Cardiovascular Indices of Peripheral and Central Sympathetic Activation

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Objective: A number of sympathetic nervous system (SNS) parameters have been used in cardiovascular psychophysiology. This study aimed to describe the pattern and redundancy of a set of SNS parameters during peripherally induced changes of cardiac sympathetic activation and reflex modulation of central SNS control. Preejection period (PEP) was assessed as a marker of peripheral sympathetic activation. Low-frequency blood pressure variability (BPV) was assessed as an estimate of central SNS control. **Methods:** Peripheral β-sympathetic stimulation and blockade were achieved with epinephrine and esmolol hydrochloride (β_1-blockade), respectively. Changes in central SNS output were induced by loading and unloading arterial baroreceptors with norepinephrine and nitroprusside sodium, respectively. This single-blinded, crossover study in 24 healthy men also included two placebo control periods. PEP was derived from impedance cardiography and adjusted individually for heart rate. BPV was calculated by power spectral analyses of beat-to-beat heart rate and systolic blood pressure (Finapres system) data. **Results:** PEP decreased during epinephrine infusion (-40.1 ± 3.8 ms, $p < .0001$) and increased during esmolol infusion ($+6.6 \pm 3.5$ ms, $p = .05$). PEP was shortened after central SNS activation by nitroprusside (-16.8 ± 2.9 ms, $p < 0.0001$). Systolic BPV in the low-frequency range (0.07–0.14 Hz, Mayer waves) increased during nitroprusside infusion ($+0.44 \pm 0.19$ ln mm Hg^2, $p = .03$) and decreased during norepinephrine infusion (-0.67 ± 0.13 ln mm Hg^2, $p < 0.0001$). Low-frequency BPV did not change significantly during epinephrine or esmolol infusion. **Conclusions:** Our data provide empirical evidence of separable peripheral and central sympathetic response components. The combined report of low-frequency BPV and PEP gives distinct information on both central SNS control and the level of sympathetic cardiac activation achieved. **Key words:** blood pressure variability, preejection period, esmolol hydrochloride, nitroprusside sodium, epinephrine, norepinephrine.

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bpm = beats per minute; BPV = blood pressure variability; HRV = heart rate variability; LVET = left ventricular ejection time; PEP = preejection period; SNS = sympathetic nervous system.

INTRODUCTION

The SNS plays an important role in psychosomatic medicine. Sympathetic activation is related to cardiovascular morbidity and mortality (1–3), may be a target of psychosomatic interventions (4), and has consequences for cognitive and emotional processes (5). There is, however, no general agreement on the usage of distinct sympathetic indices in psychosomatic medicine. Indeed, it is likely that different response components (reflecting peripheral or central sympathetic effects) may be present. Changes in peripheral sympathetic activation may result from altered organ sensitivity (ie, expression, density, and distribution of peripheral adrenergic receptors and presence of counteracting mechanisms) as well as from direct changes of central sympathetic output. Psychological effects can be expected from both, changing activity of peripheral organs or changing central SNS activity. Increased sympathetic activation of peripheral organs may cause distraction, discomfort, symptoms (ie, palpitations), and direct attention toward internal sensations. Central SNS activation may be involved more directly in cognitive and emotional processes, as suggested by the existence of multiple neural associations from SNS output areas to higher cortical structures (6–9). It would be helpful in psychosomatic research to establish a set of methods that differentiate central sympathetic control from peripheral sympathetic effects. The importance of such an approach is further emphasized by the fact that central SNS control and peripheral sympathetic activity do not necessarily change in parallel; instead, counter-regulatory phenomena have to be considered. In post-stress periods, for example, peripheral organs may still be stimulated by not-yet-inactivated circulating catecholamines even though central SNS output soon returns to normal. Some behavioral interventions, such as low-salt diet (10–14), may have different impacts on peripheral sympathetic indices (such as blood pressure) and central SNS output. Central SNS activity may be lowered during administration of peripherally acting sympathomimetic drugs (15). Such drugs induce a state of increased SNS activity (indicated by increased blood pressure and/or heart rate), although central SNS output may be reduced as a consequence of arterial baroreceptor loading.

Today it is possible to assess human sympathetic

nervous discharge by direct recordings of the peroneus nerve (16). However, substantial regional differences in sympathetic nervous activity exist. Thus, muscle or skin sympathetic nervous activity recorded in the peroneus nerve does not equal sympathetic discharge directed to the heart. Furthermore, the technique is delicate and limited by the availability of elaborate equipment. Instead, spectral analysis of HRV and BPV have been proposed as estimates of central SNS control (17, 18). Systolic time intervals have been suggested as markers of cardiac sympathetic activation (19). Simultaneous assessment of these parameters has never been reported during specific modulation of SNS activity. Thus, the current study investigated the pattern and redundancy of these noninvasive cardiovascular SNS parameters during distinct pharmacological stimulation and inhibition of central and peripheral SNS components.

