Dynamic control of maximal ventricular elastance via the baroreflex and force-frequency relation in awake dogs before and after pacing-induced heart failure

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Chen X, Sala-Mercado JA, Hammond RL, Ichinose M, Soltani S, Mukkamala R, O’Leary DS. Dynamic control of maximal ventricular elastance via the baroreflex and force-frequency relation in awake dogs before and after pacing-induced heart failure. Am J Physiol Heart Circ Physiol 299: H62–H69, 2010. First published April 30, 2010; doi:10.1152/ajpheart.00922.2009.—We investigated to what extent maximal ventricular elastance \( E_{\text{max}} \) is dynamically controlled by the arterial baroreflex and force-frequency relation in conscious dogs and to what extent these mechanisms are attenuated after the induction of heart failure (HF). We mathematically analyzed spontaneous beat-to-beat hemodynamic variability. First, we estimated \( E_{\text{max}} \) for each beat during a baseline period using the ventricular unstressed volume determined with the traditional multiple beat method during vena cava occlusion. We then jointly identified the transfer functions (system gain value and time delay per frequency) relating beat-to-beat fluctuations in arterial blood pressure (ABP) to \( E_{\text{max}} \). During the control condition, the ABP–\( E_{\text{max}} \) transfer function revealed that ABP perturbations caused opposite direction \( E_{\text{max}} \) changes with a gain value of \(-0.023 \pm 0.012 \text{ ml}^{-1}\), whereas the HR–\( E_{\text{max}} \) transfer function indicated that HR alterations caused same direction \( E_{\text{max}} \) changes with a gain value of \(0.013 \pm 0.005 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{beats}^{-1}\). Both transfer functions behaved as low-pass filters. However, the ABP–\( E_{\text{max}} \) transfer function was more sluggish than the HR–\( E_{\text{max}} \) transfer function with overall time constants (indicator of full system response time to a sudden input change) of 11.2 ± 2.8 and 1.7 ± 0.5 s (\( P < 0.05 \), respectively). During the HF condition, the ABP–\( E_{\text{max}} \) and HR–\( E_{\text{max}} \) transfer functions were markedly depressed with gain values reduced to \(-0.0002 \pm 0.0007 \text{ ml}^{-1}\) and \(-0.001 \pm 0.004 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{beats}^{-1}\) (\( P < 0.1 \)). \( E_{\text{max}} \) is rapidly and significantly controlled at rest, but this modulation is virtually abolished in HF.

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The control of ventricular contractility importantly contributes to the modulation of cardiac output and therefore cardiovascular homeostasis. Specific control mechanisms involved include the arterial baroreflex and force-frequency relation (i.e., the Treppe or Bowditch effect). Both of these mechanisms may occur simultaneously. For example, in response to a fall in arterial blood pressure (ABP), there will be a baroreflex-mediated sympathoexcitation, which could increase the inotropic state. The concurrent tachycardia could also increase the inotropic state independently via the force-frequency relation. Previous studies have described these mechanisms through various indexes of ventricular contractility including Frank-Starling curves \((9, 17, 44)\), cardiac sympathetic nerve discharge \((10)\), maximal temporal derivative of ventricular pressure \((8, 17, 26, 51)\), and maximal ventricular elastance \( E_{\text{max}} \) \((2, 3, 12, 18, 24, 27, 48)\). However, \( E_{\text{max}} \) is generally recognized as the most specific index available.

