess a degree of plasticity with exercise, we hypothesized that both the mechanical and neural components would be equally involved in BRS changes after exercise. Furthermore, because of circulatory collapse (ie, vasovagal syncope) after exercise, we hypothesized that a greater decrease in BRS to falling BP (G\text{down}), and consequent increase in hysteresis, would be manifest after aerobic exercise.

**Methods**

**Subjects**

Twelve healthy subjects (6 men; aged 25.2 ± 0.6 years [mean ± SD]; range: 17 to 36 years; body mass index: 22.8 ± 3.0 kg · m⁻²) were recruited to the study, which was approved by the New Zealand Central Regional Ethics Committee and conformed to the standards set by the Declaration of Helsinki. Subjects were excluded for any history of cardiovascular, respiratory, or endocrine diseases; medications; or smoking; and all were screened for carotid stenosis. All of the participants were recreationally active, measured via a self-reported questionnaire, and typically engaged in low- (eg, walking) and moderate- (eg, jogging or cycling) intensity aerobic activities (2 to 3 days per week). None were highly trained athletes. Participants abstained from any alcohol consumption or exercise for ≥ 24 hours before the experiment, had no caffeine the day of testing, and were instructed to eat a light meal 2.5 hours before arriving in the laboratory. Subjects were informed of the experimental procedures and possible risks before giving written informed consent.

**Measurements**

ECG, respiratory flow (Hans Rudolph Heated Pneumotach, HR 800), end-tidal P\text{CO}_2 sampled from a face mask (gas analyzer model CD-3A, AEL Technologies, Pittsburgh, PA), and noninvasive beat-to-beat BP via finger photoplethysmography (Finometer, TNO-TPD Biomedical Instrumentation) were acquired continuously at 1 kHz per channel via an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO) interfaced with a computer and stored for offline analysis. To account for potential drift, finger BP measures were verified at the brachial artery in the contralateral arm by sphygmomanometry. From the recorded ECG and arterial BP waveforms, beat-to-beat RRI, HR, and values for systolic (SBP), diastolic BP, and mean arterial BP were, respectively, determined. All of the offline data processing was done using custom-written software in LabView 8.2 (National Instruments) on a Macintosh 2.26 GHz MacBook Pro computer.

**Experimental Protocol**

Experiments were carried out in a temperature-controlled laboratory (22°C to 23°C). All pre-exercise and postexercise measurements were completed with the subject in the supine position. After placement of a venous cannula in the right or left antecubital vein, subjects rested for ≥15 minutes. Acquisition of 5 minutes of baseline measurements preceded 1 or 2 modified Oxford trials to assess BRS. Subjects then rode an upright stationary bike at 60% predicted maximal oxygen uptake for 40 minutes. Immediately on cessation of exercise supine baseline measurements were recorded for 10 minutes before the first Oxford trial (see “Baroreflex Sensitivity,” below), which was repeated at 30 and 60 minutes postexercise cessation. Because changes in BP tend to induce changes in minute ventilation, a computer-generated auditory metronome, set to the subjects spontaneous baseline breathing rate, was used to assist in the maintenance of end-tidal CO₂. No tests exhibited a change in end-tidal CO₂ > 2.5 mm Hg. No restrictions were imposed on subject tidal volume, because paced breathing without tidal volume control allows for the most efficient assessment of respiratory-related autonomic fluctuations. In our experience, paced breathing by rate only does not significantly alter HR, SBP, mean arterial BP, diastolic BP, tidal volume, or end-tidal CO₂ compared with spontaneous breathing.

**Carotid Diameter Measurement**

A 12.5-MHz linear array probe (Terson 13000, Burlington, MA) was used for duplex ultrasound imaging of a longitudinal section of the left carotid artery, < 2 cm proximal to the bifurcation, for the duration of each Oxford trial by 1 trained person (C.K.W.). A continuous digital video screen shot was recorded and saved for offline analysis (Camtasia Studio, TechSmith Co, Ltd, Okemos, MI) using previously described custom edge tracking software. Briefly, the region of the carotid artery where the diameter would be measured was identified on the video recording of the B-mode image. This region of interest was calibrated for length, and using a pixel-density algorithm the vessel walls were tracked and diameter measured at 30 Hz for the entire video that encompassed the Oxford trial and time-aligned to ECG and BP waveforms for subsequent analysis.

