Cascade model of ventricular-arterial coupling and arterial-cardiac baroreflex function for cardiovascular variability in humans

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QUANTIFICATION OF CARDIOVASCULAR variability has been established as a tool to examine autonomic function in patients with cardiovascular disease (40). For example, patients with congestive heart failure (CHF) (4, 34, 39) or with myocardial infarction (24, 44) show significantly depressed heart rate (HR) variability associated with increases in mortality. These observations have been attributed to the presence of impaired autonomic function interacting with the presence of cardiovascular disease. However, because HR variability is only the output variable of complicated cardiovascular and respiratory control systems, both neural and nonneural control mechanisms may contribute to the changes in HR variability (12, 37, 46, 48).

Short-term HR variability at respiratory frequencies is likely to be produced by the complicated interactions between the arterial-cardiac baroreflex (3, 31, 37) and central respiratory control mechanisms (13). Although the specific mechanisms underlying short-term HR variability are still under debate (3, 13, 31, 37), it is generally accepted that HR variability at the respiratory frequency is modulated by efferent vagal activity to the sinus node, because it is largely eliminated by atropine (12, 37).

Conversely, recent studies demonstrated significant contributions of nonneural control mechanisms to blood pressure (BP) variability at the respiratory frequency because BP variability at the respiratory frequency did not change after complete autonomic blockade (37, 48). In addition, several studies demonstrated the existence of stroke volume (SV) variability at the respiratory frequency (14, 16, 21, 42), suggesting that SV variability may lead to BP variability via nonneural ventricular-arterial coupling. Specifically, we have speculated (2, 26) that changes in cardiac filling volume during respiration produce changes in left ventricular end-diastolic pressure (LVEDP) via the left ventricular pressure-volume relationship (Fig. 1). Sequentially, changes in LVEDP (preload) produce changes in SV and hence systolic BP (SBP) (afterload) via the Starling mechanism (Fig. 1) (2, 26). Of note, both of these relationships also are affected by changes in intrathoracic pressure per se during respiration via ventricular interdependence and/or transmural pressure changes (16, 21). Therefore, it is conceivable that the dynamic transmission properties between the LVEDP and SBP (dynamic ventricular-arterial coupling) are likely to be determined by the specific slopes of the cardiac mechanical curves as illustrated in Fig. 1.

It is generally accepted that the baroreflex transfers SBP variability into changes in HR via the modulation of autonomic neural activity (47). Because SBP variability at the respiratory frequency is produced primarily by the nonneural control of dynamic ventricular-arterial coupling (14, 16, 21, 37, 42, 48), HR variability at the respiratory frequency would be produced at least partly by the cascade mechanism of dynamic ventricular-arterial coupling with the arterial-cardiac baroreflex (Fig. 1).

The primary aim of the present study was to test the hypothesis that dynamic ventricular-arterial coupling is modulated by changes in left ventricular compliance associated
with changes in left ventricular preload. Furthermore, we hypothesized that a cascade control mechanism of ventricular-arterial coupling with arterial-cardiac baroreflex function contributes to the genesis of cardiovascular variability at the respiratory frequency.

For these aims, we used a two-component cascade model to determine both the individual and the combined effects of dynamic ventricular-arterial coupling and the arterial-cardiac baroreflex for the genesis of SBP and HR variability under hypo- and hypervolemic conditions. Hypovolemia was induced after administration of a diuretic agent (furosemide), and hypervolemia was induced with normal saline infusion. The purpose of these interventions was to alter the operating points of dynamic ventricular-arterial coupling located on the cardiac mechanical curves as indicated in Fig. 1 in order to test the specific hypothesis of this study.