Instead of more common behavioral stimulation (ie, psychological or physical stress tests), a pharmacological design was chosen because of its relatively unambiguous effects on sympathetic function. A protocol including infusions of epinephrine, esmolol hydrochloride, nitroprusside sodium, and norepinephrine was developed to directly stimulate or block peripheral β-adrenergic receptors (β-adrenoceptors) and to indirectly activate or inhibit central SNS output by unloading or loading arterial baroreceptors. In detail, epinephrine was infused to induce peripheral sympathetic activation. Epinephrine is a natural, direct-acting, sympathomimetic agent that exerts its effects on both α- and β-adrenoceptors. It is approximately 10-fold more selective for β_2- than for β_1-adrenoceptors (20). Metabolites have been detected in cerebrospinal fluid, indicating that epinephrine may pass the blood-brain barrier to some extent (20). However, the principal site of action is peripheral tissue, accounting for increased systolic blood pressure and tachycardia (21). Esmolol hydrochloride is a water-soluble, short-acting β-blocker. No direct effects of esmolol inside the central nervous system have been reported. When esmolol is administered as a bolus followed by continuous infusion, β_1-blockade occurs within 2 minutes (20). Esmolol is highly specific for β_1 and therefore acts mainly on cardiac adrenoceptors; it has also been found to abolish adrenal medullary and plasma epinephrine responses to hypotension (22). Clearly esmolol attenuates sympathetic cardiac activity by peripheral β_1-blockade. Sodium nitroprusside is a potent, rapid-acting, and short-lasting vasodilating drug. Sodium nitroprusside releases nitric oxide (23), which is responsible for an immediate decrease in total peripheral resistance and an associated fall in blood pressure. Nitroprusside has no direct effect on adrenergic recep-

tors. However, its hypotensive activity (baroreceptor unloading) causes a reflex increase in sympathetic tone (24) and a rise in plasma norepinephrine and epinephrine (25). We do not know whether nitroprusside itself crosses the blood-brain barrier, but nitric oxide does. It remains unclear whether centrally acting nitric oxide contributes to the sympatho-excitatory effect of nitroprusside (26, 27). In the current study, infusion of nitroprusside sodium served as a model to increase central SNS output (28). Norepinephrine is an α-adrenergic agonist. It also possesses β-stimulating properties and is equipotent to epinephrine at β_1-receptors, but it has little action on β_2-receptors. Norepinephrine is an endogenous catecholamine released from sympathetic nerve endings. Infusion of norepinephrine increases total peripheral resistance and blood pressure (baroreceptor loading), accompanied by reflex augmentation of parasympathetic tone (20, 29). According to what is known of other α-adrenergic vasoconstrictor agents (ie, phenylephrine), reflex inhibition of central sympathetic output (15) can be expected. Phenylephrine would have been the better agent to induce reflex inhibition of central SNS output because of its high selectivity for α-adrenoceptors. However, because phenylephrine has a rather long half-life, it could not be included in the current study, and norepinephrine was chosen instead.

All pharmacological procedures were used in an attempt to equate heart rate and blood pressure responses to the presumed central and peripherally acting agents.

METHODS

The research protocol was approved by the local ethics committee of the University Hospital of Basel. Twenty-four male volunteers participated in the study. All had normal findings on physical examination, routine blood chemistry and hematologic studies, urine sediment test, and standard electrocardiographic study. Only nonsmokers with no evidence or history of any illicit drug use were included. Participants were asked to refrain from alcohol- or caffeine-containing beverages the night before and the day of the experiment. Volunteers gave informed consent.

Study Protocol

After entering the hospital at 7 AM, subjects were briefly introduced to the psychophysiological laboratory. A small venous line was placed at the forearm for drug infusions. The examination was divided into two parts of 4.5 hours duration each, one lasting from 8:30 AM to 1:00 PM, the other from 1:30 to 6:00 PM. During part 1 (the "peripheral β-adrenergic set"), epinephrine (peripheral β-adrenergic stimulation and to a lesser extent α-adrenergic stimulation), esmolol hydrochloride (β_1-blockade), and a control placebo (saline) infusion were administered consecutively. During part 2 (the "baroreceptor loading and unloading set"), additional placebo, norepinephrine, and nitroprusside sodium (vasodilatation) were given. Following a balanced crossover design, half of the subjects started

with the peripheral β-adrenergic set, and half started with the baroreceptor set. Within each set the succession of drug periods was such that for six consecutive subjects each infusion period was equally often the first, second, and third intervention. Thus, within each set potential sequence effects were counterbalanced. Each infusion period lasted 90 minutes, with the first 10 to 15 minutes being used to titrate doses so that a ±15% change in blood pressure and/or heart rate was achieved. The infusion dosage was then kept constant for the next 60 minutes, during which several psychophysiological interventions were tested (resting baseline period, startle measurements during presentation of emotion-inducing slides (30), facial expression ratings, cardioception, and emotion questionnaires). Each infusion period was followed by a 10- to 30-minute washout period. Here we report only drug-related changes of cardiovascular SNS parameters during resting baseline conditions; the results of the other procedures and tests will be reported elsewhere.

