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Dynamic Control of Maximal Ventricular Elastance in Conscious Dogs Before and After Pacing-Induced Heart Failure

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Abstract—**We identified the transfer functions relating beat-to-beat fluctuations in arterial blood pressure to maximal ventricular elastance (ABP→E_{max}) and beat-to-beat fluctuations in heart rate to E_{max} (HR→E_{max}) to characterize the dynamic properties of the arterial ventricular contractility baroreflex and force-frequency relation, respectively, in three conscious dogs before and after pacing-induced heart failure. During the control condition, the average gain value, dominant time constant, and time delay were respectively -0.0374 ml^{-1}, 12.8 sec, and 2 sec for the ABP→E_{max} transfer function and 0.0137 mmHg/ml-bpm, 1.77 sec, and 0 sec for the HR→E_{max} transfer function. During the heart failure condition, both transfer functions were markedly depressed. These results are consistent with known physiology and previous studies and provide perhaps the first quantitative information on the dynamic control of E_{max} during normal closed-loop operation.**

I. Introduction

It is well appreciated that the control of ventricular contractility plays an important role in extrinsic cardiovascular regulation. The specific mechanisms involved include the arterial baroreflex and the force-frequency relation (also known as the Bowditch or Treppe effect). Previous studies have elucidated these mechanisms through various indices of ventricular contractility (e.g., [1-3]). However, the studies involving the maximal ventricular elastance (E_{max}), which is perhaps the least sensitive index to loading conditions [4-6], are amongst the most illuminating.

A number of investigations have described the steady state behavior (e.g., gain value) of E_{max} control in both health and disease [7-11]. However, to our knowledge, only two studies have delineated its dynamic nature (e.g., time constants and delays). Sunagawa and colleagues characterized the dynamic properties of the baroreflex control of E_{max} by identifying the transfer function relating randomly perturbed carotid sinus pressure to beat-to-beat fluctuations in E_{max} in anesthetized and vagotomized dogs [12]. This same group then gleaned dynamic information pertaining to the efferent baroreflex limb and the force-frequency relation by identifying the transfer functions relating randomized left and right stellate ganglion stimulations to beat-to-beat fluctuations in E_{max} and heart rate (HR) in an isolated canine heart [13]. Thus, despite the unique insights provided by these two open-loop studies, the dynamic control of E_{max} is generally not well understood.

In this study, we aimed 1) to separately quantify the dynamic control of E_{max} via the arterial baroreflex and force-frequency relation during normal closed-loop operation and 2) to determine if and how the two dynamic E_{max} control mechanisms are altered in the presence of a failing heart. To achieve these aims, we analyzed spontaneous beat-to-beat hemodynamic variability recorded from conscious dogs before and after pacing-induced heart failure. For each of these two conditions, we jointly identified the transfer function relating beat-to-beat fluctuations in arterial blood pressure (ABP) to E_{max} (ABP→E_{max}) to characterize the dynamic properties of the arterial ventricular contractility baroreflex and the transfer function relating beat-to-beat fluctuations in HR to E_{max} (HR→E_{max}) to characterize the dynamic properties of the force-frequency relation.

II. Methods

A. Hemodynamic Data

We studied hemodynamic data from three adult dogs (20-25 kg). These data were previously collected by us, and the materials and methods are described in detail elsewhere [14, 15]. Briefly, the data included continuous measurements of left ventricular pressure (LVP; via a fully implanted micromanometer-tipped catheter system), left ventricular volume (LVV; via two pairs of sonomicrometry crystals), ABP (via a fluid-filled catheter in the terminal aorta), and cardiac output (via an ultrasonic flow probe around the ascending aorta) during a baseline period of 4-6 min and transient vena cava occlusion while the dogs were standing quietly. The data also comprised the same measurements following rapid chronic ventricular pacing, which induced a moderate level of congestive heart failure in the dogs.

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B. Data Analysis

We analyzed the hemodynamic data for each condition of each dog. The major steps of our analysis were to first determine E_{max}, ABP, and HR on a beat-to-beat basis from the continuous measurements during the baseline period and to then identify the ABP→E_{max} and HR→E_{max} transfer functions from the spontaneous beat-to-beat fluctuations.