Nearly all investigations of \( E_{\text{max}} \) control have focused on its steady-state performance (e.g., gain values). To our knowledge, only two studies have examined its dynamic behavior (e.g., time constants and delays). Sunagawa and colleagues \((18)\) characterized the dynamic properties of the baroreflex control of \( E_{\text{max}} \) by identifying the transfer function relating randomly perturbed carotid sinus pressure to estimated beat-to-beat fluctuations in \( E_{\text{max}} \) of anesthetized, vagotomized dogs. Their identified transfer function exhibited the expected negative feedback dynamics with an overall time constant indicative of sympathetic nervous mediation and could be parameterized as a second-order delay system. This same group then characterized the dynamic properties of \( E_{\text{max}} \) control via the efferent baroreflex limb, while also obtaining information about the force-frequency relation, by identifying the transfer functions relating the randomized left and right stellate ganglion stimulations to the estimated beat-to-beat fluctuations in \( E_{\text{max}} \) of isolated canine hearts with and without atrial pacing \((27)\). Their identified transfer functions could also be represented with second-order delay systems and suggested that \( E_{\text{max}} \) is controlled by the left sympathetic nerve through direct inotropic action and by the right sympathetic nerve via both direct inotropic action and indirect chronotropic effects. While these two studies provide unique and valuable insights, they were performed in either isolated hearts or anesthetized animals with acute surgical trauma, which may markedly affect the dynamic control of \( E_{\text{max}} \). The open-loop identification approach may also alter the compensatory mechanisms.

Hallmark features of heart failure (HF) are low basal \( E_{\text{max}} \) and depressed ability to control \( E_{\text{max}} \). Furthermore, reflexes such as the arterial baroreflex are depressed in HF \((2, 6, 33)\), and Olivier and Stephenson \((33)\) attributed the majority of the baroreflex impairment in the maintenance of ABP to the loss of the cardiac output component of the reflex. Other reflexes that depend on substantial cardiac responses, such as the muscle metaboreflex during exercise, are also markedly affected in HF because of the loss of the cardiac output component \((42)\). Attenuation or loss of the ability to rapidly change \( E_{\text{max}} \) could...
contribute importantly to this impaired ability to raise cardiac output. To our knowledge, no study has assessed the effects of HF on the dynamic control of \( E_{\text{max}} \).

In this study, we aimed 1) to separately characterize the dynamic control of \( E_{\text{max}} \) via the arterial baroreflex and force-frequency relation during normal closed-loop operation in conscious, chronically instrumented animals and 2) to determine in what way the two dynamic \( E_{\text{max}} \) control mechanisms are altered by HF. To accomplish these aims, we mathematically analyzed naturally occurring, beat-to-beat hemodynamic variability from fully conscious dogs before and after pacing-induced HF. A preliminary version of this study has been reported in abbreviated form (7).

MATERIALS AND METHODS

We collected continuous hemodynamic data from dogs standing quietly before and after rapid chronic pacing-induced HF. We then analyzed the spontaneous hemodynamic variability as follows. First, rather than using single beat methods (45, 49) to estimate the \( E_{\text{max}} \) fluctuations on a beat-to-beat basis as previously done, we employed a simple and potentially more reliable method in which the ventricular unstressed volume \( (V_0) \) was assumed to be relatively constant and determined with the traditional multiple beat method during vena cava occlusion. We then jointly identified the transfer function relating beat-to-beat fluctuations in ABP to \( E_{\text{max}} \) (ABP \( \rightarrow E_{\text{max}} \)) to characterize the frequency relation during normal closed-loop operation in conscious, chronically instrumented animals. We then statistically compared the results before and after HF.

Hemodynamic Data

The collection of the hemodynamic data for analysis in this study is described in detail elsewhere (42). Below, we briefly describe the instrumentation employed and the relevant aspects of the executed protocol. All procedures were approved by the Wayne State University Animal Investigation Committee and conformed to the National Institutes of Health guidelines.