METHODS

Subjects

Seven sedentary nonsmoking healthy men (ages 20–35 yr) with a body mass index of 25 ± 0.6 kg/m² participated in this study. All subjects were screened with a detailed medical history, a physical examination, and a baseline 12-lead ECG. The study was performed in accordance with the Declaration of Helsinki. The experimental procedures were explained to all subjects, with informed consent obtained as approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

Measurements

For each subject, the R-R interval was continuously monitored with a three-lead ECG (Hewlett-Packard). Photoplethysmography (Finapres, Ohmeda) was used to continuously measure finger arterial BP (ABP) with the transducer positioned at heart level. For measurements of pulmonary capillary wedge pressure (PCWP) and pulmonary arterial pressure (PAP), a 6-F balloon-tipped, fluid-filled catheter (Swan-Ganz, Baxter) was placed through an antecubital vein into the pulmonary artery under fluoroscopic guidance. All intracardiac pressures were referenced to atmospheric pressure, with the pressure transducer (Transpac IV, Abbott) zero-reading set at 5 cm below the sternal angle. Mean PCWP was determined visually at end expiration. Beat-by-beat pulmonary artery diastolic pressure (PAD) was used as an index of beat-by-beat LVEDP to avoid prolonged balloon inflation for safety reasons (15). Cardiac output was measured with a modified acetylene rebreathing technique using acetylene as the soluble and helium as the insoluble gas (27, 43). Then cardiac output and HR during the rebreathing were used to calculate the SV. Baseline plasma volume (PV) was measured by Evans blue dye, and then changes in PV were estimated during hypervolemia and hypovolemia from hematocrit changes according to the method of Van Beaumont (45).

Experimental Protocol

All experiments were performed in the morning at least 2 h after a light breakfast in a quiet environmentally controlled laboratory with an ambient temperature of 25°C. The subjects were asked to refrain from heavy exercise and caffeinated or alcoholic beverages for at least 24 h before the tests. To assess the effect of central volume changes, two specific conditions of hypervolemia and hypovolemia were utilized. Subjects rested for at least 30 min in the supine position to stabilize their hemodynamics. Hypervolemia was then induced with warm (37°C) isotonic saline infusion of 30 ml/kg at a rate of 100–150 ml/min with an 18-gauge intravenous catheter and an infusion bag pressurized to 250 mmHg. Our previous studies (2, 26) showed that this amount and rate of saline infusion lead clearly to higher left ventricular end-diastolic volume, SV, and PCWP. PAP was monitored continuously, and PCWP was measured intermittently during saline infusion for safety reasons. Immediately after saline infusion, SV and PCWP were measured, and then subjects were asked to breathe at a rate of 10 breaths/min for 5 min while breathing room air or a 20% O2 and 80% N2 mixture. To assess the effect of respiratory changes on cardiovascular variability, respiratory sinus arrhythmia (RSA) was recorded in a supine position while breathing at 10 breaths/min and in a recumbent position at 30 breaths/min.
controlled 12 min\(^{-1}\) frequency for 6 min by following a moving
cursor on a breathing pattern displayed on a computer. The breathing
pattern used was an equal amplitude and an equal time interval of
sawtooth waveforms. All subjects followed the breathing protocol
very well without complaint of any discomfort. We selected con-
trolled-frequency breathing to avoid changes in HR variability ind-
uced by changes in respiratory patterns during spontaneous breathing
(6, 18) and to avoid changes in BP variability at the respiratory
frequencies being contaminated by those fluctuations at the lower
frequencies (<0.15 Hz) (30). Six-minute data segments of PAP, ABP,
and ECG were recorded for spectral and transfer function analysis.
Hypovolemia was induced on a separate occasion with intravenous
administration of 20 mg of furosemide (Lasix). After administration
of furosemide, the change in PCWP was monitored continuously over
2 h to confirm an ~25% reduction of PCWP (33). The same mea-
surements for spectral and transfer function analysis as during hyper-
volemia were performed under hypovolemic conditions. These two
experiments were separated by at least 3 days but no more than 3 wk.
In addition, a 6-min random-frequency breathing protocol with an
averaged frequency of 15 ± 11 min\(^{-1}\) was performed before the
controlled-breathing protocol during both hypervolemia and hypovo-
lemia to confirm our assumption that beat-by-beat changes in LVEDP
are induced mainly by respiration and that changes in SBP and HR
variability during changes in central volume have little if any effect on
the changes in LVEDP.