More specifically, we estimated beat-to-beat E_{max} during the baseline period according to the procedure shown in Fig. 1. First, we applied the traditional method for determining E_{max} by performing linear regression on the end-systolic LVP-LVV points during the transient vena cava occlusion [16]. The slope of the resulting line represents the average E_{max}, while the x-intercept indicates the LV unstressed volume (V_0). Then, assuming constant V_0, we computed the time-varying LV elastance (LVE) curve from the continuous LVP and LVV during the baseline period by dividing the former measurement by the difference between the latter measurement and V_0. Finally, we determined E_{max} on a beat-to-beat basis by identifying the maximum of the LVE curve over each beat. In this way, beat-to-beat fluctuations in E_{max} may be more reliably estimated than previously proposed single beat methods, which are based on more stringent assumptions [17, 18].

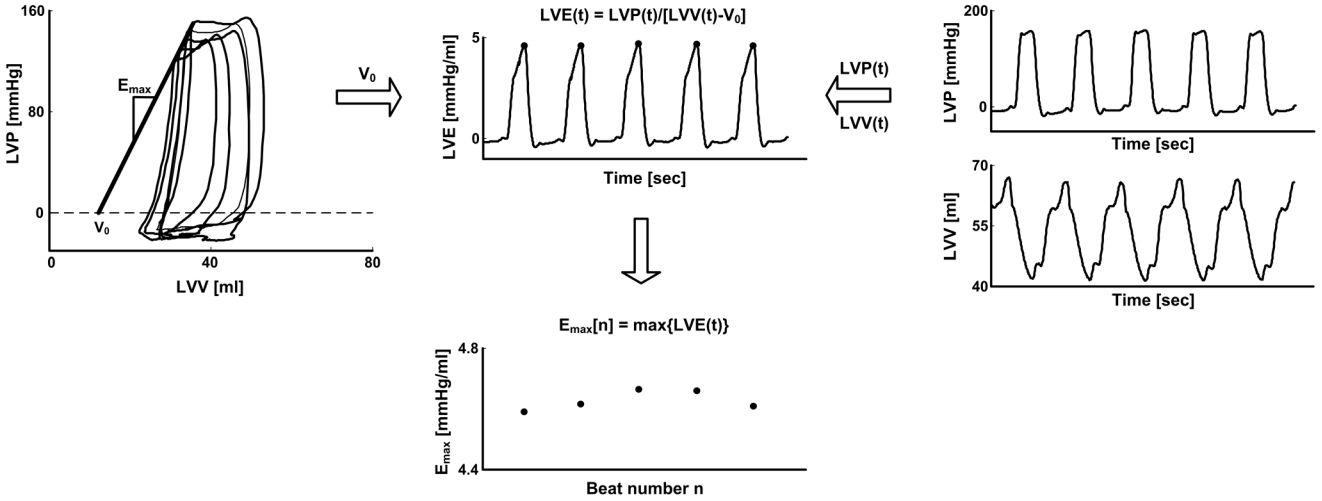

Fig. 1. Procedure for estimating beat-to-beat E_{max} from continuous LVP and LVV measurements during transient vena cava occlusion (left panel) and a baseline period (right panel).

We calculated ABP on a beat-to-beat basis by averaging the continuous ABP over each beat during the baseline period and detected HR for each beat from the continuous cardiac output during the same period. We then converted the E_{max}, ABP, and HR beat sequences to 1 Hz time series as described in [19].