Drug Interventions and Rationale of Dosages

All drugs that were used are highly hydrophilic. Their principal site of action is in the periphery and not beyond the blood-brain-barrier. All drugs have a short half-time (epinephrine, <120 s; norepinephrine, <120 s; nitroprusside, 150 s; esmolol, 7.8 min) (31, 32), well-established effects, and excellent dose-response properties so that the hemodynamic goals could be achieved by carefully titrating the substances. Patients were blind to the content of the infusion they actually received. The starting dose of epinephrine, 40 ng/kg per min, was increased by increments of 20 ng/kg per minute every 3 minutes until either a 15% increase in heart rate or mean arterial blood pressure was achieved. The maximal allowed dose was 80 ng/kg per minute because higher doses were expected to result in plasma epinephrine levels above those achieved during physiological conditions (33). The starting dose of norepinephrine was 20 ng/kg per minute. It was increased by increments of 20 ng/kg per min (every 3 minutes) until the intended hemodynamic effect (15% increase in mean arterial blood pressure or 15% decrease in heart rate) was achieved. The maximal allowed dose was 100 ng/kg per min. The starting dose of nitroprusside sodium was 12.5 μg/min. It was increased by 25 μg/min every 3 minutes until a 15% decrease in mean arterial blood pressure or a 15% increase in heart rate was achieved. The maximal allowed dose was 150 μg/min. The esmolol period was started with an initial dose of esmolol hydrochloride 500 μg/kg per min, administered over 1 minute, followed by a constant infusion of 50 μg/kg per min. If heart rate or mean arterial blood pressure did not decrease by at least 15% during the following 4 minutes, the loading doses was readministered and followed by a continuous infusion, which was increased in increments of 50 μg/kg per min. This procedure was repeated until either the effect or the maximal allowed continuous dose (200 μg/kg per min) was achieved.

Baseline Recording and Parameter Calculation

During the 5-minute resting baseline period, subjects were in the supine position. They were instructed to close their eyes, relax, and to neither voluntarily move nor speak. Respiratory frequency was not externally controlled. The following signals were recorded: a standard lead II electrocardiogram, continuous noninvasive finger blood pressure (Finapres 2000 system, Ohmeda, Englewood, CO), intermittent cuff blood pressure (Dinamap system, Critikon, FL), impedance cardiogram (modified Minnesota device, Diefenbach, Frankfurt A. M., Germany), and respiratory frequency (Respitrace system, Med. Elektronic, KSB, Basel, Switzerland). Analog-to-digital conversion was performed at 1000 Hz. Data were stored on a per-

sonal computer. Off-line analysis with ACTS software (34) revealed beat-to-beat heart rate and interbeat interval length from the electrocardiogram, systolic and diastolic blood pressures from Finapres output, and systolic time intervals from the impedance cardiogram (dz/dt signal). PEP was calculated from the onset of the Q interval (electrocardiogram) to point B of the dz/dt signal (beginning of ventricular ejection). LVET was calculated from point B to the X point minimum (closure of aortic valve). To correct PEP and LVET for changes in heart rate, the following procedure was used: a weighted regression model between systolic time intervals and interbeat interval length was constructed for each subject and for each infusion period to predict LVET or PEP at an interbeat interval length of 925 ms. The interbeat interval length of 925 ms was chosen because it corresponds to the subjects' mean heart rate during placebo (saline) infusion (about 65 bpm).

HRV and BPV were assessed according to published standards (35, 36). In brief, BPV was calculated by Fourier transformation after equidistant representation of systolic blood pressure data. HRV was determined by Low-Pass Filtering of Event Series (LPFES method) as suggested by Rompelman et al. (37). This method is in accordance with the integral pulse frequency modulator concept, which represents a rational model for the modulation of heart beat generation by autonomic nervous system influences (38). Power of BPV and HRV was analyzed over the entire spectrum of 0.01 to 0.50 Hz with a frequency resolution of 0.01 Hz. Low-frequency power of HRV and BPV was determined by integrating spectral power in the low-frequency range between 0.07 Hz and 0.14 Hz. Two procedures were used to normalize power values. First, the percentage of total power was calculated for the low-frequency band of HRV and BPV. Second, HRV was adjusted to mean heart rate according to a method proposed by Akselrod et al. (39) and Althaus et al. (40) and expressed as the modulation index. However, this second procedure did not alter the results in any substantial way relative to the untransformed numbers. Log transformation of power measures was performed to yield normally distributed values. Because respiratory frequency is a strong determinant of HRV (41, 42) and BPV (43), the dominant respiratory frequency was calculated for each subject and period.