Data Analysis

Spectral and transfer function estimation. PAP, ABP, and ECG
waveforms were sampled at 1 kHz and digitized at 12 bits with an
analog-to-digital converter (Daq-20, Metabyte). Digitized signals
were stored in a laboratory computer and processed with a custom-
designed program for PAD, SBP, and R-wave detection. Beat-to-beat
LVEDP (estimated from PAP), SBP, and HR (calculated from R-R
interval) were linearly interpolated and then resampled at 2 Hz for
spectral analysis. The time series of LVEDP, SBP, and HR were first
detrended with third-order polynomial fitting and then subdivided into
256-point segments with 50% overlap for spectral estimation. This
process resulted in five segments of data over the 6-min period
recordings. Fast Fourier transforms were implemented with each
Hanning-windowed data segment and then averaged to calculate
autospectra \(X(f)\) and cross-spectra \(X_y(f)\) for LVEDP, SBP, and
HR variability, respectively. The spectral resolution for these esti-
mates is 0.0078 Hz.

To quantify the dynamic relationship between SBP and HR vari-
ability, transfer function analysis between these variables was used
(20, 25, 31, 37). Similarly, transfer function between changes in
preload (LVEDP) and afterload (SBP) of the left ventricle was
estimated to quantify dynamic ventricular-arterial coupling (49).
Therefore, transfer functions \(H(f)\) of dynamic ventricular-arterial
coupling \(H_{L,SV}(f)\), arterial-cardiac baroreflex function \(H_{S,H}(f)\), and
the total transfer function \(H_{L,H}(f)\) between LVEDP and HR
variability were obtained with the following equations:

\[
H_{L,SV}(f) = \frac{S_{L,SV}(f)}{S_{L,SV}(f)}
\]

\[
H_{S,H}(f) = \frac{S_{S,H}(f)}{S_{S,H}(f)}
\]

\[
H_{L,H}(f) = \frac{S_{L,H}(f)}{S_{L,H}(f)}
\]

where \(S_{L,SV}(f)\), \(S_{S,H}(f)\), and \(S_{L,H}(f)\) are cross-spectra
between LVEDP and SBP, SBP and HR, and LVEDP and HR,
respectively, and \(S_{L,SV}(f)\) and \(S_{S,H}(f)\) are the autospectra
of LVEDP and SBP, respectively. Transfer function gain and phase
were derived from the real part \(H_R(f)\) and the imaginary part \(H_I(f)\)
of the complex transfer function as

\[
|\text{gain}(f)| = \sqrt{(H_R(f)^2 + H_I(f)^2)}
\]

\[
\text{phase}(f) = \tan^{-1}[H_I(f)/H_R(f)]
\]

Gain and phase reflect the relative amplitude and time relationships
between the input and output signals of the system modeled by \(H(f)\)
over a specified frequency range.

Coherence function was derived from \(X_y(f)\), \(X_y(f)\), and \(X_y(f)\) as

\[
\text{coherence} = \frac{|S_{X_y}(f)|^2}{|S_{X_y}(f)|} \frac{|S_{X_y}(f)|}{|S_{X_y}(f)|} \frac{|S_{X_y}(f)|}{|S_{X_y}(f)|}
\]

The reliability of linear transfer function estimation was evaluated by
the estimates of coherence function in this study.

Because coherence function between LVEDP and SBP variability
was low (<0.5) at the frequency range below 0.15 Hz even when
random breathing was applied (see Figs. 2 and 4), we used data at the
high-frequency range between 0.18 and 0.22 Hz during controlled-
frequency breathing (0.2 Hz) to estimate transfer functions between
LVEDP, SBP, and HR variability, where coherence function was high
(>0.5) under all experimental conditions.