We studied five healthy adult mongrel dogs (~20–25 kg). We installed chronic instrumentation in each dog through two recovery surgeries. The instrumentation included a fully implanted, high-fidelity pressure transducer (Data Sciences International) for left ventricular (LV) pressure (LVP) measurement; two pairs of sonomicrometry crystals (Sonometrics) for LV short-axis and long-axis dimensions (\( D_{\text{SA}} \) and \( D_{\text{LA}} \)) measurement and subsequent computation of LV volume (LVV) via the modified ellipsoid formula \( \frac{4}{3} \pi \times D_{\text{SA}} \times D_{\text{LA}} \times D_{\text{LV}} \); a fluid-filled catheter that was connected to a standard extracorporeal pressure transducer (Abbott) for ABP measurement; an ultrasonic flow probe (Transonic Systems) for aortic flow rate measurement; two hydraulic vascular occluders (In Vivo Metrics) for superior and inferior vena cava occlusion; and three stainless steel sutures (Ethicon) that served as electrodes for ventricular pacing. (For studies unrelated to the present investigation, we also instrumented each dog during the surgery for measurement of hindlimb blood flow via a retroperitoneal approach.) After allowing each dog at least 2 wk to recover from the thoracotomy and at least 1 wk to recover from the follow-up surgery, we continuously recorded the hemodynamic data at a sampling frequency of ~300 Hz during a baseline period and multiple transient vena cava occlusions while the dog was standing quietly. Thereafter, we connected the ventricular pacing leads to a pacemaker set at a rate of 240 beats/min for ~30 days to induce a moderate level of HF. We then discontinued the ventricular pacing and likewise recorded the hemodynamic data. We did not record data within the HF induction period.

Data Analysis

Determination of spontaneous beat-to-beat variability. We estimated \( E_{\text{max}} \) on a beat-to-beat basis from the hemodynamic data during the baseline periods according to the method illustrated in Fig. 1. First, we employed the traditional multiple beat method for determining \( E_{\text{max}} \), that is, linear regression on the end-systolic LVP-LVV points during transient vena cava occlusion (41). The slope and x-intercept of the resulting line respectively represent the average \( E_{\text{max}} \) and the LV \( V_0 \). Assuming a constant \( V_0 \), we then computed the LV elastance \( (E_{\text{max}}) \) waveform from the LVP and LVV waveforms during the baseline periods by dividing the former waveform by the difference between the latter waveform and \( V_0 \) (averaged over the respective multiple transient vena cava occlusions to reduce noise). Finally, we established beat-to-beat \( E_{\text{max}} \) by identifying the maximum of the LV waveform over each beat.

We calculated the corresponding HR and ABP on a beat-to-beat basis by detecting each beat from the aortic flow rate waveform and averaging the ABP waveform over each beat during the baseline periods. We used HR rather than the standard cardiac cycle interval for the analysis, because the force-frequency relation has customarily been reported in terms of the former variable (12, 24). However, the use of the latter...

Fig. 1. Method for estimating spontaneous beat-to-beat maximal ventricular elastance \( (E_{\text{max}}) \) variability from left ventricular pressure (LVP) and volume (LVV) measurements during transient vena cava occlusion (left) and a baseline period (right). \( V_0 \) is the ventricular unstressed volume and is assumed to be constant (i.e., not modulated by control mechanisms), and LVE is the time-varying left ventricular elastance. \( t \), Time.
variable would not have materially altered the results that follow. We then converted the spontaneous \(E_{\text{max}}\) ABP, and HR beat sequences to time series by first forming stepwise continuous time signals in which the value for each beat is held for the duration of the beat and then sampling these signals to 1 Hz using an anti-aliasing filter whose impulse response is a unit-area rectangular pulse of 2-s width.

Identification of transfer functions. From these three time series, we identified the \(\text{ABP} \rightarrow E_{\text{max}}\) and \(\text{HR} \rightarrow E_{\text{max}}\) transfer functions according to the block diagram shown in Fig. 2. The perturbing noise source \(N_{E_{\text{max}}}\) in the block diagram is also estimated and represents the residual variability in \(E_{\text{max}}\) due to, for example, an \(E_{\text{max}}\) estimation error as well as other control mechanisms such as the cardiopulmonary baroreflex. We mathematically represented the block diagram with the following dual-input, autoregressive exogenous input model:

\[
E_{\text{max}}(t) = \sum_{i=1}^{a} a_i E_{\text{max}}(t-i) + \sum_{i=q}^{b} b_i \text{ABP}(t-i) + \sum_{i=0}^{c} c_i \text{HR}(t-i) + W_{E_{\text{max}}}(t).
\]

