Arterial Baroreflex Control of the Sinus Node During Dobutamine Exercise Stress Testing

Philippe van de Borne, Shirley Heron, Hung Nguyen, Philippe Unger, Marc Leeman, Jean Louis Vincent, Jean Paul Degaute

Abstract—The contributions of increases in circulating catecholamines, changes in central command, and muscle afferents on baroreflex control of the sinus node during exercise are unclear. We used a dobutamine infusion to induce hemodynamic changes comparable to those of moderate physical exercise in the absence of changes in central command and muscle afferents in 13 healthy subjects. Dobutamine (up to 9 μg/kg body weight per minute) increased systolic blood pressure, shortened the RR interval, increased systolic blood pressure variability, but blunted RR interval variability (P<0.05 versus placebo). Consequently, dobutamine decreased the coherence between variations in systolic blood pressure and RR interval and decreased arterial baroreflex sensitivity from 12±2 to 3±1 ms/mm Hg (P<0.01). The largest increases in systolic blood pressure with dobutamine were paralleled by the greatest impairments in arterial baroreflex sensitivity (0.50<r<0.56, P<0.01). The chronotropic effects of dobutamine prevented a reflex bradycardia in response to the blood pressure increase. However, less predominant low-frequency oscillations in systolic blood pressure (P<0.0001) suggested preserved sympathetic withdrawal in response to the blood pressure increase induced by dobutamine. In conclusion, this study revealed that a shift in the operating point of the arterial baroreceptors and the chronotropic effects of adrenergic stimulation impair baroreflex control of the sinus node during dobutamine exercise stress testing. Baroreflex control of the sinus node is not reset when hemodynamic characteristics of exercise are reproduced in the absence of modifications in central command and muscles afferents. (Hypertension. 1999;33:987-991.)

Key Words: dobutamine ■ baroreflex ■ exercise ■ blood pressure

Both arterial blood pressure (BP) and heart rate increase rapidly after the onset of physical exercise and continue to rise with increases in work rate.1–10 This contrasts with the cardiovascular responses elicited by increases in BP in resting humans,11 in whom increases in BP, sensed by the carotid and aortic baroreceptors, result in a reflex reduction in both cardiac sympathovagal balance and in sympathetic nerve traffic to peripheral blood vessels.10,11 The absence of reflex bradycardia and peripheral vasodilatation in response to exercise-induced increases in BP continues to intrigue many investigators1–10 and suggests marked changes in arterial baroreflex control during physical exercise.

The stimulus-response curve of the arterial baroreceptors is sigmoidal.1–10 The sensitivity of the baroreceptors assessed by the slope of the stimulus-response curve is largest around the centering point, where there is a comparable depressor and pressor response to a given change in BP.1–10 However, there is a point where no further response will be elicited with a further increase in BP. Consequently, baroreflex sensitivity is markedly lower at the saturation point of the reflex than at the centering point.1–10 Thus, the acute increases in BP elicited by exercise would normally be expected to shift the operating point of the baroreceptors toward their saturation point and thereby to reduce arterial baroreflex sensitivity. However, there are as many reports of reduced1–3,9 as of unchanged4–10 baroreflex sensitivity during exercise in humans. Thus, whether a reduction in the sensitivity of arterial baroreflex control of the sinus node permits the concomitant increase in BP and heart rate during physical exercise or whether arterial baroreflex sensitivity is simply reset (unchanged sensitivity in the presence of a heightened BP) during exercise is unclear.1–10 Variable contributions of changes in central command (which activates concomitantly regions of the brain responsible for the recruitment of skeletal muscle motor units and cardiovascular areas within the medulla9,10), muscle chemoreflex stimulation,8,9 sustained adrenergic stimulation,11 and mechanosensitive stimulation9 may explain why arterial baroreflex sensitivity remained unchanged (ie, was reset) despite increases in BP during exercise in some4–10 but not all studies.1–3,9

We tested the hypothesis that baroreflex resetting does not occur when the hemodynamic changes of exercise are in-
duced in the absence of modifications in central command and muscle afferents. In a double-blind, randomized, placebo-controlled crossover study, we used an infusion of dobutamine, an agent with predominant β$_1$ and weaker β$_2$ and α$_1$, adrenoreceptor agonist activity, to induce hemodynamic changes comparable to those of moderate physical exercise. Such a procedure is commonly used to replicate the effects of exercise in patients with coronary artery disease.\textsuperscript{12}

Subjects were unaware that the aim of the study was to reproduce the hemodynamic changes of exercise to avoid the possibility that modifications in their central command might affect their baroreflex control. In addition, subjects were kept in strict resting conditions. Thus, hemodynamic changes induced by exercise were reproduced, but in the absence of modifications in central command and changes in afferents from receptors within the skeletal muscle.

