31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Pilot Canine Investigation of the Cardiopulmonary Baroreflex Control of Ventricular Contractility

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Abstract—**We performed a pilot investigation of the cardiopulmonary baroreflex control of ventricular contractility in two conscious dogs. We specifically measured spontaneous beat-to-beat hemodynamic variability before and after the administration of propranolol. We then identified the transfer function relating beat-to-beat fluctuations in central venous pressure (CVP) to maximal ventricular elastance (E_{max}) to characterize the cardiopulmonary baroreflex control of ventricular contractility, while accounting for the influences of arterial blood pressure fluctuations on E_{max} via the arterial baroreflex and heart rate fluctuations on E_{max} via the force-frequency relation. Our major finding is that the cardiopulmonary baroreflex responds to an increase (decrease) in CVP by increasing (decreasing) E_{max} via the β-sympathetic nervous system.**

I. Introduction

The baroreflex systems are primarily responsible for maintaining blood pressures over short time scales of seconds to minutes. It is well known that the arterial baroreflex senses arterial blood pressure (ABP) via baroreceptors lying in the carotid sinus and aortic arch and buffers a decrease (increase) in ABP by increasing (decreasing) heart rate (HR), total peripheral resistance, and ventricular contractility. However, the cardiopulmonary baroreflex is less understood. The sensory receptors of this system are more complex, residing mainly in the cardiac chambers but also in the walls of the pulmonary artery [1]. These receptors have been shown to be very responsive to central venous pressure (CVP) [2, 3]. The cardiopulmonary baroreflex responds to a change in CVP by inducing an opposite change in total peripheral resistance [3, 4]. An increase in CVP also leads to an increase in HR (i.e., Bainbridge effect) in dogs [5], but an opposite change may occur in humans [2].

To our knowledge, the cardiopulmonary baroreflex control of ventricular contractility has not been elucidated. A change in CVP could induce a same directional change in ventricular contractility so as to maintain CVP, much like the Bainbridge effect. On the other hand, a change in CVP could cause an opposite change in ventricular contractility in order to blunt the forthcoming change in ABP due to the altered preload, much like the cardiopulmonary baroreflex control of total peripheral resistance.

We performed a pilot canine investigation of the cardiopulmonary baroreflex control of ventricular contractility. More specifically, we measured spontaneous beat-to-beat hemodynamic variability from two conscious dogs during control conditions and from one of the dogs after the administration of propranolol to abolish the neural control of ventricular contractility. We then identified the transfer function relating beat-to-beat fluctuations in CVP to maximal ventricular elastance (E_{max}), which is perhaps the best available index of ventricular contractility [6-8], while accounting for other influences on E_{max} including ABP fluctuations via the arterial baroreflex.

II. Methods

A. Data Collection

We collected pilot hemodynamic data for this study from two adult dogs (20-25 kg) in the context of performing experiments to address unrelated specific aims. We describe only those aspects of the experimental procedures that were relevant to the present study. All procedures were reviewed and approved by the Wayne State University Animal Investigator Committee.

We studied each dog on three experimental days with suitable recovery periods in between as follows. On the first day, we performed a midline sternotomy under sterile conditions. We installed instrumentation including two pairs of sonomicrometry crystals (Sonometrics) on the left ventricular (LV) endocardium for continuous LV volume (LVV) as described in [9]; a fully implanted system with a micromanometer-tipped catheter (Data Sciences International) in the left ventricle (LV) for continuous LV pressure (LVP); an ultrasonic flow probe (Transonic Systems) around the ascending aorta for continuous cardiac output; and hydraulic vascular occluders (In Vivo Metrics) on the superior and inferior vena cava to diminish cardiac preload. Then, on the second day, we installed additional instrumentation under sterile conditions including fluid-filled

Manuscript received April 7, 2009. This work was supported by the National Institutes of Health (HL-55473, HL-080568) and the National Science Foundation (CAREER 0643477).

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catheters in the terminal aorta for continuous ABP and in the right atrium for continuous CVP. Finally, on the third day, we recorded the cardiovascular measurements during a baseline period of 5-8 min and transient vena cava occlusion while the dogs were standing quietly. For the second dog, we then administered propranolol to achieve complete β-sympathetic nervous blockade and likewise recorded the measurements.