Transfer function analysis of beat-to-beat changes of interbeat interval length and systolic blood pressure data were performed using ACTS software in accordance with previous publications (34, 44, 45). The transfer magnitude (modulus gain) function was calculated over the frequency range of 0.02 to 0.5 Hz (this function is expressed in ms/mm Hg). For further statistical analysis, it was adjusted to the weighted coherence function (46) as previously suggested (44). We separately calculated the low- and high-frequency parts of the transfer function between systolic blood pressure and interbeat interval by integrating the modulus gain function over the low- and the high-frequency bands (0.15–0.4 Hz), respectively, which yielded two parameters.

Safety Considerations and Adverse Effects

All drugs used have well-known cardiovascular effects, side effects, and a short half-time. Drug infusion could have been interrupted immediately. A physician was always present during drug administration. In two subjects superficial phlebitis, probably induced by the esmolol infusion, occurred. After further dilution of the esmolol solution, no more phlebitis occurred. No other adverse reactions were observed.

Statistics and Power Analysis

A multivariate analysis of variance suitable for repeated measures was used to test drug effects. Contrasts were constructed a

priori, testing β-adrenergic stimulation and blockade against placebo and testing baroreceptor loading and unloading against placebo. Test-retest reliability coefficients (Pearson correlation) of all dependent variables were calculated for the two placebo periods. Statistical analysis was performed using SAS software (version 6.12 for Windows NT). Mean (±SEM) values are provided in the text, tables, and figures. For illustration of the dz/dt impedance cardiogram, a signal-averaging technique was used with respect to interbeat interval length. Intervals of 600 to 750, 750 to 900, 900 to 1050, 1050 to 1200, and 1200 to 1350 ms were averaged separately. Power analysis (47) of the current study was based on data of low-frequency BPV as reported previously (45). Power was greater than 90% for the detection of a 10% change in normalized low-frequency BPV.

RESULTS

Subjects' age was 24.7 ± 0.7 years. Body weight was 74.6 ± 1.5 kg. Average infusion doses were as follows: epinephrine, 60.6 ± 2.9 ng/kg per min; norepinephrine, 64.1 ± 3.5 ng/kg per min; nitroprusside sodium, 76.8 ± 3.8 μg per min; and esmolol hydrochloride, 168.7 ± 9.4 μg/kg per min. The average number of esmolol hydrochloride loading doses necessary to induce the desired effect was 3.2 ± 0.2. Blood pressure or heart rate criteria were met in all subjects under all conditions. Data on blood pressure, heart rate, and respiratory frequency during infusion periods are provided in Table 1. All comparisons of blood pressure and heart rate between drug and placebo periods were statistically significant (at least <.05) except for diastolic blood pressure during epinephrine infusion. Respiratory frequency during drug infusion did not differ from that during either placebo period. Epinephrine- and norepinephrine-induced increases in systolic blood pressure did not differ significantly from each other, nor did epinephrine- and nitroprusside-induced heart rate responses. Esmolol- and nitroprusside-induced decreases in systolic blood pressure were not statistically different, although norepinephrine was more effective ($p < .03$) than esmolol in inducing a decrease in heart rate.

Average PEP values during placebo periods were 100 ± 4.7 and 103.3 ± 2.1 ms. PEP was shorter during epinephrine infusion than during placebo periods. The same was true during central SNS activation with nitroprusside sodium. During esmolol infusion, PEP increased. Compared with placebo, norepinephrine was associated with a decrease in PEP (for details and statistical significance data, see Figure 1). LVET increased significantly during epinephrine infusion (by 19.5 ± 6 ms, $p = .003$), esmolol infusion (by 5.2 ± 2.4 ms, $p = .05$), and norepinephrine infusion (by 13.6 ± 3.9 ms, $p = .002$), but it did not change during nitroprusside infusion ($+1.4 \pm 2.5$ ms, NS). The PEP/LVET ratio (data not presented) decreased significantly ($p < .0001$) during epinephrine infusion, increased slightly during esmolol infusion (NS), and decreased during nitroprusside ($p = .003$) and norepinephrine ($p = .003$) infusion.