Here, \(t\) indicates discrete time; the three sets of unknown parameters \((a, b, c)\) define the \(\text{ABP} \rightarrow E_{\text{max}}\) and \(\text{HR} \rightarrow E_{\text{max}}\) transfer functions; the unmeasured residual error \(W_{E_{\text{max}}}\) together with the set of parameters \((a, b, c)\) specify \(N_{E_{\text{max}}}\); and the unknown model order terms, \(p, q, r,\) and \(m\), limit the number of parameters to be estimated (22). For a fixed model order, we estimated the parameters in closed form from 3–6-min stationary intervals of zero-mean fluctuations in the ABP, HR, and \(E_{\text{max}}\) time series by linear least squares minimization of \(W_{E_{\text{max}}}\) (22). We established the model order by setting \(p\) and \(r\) to, respectively, 2 and \(q\) (i.e., second-order delay representation of the arterial \(E_{\text{max}}\))

\[
H_{\text{HR} \rightarrow E_{\text{max}}} = \frac{-0.0013 e^{-2j\omega}}{1 - 1.3858 e^{-2j\omega} + 0.4585 e^{-3j\omega}}
\]

where \(H\) indicates transfer function and \(\omega\) indicates normalized frequency.

During the control condition, the \(\text{ABP} \rightarrow E_{\text{max}}\) and \(\text{HR} \rightarrow E_{\text{max}}\) transfer functions exhibited negative and positive gain values, respectively. Thus \(E_{\text{max}}\) would decrease (increase) in the steady state in response to an increase (decrease) in mean ABP but in the absence of any change to mean HR as a result of the arterial baroreflex, whereas \(E_{\text{max}}\) would increase (decrease) in the steady state in response to an increase (decrease) in mean HR without any change to mean ABP because of the force-frequency relation. The two transfer functions were similar in that they both behaved as low-pass filters. Thus \(E_{\text{max}}\) would reach steady state without oscillating in response to a change in mean HR or mean ABP. However, the \(\text{ABP} \rightarrow E_{\text{max}}\) transfer function was more sluggish. This transfer function showed a notable time delay and an overall time constant that was over five times as large as that of the \(\text{HR} \rightarrow E_{\text{max}}\) transfer function. Thus \(E_{\text{max}}\) would reach steady state faster in response to a change in mean HR than a perturbation to mean ABP.

Table 1 shows the group average mean of the ABP, HR, and \(E_{\text{max}}\) time series as well as the group average \(V_0\) before and after pacing induced HF. Figure 3 illustrates the group average power spectra of these time series, and Table 2 provides their low-frequency, high-frequency, and total powers. Mean ABP and mean \(E_{\text{max}}\) decreased, whereas mean HR and \(V_0\) increased, from the control condition to the HF condition. (Mean \(E_{\text{max}}\) as determined with the traditional multiple beat method during vena cava occlusion, revealed a similar result.) The \(E_{\text{max}}\) spectra appeared more narrowband than their ABP and HR counterparts. All of the power spectra looked depressed following the induction of HF. The corresponding low-frequency, high-frequency, and total powers all decreased, but only the low-frequency power of the ABP spectrum reached the \(P = 0.1\) level of significance. The HR spectrum in particular also appeared shifted toward lower frequencies after HF induction, but this shift was likewise statistically insignificant.

Figure 4 illustrates the group average \(\text{ABP} \rightarrow E_{\text{max}}\) and \(\text{HR} \rightarrow E_{\text{max}}\) transfer functions in terms of the magnitude and phase responses as well as the intuitive step responses before and after HF. The computation of the magnitude and phase responses at frequencies outside the range of the 3–6-min time series was feasible because of the use of a parametric model.

Table 3 shows the gain values and the overall time constants of these transfer functions. The transfer functions during the control condition are precisely defined as follows:

\[
H_{\text{ABP} \rightarrow E_{\text{max}}} = \frac{-0.0013 e^{-2j\omega}}{1 - 1.3858 e^{-2j\omega} + 0.4585 e^{-3j\omega}}
\]
During the HF condition, the ABP→E<sub>max</sub> and HR→E<sub>max</sub> transfer functions were markedly blunted, except for the higher-frequency regime of the latter transfer function. The gain values of the two transfer functions were, in particular, reduced to negligible values. The time constants and delays were not well defined because of the small transfer function magnitudes. Thus E<sub>max</sub> would not change much transiently and especially in the steady state in response to a variation in either mean ABP or mean HR.