The spectral power of LVEDP, SBP, and HR also was calculated in
the high-frequency range (0.18–0.22 Hz) by integrating the cor-
responding autospectra (20, 37, 48). Mean values of gain, phase,
and coherence were calculated in the high-frequency range and averaged
for all subjects under hypovolemic and hypervolemic conditions (20, 37, 48).

Finally, to validate the proposed two-component cascade model,
the relationship between the product of Gain LVEDP-SBP and Gain
SBP-HR and the estimation of Gain LVEDP-HR was assessed by
using linear regression of all the data obtained under hypovolemic
and hypervolemic conditions (23, 38).

Statistics. Variables were compared between hypovolemia and
hypervolemia by paired \(t\)-test. A \(P\) value of <0.05 was considered
statistically significant. Data are presented as means ± SE.

RESULTS

Steady-State Hemodynamics

PCWP, PAD, SV, and PV all were significantly higher during
hypervolemia than during hypovolemia (Table 1), consist-
ent with the expected increases in central volume. HR and
SBP were significantly higher during hypervolemia than during
hypovolemia (Table 1). Total HR and SBP variability quanti-
Table 1. Steady-state hemodynamics and spectral analysis of
LVEDP, SBP, and HR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypovolemia</th>
<th>Hypervolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV, ml</td>
<td>3,119±100</td>
<td>4,398±158*</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>7.4±1.0</td>
<td>16.8±1.6*</td>
</tr>
<tr>
<td>PAD, mmHg</td>
<td>6.9±1.1</td>
<td>14.8±1.3*</td>
</tr>
<tr>
<td>PAD SD, mmHg</td>
<td>1.5±0.2</td>
<td>1.8±0.2*</td>
</tr>
<tr>
<td>SV, ml</td>
<td>86±7</td>
<td>105±8*</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>125±5.5</td>
<td>140±5*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>74±4</td>
<td>74±4</td>
</tr>
<tr>
<td>HR SD, mmHg</td>
<td>4±2</td>
<td>3±0*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69±3</td>
<td>80±3*</td>
</tr>
<tr>
<td>HR SD, bpm</td>
<td>6.1±1</td>
<td>5±1*</td>
</tr>
<tr>
<td>HF LVEDP, mmHg²</td>
<td>1.1±0.2</td>
<td>2.2±0.2*</td>
</tr>
<tr>
<td>HF SBP, mmHg²</td>
<td>2.0±0.4</td>
<td>2.5±0.6</td>
</tr>
<tr>
<td>HF HR, bpm²</td>
<td>5.6±2.3</td>
<td>3.1±0.9*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Hypovolemia, after intravenous furosemide injec-
tion; hypervolemia, after acute saline infusion; SD, standard deviation of time
series; PV, plasma volume; PCWP, pulmonary capillary wedge pressure; PAD,
pulmonary artery diastolic pressure; SV, stroke volume; SBP and DBP,
systolic and diastolic blood pressure, respectively; HR, heart rate; HF, spectral
power in high-frequency ranges (0.18–0.22 Hz); bpm, beats per minute. *\(P <
0.05; †P = 0.08.  

fied by standard deviation of the time series were significantly lower during hypervolemia (Table 1).

**Spectral and Transfer Function Analysis**

Representative data of time series and autospectra in LVEDP, SBP, and HR during controlled breathing from one subject are shown in Fig. 2. Averaged data of autospectra in LVEDP, SBP, and HR in hyper- and hypovolemia during controlled breathing are also shown in Fig. 2. Averaged data of transfer function and coherence function in hyper- and hypovolemia during controlled breathing are shown in Fig. 3. Averaged data of autospectra in LVEDP, SBP, and HR and coherence function during random breathing are shown in Fig. 4.