To exclude the possibility that impedance cardiography results simply reflect the changes in heart rate induced by the protocol, dz/dt signals were individually averaged following the R peak of the electrocardiogram for different interbeat interval lengths. The resulting changes in the impedance cardiogram are illustrated in Figure 2. During epinephrine infusion, a higher and earlier ejection component is clearly visible in comparison with placebo or esmolol infusion. This is true for each heart rate (interbeat interval) level.

Average low-frequency systolic BPV during the placebo periods was 1.71 ± 0.15 and 1.9 ± 0.17 ln mm Hg^2. Systolic BPV in the low-frequency range increased during infusion of nitroprusside sodium and decreased during norepinephrine infusion irrespective of whether log-transformed raw power values (Figure 1) or percentage of total power was analyzed (percentage of total power increased by 10.5 ± 3.0, $p < .0001$, during nitroprusside infusion and decreased by -10.5 ± 2.2, $p < .0001$, during norepinephrine infusion). Neither epinephrine nor esmolol had a significant impact on low-frequency BPV (Figure 1). A similar pattern emerged for low-frequency HRV. Average low-frequency HRV during the placebo periods was 1.66 ± 0.18 and 1.81 ± 0.16 ln bpm^2. During nitroprusside infusion the low-frequency component of HRV increased, and it decreased during norepinephrine infusion (Figure 1). When low-frequency HRV was expressed as a percentage of total power, a significant decrease of 13.3 ± 3.2 ($p = .0004$) was detectable during norepinephrine infusion; however,

TABLE 1.   **Heart Rate, Blood Pressures (Systolic, Diastolic, and Mean Arterial), and Respiratory Frequency During Drug Infusion**

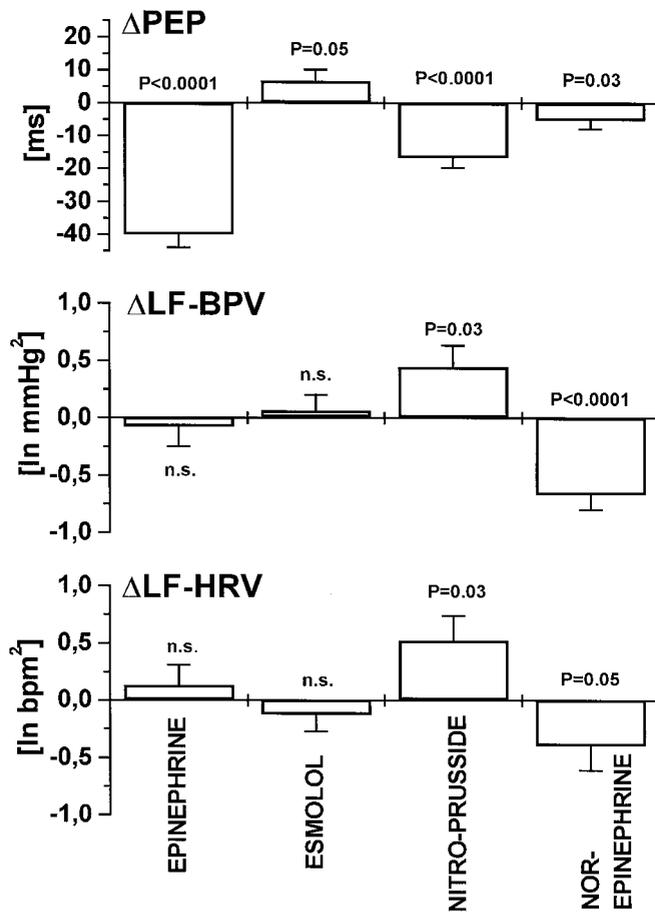|	Epinephrine	Norepinephrine	Esmolol	Nitroprusside	Placebo A	Placebo B
Blood pressure, mm Hg						
Systolic	130.3 ± 1.8	131.1 ± 1.2	113.9 ± 1.4	115.3 ± 1.0	120.6 ± 1.5	121.5 ± 1.4
Mean arterial	82.5 ± 1.3	92.1 ± 1.1	79.6 ± 1.0	77.3 ± 1.1	81.7 ± 1.1	82.3 ± 1.1
Diastolic	57.9 ± 1.1	69.6 ± 1.5	56.2 ± 1.4	50.5 ± 1.2	59.4 ± 1.1	60.6 ± 1.4
Heart rate, beats/min	77.7 ± 2.2	57.3 ± 1.5	64.4 ± 1.7	77.6 ± 1.9	68.9 ± 2.1	64.8 ± 1.4
Respiratory frequency, Hz	0.271 ± 0.010	0.264 ± 0.010	0.258 ± 0.007	0.239 ± 0.009	0.265 ± 0.009	0.263 ± 0.011

Fig. 1. Effects of epinephrine, esmolol, nitroprusside, and norepinephrine on PEP (*top*), low-frequency systolic blood pressure variability (LF-BPV) (*middle*), and low-frequency heart rate variability (LF-HRV) (*bottom*) as compared with placebo. Nitroprusside increased LF-BPV and LF-HRV, whereas norepinephrine decreased LF-BPV and LF-HRV. Neither epinephrine nor esmolol had any effect on LF-BPV or LF-HRV.

the increase of 3.5 ± 3.9 during nitroprusside infusion was not statistically significant. Neither epinephrine nor esmolol infusion had a significant impact on low-frequency HRV irrespective of whether percentage of total power or log-transformed absolute power values were considered.