**DISCUSSION**

This study is the first to examine the dynamic control of E<sub>max</sub> in conscious subjects. Furthermore, this study is the first to determine the effects of HF on the dynamic control of E<sub>max</sub> in isolated hearts, anesthetized preparations, or conscious subjects. Through mathematical analysis of spontaneous beat-to-beat hemodynamic variability, we were able to reveal quantitatively the strength and temporal (or frequency) characteristics of the arterial baroreflex and force-frequency relation in modulating ventricular contractility during normal closed-loop operation in healthy and HF conditions. In particular, we found that both of these mechanisms significantly and independently controlled E<sub>max</sub> with response times on the order of seconds during healthy conditions. Furthermore, the strength of both the arterial baroreflex and force-frequency relation was severely reduced in HF, not only in the steady state but also in the transient phase. This reduced ability to elicit beat-to-beat changes in E<sub>max</sub> likely contributes importantly to the loss of the cardiac output component in the reflex cardiovascular control mechanisms seen in HF (33, 42).

**Dynamic E<sub>max</sub> Control**

**Control condition.** The ABP→E<sub>max</sub> transfer function showed negative feedback dynamics during the control condition (see Fig. 4), which is consistent with the arterial baroreflex mechanism. More specifically, the transfer function behaved as a low-pass filter (see Fig. 4) with a time delay and overall time constant of 2.6 ± 0.5 and 11.2 ± 2.8 s, respectively (see Table 3). These dynamics are indicative of the well-known sympathetic nervous mediation of the arterial E<sub>max</sub> baroreflex (5). Sunagawa and colleagues (18) reported that the transfer function relating randomly perturbed carotid sinus pressure to beat-to-beat E<sub>max</sub> fluctuations in anesthetized, vagotomized dogs similarly exhibited low-pass frequency characteristics with a time delay and overall time constant of 2.3 and 11 s,

### Table 1. Group average mean of the hemodynamic variables before and after HF

<table>
<thead>
<tr>
<th>Hemodynamic Variable Mean</th>
<th>Control</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP, mmHg</td>
<td>111.4 ± 2.3</td>
<td>86.6 ± 1.5†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>109.4 ± 5.9</td>
<td>128.3 ± 3.9*</td>
</tr>
<tr>
<td>E&lt;sub&gt;max&lt;/sub&gt;, mmHg/ml</td>
<td>5.5 ± 0.1</td>
<td>3.1 ± 0.1*</td>
</tr>
<tr>
<td>V&lt;sub&gt;0&lt;/sub&gt;, ml</td>
<td>10.5 ± 4.7</td>
<td>23.3 ± 10.4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. HF, heart failure; ABP, arterial blood pressure; HR, heart rate; E<sub>max</sub>, maximal ventricular elastance; V<sub>0</sub>, ventricular unstressed volume. †P < 0.05; *P < 0.005.

### Table 2. Group average powers of the beat-to-beat fluctuations in the hemodynamic variables before and after HF

<table>
<thead>
<tr>
<th>Hemodynamic Variable Power</th>
<th>Control</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP, mmHg&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Low frequency</td>
<td>7.51 ± 1.11</td>
</tr>
<tr>
<td>High frequency</td>
<td>4.35 ± 2.63</td>
<td>1.16 ± 0.48</td>
</tr>
<tr>
<td>Total</td>
<td>22.59 ± 4.58</td>
<td>10.33 ± 2.31</td>
</tr>
<tr>
<td>HR, (beats/min)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Low frequency</td>
<td>25.56 ± 3.48</td>
</tr>
<tr>
<td>High frequency</td>
<td>64.93 ± 33.08</td>
<td>20.58 ± 11.68</td>
</tr>
<tr>
<td>Total</td>
<td>116.03 ± 36.80</td>
<td>65.62 ± 21.05</td>
</tr>
<tr>
<td>E&lt;sub&gt;max&lt;/sub&gt;, mmHg&lt;sup&gt;2&lt;/sup&gt;/ml&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Low frequency</td>
<td>0.0080 ± 0.0025</td>
</tr>
<tr>
<td>High frequency</td>
<td>0.0041 ± 0.0020</td>
<td>0.0024 ± 0.0008</td>
</tr>
<tr>
<td>Total</td>
<td>0.0290 ± 0.0093</td>
<td>0.0115 ± 0.0037</td>
</tr>
</tbody>
</table>