**Baroreflex Sensitivity**

BRS was assessed using the modified Oxford technique performed on each subject both before and after exercise. This consisted of a 50- to 250-μg IV bolus injection of sodium nitroprusside (SNP), followed 1 minute later by a 150- to 300-μg bolus of phenylephrine hydrochloride (PE). Dosages were estimated based on the weight of the subject and/or previous experience with that subject’s pharmacological sensitivity; doses of 150 μg of both SNP and PE were typically given, except for the following: (1) when that dose failed to produce ≥ 15 mm Hg of change in SBP; (2) in female volunteers with body weight < 55 kg, in which case a lower dose was initially used; or (3) 10 minutes after exercise when less drug was required for a given BP response. If a given dose failed to produce the requisite change in SBP before exercise, ≥ 10 minutes of rest was allowed before a replicate test with adjusted dosage was performed; after exercise, an adequate change in SBP was achieved in all of the subjects included in the data set.

Data were binned to 3-mm Hg segments of SBP to account for respiratory-related oscillations in BP and HR. BVP values were matched to either the concurrent heartbeat for RRI > 800 or a 1-beat delay for RRI between 500 and 800 ms. BRS was calculated separately using both HR and RRI; for each analysis, the cardiac responses to SNP and PE injections were individually analyzed to identify integrated, mechanical, and neural gains for falling and rising BPs. These gain values are referred to henceforth as rising BP for BRS gains calculated during PE-induced rising BP and G\text{up} as BRS values during SNP-mediated falling BP. There are, thus, 8 gain values, rising BP (G\text{up}) and G\text{down} for integrated and neural HR and RRI BRS gains (4 total) and G\text{up} and G\text{down} for mechanical BRS.
Integrated BRS was determined by plotting the SBP-RRI and the SBP-HR relationships and excluding the threshold and saturation regions; a linear regression was then applied to the linear portion of the curve. Mechanical BRS was calculated as the slope of the SBP-carotid diameter relationship and neural BRS as the slope of the carotid diameter-RRI and the carotid diameter-HR relationships. The threshold and saturation regions for the integrated, mechanical, and neural BRSs were independently visually identified and excluded. The slope of the linear regression for integrated BRS gain was only taken as an estimate of BRS if the coefficient of determination, \( R^2 \), was \( >0.6 \).

Statistics
Data were normally distributed as determined using a Shapiro-Wilk normality test. Consistent with a previous report,28 there were no statistical differences between men and women; therefore, data were pooled for statistical analysis. One and 2-way repeated-measures ANOVA were used to assess differences across conditions (Huynh-Feldt corrected). A priori defined comparisons between postexercise conditions to pre-exercise values and between SNP to PE BRS values within each time point were made using the Dunnet test and Student paired \( t \) test (Bonferroni corrected) respectively. \( \alpha \) was set to 0.05. Statistical analyses were completed with SPSS 16.0.2 (SPSS Inc) and Prism 4.0 (GraphPad Software, Inc, La Jolla, CA). All values are mean±SD.

Results

Subjects
All of the subjects completed the protocol; however, in 1 female subject, a >15-mm Hg change in BP could not be achieved during the pre-exercise Oxford tests, despite increased drug doses, and her data were consequently excluded. One other male subject was excluded because of a lack of BP change at 30 minutes postexercise, and poor carotid images at 10 minutes postexercise, and was consequently excluded from analysis that was, therefore, based on \( n=10 \) (5 men).