B. Data Analysis

We analyzed the hemodynamic data for the three conditions of the two dogs. First, we determined E_{max} and CVP, along with ABP and HR, on a beat-to-beat basis from the continuous measurements during the baseline period. Then, we identified the transfer function relating the spontaneous beat-to-beat fluctuations in CVP to E_{max} (CVP→E_{max}), while effectively eliminating the known influences of beat-to-beat ABP and HR fluctuations on E_{max}.

More specifically, as described in a companion study of dynamic E_{max} control before and after heart failure [10], 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 [11]. 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.

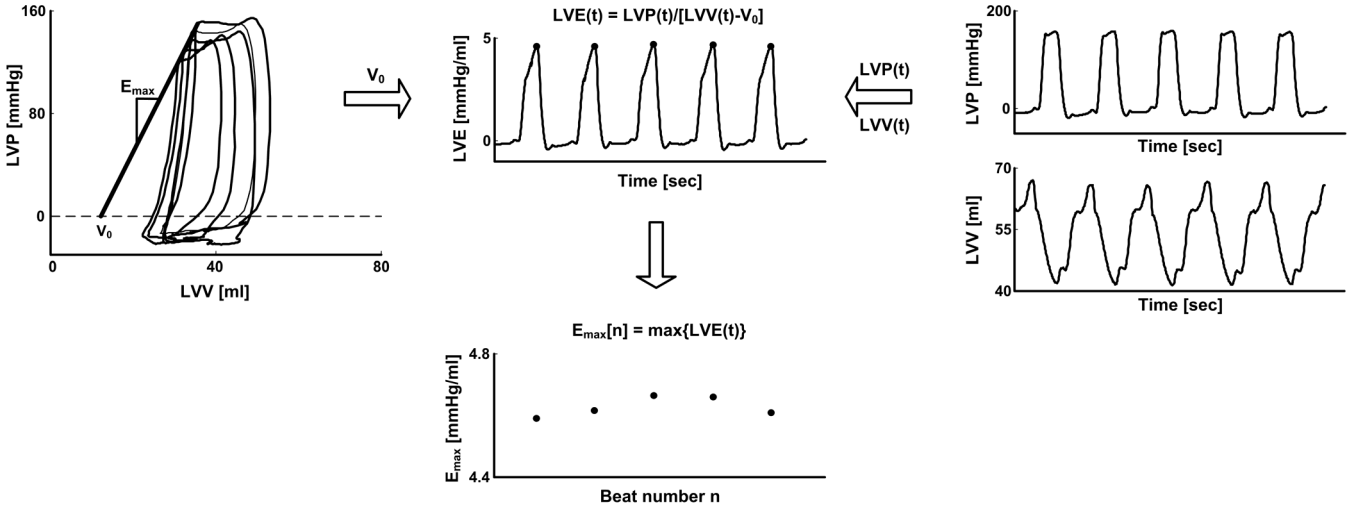

Fig. 1. Procedure for estimating beat-to-beat E_{max} from continuous LVP and LVV measurements during transient vena cava occlusion (left panel) and a baseline period (right panel).

We computed beat-to-beat CVP and ABP by respectively time averaging the continuous CVP and ABP over each beat during the baseline period and identified beat-to-beat HR from the continuous cardiac output during the same period. We then re-sampled the E_{max}, CVP, ABP, and HR beat series to time series at a sampling frequency of 1 Hz as described in [12].

We identified the CVP→E_{max} transfer function by analyzing all four of the time series according to the block diagram illustrated in Fig. 2. As indicated in this diagram, we simultaneously identified the transfer function relating beat-to-beat fluctuations in ABP to E_{max} (ABP→E_{max}), which characterizes the arterial baroreflex, and the transfer function relating beat-to-beat fluctuations in HR to E_{max} (HR→E_{max}), which characterizes the force-frequency relation. In this way, the influence of beat-to-beat fluctuations in CVP on E_{max} was isolated from other major confounding factors. We also estimated the perturbing noise source $N_{E_{max}}$ in the block diagram, which represents the residual variability in E_{max} not explained by the analyzed fluctuations. In particular, we mathematically represented the block diagram with the following autoregressive exogenous input structure:

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

where t is discrete time; the four sets of unknown parameters $\{a_i, b_i, c_i, d_i\}$ fully define the three transfer functions; the unmeasured residual error $W_{E_{max}}$ together with the set of parameters $\{a_i\}$ specify $N_{E_{max}}$; and the unknown model order, p, q, r, s, m, and n, limit the number of parameters [13]. For a fixed model order, we analytically estimated the parameters from zero-mean fluctuations in the 1 Hz CVP, ABP, HR, and E_{max} time series by linear least squares minimization of $W_{E_{max}}$ [13]. We set p, r, and m to two, q, and s, respectively, on the basis of a compelling previous study demonstrating that the arterial baroreflex control of E_{max}

could be well represented as a second-order delay system [14]. We determined q, s, and n by minimization of the popular minimum description length criterion [13].

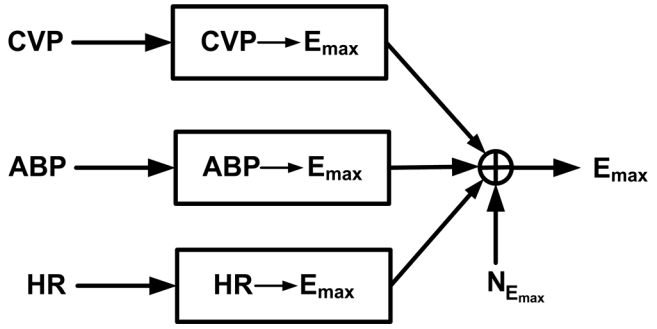

Fig. 2. Block diagram for identifying the CVP→E_{max}, ABP→E_{max} and HR→E_{max} transfer functions from beat-to-beat fluctuations in CVP, ABP, HR, and E_{max}.

III. Results

Figs. 3 and 4 illustrate the CVP→E_{max}, ABP→E_{max}, and HR→E_{max} transfer functions in terms of intuitive step responses, respectively, from the first dog during the control condition and the second dog during the control and propranolol conditions. During the control condition, both CVP→E_{max} step responses indicate that E_{max} would increase in response to a step increase in CVP. Quantitatively, the average gain value and dominant time constant of these steps responses are 0.2097 ml^{-1} and 11.17 sec. The corresponding pairs of ABP→E_{max} and HR→E_{max} step responses show that E_{max} would decrease and increase, respectively, in response to step increases in ABP and HR. The average gain value of the ABP→E_{max} step response and the average dominant time constant of the HR→E_{max} step response are smaller than those of the CVP→E_{max} step response. During the propranolol condition, the CVP→E_{max} step response indicates that E_{max} would not change in response to a step increase in CVP. The corresponding ABP→E_{max} and HR→E_{max} step responses similarly reveal blunted responses to steps increases in ABP and HR.

IV. Discussion

In summary, we have investigated the cardiopulmonary baroreflex control of ventricular contractility in terms of E_{max} in two conscious dogs. Our results suggest that, similar to the Bainbridge effect, the cardiopulmonary baroreflex responds to an increase (decrease) in CVP by increasing (decreasing) E_{max}. This mechanism appears to be mediated by the β-sympathetic nervous system, as the E_{max} response to a change in CVP was abolished following the administration of propranolol. These pilot results may be amongst, if not, the first to illustrate how the cardiopulmonary baroreflex controls ventricular contractility.

Further, our ancillary results here on the E_{max} response to changes in ABP and HR are consistent with known physiology. In particular, we found that an ABP change produces an opposing change in E_{max}, which is consistent with the negative feedback dynamics of the arterial baroreflex, while a HR change induces the same directional change in E_{max}, which is congruent with the force-frequency relation. Moreover, the E_{max} response to a HR change was markedly faster than to an ABP change. This result is in accord with the force-frequency relation being mediated by fast mechanical effects and the arterial baroreflex being governed by the sluggish sympathetic nervous system. Finally, as expected, the E_{max} response to a change in ABP was eliminated after the administration of propranolol. (However, it is unclear why the E_{max} response to a HR change was also blunted after the drug administration.) These physiologically consistent results add confidence to our new findings on the cardiopulmonary baroreflex control of ventricular contractility.