Values are means ± SE. Low frequency is 0.04–0.15 Hz, and high frequency is 0.15–0.50 Hz. *P < 0.05.
respectively. However, the gain value of \(-0.085 \text{ ml}^{-1}\) that they found is nearly four times as large as the \(-0.023 \pm 0.012 \text{ ml}^{-1}\) ABP→\(E_{\text{max}}\) gain value that we obtained (see Table 3). This difference is in accord with a previous study showing that the steady-state carotid sinus baroreflex control of the normalized maximal temporal derivative of ventricular pressure was smaller in conscious than in anesthetized dogs (51).

The HR→\(E_{\text{max}}\) transfer function indicated that HR changes directionally cause the same \(E_{\text{max}}\) changes during the control condition (see Fig. 4), which is consistent with the force-frequency relation. In particular, when compared with the ABP→\(E_{\text{max}}\) transfer function, this transfer function likewise acted as a low-pass filter (see Fig. 4) but with a minimal time delay and a significantly smaller overall time constant of 1.7 ± 0.5 s (see Table 3). These dynamics are coherent with the belief that the force-frequency relation is mediated by fast intracellular calcium handling mechanisms (though the more sluggish sympathetic nervous system does appear to set its operating point and thus its gain value) (34, 38). The HR→\(E_{\text{max}}\) gain value of \(0.013 \pm 0.005 \text{ mmHg·ml}^{-1}\cdot(\text{beats/min})^{-1}\) (see Table 3) is about three times smaller than the 0.03 mmHg·ml\(^{-1}\cdot(\text{beats/min})^{-1}\) gain value previously obtained from isolated canine hearts at the same mean HR (24). Deviations in these values are likely due at least in part to the different experimental conditions.

These results indicate that the combined effect of the arterial baroreflex and force-frequency relation can significantly increase ventricular contractility and thereby importantly aid in pressure homeostasis. In response to pressure challenges, changes in autonomic activity elicit both changes in ventricular performance as well as changes in HR. For example, if mean ABP fell by 10 mmHg, our results predict that the arterial baroreflex would increase \(E_{\text{max}}\) by 0.23 ml/mmHg. Based on recent studies from our laboratory on dynamic baroreflex control of HR using the same animal model, HR would be...
expected to increase by nearly 60 beats/min in response to this pressure insult (43). Our results here predict that this tachycardia would, in turn, cause the force-frequency relation to increase $E_{\text{max}}$ by nearly 0.8 ml/mmHg. Together, the direct baroreflex-mediated increase in ventricular contractility coupled with that elicited indirectly by the force-frequency relation would increase $E_{\text{max}}$ by nearly 20%. Using data from previous studies on $E_{\text{max}}$ control (18, 24) would overestimate this change. Since the time constants governing the baroreflex control of HR and $E_{\text{max}}$ are similar (5), the time for $E_{\text{max}}$ to reach steady state in response to the fall in ABP would be within 1 min. Finally, the standard deviation of $E_{\text{max}}$ variability because of ABP fluctuations was about the same as that due to HR fluctuations during healthy conditions (result not shown). Thus ABP and HR fluctuations contribute roughly the same to the genesis of normal $E_{\text{max}}$ variability.

**HF condition.** The ABP→$E_{\text{max}}$ transfer function including its gain value was blunted essentially to zero following the induction of HF (see Fig. 4 and Table 3). This alteration is likely due to the diminished total baroreflex control mechanisms. This assumption originates from the classic studies of Sagawa and colleagues demonstrating that average contractility, thereby assuming that the ventricular end-diastolic pressure-volume relationship was linear. Although nonlinearity has been observed over wide pressure and volume ranges (32, 50), the relationship indeed appears to be linear over more physiological pressure and volume ranges in conscious dogs (46, 47) as well as humans in health (25) and with severe HF (1).

