Emax Monitoring by Aortic Pressure Waveform Analysis

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Abstract—Emax – the maximal left ventricular elastance – is perhaps the best available scalar index of contractility. However, the conventional method for its measurement involves obtaining multiple ventricular pressure-volume loops at different loading conditions and is thus impractical. We previously proposed a more practical technique for tracking Emax from just a single beat of an aortic pressure waveform based on a lumped parameter model of the left ventricle and arteries. Here, we tested the technique against the conventional Emax measurement method in animals during inotropic interventions. Our results show that the estimated Emax changes corresponded fairly well to the reference changes, with a correlation coefficient of 0.793. With further development and testing, the technique could ultimately permit continuous and less invasive monitoring of Emax.

I. INTRODUCTION

The Emax concept was introduced by Suga and Sagawa [1][2] and is as follows. The left ventricular elastance, which is the ratio of pressure to stressed volume (i.e., volume minus unstressed volume (V_0)), is linear and time-varying. That is, in electrical terms, the left ventricle behaves as a variable capacitor. Further, the maximal elastance (Emax) attained is sensitive to contractility but not preload or afterload. While ensuing studies have challenged the concept (see references in [3]), Emax is still considered by many to be the most load independent scalar index of inotropic state that is available.

The conventional method for measuring Emax involves (1) measuring ventricular pressure and volume at different preloads and/or afterloads; (2) plotting the multiple pressure-volume loops; and (3) finding the line that best fits the end-systolic pressure-volume points. The slope of the line is approximately Emax, whereas the x-intercept is V_0.

However, there are three practical difficulties with this method. Firstly, measurement of ventricular pressure is very invasive and carries great risk. Secondly, reliable measurement of ventricular volume is challenging. Thirdly, the loading condition change, which is often achieved with vena cava occlusion, is likewise intrusive and could reflexively alter Emax. These practical difficulties have limited the use of Emax despite its recognized value.

As a result, several methods have been proposed towards practical measurement of Emax [3]-[7]. These methods determine Emax from a single beat and thereby eliminate the need for the loading condition change. However, most of the "single-beat" methods still require measurements of ventricular pressure and ventricular volume or stroke volume, which is also difficult. While one method does preclude measurement of ventricular pressure and could thus be non-invasive, it is based on population values [5].

Our broad objective is to achieve practical and reliable Emax monitoring. Previously, we proposed a technique to estimate parameters indicative of the ventricle and arteries including Emax from just a single beat of an aortic pressure waveform [8]. We computed ejection fraction, a widely used but load dependent index of contractility, from the lumped parameter estimates. We showed that the computed ejection fraction agreed fairly well with periodic echocardiographic ejection fraction measurements. Our specific objective in this study was to compare the Emax estimates of the lumped parameter model-based analysis technique with conventional Emax measurements during inotropic interventions.

II. METHODS

A. Lumped Parameter Model-Based Analysis Technique

The technique calculates relative Emax changes (as well as absolute ejection fraction) from an aortic pressure waveform without the need for a loading condition change or a ventricular or stroke volume measurement. This technique is illustrated in Fig. 1 and described in detail elsewhere [8].

Briefly, an aortic pressure waveform [$P_a(t)$] is represented with a lumped parameter model of the left ventricle and arteries (Fig. 1a). In this model, the left ventricle is represented with a linear, time-varying elastance [$E_{lv}(t)$]; the left ventricular outflow valve is characterized by an ideal diode; and the arteries are represented with a Windkessel accounting for the compliance of the large arteries [C_a] and the resistance of the small arteries [R_a]. Further, C_a is assumed to be relatively constant.

During arterial systole, the following equation governs the model:

$$\frac{P_a(t_{bs})}{C_a E_{lv}(t_{bs})} - \frac{P_a(t)}{C_a E_{lv}(t)}$$
$$= P_a(t) - P_a(t_{bs}) + \frac{1}{\tau} \int_{t_{bs}}^{t} P_a(\lambda)\, d\lambda, \quad t_{bs} < t \le t_{es}, \qquad (1)$$

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where $\tau = R_a C_a$, and the subscripts bs and es respectively stand for the beginning and end of systole. In this equation, $E_{lv}(t)$ is succinctly represented with the following parametric raised cosine function:

$$E_{lv}(t) = \begin{cases} E_{min} + \dfrac{E_{max} - E_{min}}{2}\left\{1 - \cos\left(\dfrac{\pi\left(t - t_{bi}\right)}{T_s}\right)\right\}, \\ \qquad\qquad\qquad\qquad t_{bi} \le t < t_{bi} + T_s \\[6pt] E_{min} + \dfrac{E_{max} - E_{min}}{2}\left\{1 + \cos\left(\dfrac{2\pi t\left(t - \left(t_{bi} + T_s\right)\right)}{T_s}\right)\right\}, \\ \qquad\qquad\qquad\qquad t_{bi} + T_s \le t < t_{bi} + 1.5 T_s \\[6pt] E_{min}, \qquad\qquad\qquad t_{bi} + 1.5 T_s \le t \end{cases} \quad (2)$$