High-frequency power of LVEDP was significantly higher during hypervolemia than during hypovolemia (Table 1; Fig. 5) \( P < 0.05 \). High-frequency power of HR variability tended to decrease during hypervolemia but did not reach statistical significance (Table 1) \( P = 0.08 \). High-frequency power of SBP variability was not changed (Table 1).

Peak values of coherence (\( > 0.8 \)) were observed around the respiratory frequency for all transfer functions (LVEDP-HR, LVEDP-SBP, and SBP-HR) (Fig. 3). The mean values of coherence function were \( > 0.5 \) for all transfer functions in the high-frequency range, indicating the reliability of transfer function gain and phase estimates in the high-frequency range.

Gain LVEDP-SBP was significantly lower during hypervolemia than during hypovolemia (Figs. 3 and 5; see Fig. 7) (hypovolemia 1.31 ± 0.09 and hypervolemia 0.97 ± 0.12 mmHg/mmHg; \( P = 0.009 \)). However, no change in Gain SBP-HR was observed between hypovolemia and hypervolemia (Fig. 3; see Fig. 7) (hypovolemia 1.31 ± 0.19 and hypervolemia 1.18 ± 0.22 beats·min⁻¹·mmHg⁻¹; \( P = 0.19 \)). Gain LVEDP-HR was significantly lower during hypervolemia than during hypovolemia (Fig. 3; see Fig. 7) (hypovolemia 2.09 ± 0.56 and hypervolemia 1.25 ± 0.28 beats·min⁻¹·mmHg⁻¹; \( P = 0.04 \)).

As expected, a strong linear relationship \( (R^2 = 0.93, P < 0.001) \) was observed between the product of Gain LVEDP-SBP and Gain SBP-HR and the estimate of Gain LVEDP-HR (Fig. 6).

Phase of LVEDP-SBP was significantly lower in hypervolemia than in hypovolemia (Fig. 3) (hypovolemia −0.24 ± 0.23 and hypervolemia −0.68 ± 0.20 rad; \( P = 0.01 \)). Phase of
LVEDP-SBP was negative in the high-frequency ranges in 11 of 14 data sets (7 subjects tested during hyper- and hypovolemia). Phases of SBP-HR and LVEDP-HR were positive in all data and were not different between hypervolemia and hypovolemia (Fig. 3).

**DISCUSSION**

We obtained three major results that provide new evidence for the presence of nonneural control mechanisms for the genesis of cardiovascular variability in humans. First, we found that dynamic ventricular-arterial coupling gain (Gain LVEDP-SBP) was reduced significantly during hypervolemia compared with hypovolemia. These data suggest that a reduction in dynamic left ventricular compliance due to hypervolemia results in smaller changes in SV per unit changes in LVEDP, and hence smaller changes in SBP under dynamic conditions (Fig. 5). Second, the presence of a strong linear relationship between the product of Gain LVEDP-SBP and Gain SBP-HR and the estimation of Gain LVEDP-HR demonstrates the validity of using a cascade model of cardiac mechanics with arterial-cardiac baroreflex function to identify the nonneural control mechanisms of cardiovascular variability in humans (23, 38) (Figs. 6 and 7). Finally, these findings suggest that left ventricular diastolic function may affect HR variability at the respiratory frequency via dynamic ventricular-arterial coupling rather than exclusively via an autonomic mechanism (Figs. 1 and 7).

**Steady-State Hemodynamics**

As expected by protocol and confirmed from PV changes, both PCWP and SV increased during hypervolemia, suggesting an upward shift of the operating point on both the left ventricular pressure-volume and Starling curves (Fig. 1). The increase in steady-state SBP during hypervolemia was likely caused by an increase in SV and cardiac output. HR was higher in hypervolemia than in hypovolemia, consistent with the presence of a Bainbridge reflex during hypervolemia (17, 32).