We used $V_0$ determined with the traditional multiple beat method during vena cava occlusion to estimate the requisite beat-to-beat $E_{\text{max}}$ during the corresponding baseline period (see Fig. 1). We therefore assumed that $V_0$ was constant within an experimental condition of a dog (i.e., not modulated by control mechanisms). This assumption originates from the classic studies of Sagawa and colleagues demonstrating that inotropic agents selectively alter $E_{\text{max}}$ (e.g., Ref. 41) as well as subsequent work showing that average $E_{\text{max}}$, but not $V_0$, is controlled over a wide HR range via the force-frequency relation (24). Although single-beat methods for estimating $E_{\text{max}}$ on a beat-to-beat basis do not involve such a constant $V_0$ assumption, they are based on other, seemingly more stringent, assumptions such as that LVE function, normalized in amplitude and time over each beat, is invariant (45) or that peak intraventricular pressure at end-diastolic volume can be extrapolated from the isovolumic phase LVP of ejecting beats (49). These methods have been verified during large perturbations to $E_{\text{max}}$ but not smaller, spontaneous $E_{\text{max}}$ changes. We did attempt to implement several variants of the single-beat method based on an invariant normalized LVE function to estimate beat-to-beat $E_{\text{max}}$. However, the resulting $E_{\text{max}}$ fluctuations were fast and large, even extending to nonphysiological, negative values. For example, the arterial baroreflex gain value determined from these fluctuations was often positive.

<table>
<thead>
<tr>
<th>Transfer Function Parameters</th>
<th>Control</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_{\text{ABP} \rightarrow E_{\text{max}}}$, ml⁻¹</td>
<td>$-0.023 \pm 0.012$</td>
<td>$-0.0002 \pm 0.0007$†</td>
</tr>
<tr>
<td>$G_{\text{HR} \rightarrow E_{\text{max}}}$, (beats/min)⁻¹</td>
<td>$0.013 \pm 0.005$</td>
<td>$-0.0010 \pm 0.0004$‡</td>
</tr>
<tr>
<td>$T_{\text{ABP} \rightarrow E_{\text{max}}}$, S</td>
<td>$11.2 \pm 2.8^*$</td>
<td>‡</td>
</tr>
<tr>
<td>$T_{\text{HR} \rightarrow E_{\text{max}}}$, S</td>
<td>$1.7 \pm 0.5^*$</td>
<td>‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. G, gain value. *$P < 0.05$, two values marked with asterisk are significantly different from each other. †$P < 0.10$. ‡Overall time constant ($\tau$) was not well defined because of the small transfer function input. Thus not only are baroreflex-mediated changes in HR fluctuations during healthy conditions (result not shown). Therefore, the force-frequency relation was reduced or even inverted in the HF steady state in isolated myocardium from failing human hearts (11, 29); conscious, but autonomically blocked, dogs following pacing induced HF (2); and HF patients (11, 13). The mechanisms involved appear to be abnormal intracellular calcium handling (37). Another potential mechanism for the diminished strength of the force-frequency relation in our study may be the significant increase in mean HR (i.e., shift in operating point; see Table 3) as previously shown in isolated canine hearts (24). The abolishment of the ABP→$E_{\text{max}}$ transfer function and the marked attenuation of the HR→$E_{\text{max}}$ transfer function coupled with lower baroreflex control of HR likely contribute to the markedly attenuated control of cardiac output in HF (15, 33).