where E_{min} is the minimum ventricular elastance, T_s is the time duration to reach E_{max} from E_{min}, and the subscript bi stands for the beginning of the isovolumic contraction phase (lower panel of Fig. 1b). Hence, the governing equation above has five unknown parameters: τ, $C_a E_{max}$ (proportional E_{max}), $C_a E_{min}$, $C_a E_{lv}(t_{bs})$, and T_s (Fig. 1b). Since E_{min} is not observable in $P_a(t)$, $C_a E_{min}$ is assumed to be a fixed fraction of $C_a E_{max}$ (lower panel of Fig. 1b), thereby reducing the unknown parameters to four.

The parameters are estimated from the entire beat of $P_a(t)$ as follows. First, τ is estimated by least squares fitting of an exponential to $P_a(t)$ during diastole (upper panel of Fig. 1b). Then, after substituting this estimate into Eqn. (1), the other three parameters are estimated by least squares matching of both sides of the equation using $P_a(t)$ during systole.

Finally, the $C_a E_{max}$ estimate is used to track relative Emax changes. Alternatively, if desired, the proportional estimate can be calibrated with a stroke volume measurement to obtain absolute Emax.

B. Data Collection

To test the technique, we collected hemodynamic data from six healthy adult beagles (10-12 kg) under an experimental protocol approved by the Michigan State University All-University Committee on Animal Use and Care. Under general anesthesia and with fluoroscopic guidance (GE), we positioned the following instruments in each dog: a high fidelity catheter (Millar Instruments) in the aorta to measure an aortic pressure waveform; a high fidelity pressure-volume admittance catheter (Scisense) in the left ventricle to measure ventricular pressure and volume waveforms; an echocardiographic probe (Philips) in the esophagus to calibrate the ventricular volume waveform; and a balloon catheter in the inferior vena cava to adjust the loading condition. We also placed a catheter in a cephalic vein for drug infusion as well as other instruments to address different objectives. We interfaced all analog transducer outputs to a personal computer via a data acquisition system (DataQ Instruments). We then recorded the measurements at a sampling rate of 500 Hz during a baseline period and after dobutamine infusions to increase Emax in three of the dogs and after esmolol infusions to decrease Emax in the remaining dogs. We employed several infusion rates per inotropic intervention. During the baseline period and each inotropic infusion rate, we obtained a several beat long cine echocardiographic recording via a four chamber view and
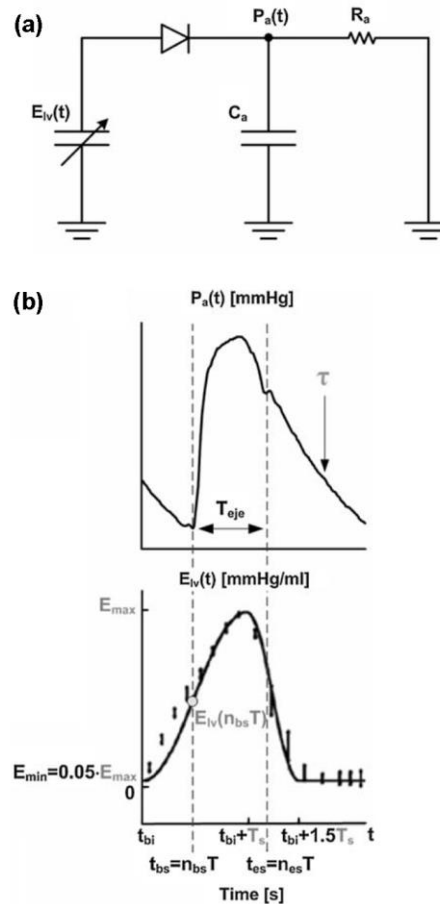

Fig. 1. Lumped parameter model-based analysis technique for estimating proportional Emax [$C_a E_{max}$] from an aortic pressure waveform [$P_a(t)$]. (a) Model of the left ventricle and arteries. (b) Model parameter estimation.

transiently inflated and deflated the inferior vena cava balloon to adjust the loading condition multiple times.

