Monitoring Left Ventricular Contractility from Respiratory-Induced Blood Pressure Variability

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Abstract

The maximum left ventricular elastance (E_{lv}^{max}) is a valuable index of ventricular contractility. However, traditional methods for its measurements are too invasive for practical use. We introduce a minimally invasive technique for monitoring E_{lv}^{max} by mathematical analysis of beat-to-beat fluctuations in arterial blood pressure and intrathoracic (esophageal) pressure obtained during random-interval breathing. The technique exploits the concept that the magnitude of the blood pressure drop immediately initiated by inspiration is due to E_{lv}^{max} and the nearly constant arterial compliance (C_a). The technique estimates $C_a E_{lv}^{max}$ and may be utilized to monitor changes in E_{lv}^{max}. We theoretically evaluated the technique by applying it to realistic beat-to-beat variability generated by a cardiovascular model. Our simulation results show that the technique is able to quantify $C_a E_{lv}^{max}$ with little bias and can detect actual changes to the model E_{lv}^{max}.

1. Introduction

Due to recent advances in the treatment of heart attacks and other cardiac disorders, the incidence of heart failure is rapidly growing. The disease presentation and therapeutic response are variable, and the treatment options are growing in complexity. It is therefore becoming increasingly important to be able to measure specific indices of cardiac function in order to help guide therapy. The clinical method for monitoring cardiac function typically involves employing echocardiography to estimate the ejection fraction. Although this index of ventricular contractility is relatively easy to estimate, it is dependent on ventricular preload and afterload as well.

Suga and Sagawa were able to identify a relatively specific or pure index of ventricular contractility [1]. These investigators demonstrated that the pressure-volume relationship of the isolated canine left ventricle may be represented by a line whose slope (elastance) varies from its minimum value at the end of diastole to its maximum value at the end of systole. That is, the left ventricle operates analogously to a variable capacitor (where capacitance is the reciprocal of elastance). They showed that the maximum elastance was highly sensitive to changes in ventricular inotropy but insensitive to alterations in preload and afterload. They referred to this specific index of left ventricular contractility as E_{lv}^{max}.

Although the significance of the E_{lv}^{max} concept is well appreciated, it is rarely employed because of difficulties involved in its measurement. The traditional measurement method involves measuring multiple ventricular pressure-volume loops during interventions that ideally alter only the loading conditions. Ventricular pressure can be measured with high fidelity, but very invasive techniques are required to do so. Moreover, while ventricular volume can be estimated non-invasively via echocardiography, even very invasive ventricular volume measurements may not be reliable. Finally, the adjustment of loading conditions is not only invasive but may also reflexively alter the contractile state.

In this paper, we introduce a practical technique for monitoring E_{lv}^{max} that may ultimately be employed to help guide the clinical management of heart failure patients. The technique specifically estimates *changes* in E_{lv}^{max} by mathematically analyzing beat-to-beat fluctuations in arterial blood pressure (P_a) and respiratory activity in terms of intrathoracic pressure (P_{th}) obtained during a random-interval breathing protocol [2]. The key idea of the technique is to identify changes in the magnitude of the immediate P_a drop mechanically induced by inspiration (*i.e.*, direct capacitive effects), which are mainly due to changes in E_{lv}^{max}. Importantly, minimally invasive methods exist for continuously measuring P_a (radial artery catheterization) and P_{th} (esophageal balloon). We then theoretically evaluate the technique with respect to realistic beat-to-beat variability generated by a cardiovascular model in which E_{lv}^{max} can be exactly controlled [3].

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2. The technique

2.1. Respiratory-induced P_a variability mechanisms

Beat-to-beat fluctuations due to respiration are readily apparent in P_a waveforms. These fluctuations are usually slower than the heart rate (HR) and are caused by multiple, distinct physiologic mechanisms operating over different time courses. These mechanisms may be categorized into those mediated by the autonomic nervous system and those governed by mechanical phenomena.