**Beat-to-Beat Hemodynamic Variability**

The power spectra of the beat-to-beat ABP, HR, and $E_{\text{max}}$ fluctuations during the control condition showed a high-frequency peak around 0.25 Hz but did not reveal a low-frequency peak near 0.1 Hz (see Fig. 3), which has previously been reported in conscious dogs (40). These power spectra all showed a tendency to decrease during HF (see Fig. 3 and Table 2). A number of previous studies have shown that HR variability is reduced in HF including after rapid chronic pacing in conscious dogs (36) due to aberrant autonomic nervous system functioning, and at least one study has demonstrated that ABP variability is smaller in HF patients than control subjects (39). We are not aware of any previous study addressing $E_{\text{max}}$ variability during HF. The lack of statistical significance of the reductions in spectral powers in our study may be due to the smaller sample size as well as an error in the beat-to-beat $E_{\text{max}}$ estimates. Importantly, however, the identified transfer functions coupling the beat-to-beat fluctuations were able to show greater levels of statistical significance, since a major portion of the beat-to-beat $E_{\text{max}}$ estimation error was likely uncorrelated with the independently measured ABP and HR fluctuations and therefore ascribed to the perturbing noise term $N_{E_{\text{max}}}$ rather than the transfer functions (see Fig. 2). Indeed, it is for this reason that we have focused the study on the transfer functions rather than the beat-to-beat variability.

**Data Analysis: Assumptions, Limitations, and Strengths**

We employed $E_{\text{max}}$ as the quantitative index of ventricular contractility, thereby assuming that the ventricular end-diastolic pressure-volume relationship was linear. Although nonlinearity has been observed over wide pressure and volume ranges (32, 50), the relationship indeed appears to be linear over more physiological pressure and volume ranges in conscious dogs (46, 47) as well as humans in health (25) and with severe HF (1).
We characterized dynamic $E_{\text{max}}$ control via the arterial baroreflex and the force-frequency relation through the ABP$\rightarrow E_{\text{max}}$ and HR$\rightarrow E_{\text{max}}$ transfer functions, respectively. Thus we assumed that these control mechanisms were linear and time invariant. Sunagawa and colleagues (18, 27) showed that the coherence of the transfer functions relating randomly perturbed carotid sinus pressure and randomized left and right stellate ganglion stimulations to estimated beat-to-beat fluctuations in $E_{\text{max}}$ during stable conditions was between 0.5 and 0.8 over the lower-frequency range. Since the spontaneous hemodynamic fluctuations analyzed herein were smaller and likewise obtained at rest, our linearity and time invariance assumption appears to be quite tenable. However, the trade-off is that the transfer functions are only valid over the limited range of the naturally occurring hemodynamic variability.

Finally, we jointly identified the ABP$\rightarrow E_{\text{max}}$ and HR$\rightarrow E_{\text{max}}$ transfer functions from spontaneous beat-to-beat ABP, HR, and $E_{\text{max}}$ fluctuations using a new dual-input autoregressive exogenous input model (see initial equation and Fig. 2). We therefore made the following additional assumptions. First, the transfer functions may be succinctly represented with pole-zero structures. Such structures have proven successful in representing various physiological control systems in the past (e.g., Refs. 28, 30). Second, the residual error term $W_{E_{\text{max}}}$ in the model is a white noise process that is uncorrelated with the HR fluctuations and a similar process inducing the ABP fluctuations, whereas the model order term $q$ is nonnegative to enforce causality in the closed-loop path between the ABP and $E_{\text{max}}$ fluctuations. This assumption is needed for a unique and consistent estimation of the model parameters ($a_0$, $b$, and $c_i$) (53). Although a lack of correlation may not strictly hold, the baroreflex has a time delay (5) and is therefore causal. Third, the model order terms $p$ and $r$ are set to 2 and $q$, respectively. This assumption arises from the aforesaid non-parametric modeling results of Sunagawa and colleagues (18, 27) obtained from anesthetized, vagotomized dogs and isolated canine hearts. (Note that, like the model parameters, the model order terms $q$ and $m$ were estimated from the measured fluctuations.)

With the above assumptions, we were able obtain results uniformly consistent with known qualitative physiology. A novelty of these results is in quantitatively revealing how $E_{\text{max}}$ is dynamically controlled during relevant physiological conditions. Furthermore, the HR$\rightarrow E_{\text{max}}$ transfer function may not have been reported before even during nonphysiological conditions.

**REFERENCES**