Baroreflex function was assessed throughout the study as the gain of the transfer function between variations in RR interval in response to beat-by-beat changes in systolic arterial pressure,\textsuperscript{13–15} thereby avoiding the need for additional interventions to alter BP during dobutamine infusion.

**Methods**

**Subjects**

Thirteen healthy subjects (6 women and 7 men; mean age, 32±6 (SD) years) participated in the study. None was taking any medication. Informed written consent was obtained from all subjects. The study was approved by the Institutional Human Subjects Review Committee. All procedures were in accordance with institutional guidelines.

**Measurements**

Systolic BP (SBP) was recorded continuously using a volume oscillometric method (Finapres, Ohmeda 2300).\textsuperscript{16–18} The cuffed finger was kept at heart level during the entire recording procedure. Finger BP, an ECG (Sirecust 404, Siemens AG, UB Medical), and ribcage and abdominal motion (Respitrace, Ambulatory Monitoring) were recorded online on a Compaq 386/25 E computer for subsequent analysis. Analog-to-digital conversion was performed at 1000 s$^{-1}$ for the ECG and at 200 s$^{-1}$ for the BP and respiratory signals.

**Protocol and Interventions**

The study used a randomized, double-blind, crossover, and vehicle-controlled design. Studies were conducted with subjects under quiet resting conditions in the same room by the same investigator (S.H.). Subjects were in the supine position, and measurements were obtained during relaxed free breathing. All subjects were instructed to avoid talking during the recordings. Sleep was not permitted and was carefully prevented by continuous monitoring of the subjects. After 10-minute baseline measurements were obtained, dobutamine (or placebo) was infused in random order for 10 minutes at 3 μg/kg body weight per minute, followed by a 10-minute infusion at 6 μg/kg body weight per minute and a 10-minute infusion at 9 μg/kg body weight per minute. A 20-minute recovery period between dobutamine and placebo infusions was observed for all subjects.

**Analyses**

A derivative/threshold algorithm provided the continuous series of RR intervals (tachogram) and SBP. The signals of respiratory activity were sampled once every cardiac cycle, allowing us to obtain respirograms synchronized with the tachograms. Isolated artifacts were detected and removed, and all interpolated values were visually checked. Stationary segments devoid of artifacts and rhythm disturbances were analyzed with discrete Fourier algorithms with a frequency resolution of 0.01 s$^{-1}$\textsuperscript{13–15,19} Arterial baroreflex sensitivity was determined as the gain of the transfer function between SBP variability and RR interval variability among the low-frequency (LF, 0.04 to 0.14 s$^{-1}$) and high-frequency (HF, 0.15 to 0.35 s$^{-1}$) points with a coherence of >0.50.\textsuperscript{13,19,20} The coherence function determines the amount of linear coupling between series of SBP and RR interval and has the same meaning as the squared coefficient of correlation (percentage of explained variance) in a linear regression equation.\textsuperscript{13,19} This method of determination of arterial baroreflex sensitivity has been validated against the classic phenylephrine methods\textsuperscript{13,20} and the pulse interval method.\textsuperscript{20} This technique has several advantages over the phenylephrine and neck suction methods because there is no need for additional pharmacological or mechanical interventions. Moreover, arterial baroreflex sensitivity is determined over a wide range of SBP variations and integrated over long sequences of beat-to-beat SBP variations. This is particularly important for the marked short-term intraindividual variability of arterial baroreflex gain.\textsuperscript{14,21} In addition, frequency domain analysis of arterial baroreflex sensitivity has the additional advantage over the phenylephrine and pulse interval methods of being able to analyze separately baroreflex gain in responses to fast respiratory-related SBP oscillations (HF, 0.15 to 0.35 s$^{-1}$) and to slower Mayer wave oscillations in SBP (LF, 0.04 to 0.14 s$^{-1}$). In this study, the LF and HF variability of SBP and RR interval were expressed in normalized units, obtained by calculating the percentage of LF and HF variability with respect to the total power after subtraction of the power of the very LF component (frequency of <0.03 s$^{-1}$).\textsuperscript{22–24} All recordings received an anonymous code and were analyzed in a completely blinded manner.