With these three time series, we simultaneously identified the ABP→E_{max} and HR→E_{max} transfer functions according to the block diagram illustrated in Fig. 2. This block diagram includes a perturbing noise source $N_{E_{max}}$, which is also estimated and represents the residual variability in E_{max} not explained by the ABP and HR fluctuations. We mathematically represented the block diagram with the following autoregressive exogenous input structure:

$$E_{max}(t)=\sum_{i=1}^{p} a_i \cdot E_{max}(t-i)+\sum_{i=q}^{r} b_i \cdot ABP(t-i)+\sum_{i=0}^{m} c_i \cdot HR(t-i)+W_{E_{max}}(t)$$

where t indicates discrete time. The three sets of unknown parameters $\{a_i, b_i, c_i\}$ completely specify the ABP→E_{max} and HR→E_{max} transfer functions, and the unmeasured residual error $W_{E_{max}}$ together with the set of parameters $\{a_i\}$ fully define $N_{E_{max}}$ [20]. The unknown model order, p, q, r, and m, limit the number of parameters. We estimated the parameters, for a fixed model order, in closed-form from zero-mean fluctuations in the 1 Hz ABP, HR, and E_{max} time series by linear least squares minimization of $W_{E_{max}}$ [20]. Since Sunagawa and colleagues showed that the arterial baroreflex control of E_{max} could be well represented as a second-order delay system [12], we set p and r to two and q, respectively. We determined q and m by minimization of the popular minimum description length criterion [20].

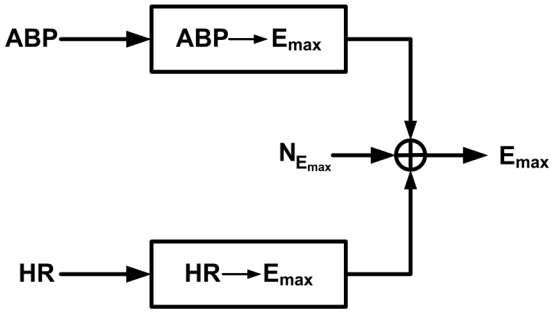

Fig. 2. Block diagram for identifying the ABP→E_{max} and HR→E_{max} transfer functions from beat-to-beat fluctuations in ABP, HR and E_{max}.

III. Results

The Table shows the group average values during the baseline period for mean ABP, HR, and E_{max}, as well as V_0

before and after pacing-induced heart failure. As expected, mean ABP and E_{max} markedly decreased, while mean HR and V_0 substantially increased, from the control condition to the pathophysiologic condition.

Fig. 3 illustrates the group average ABP→E_{max} and HR→E_{max} transfer functions before and after pacing-induced heart failure in terms of intuitive step responses. The step responses during the control condition generally indicate that E_{max} would decrease in response to a step increase in ABP and increase in response to a step increase in HR. Quantitatively, the average gain value, dominant time constant, and time delay here were respectively -0.0374 ml^{-1}, 12.8 sec, and 2 sec for the ABP→E_{max} step response and 0.0137 mmHg/ml-bpm, 1.77 sec, and 0 sec for the HR→E_{max} step response. The step responses during the heart failure condition generally indicate that E_{max} would not change much in response to a step increase in either ABP or HR.

TABLE
GROUP AVERAGE HEMODYNAMIC VALUES (MEAN ± SE).

	Control	Heart Failure
mean ABP [mmHg]	108.84 ± 3.63	84.63 ± 4.79
mean HR [bpm]	114.97 ± 8.87	134.12 ± 12.78
mean E_{max} [mmHg/ml]	5.81 ± 1.07	3.05 ± 0.20
V_0 [ml]	12.95 ± 5.37	21.87 ± 6.46