Our future efforts will focus on confirming the results reported herein in a larger number of animals. Ultimately, we believe that this line of research will translate to a significant advance in the understanding of baroregulatory physiology.

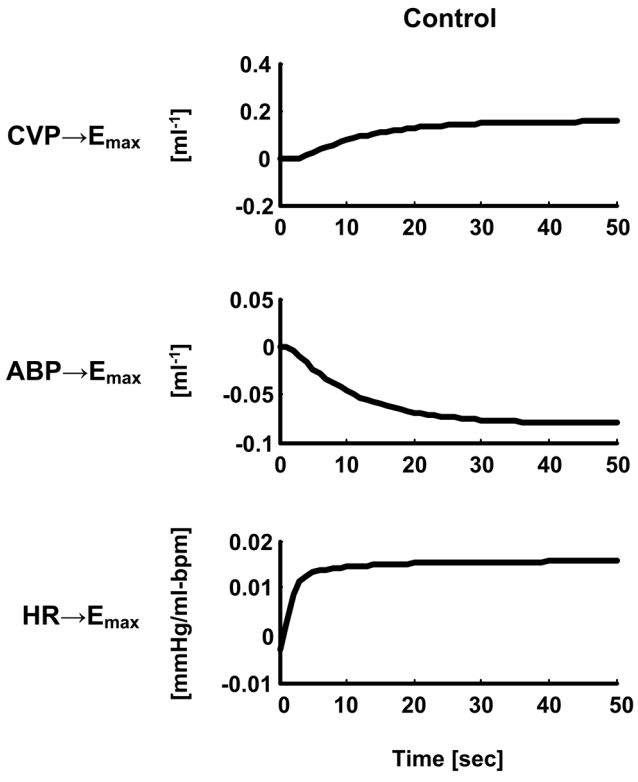

Fig. 3. Transfer functions in terms of step responses from the first dog during the control condition.

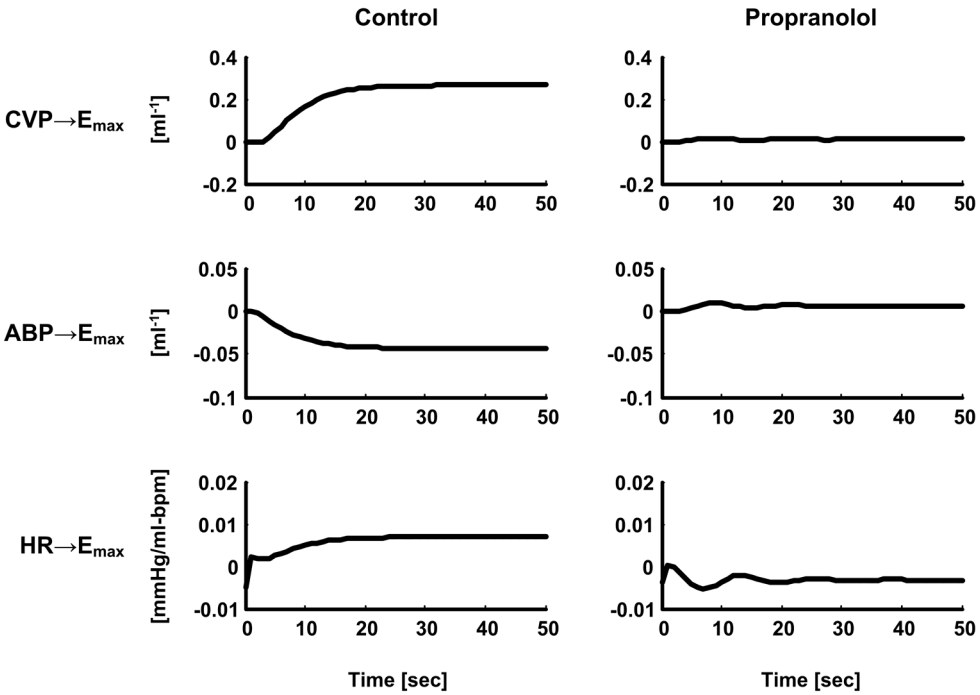

Fig. 4. Transfer functions in terms of step responses from the second dog during the control and propranolol conditions.

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