C. Data Analysis

We analyzed the data from the baseline period and each inotropic infusion rate of each dog as follows. We applied the lumped parameter model-based analysis technique to 20-50 sec steady intervals of the aortic pressure waveforms and then averaged the resulting beat-to-beat $C_a E_{max}$ to arrive at proportional Emax estimates. We determined reference Emax values in three steps. First, we measured end-diastolic and end-systolic ventricular volumes by manually tracing the endocardial borders of the single-plane echocardiographic images, excluding papillary muscles, at end-diastole and end-systole and then applying Simpson's rule. We likewise averaged the ventricular volumes over multiple beats. Second, we used the echocardiographic volumes to calibrate the ventricular volume waveforms obtained via the admittance catheter. Third, we applied the conventional Emax measurement method to the ventricular pressure and calibrated ventricular volume waveforms during transient inferior vena cava balloon inflation. We again averaged Emax over multiple inflations to arrive at reference Emax values. Finally, we quantitatively compared the proportional
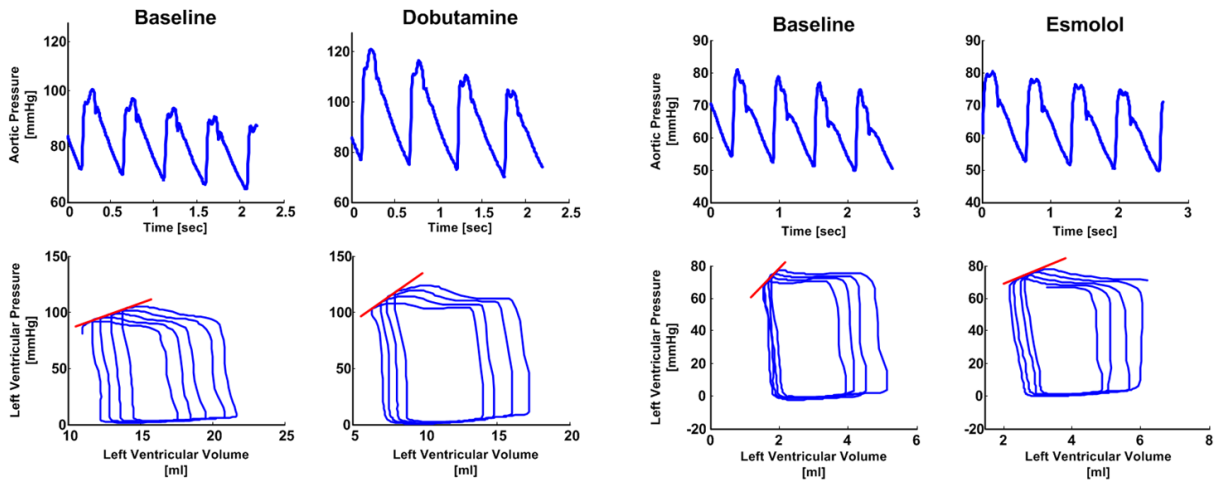
Fig. 2. Sample aortic pressure waveforms and ventricular pressure-volume loops with reference Emax indicated before and after inotropic interventions.

Emax estimates to the reference Emax values in terms of their relative percent change from the baseline period to each inotropic infusion rate.

III. RESULTS

Fig. 2 illustrates sample aortic pressure waveforms and ventricular pressure-volume loops during baseline periods and following inotropic interventions. As indicated in this figure and consistent with the employed lumped parameter model, the aortic pressure waveforms generally showed exponential diastolic decays. The Table shows aortic mean and pulse pressure (MAP and PP), and reference Emax values for each dog during the baseline period and following inotropic intervention at the maximum infusion rate. These values changed significantly with the interventions. Fig. 3 illustrates the estimated relative Emax changes from the baseline period to each inotropic infusion rate versus the reference Emax changes over all the dogs. The correlation coefficient between the estimates and reference values was 0.793. So, the technique was able to track Emax fairly well.

IV. DISCUSSION

In summary, we tested a lumped parameter model-based analysis technique for monitoring Emax from an aortic pressure waveform against the conventional Emax measurement method. Our laboratory results show that the technique can estimate relative Emax changes induced by positive and negative inotropes reasonably well.

While more practical Emax measurement in the form of single-beat methods have previously been proposed, the technique here has the advantage of neither requiring ventricular or stroke volume measurements nor population values. Its disadvantage is that it does not yield absolute Emax or V_0. That said, in a continuous monitoring application, tracking changes in Emax may be most relevant.