Autonomic mechanisms are responsible for the well-known respiratory sinus arrhythmia phenomenon in which HR and respiratory variations are in synchrony. It has been shown that the HR variations, which may initiate P_a variations through changes in cardiac output, actually *precede* the respiratory variations [4]. The resulting blood pressure changes also stimulate the baroreflex, which responds by buffering the ensuing blood pressure changes through autonomic nervous control of HR, stroke volume, and arteriolar resistance.

The mechanical mechanisms are initiated by changes in P_{th} caused by chest wall expansion (inspiration) and contraction (expiration). For example, the act of inspiration causes P_{th} to drop. This drop is immediately transmitted to P_a due to direct capacitive effects and then causes an increase in P_a after a couple of beats due to enhanced venous return to the right heart. For a given P_{th} drop, the extent to which the enhanced venous return to the right heart affects P_a is dependent on the properties of the right heart, pulmonary circulation, left heart, and systemic arteries. So, for example, left and right ventricular failure or systolic and diastolic failure could not be distinguished by examining the extent of increase in P_a due to enhanced venous return to the right heart.

On the other hand, the direct capacitive effects essentially reflect only left ventricular contractile properties. To demonstrate this quantitatively, consider the two-compartment, electrical analog model representing the left ventricle (lv) and systemic arteries (a) in Figure 1a. Each compartment includes a resistance (R) and a capacitance (C). The external pressure (P) is P_{th} for the left ventricle and XP_{th} for the systemic arteries, where X is the fraction of the arteries residing in the thoracic compartment (normally about 1/3 in humans [5].) The capacitance of the left ventricle oscillates over time (t) according to the experimental data of Suga and Sagawa and is responsible for driving the flow of blood. Finally, the ideal diode represents the aortic valve and ensures uni-directional flow. Note that fast inertial and distributed effects are not modeled, as only slow, beat-to-beat variations are considered here.

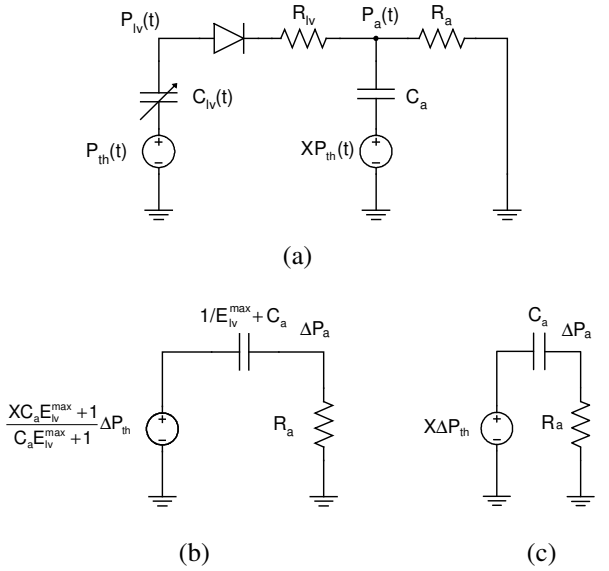

Figure 1. (a) Two-compartment model of the left ventricle and arteries. (b) Reduced systole model. (c) Reduced diastole model. See text for details.

The two-compartment model of Figure 1a is nonlinear due to the presence of the diode. However, this model may also be viewed as two distinct linear systems, one during systole and the other during diastole. To calculate the immediate P_a model response to a change in P_{th} (*i.e.*, direct capacitive effects) during systole, we assume that R_{lv}=0 (*i.e.*, no stenosis of the aortic valve). We also assume that the difference between $C_{lv}(t)$ and the reciprocal of E_{lv}^{max} during the systolic ejection phase is small and likely to be within the estimation error (see below), since the systolic ejection time and time derivative of left ventricular elastance near its maximal value are both small, especially for failing hearts [1]. Thus, the reduced systole model in Figure 1b results. Because the systolic ejection interval is usually much smaller than the time constant of the reduced systole model (*i.e.*, capacitor shorted), the average change in P_a with respect to its mean value in response to a known change in P_{th} with respect to its mean value during systole as a result of only the direct capacitive effects is given as follows:

$$\Delta P_a \approx \frac{XC_a E_{lv}^{\max} + 1}{C_a E_{lv}^{\max} + 1} \Delta P_{th} \qquad (1)$$