**Dynamic Ventricular-Arterial Coupling**

We assessed the transmission properties of preload (LVEDP) to afterload (SBP) of the left ventricle by using the cross-spectral method. In previous studies (2, 26), we have shown that the operational slope on the Starling curve, which
determines the dynamic transmission properties between the beat-by-beat change in LVEDP and SV, decreased during hypervolemia. Consistent with these observations, a significant decrease in dynamic ventricular-arterial coupling gain (Gain LVEDP-SBP) was observed during hypervolemia in the present study (Fig. 5).

As we expected, a prominent power of LVEDP variability and the highest coherence function between LVEDP and SBP were observed at the controlled respiratory frequency of 0.2 Hz (Figs. 2 and 3). Moreover, LVEDP power at frequencies lower than 0.15 Hz was much larger during random- than fixed-frequency breathing (Figs. 2 and 4). These findings support our assumption that LVEDP changes are caused primarily by respiration and that LVEDP changes produce SV and thus SBP variability via the pressure-volume and Starling mechanisms. Our results showed that the phase relationship of LVEDP-SBP was negative for most subjects under either hypo- or hypervolemic conditions, suggesting that changes in LVEDP precede SBP. These findings also are consistent with our assumption that changes in LVEDP produce changes in SBP via ventricular-arterial coupling. Furthermore, it is also possible that a dilated right ventricular chamber during hypervolemia alters the operational slopes of the pressure-volume and Starling curves via ventricular interdependence (16, 21). In addition, changes in intrathoracic pressure during respiration per se also may alter the operational slopes of cardiac mechanical curves by changing transmural pressure (16, 21). However, regardless of the specific underlying mechanisms, the results of the present study support the hypothesis that dynamic ventricular-arterial coupling is dependent on cardiac preload due to changes in operational slopes on the cardiac mechanical curves that lead to the changes in SBP variability at respiratory frequencies.

High-frequency power of LVEDP increased in hypervolemia compared with hypovolemia. These changes may be explained by the pressure-volume relationship of the left ventricle. For example, if changes in cardiac filling volume due to respiration were equal between hypervolemia and hypovolemia, the pressure changes would be larger during hypervolemia than during hypovolemia because of the upward shifting of the operating point to a less compliant portion on the pressure-volume curve (Fig. 5). This finding implies that the input variable of dynamic ventricular-arterial coupling, i.e., LVEDP variability, is also affected by left ventricular preload conditions.

Reliability of Cascade Model

LVEDP spectral power at a frequency range of <0.15 Hz in fixed-frequency breathing was much less than that during random-frequency breathing, while similar SBP and HR spec-
Central powers were observed between these conditions (Figs. 2 and 4). These findings suggest, but do not necessarily prove, that “feedback” effects of SBP and HR variability on LVEDP variability, if any, are negligible under the current experimental conditions, supporting the “open-loop” cascade model hypothesis of this study. Furthermore, the presence of a strong linear relationship ($R^2 = 0.93$, $P < 0.001$) between the estimate of Gain LVEDP-HR and the product of Gain LVEDP-SBP and Gain SBP-HR suggests the feasibility of using the proposed cascade model to represent both nonneural and neural control of cardiovascular variability at respiratory frequencies in humans (23, 38).

In the high-frequency range, mean values of coherence function were $0.5$ for all transfer function estimates. These data support the statistical reliability of transfer function gain estimation in this study.

High-frequency power of HR variability tended to decrease during hypervolemia. We attribute these changes at least partially to the reductions in the transfer function gain of LVEDP-SBP as suggested by the cascade model (Figs. 1 and 7). In addition, HR variability also could be influenced directly by changes in respiration (6, 18). Because carefully frequency-controlled breathing was used to avoid the effect of changes in respiratory patterns on HR variability, the direct effects of respiration on changes in HR variability are likely to be small between the experimental conditions in the present study (6, 18). We also cannot exclude mechanisms other than the cascade model to explain the reduction in HR variability at respiratory frequency during hypervolemia. For example, changes in LVEDP may affect autonomic nervous system activity and hence HR variability via cardiopulmonary receptors (13). Furthermore, at least theoretically the Bainbridge reflex could directly contribute to changes in Gain LVEDP-HR and hence HR variability, although the exact mechanism and neural pathways underlying this reflex in humans are uncertain (32).