The lumped parameter model-based analysis technique can be improved in at least two ways. Firstly, measurement of an aortic pressure waveform is still too invasive. On the

TABLE HEMODYNAMIC VALUES PER SUBJECT

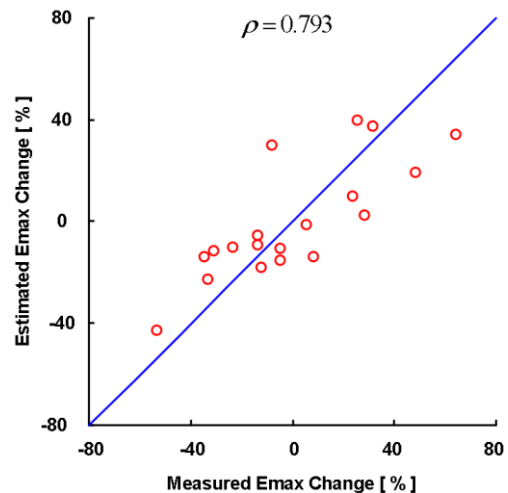| Dog	Drug	MAP [mmHg]	PP [mmHg]	Ref.. Emax [mmHg/ml]
1	Baseline	73	31	2.5
	Dobutamine	94	38	6.9
2	Baseline	99	30	1.6
	Dobutamine	107	38	3.6
3	Baseline	92	29	4.9
	Dobutamine	101	42	7.4
4	Baseline	91	29	3.7
	Esmolol	69	27	1.5
5	Baseline	82	25	4.1
	Esmolol	72	24	2.5
6	Baseline	80	28	2.5
	Esmolol	71	26	2.2

Fig. 3. Estimated relative Emax changes induced by each inotropic intervention versus reference Emax changes over all the subjects.

other hand, a peripheral artery pressure waveform can be measured with minimally invasive or even non-invasive methods. However, unlike an aortic pressure waveform, peripheral artery pressure waveforms do not typically exhibit exponential diastolic decays. So, one potential improvement is to mathematically derive an aortic pressure waveform from a peripheral artery pressure waveform using an adaptive transfer function [9] and then apply the technique to the derived aortic pressure waveform so as to calculate proportional Emax from a peripheral artery pressure waveform. Secondly, while arterial compliance (C_a) must have been relatively constant here, this assumption cannot always hold. So, a second potential improvement is to correct for any C_a change using pulse transit time. This variable goes with the square root of C_a and could be easily obtained from non-invasive measurements. If these improvements can be realized, then Emax may be tracked less invasively, continuously, and more accurately.

REFERENCES

[1] H. Suga, K. Sagawa, and a. a. Shoukas, "Load Independence of the Instantaneous Pressure-Volume Ratio of the Canine Left Ventricle and Effects of Epinephrine and Heart Rate on the Ratio," *Circ. Res.*, vol. 32, no. 3, pp. 314–322, Mar. 1973.

[2] H. Suga and K. Sagawa, "Instantaneous Pressure-Volume Relationships and Their Ratio in the Excised, Supported Canine Left Ventricle," *Circ. Res.*, vol. 35, no. 1, pp. 117–126, Jul. 1974.

[3] M. Hideaki Senzaki, M. Chen-Huan Chen, and M. David A. Kass, "Single-Beat Estimation of End-Systolic Pressure-Volume Relation in Humans," *Circulation*, vol. 94, pp. 2497–2506, 1996.

[4] T. Nakamoto, C. P. Cheng, W. P. Santamore, and M. Iizuka, "Estimation of left ventricular elastance without altering preload or afterload in the conscious dog," *Cardiovasc. Res.*, vol. 27, no. 5, pp. 868–73, May 1993.

[5] C. H. Chen, B. Fetics, E. Nevo, C. E. Rochitte, K. R. Chiou, P. a Ding, M. Kawaguchi, and D. a Kass, "Noninvasive Single-Beat Determination of Left Ventricular End-Systolic Elastance in Humans," *J. Am. Coll. Cardiol.*, vol. 38, no. 7, pp. 2028–34, Dec. 2001.

[6] T. Shishido, K. Hayashi, K. Shigemi, T. Sato, M. Sugimachi, and K. Sunagawa, "Single-Beat Estimation of End-Systolic Elastance Using Bilinearly Approximated Time-Varying Elastance Curve," *Circulation*, vol. 102, no. 16, pp. 1983–1989, Oct. 2000.

[7] M. Takeuchi, Y. Igarashi, S. Tomimoto, M. Odake, T. Hayashi, T. Tsukamoto, K. Hata, H. Takaoka, and H. Fukuzaki, "Single-beat estimation of the slope of the end-systolic pressure-volume relation in the human left ventricle," *Circulation*, vol. 83, no. 1, pp. 202–212, Jan. 1991.

[8] G. Swamy, J. Kuiper, M. S. R. Gudur, N. B. Olivier, and R. Mukkamala, "Continuous left ventricular ejection fraction monitoring by aortic pressure waveform analysis.," *Ann. Biomed. Eng.*, vol. 37, no. 6, pp. 1055–68, Jun. 2009.

[9] G. Swamy, D. Xu, N. B. Olivier, and R. Mukkamala, "An adaptive transfer function for deriving the aortic pressure waveform from a peripheral artery pressure waveform.," *Am. J. Physiol.*, vol. 297, no. 5, pp. H1956–63, Nov. 2009.