With similar arguments, we derive the reduced diastole model in Figure 1c, and the average change in P_a with respect to its mean value to a known change in P_{th} with respect to its mean value during diastole due to only direct capacitive effects is given as follows:

$$\Delta P_a = X \Delta P_{th} \qquad (2)$$

Thus, the quantity $C_a E_{lv}^{max}$ is uniquely specified by the direct capacitive effects during systole and diastole. Since C_a is relatively constant on the time scale of months and over a wide pressure range [6,7], changes in $C_a E_{lv}^{max}$ would reflect only changes in left ventricular contractility.

2.2. Measurement of the direct capacitive effects

The direct capacitive effects cannot be measured from naturally occurring, beat-to-beat variability by simply computing ratios of changes in systolic and diastolic P_a over a given time period to the change in P_{th} over the same time period (as implied in Equations (1) and (2)). The reason is that the systolic and diastolic P_a changes are also due to the past histories of P_{th} changes (*e.g.*, enhanced venous return to the right heart) and P_a changes (*e.g.*, baroreflex control of R_a and stroke volume). Additionally, the P_a changes are due to HR, which, unlike the other baroreflex controllable parameters, may not be adequately reflected in the past history of P_a due to fast parasympathetic modulation of HR.

To measure the direct capacitive effects, we therefore employ the powerful system identification analysis to continuous segments of the P_a and P_{th} measurements [8]. This analysis permits the determination of the effect of one input variable (present value of P_{th}) on an output variable (present value of systolic or diastolic P_a) independent of all confounding input variables (past values of P_{th} and P_a and present and past values of HR). Thus, system identification mathematically "turns off" all of the confounding factors. Since system identification is most effective when the input is rich in spectral content, we employ a broadband excitation protocol in which the subjects breathe according to a sequence of randomly spaced auditory tones (with a mean of five seconds and a range of one to fifteen seconds) [2]. Finally, note that E_{lv}^{max} may vary over the analysis interval due to the baroreflex. Thus, system identification essentially determines the average $C_a E_{lv}^{max}$ value over this interval.

We specifically analyze six-minute intervals of the P_a and P_{th} signals measured during random-interval breathing and sampled at 90 Hz. To quantify the direct capacitive effects during both systole and diastole, we separate the measurements into systolic and diastolic signals as follows. First, we remove the pulsatile component (*i.e.*, HR variability) from the P_a signal according to a previous technique [4]. Then, we determine the average values of this signal during systole and diastole for each beat. These two steps produce systolic P_a (P_a^s) and diastolic P_a (P_a^d) beat sequences, which are both independent of HR. Next, we likewise determine the average values of the P_{th} signal over systole and diastole for each beat. This step produces systolic P_{th} (P_{th}^s) and diastolic P_{th} beat sequences (P_{th}^d). Then, we remove the mean values from the four beat sequences and resample them to 1.5 Hz time series.

To estimate the immediate P_a change with respect to its mean value in response to a change in P_{th} with respect to its mean value during systole, we utilize the following three-input autoregressive moving average (ARMA) equation:

$$P_a^s(t) = \sum_{i=1}^{o} a_i P_a^s(t-i) + \sum_{i=1}^{p} b_i P_a^d(t-i) + \sum_{i=0}^{q} c_i P_{th}^s(t-i) + \sum_{i=1}^{r} d_i P_{th}^d(t-i) + w_s(t) \quad (3)$$

where $\{a_i, b_i, c_i, d_i\}$ are sets of unknown parameters, o, p, q, and r limit the number of parameters in the model (model order), and w_s is an unobserved noise term. The parameters are estimated from the processed P_a and P_{th} signals according to the linear least squares method, while the model order is chosen by minimizing the Final Prediction Error [8]. The resulting estimate of c_0 specifically indicates the immediate P_a response to a unit change in P_{th} during systole. To estimate the immediate P_a change with respect to its mean value in response to a change in P_{th} with respect to its mean value during diastole, we likewise identify the following three-input ARMA equation:

$$P_a^d(t) = \sum_{i=1}^{s} e_i P_a^d(t-i) + \sum_{i=0}^{u} f_i P_a^s(t-i) + \sum_{i=0}^{v} g_i P_{th}^d(t-i) + \sum_{i=0}^{y} h_i P_{th}^s(t-i) + w_d(t) \quad (4)$$

where g_0 represents the immediate P_a response to a unit change in P_{th} during diastole. From Equations (1) and (2), $C_a E_{lv}^{max}$ may be computed from c_0 and g_0 as follows:

$$C_a E_{lv}^{max} = \frac{1 - c_0}{c_0 - g_0}. \quad (5)$$

3. Theoretical evaluation

We theoretically evaluated the technique based on a human cardiovascular model that we developed and demonstrated to generate realistic short-term, beat-to-beat variability [3]. Briefly, the major components of the model are a heart and circulation, a short-term regulatory system, and resting perturbations. The heart and circulation include contracting left and right ventricles, system arteries and veins, and pulmonary arteries and veins. The short-term regulatory system consists of the arterial and cardiopulmonary baroreflex systems and a

direct neural coupling between respiration and HR. The resting perturbations include respiratory activity and stochastic representations of the autoregulation of local vascular beds and *1/f* HR fluctuations. The model-generated signals are also corrupted with Gaussian white noise to model measurement noise. Finally, we conducted Monte Carlo simulations to establish the mean and 95% confidence intervals of the $C_a E_{lv}^{max}$ estimates.

4. The technique

Figure 2 illustrates the $C_a E_{lv}^{max}$ estimates (mean (X) ± 95% confidence intervals (bar)) obtained by applying the technique to the model P_a and P_{th} signals during simulated random-interval breathing plotted against the actual model E_{lv}^{max} values. The O symbol indicates the actual $C_a E_{lv}^{max}$ model values. This figure demonstrates that the technique is able to estimate $C_a E_{lv}^{max}$ with little bias and can detect actual changes to the model E_{lv}^{max}. Moreover, the technique is more reliable at smaller values of E_{lv}^{max}, which may be desirable in the context of heart failure monitoring. Finally, we note that the technique may also be employed without separating P_a and P_{th} into systolic and diastolic components. In this way, the sensitivity in detecting E_{lv}^{max} changes is enhanced (as fewer parameters are needed for estimation); however, the estimated quantity is not $C_a E_{lv}^{max}$ but rather what may be thought of as some average of Equations (1) and (2).

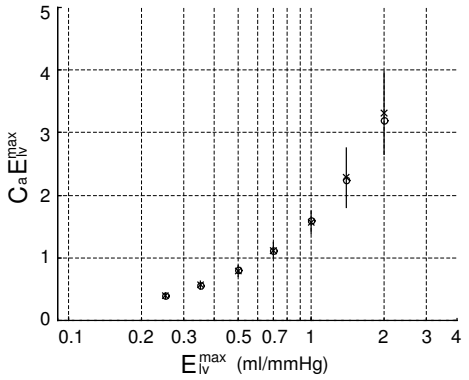

Figure 2. Estimated $C_a E_{lv}^{max}$ from the cardiovascular model vs. the actual E_{lv}^{max} values. See text for details.

5. Summary and conclusions

In summary, we have presented a new, minimally invasive technique for monitoring changes in left ventricular contractility in terms of E_{lv}^{max} from only respiratory-induced P_a variations obtained during a random-interval breathing protocol. While we have described the technique in the context of negative pressure breathing, in principle, it could also be applied to patients under programmable mechanical ventilation. We also have demonstrated the validity of the technique with respect to a realistic human cardiovascular model. Importantly, this precise theoretical validation could not have been achieved in an experimental model in which all of the actual parameter values would be difficult to ascertain. The theoretical validation justifies and promotes experimental testing of the technique against the traditional method for measuring E_{lv}^{max} during different levels of ventricular contractile state. We indeed plan to conduct such testing with the ultimate aim of establishing a clinical technique that helps guide therapy in heart failure patients.

Acknowledgements

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