Average transfer magnitude in the low-frequency range between systolic blood pressure and interbeat interval length during placebo periods was 11.4 ± 0.84 and 11.3 ± 0.68 ms/mm Hg. Drug-induced changes of transfer magnitude in the low-frequency band were small and not statistically significant during epinephrine infusion (increase of 1.2 ± 1.5 ms/mm Hg), esmolol infusion (increase of 1.6 ± 1.4 ms/mm Hg), and nitroprusside infusion (decrease of -1.7 ± 1.2 ms/mm Hg). Only during norepinephrine infusion did

transfer function magnitude in the low-frequency band increase (by 6.3 ± 1.8 ms/mm Hg, $p = .002$).

Table 2 summarizes the drug-induced changes in the high-frequency band. High-frequency HRV is reduced during nitroprusside infusion and enhanced during norepinephrine infusion even though significant opposite changes in BPV are detectable. Average transfer magnitude in the high-frequency range between systolic blood pressure and interbeat interval length during the placebo periods was 16.6 ± 2.3 and 16 ± 1.84 ms/mm Hg. Changes in transfer magnitude in the high-frequency band reveals decreasing magnitude during nitroprusside infusion (-5.8 ± 1.4 ms/mm Hg, $p = .0004$) and increasing magnitude during norepinephrine infusion ($+19.9 \pm 4$ ms/mm Hg, $p < 0.0001$), but no significant changes during esmolol ($+1.8 \pm 1.3$ ms/mm Hg) or epinephrine ($+1.5 \pm 2.1$ ms/mm Hg) infusion.

Nitroprusside-induced changes of low-frequency BPV were modestly correlated ($r = -0.34$) with nitroprusside-induced changes in PEP; however, this association failed to reach statistical significance. The correlation of nitroprusside-induced changes in low-frequency HRV and PEP was $r = -0.30$ (NS). None of the drug-induced changes in low-frequency HRV or BPV showed a significant correlation with changes in systolic time intervals.

The sympathetic indices all yield statistically significant but modest test-retest (placebo period to placebo period) correlations. Test-retest correlations of PEP and LVET were 0.57 and 0.48; similarly, all low-frequency variability indices showed correlations between 0.44 and 0.58. High-frequency HRV test-retest correlations were higher (0.72–0.76), but high-frequency BPV indices were only modestly stable (0.32–0.59).

DISCUSSION

This study was designed to investigate the value of BPV and systolic time intervals as markers of stimulation or inhibition of cardiac sympathetic activation and central SNS output. PEP was shortened during peripheral adrenergic stimulation and increased during peripheral β_1-adrenergic blockade. Thus, PEP clearly mirrored cardiac sympathetic activation and inhibition. Systolic BPV in the low-frequency range increased during nitroprusside infusion and decreased during norepinephrine infusion, thereby reflecting central SNS output. Systolic BPV and PEP changes did not correlate with each other, indicating different sources of variation.