Baseline Hemodynamic Variables
Table 1 shows 30-second average resting values before exercise and before each Oxford BRS trial. HR was elevated from baseline after exercise cessation and remained elevated up to 60 minutes postexercise. Mean arterial BP fell from...
82±9 mm Hg before exercise to 71±12 (P<0.05), 73±9, and 78±13 mm Hg at 10, 30, and 60 minutes postexercise, respectively. Therefore, the 13±10% mean arterial BP reduction at 10 minutes postexercise was restored to baseline levels by 60 minutes. SBP was reduced at 10 and 30 minutes postexercise from 136±12 to 112±14 and 116±13 mm Hg, respectively, returning to baseline values by 60 minutes postexercise (Table 1). Carotid diameter was significantly narrowed from 6.0±0.7 mm before exercise to 5.7±0.5 mm at 10 minutes and 30 minutes, respectively, and 5.7±0.6 mm at 60 minutes postexercise (each P<0.05; Table 1).

**BRS After Exercise**

Figures 1 and 2 and Table 2 show baseline and postexercise values for G_up and G_down for integrated, neural, and mechanical gains, as calculated using both HR and RRI. Coefficients of determination for all of the BRS calculations are also reported in Table 2.

Every gain value with the exception of neural G_up was decreased at 10 minutes postexercise, both in terms of HR and RRI BRS gains. Both integrated G_up and G_down were decreased at 10 minutes postexercise, with RRI G_down by ~70% (Δ9.63 ms·mm Hg⁻¹), HR G_down by ~54% (Δ−0.59 beats·min⁻¹·mm Hg⁻¹), RRI G_up by ~−53% (Δ11.89 ms·mm Hg⁻¹), and HR G_up by ~−28% (Δ−0.37 beats·min⁻¹·mm Hg⁻¹). By 60 minutes postexercise, integrated HR and RRI G_up and G_down had returned to baseline values (Figure 1).

Neural gain with falling BP was lower than baseline at 10 minutes postexercise with RRI G_down decreasing by ~67% (Δ620.5 ms·mm⁻¹) and HR G_down by ~48% (Δ32.47 beat·min⁻¹·mm⁻¹). Neural RRI and HR G_up did not differ from pre-exercise values at any point (Figure 1).

Mechanical G_down and G_up were reduced at 10 minutes postexercise by ~42% (Δ0.006 mm·mm Hg⁻¹) and ~47% (Δ0.009 mm·mm Hg⁻¹), respectively (Figure 2). Pressure-diameter curves were generated to compare pre-exercise and postexercise compliance; examination of these relations revealed a clear left and downward shift corresponding with lower pressures and smaller vessel diameters observed postexercise.

**Baroreflex Hysteresis**

BRS calculated using HR and RRI produced similar relationships with respect to hysteresis. Integrated G_down was less than G_up at every point after exercise; HR G_down was not statistically different from G_up at 60 minutes postexercise, although the trend remained intact. There was no neural hysteresis before exercise, but at each point postexercise G_down was significantly less than G_up (Figure 1). Mechanical G_up was not significantly different from mechanical G_down at any point (Figure 2).

**Discussion**

The new findings of the present study were that the attenuation in G_down is mediated by reductions in both neural and mechanical gains, whereas the reduced G_up after exercise is mediated by a decrease in mechanical G_up only; thus, both the mechanical and neural components of the cardiac baroreflex are implicated in postexercise baroreflex attenuation. Also, baroreflex hysteresis is manifest for at least the first 60 minutes after aerobic exercise, regardless of whether it is calculated using HR or RRI. Before these findings are expli-
cated further, certain methodological aspects of this study warrant discussion.

Methodological Considerations
Spontaneous measures of BRS (spontaneous ramp method and spectral analysis) were not used herein for comparison to the Oxford BRS. The combination of a high HR and/or shorter respiratory intervals postexercise meant that spontaneous ramps (data not shown) occurred infrequently, such that in many cases no ramps could be identified to yield a BRS measurement. Although it is possible to use spectral measures such as the α-index to characterize BRS, the validity of spectral indexes in the high (respiratory)-frequency range has been questioned, and indexes in the low-frequency range require at minimum 3 to 5 minutes of stationary data, which may not be obtainable during dynamic exercise recovery.24