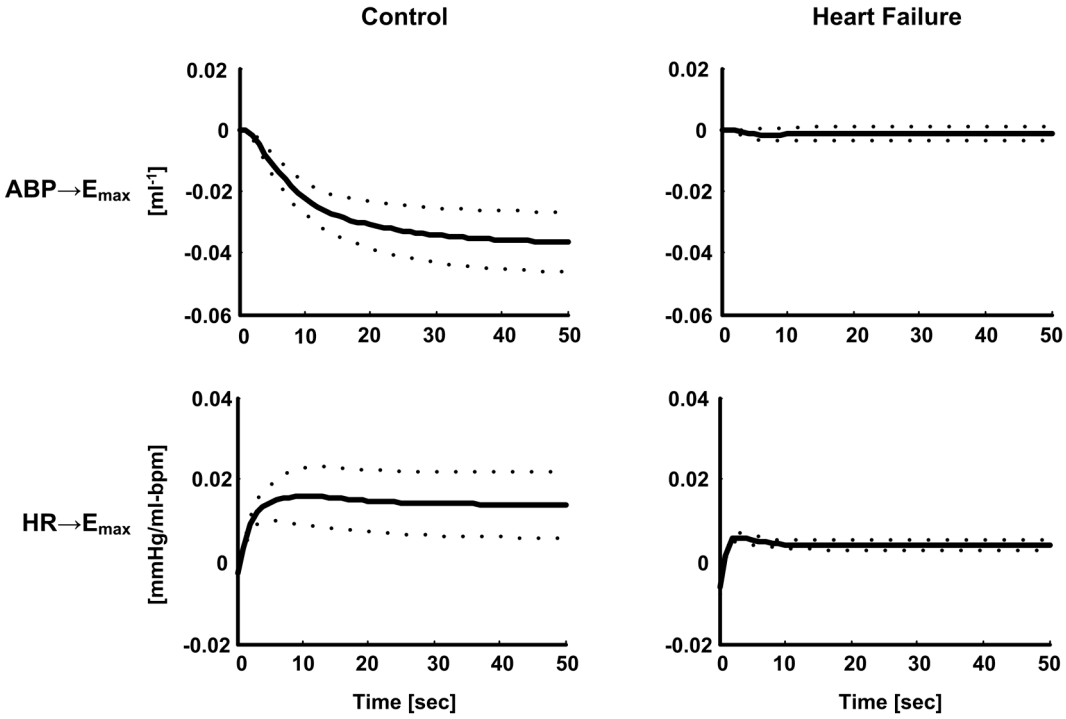

Fig. 3. Group average transfer functions (mean ± SE) in terms of step responses.

IV. Discussion

In summary, we have identified the ABP→E_{max} and HR→E_{max} transfer functions, which respectively characterize the dynamic properties of the arterial ventricular contractility baroreflex and force-frequency relation, by analysis of spontaneous hemodynamic variability from three conscious dogs before and after pacing-induced heart failure. Our results are congruent with both known physiology and previous studies

The ABP→E_{max} transfer function reveals negative feedback dynamics during the control condition, which is consistent with the arterial baroreflex mechanism. Further, its gain value, dominant time constant, and time delay compare reasonably well with the corresponding -0.085 ml^{-1}, 11 sec, and 2.28 sec values reported by Sunagawa and colleagues [12]. Differences in these values may be attributed to the widely varying experimental conditions employed in the two studies as well as isolation of the carotid sinus baroreflex in the previous study as opposed to identification of what may be though of as a combined aortic arch-carotid sinus baroreflex herein. Finally, the ABP→E_{max} transfer function was blunted essentially to zero following induction of heart failure, which is expected due to depressed sympathetic nervous *responsiveness* in this pathophysiologic condition.

The HR→E_{max} transfer function indicates that HR changes cause directionally same E_{max} changes during the control condition, which is consistent with the force-frequency relation. Moreover, its gain value is not far from the 0.03 mmHg/ml-bpm value at the same mean HR reported by Maughan et al. who determined the steady state HR to E_{max} relationship over a wide HR range in an isolated canine heart [11]. Again, deviations in these values should be mainly due to the differing experimental conditions. In addition, both the

time constant and delay of the HR→E_{max} transfer function are much smaller than those of the ABP→E_{max} transfer function. These results are not surprising, as the force-frequency relation is mediated via fast mechanical effects, whereas the arterial ventricular contractility baroreflex is governed by the more sluggish sympathetic nervous system. Finally, the HR→E_{max} transfer function was depressed, though not to zero, following the induction of heart failure. Asanoi et al. reported a similar finding by determining the steady state HR to E_{max} relationship before and after pacing-induced heart failure in conscious, but autonomically blocked, dogs [7]. The mechanism for the diminished strength of the force-frequency relation here is likely due to the increase in mean HR (i.e., change in operating point), as shown by Maughan et al. [11].

Our ongoing efforts are geared towards increasing the sample size of this study to reduce the standard error and achieve statistical significance. We believe that these efforts will significantly add to the knowledge base on the dynamic control of E_{max} by yielding quantitative data during normal closed-loop operation in both health and disease.

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