One strength of the current pharmacological design is that it offers distinct modulation of the SNS and
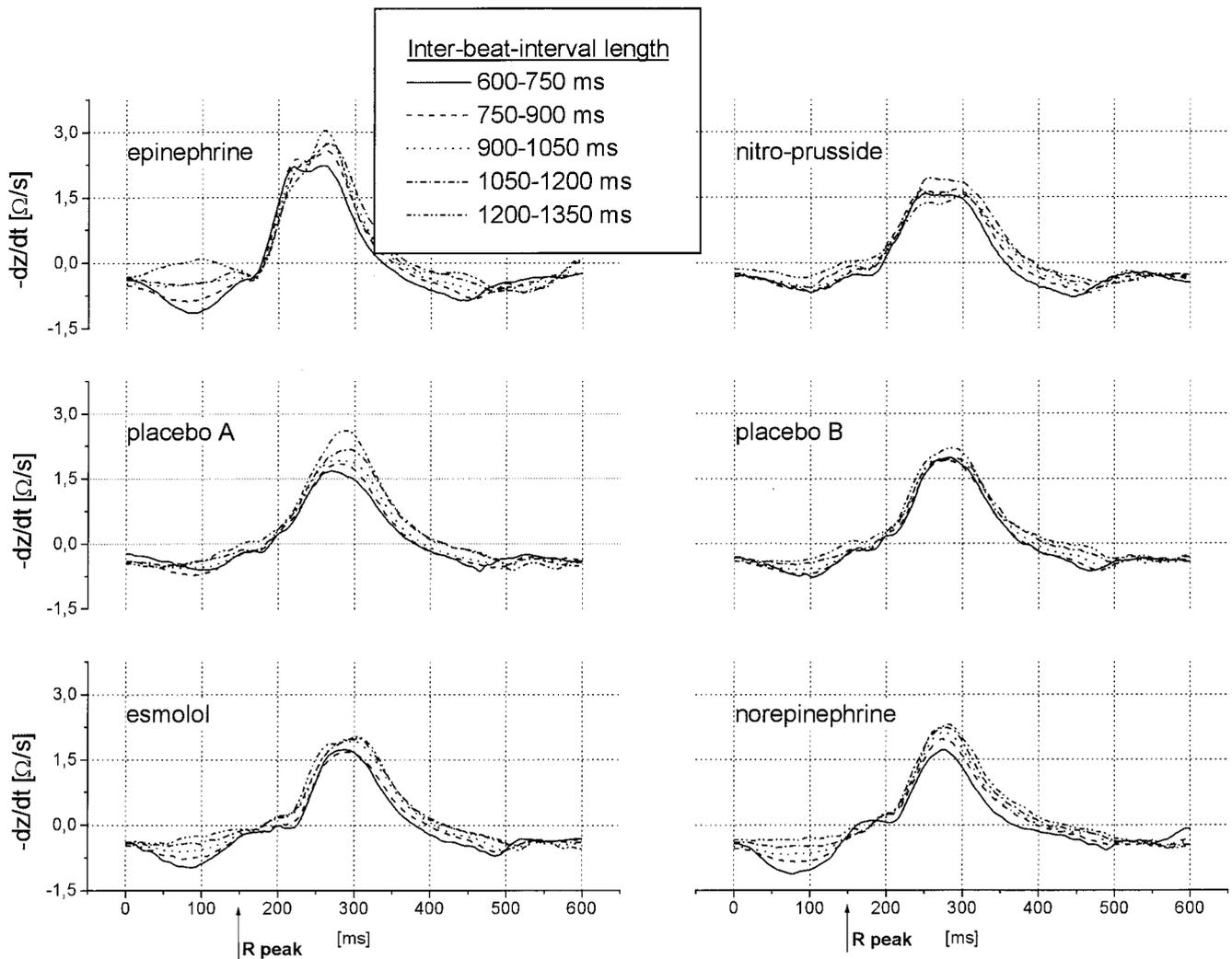
Fig. 2. Signal-averaged impedance cardiograms during infusion epinephrine, esmolol, nitroprusside, and norepinephrine as compared with the two placebo periods (A and B). Averaging was done with respect to interbeat interval length. Independent of interbeat interval length, epinephrine infusion caused a higher and earlier ejection component as compared with placebo; esmolol had the opposite effect.

TABLE 2. Changes in High-Frequency (HF) BPV and HRV During Drug and Placebo Infusion[a]

	Epinephrine	Esmolol	Nitroprusside	Norepinephrine
HF-BPV				
ln mm Hg^2	-0.04 ± 0.09 (NS)	0 ± 0.09 (NS)	0.71 ± 0.15 (.0001)	-0.68 ± 0.16 (.0003)
% of total BPV	-0.6 ± 1.7 (NS)	0.1 ± 1.1 (NS)	10.1 ± 3.1 (.003)	-5.9 ± 1.9 (.005)
HF-HRV				
ln bpm^2	0.23 ± 0.17 (NS)	-0.05 ± 0.09 (NS)	-0.1 ± 0.15 (NS)	0.39 ± 0.13 (.006)
% of total HRV	1.3 ± 3.2 (NS)	-0.5 ± 2.5 (NS)	-6.9 ± 2.8 (.02)	11.2 ± 3.8 (.0001)

[a] p values are shown in parentheses.

simultaneously controls for accompanying changes in average blood pressure and heart rate. This is important because there remains some uncertainty about the effects of mean blood pressure on BPV as well as the effects of mean heart rate on HRV. In the current re-

search we can contrast the effect of nitroprusside on HRV to that of epinephrine because both drugs resulted in comparable increases in heart rate. We can also contrast the effect of nitroprusside on BPV to the effect of esmolol because both drugs resulted in com-

parable decreases in blood pressure. The same is true for the effects of norepinephrine on HRV, which can be contrasted with those of esmolol (because heart rate declines during infusion of both drugs), and the effects of norepinephrine on BPV, which can be contrasted with those of epinephrine (because blood pressure increases during infusion of both drugs). Thus, we exclude the possibility that our findings are simple epiphenomena of either lowered and elevated blood pressure or increased and decreased heart rate.