The modified Oxford technique allows perturbation of systemic vascular resistance such that transient increases and decreases in BP can be reliably produced to assess baroreflex hysteresis. Previous studies suggest that carotid diameter is not affected by vasoactive drug administration and passively follows BP during the modified Oxford test.17,29 However, the time course of the response was not evaluated in these studies, and, therefore, direct drug effects on our measurements cannot be discounted. If a drug effect were manifest, the BRS values at 30 minutes postexercise would be most affected, because there was only a 20-minute gap between drug administrations. Nonetheless, we have found previously that cardiovascular parameters typically normalize within 15 minutes; this is also the time interval used in previous research using the modified Oxford method.15,17,26 Furthermore, the timing of our protocol also allows direct comparison with previous studies that have used the modified Oxford method and the same time protocol with respect to exercise intervention.3,30

As opposed to neck-collar suction/pressure devices that preclude access to the neck, the use of vasoactive compounds to perturb BP allows imaging of the carotid artery. With the advent of vascular ultrasound technologies that enable high-resolution quantification of instantaneous carotid artery diameter, it is possible to assess the mechanical transduction of pressure and neural transduction of stretch as individual components of the integrated cardiac baroreflex response. Consequently, the Oxford method appears to be the only means to explore the relative contribution of mechanical transduction of BP into carotid stretch (the principle stimulus for baroreceptor activation) and the transduction of stretch into changes in cardiac vagal tone.

Because predicted maximal oxygen uptake based on estimated maximal HR was used to determine each volunteer’s exercise intensity, and because maximal oxygen consumption was not measured, it is not possible to quantify the relative fitness of this cohort. Endurance training appears to alter the mechanism through which postexercise hypotension becomes manifest31 and also results in a differential shift in postexercise BRS relative to untrained individuals.32 We controlled for training status through an activity questionnaire, and no participants were elite or endurance trained athletes. Although differences in training status might contribute to the variation that we observed in BRS values, large intersubject variation in BRS gains is consistent with previous data.3,17,18,24

Mechanical and Neural Alterations After Exercise
Both integrated \( G_{up} \) and \( G_{down} \) were significantly decreased postexercise, but the drop in \( G_{down} \) was greater than that of \( G_{up} \) at each time point. Comparable to a previous report,13 mechanical BRS was reduced after exercise. This study used the α index for BRS assessment, however, and thus could not differentiate between mechanical \( G_{up} \) and \( G_{down} \), both of which were found to decrease similarly in the present study. In contrast, neural hysteresis was clearly present after exercise (Figure 1). This change appears to be a product of a selective reduction in neural \( G_{down} \) with a concomitant maintenance of \( G_{up} \). To our knowledge there are no previous data to compare to this finding. Because the neural gain simply considers the relationship between carotid diameter and cardiac period or rate (which yield the same conclusions), it is not possible from these data to discern whether the reduction in neural \( G_{down} \) is because of attenuated neural outflow from the carotid baroreceptors or altered integration and outflow within the central nervous system. Neural BRS was shown to be augmented in endurance-trained men, which was not a function of altered carotid diameter20; but, the possibility that the reduction in neural \( G_{down} \) shown herein is a function of the observed reduction in carotid diameter after exercise cannot be excluded. Our data indicate that the reductions in mechanical \( G_{up} \) and \( G_{down} \) were accompanied by a left and downward shift of the entire pressure-carotid diameter relation rather than simply a movement to a different operating point on the baseline pressure-carotid diameter relationship.

Baroreflex Hysteresis: Rest and Exercise
The pressure-heart period relation exhibits a greater gain with rising versus falling BP,16,29,34 a finding replicated in the current data. Surprisingly, to our knowledge, no studies have examined this phenomenon after exercise; our data indicate