Clinical Implications

It is possible that the effects of diastolic dysfunction on dynamic ventricular-arterial coupling and hence HR variability...
are more prominent in patients with CHF and/or coronary artery disease rather than that caused by an experimentally increased preload condition in healthy young volunteers. Several studies support this assumption. For example, studies in CHF patients showed either a linear (1) or a logarithmic (7) relationship between the ejection fraction of the left ventricle and the high-frequency power of HR variability. Also, a positive relationship between high-frequency power of HR variability and ejection fraction or mean acceleration of aortic flow was present in patients with coronary artery disease (5). Moreover, patients with restrictive cardiac diastolic filling showed a greater reduction in HR variability (35).

The fact that continuous positive airway pressure (CPAP) improves prognosis in CHF patients has been explained by a reduction of sympathetic activity (19, 22), and hence ventricular arrhythmias (36), associated with a reduction of cardiac work caused by changes in ventricular interdependence and/or reduction in transmural pressure due to intrathoracic positive pressure (29, 41). Our present findings suggest that CPAP also may improve dynamic ventricular-arterial coupling by changing the operational slopes on the pressure-volume and Starling curves via ventricular interdependence and/or changes in transmural pressure in CHF patients (29, 41). Therefore, it is possible that improvement in dynamic ventricular-arterial coupling per se is related to the treatment effects of CPAP on CHF patients.

**Study Limitations**

There remains the possibility that HR changes affect SBP variability and hence Gain LVEDP-SBP through cardiac output changes, because cardiac output is the product of HR and SV. It has been reported, however, that systolic BP variability at the respiratory frequency is mainly determined by changes in SV, which produces pulse pressure via arterial compliance, whereas mean BP variability is more closely related with cardiac output changes (9, 14, 28, 42). Theoretically, the transfer function gain between LVEDP and SBP variability could be decomposed into two components, i.e., a gain between LVEDP and SV variability via the Starling mechanism and a gain between SV and SBP variability via end-systolic ventricular-arterial coupling, reflecting arterial compliance (10). Therefore, our findings of changes in Gain LVEDP-SBP could reflect either ventricular or arterial compliance, although it is unlikely that arterial compliance would change significantly during the present study protocol. To evaluate dynamic ventricular-arterial coupling in more detail, future studies will be required to estimate beat-to-beat SV variability, which will enable us to assess Gain LVEDP-SV and Gain SV-SBP separately.

Arterial-cardiac baroreflex function also may be affected by physiological changes other than volume status after saline infusion. For example, sodium-sensitive arterial baroreflex...
sensors may change arterial-cardiac baroreflex function because of chronic sodium loading during large changes in sodium intake (11). Furthermore, changes in plasma osmolality may also affect baroreflex function after hypertonic saline infusion (8). In addition, HR variability may be affected by physiological mechanisms such as respiratory gating (13) or the Bainbridge reflex (32) in concert with the arterial-cardiac baroreflex. Therefore, it is possible that arterial-cardiac baroreflex gain was similar between hypervolemia and hypovolemia, significantly during hypervolemia compared with hypovolemia, arterial coupling gain (Gain LVEDP-SBP) was reduced significantly in these factors is likely to be small.

In conclusion, our results show that dynamic ventricular-cardiac coupling (Gain LVEDP–SBP) was reduced significantly during hypervolemia compared with hypovolemia, probably because of a reduction in dynamic left ventricular compliance during hypervolemia. These changes may lead to a reduction in HR variability via a cascade model of dynamic ventricular-cardiac coupling with arterial-cardiac baroreflex function. These findings suggest that a reduction of HR variability in patients with CHF may be at least partially explained by nonneural mechanisms of left ventricular diastolic dysfunction.

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