**Statistical Analysis**

Results are mean±SEM. The null hypothesis of no significant differences between equal-volume infusion of dobutamine and placebo was tested for each cardiovascular parameter using repeated-measures ANOVA. Data were first transformed by natural logarithm to stabilize variance. We used $P<0.05$ as the significance level for overall analysis but adjusted the level of significance for multiple comparisons using the Bonferroni correction.\textsuperscript{25} Because we considered 4 pairwise contrasts (Figure 1), the level of significance for each contrast was $P<0.05/4=0.0125$. Correlations were estimated with the Pearson coefficient.

**Results**

**Effects of Dobutamine on BP, RR Interval, and Arterial Baroreflex Sensitivity**

Dobutamine increased SBP and shortened RR interval (both ANOVA, $P<0.0001$; Figure 1), increased BP variability (ANOVA, $P<0.0001$; Figure 1), and tended to blunt RR interval variability (ANOVA, $P<0.05$; pairwise contrasts, $P>0.10$; Figure 1). Dobutamine also decreased coherence between variations in SBP and RR interval (both ANOVA, $P<0.01$; Figure 2) and impaired arterial baroreflex function in a dose-dependent manner (ANOVA, $P<0.01$; Figure 2). The reduction in arterial baroreflex sensitivity was most evident in the HF respiratory band, where 9 μg/kg body weight per minute of dobutamine decreased arterial baroreflex sensitivity from 12±2 to 3±1 ms/mm Hg ($P<0.001$).

Higher increases in SBP with dobutamine resulted in larger decreases in arterial baroreflex sensitivity ($r=-0.56$ and $-0.50, P<0.01$, for arterial baroreflex sensitivity in the LF and HF domains, respectively; Figure 3), indicating that the dobutamine-induced BP rise decreased arterial baroreflex sensitivity through a shift in the operating point of the arterial baroreceptors.
Effects of Dobutamine on BP, RR Interval, and Respiratory Variability

The chronotropic effects of dobutamine prevented reflex bradycardia in response to the BP increase and blunted both LF and HF oscillations in RR interval (ANOVA, $P > 0.60$; Figure 4). However, less predominant LF oscillations in SBP during dobutamine infusion suggested preserved peripheral sympathetic withdrawal in response to the BP increase induced by dobutamine (ANOVA, $P < 0.0001$; Figure 4). In addition, quantitative assessment of minute ventilation by the variance of the ribcage and abdominal movements indicated that increased ventilation during dobutamine infusion could

**Figure 1.** SBP, RR interval (RRI), and their variance during equal-volume infusions of dobutamine (●) and placebo (□). Dobutamine increased SBP, shortened RR interval, increased SBP variability, and tended to blunt RR interval variability (pairwise contrasts: $§P < 0.01$ and $*P < 0.0001$, placebo vs dobutamine; other, NS).

**Figure 2.** Effects of dobutamine on the amount (coherence) and gain (baroreflex sensitivity, BRS) of linear coupling between oscillations in SBP and RR interval (RRI) present in the LF and HF domains. Dobutamine decreased coherence between variations in SBP and RRI and impaired arterial baroreflex control of the sinus node in a dose-dependent manner (pairwise contrasts: $§P < 0.01$, placebo vs dobutamine; other, NS).
also have increased the HF oscillations in SBP (ANOVA, \(P<0.01\); pairwise contrasts, \(P>0.18\); Figure 4). Dobutamine, however, did not affect respiratory frequency (ANOVA, \(P=0.43\); Figure 4).