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<th>Table 2. Continued</th>
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<tr>
<td>60 Minutes Postexercise</td>
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<tr>
<td>Condition</td>
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<tr>
<td>−1.30 ± 0.42 (0.92 ± 0.05)</td>
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<tr>
<td>−1.07 ± 0.36 (0.91 ± 0.08)</td>
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<tr>
<td>18.47 ± 8.487† (0.938 ± 0.053)</td>
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<tr>
<td>10.4 ± 4.15 (0.962 ± 0.028)</td>
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<tr>
<td>−85.6 ± 25.5† (0.81 ± 0.10)</td>
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<tr>
<td>−56.9 ± 25.0 (0.69 ± 0.17)</td>
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<tr>
<td>1183 ± 587.7† (0.853 ± 0.090)</td>
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that hysteresis in integrated BRS is augmented after exercise with both integrated $G_{up}$ and $G_{down}$ attenuated for the first 10 minutes postexercise. Studinger et al. observed marked variation in baroreflex hysteresis that was explained by between-subject variation in the relative contribution of the mechanical and neural components of integrated baroreflex gain. They concluded that this large variation represented a complexity in baroreflex function that could not be explained with their measures. Interestingly, after exercise, this inter-subject variation appears to be reduced with every individual showing similar changes in mechanical and neural BRS. Indeed, Charkoudian et al. have shown that the intersubject variability itself is relevant in describing cardiovascular variables, however, given that the general trend was for BRS values to decrease toward 0 immediately postexercise, it is not possible to know whether the reduced variance is indicative of some postexercise physiology or simply a mathematical effect of the attenuated gain values that are constrained by $G_{up}$.

Our finding of a 54% decrease in HR $G_{down}$ at 10 minutes postexercise might provide one explanation for the orthostatic intolerance often observed in humans after exercise; a reduced cardiac response to a hypotensive insult may critically attenuate the maintenance of cerebral perfusion pressure leading to syncope. Furthermore, although not significantly different, integrated $G_{down}$ remained 25% below pre-exercise levels at 60 minutes postexercise. This suggests that orthostatic tolerance and autonomic function may remain attenuated even 1 hour postexercise, a finding that is consistent with studies reporting impaired autonomic function after different types of exercise in humans. In fact, Furlan et al. showed that cardiac sympathetic modulation remained elevated after restoration of HR to pre-exercise values. It is important to note, however, that these studies using spectral means of BRS measurement cannot discern between gain values for rising and falling BPs.

This study is the first to identify neural characteristics of the cardiac baroreflex after exercise. That neural gain after exercise is differentially altered with rising versus falling BP has a number of implications. First, the fact that both mechanical and neural gains are reduced postexercise likely accounts for the greater attenuation of integrated $G_{down}$ than $G_{up}$. Indeed, plasticity of the neural BRS in postexercise hypotension has been reported previously in animals and therein suggested to manifest in attenuated inhibitory input to second-order baroreflex neurons in the nucleus tractus solitarii. However, these alterations to baroreflex signals have not been explored with respect to directionality of BRS. Although speculative, the unchanged neural $G_{up}$ after exercise may be suggestive of central baroreflex signaling that is only sensitive to falling BP. Another possibility is an active preservation of $G_{up}$ to protect against postexercise BP fluctuations providing defense against hemorrhage. These speculations clearly need to be addressed and require future research.

**Perspectives**

Regulation of BP ultimately serves to maintain adequate systemic perfusion. The brain, given its high metabolic requirement and very limited capacity for energy storage, is nearly immediately affected by a drop in perfusion pressure. Likely in consequence, the brain has evolved effective regulatory mechanisms to defend regional brain perfusion; interestingly, there is an increased incidence of fainting after exercise, which is ultimately because of loss of said perfusion. It is important to recognize that the cardiac baroreflex is only 1 part of human dynamic BP regulation; muscle sympathetic nervous activity has been shown to be attenuated 60 minutes after exercise, which, along with concomitant neurovascular uncoupling (lower resistance for given sympathetic activity), may account for a transient loss of effective BP regulation after exercise. There have been reports during syncope of associations between the decline in cardiac output and cerebral blood flow after exercise. It is, therefore, conceivable that the integrated defense against cerebral hypoperfusion and imminent syncope depends, at least in part, on an intact cardiac baroreflex and the related maintenance of cardiac output.

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**Disclosures**

None.

**References**