Respiratory frequency is known to be of major importance for HRV and BPV (41–43). Therefore, changes in respiratory frequency may cause substantial bias in HRV and BPV studies. However, in our study no differences in respiratory frequency during the different drug periods were observed. Thus, although respiration was not externally paced, it is unlikely that our results are biased by respiratory frequency.

Several previous studies have focused on SNS influence on HRV and BPV. It has been shown that centrally acting sympatholytic drugs (like clonidine) reduce low-frequency HRV (48); however, the effects of β-blockade remain controversial. Most studies have found that propranolol diminishes low-frequency BPV and HRV during resting supine conditions (34, 49) and during sympathetic activation by tilt testing (17, 34). Unlike esmolol, propranolol is a lipid-soluble nonselective β-blocker that freely crosses the blood-brain barrier. The lack of effect of esmolol on low-frequency BPV suggests that tonic modulation of peripheral β_1-adrenergic receptors is not associated with the magnitude of low-frequency blood pressure variations. It remains to be elucidated whether peripheral β_2-adrenergic or any direct effects inside the central nervous system are responsible for the β-blockade effects on low-frequency BPV and HRV observed in other studies. Nitroprusside has previously been used for the investigation of HRV and BPV, and we can confirm increased BPV and HRV in the low-frequency range during nitroprusside infusion. There is, however, debate about whether normalizing procedures enhance the likelihood of detecting such effects (50). The fraction of heart rate spectral power at low frequencies, but not the absolute value, correlated significantly with reference indices of sympathetic activation (28, 51). We are unable to explain why in our study the raw score seems to be more sensitive. On the other hand, we do not think our data really contradict these reports. In at least one of these experiments (51), the association of nonnormalized low-frequency HRV to muscle sympathetic nerve activity just missed ($p = .08$) the significance criterion. Importantly, both studies cited above (28, 51) indicated a close relationship between nonnormalized low-frequency BPV and reference sympathetic indices, a finding supporting our decision to use low-frequency BPV to describe changes in SNS control. However, some authors advocate the use of low-frequency HRV to assess changes in SNS control. At first glance, our findings, and recent findings by others (52), may support such a view because low-frequency HRV and BPV change in parallel after stimulation of central sympathetic discharge. However, it is likely that arterial baroreflexes are responsible for this coupling of BPV and HRV, and prior evidence emphasizes the importance of parasympathetic—and not sympathetic—neural factors for these mechanisms (53, 54). Thus, low-frequency HRV changes depend, at least to some extent, on vagal mechanisms rather than represent exclusive sympathetic mechanism per se. On the other hand, our analysis of high-frequency HRV indicated a decrease in cardiac vagal tone during nitroprusside infusion and an increase during norepinephrine infusion. Transfer function analysis between systolic blood pressure and interbeat interval length in the high-frequency range revealed decreasing transfer magnitude during nitroprusside infusion and the opposite effect during norepinephrine infusion. These findings would favor a decrease of low-frequency HRV during nitroprusside infusion and an increase during norepinephrine infusion. Therefore, we cannot rule out the possibility that the observed increase of low-frequency HRV during nitroprusside infusion and the observed decrease of low-frequency HRV during norepinephrine infusion depends on additional direct central sympathetic influence on HRV. However, this aspect awaits further clarification. At the moment, and in accordance with others (55), we do not advocate the use of low-frequency HRV as a simple sympathetic measure of the effects of psychological stress.

No correlation could be detected between drug-induced changes in BPV and PEP, raising the possibility that these parameters do not share a common source of variance. Thus, inclusion of these parameters is not redundant because they do provide additional information. Our results have important implications for investigations focusing on the impact of the SNS on higher central nervous system functioning. Multiple central pathways have been described, including those of sympathetic output areas in the brain stem to higher cortical centers (6–9). These findings provide a good rationale to study the association of cognitive processes (ie, impact of SNS on emotional processing, SNS-induced alterations of pain thresholds, effects of SNS on mental performance) with central SNS activity and peripheral sympathetic effects separately. Currently such studies are hampered by the confusion about the choice of parameters to describe central SNS tone and to assess peripheral sympathetic effects.

CONCLUSION

Our data provide empirical evidence of separable peripheral and central sympathetic response components. We conclude that low-frequency BPV reflects changes of central sympathetic control. Heart rate–corrected PEP is a suitable measure of actual cardiac β-sympathetic activity. Changes of these measures share only little common source of variance. They should be combined in psychophysiological research because they may provide important additive information.

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