**Discussion**

This study demonstrated that dobutamine decreases arterial baroreflex sensitivity. We are not aware of a previous study in humans on the effects of dobutamine on arterial baroreflex sensitivity, although dobutamine stress testing is increasingly used to replicate the effects of exercise.\(^{12}\) The originality of our study is that baroreflex control was determined during hemodynamic changes comparable to those of moderate exercise, but in resting subjects. This avoided confounding effects of changes in central command and in muscle afferents on baroreflex function.\(^{1–10}\) This is important because at least 5 mechanisms can affect arterial baroreflex sensitivity during exercise: (1) the rise in BP, which shifts the operating point of the baroreceptors toward their saturation point; (2) mechanosensitive stimulation, which has been reported to decrease arterial baroreflex sensitivity; (3) sustained adrenergic stimulation, which impairs heart rate variability\(^{11}\) and thus arterial baroreflex function; (4) changes in central command and (5) in muscle chemoreflex stimulation, which resets the baroreceptors.

Our results have several implications. First, they reveal a redundancy in the mechanisms that can impair baroreflex control during exercise. Not only mechanosensitive muscle stimulation\(^9\) but also the hemodynamic changes per se of exercise decrease baroreflex sensitivity. Second, we observed the largest decreases in arterial baroreflex sensitivity during the largest increases in BP induced by dobutamine. These data are in good agreement with the well-known sigmoidal stimulus–response curve of the arterial baroreceptors\(^{10}\) and suggest that the increase in BP induced by dobutamine shifted the operating point of the arterial baroreceptors toward a less sensitive region. Third, our findings support previous observations of the importance of changes in central command\(^9,10\) and in muscle chemoreflex\(^8,9\) for arterial baroreflex resetting\(^4–10\) during dynamic exercise. Last, the results of our study suggest that caution should be exercised in the inter-

![Figure 3](image3.png)

**Figure 3.** Correlation analyses between increases in SBP (Delta SBP) and reductions in arterial baroreflex gain (Delta BRS) during dobutamine infusion. Baroreflex gain was determined in the LF (DELTA LF BRS, ◆) and HF (DELTA HF BRS, □) domains.

![Figure 4](image4.png)

**Figure 4.** Effects of dobutamine on SBP variability, RR interval (RRI) variability, respiratory variance, and respiratory frequency. HF oscillations in SBP became more predominant than LF oscillation in SBP during dobutamine infusion. Also, respiratory variance tended to increase during dobutamine. Dobutamine affected neither normalized LF and HF variability in RRI nor breathing frequency (pairwise contrasts: \(P<0.01\), placebo vs dobutamine; other, NS). au indicates arbitrary units; and nu, normalized units.
pretation of studies on autonomic control in critically ill patients who receive intravenous inotropes.26

Dobutamine had similar effects on LF and HF variability of the RR interval. RR interval variability normally results from the complex interactions of phasic changes in sympathetic and vagal drive to the sinus node.27 Hence, RR interval variability decreased progressively when we added a tonic intravenous adrenergic stimulation on the modulated autonomic drive to the sinus node. These effects of dobutamine on RR interval variability contrast with our new finding of decreased predominance of LF over HF variability in BP during dobutamine infusion.

In healthy subjects, BP variability consists mainly of LF and HF respiratory-related oscillations.11,14,15,22 These LF oscillations in BP become less predominant over the HF oscillations when phenylephrine (a virtually pure α1 adrenoceptor stimulant) produces reflex peripheral sympathetic inhibition in response to graded hypertension.11 Thus, decreased predominance of LF over HF oscillations in BP during dobutamine infusion suggests a reflex peripheral sympathetic withdrawal in response to the increase in BP. Hence, it could be that the chronotropic action of dobutamine impairs baroreflex control of the sinus node more than baroreflex control of sympathetic outflow to the blood vessels. In addition, β-adrenergic stimulation increases ventilation,28 and a heightened ventilatory drive could also contribute to the increase in HF variability in BP during dobutamine infusion.

In conclusion, this study revealed that a shift in the operating point of the arterial baroreceptors and the chronotropic effects of adrenoreceptor stimulation impair baroreflex control of the sinus node during dobutamine exercise stress testing. Baroreflex control of the sinus node is not reset when hemodynamic changes of exercise are simulated in the absence of modifications in central command and muscle afferents.

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References
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