Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Continuous Left Ventricular Ejection Fraction Monitoring by Central Aortic Pressure Waveform Analysis

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***Abstract*—Left ventricular ejection fraction (EF) is perhaps the most clinically significant index of global ventricular function. EF is measured in clinical practice via imaging methods such as echocardiography. However, these methods generally require a well-trained operator and expensive capital equipment. Thus, EF measurements are only obtained in the clinical setting and are usually made few and far between. To expand the measurement of this critical hemodynamic variable, our overarching hypothesis is that EF may be continuously (*i.e.*, automatically) monitored by mathematical analysis of routinely measured blood pressure waveforms. Here, we introduce a novel technique for estimating the absolute EF by model-based analysis of only a central aortic pressure (CAP) waveform. We then demonstrate the validity of the technique with respect to five conscious dogs in which reference EF was independently measured before and after chronic pacing induced heart failure. With further successful testing, the technique may potentially be utilized for continuous EF monitoring in research and clinical settings in which an aortic catheter is employed as well as for ambulatory EF monitoring in conjunction with recently developed implantable devices for measuring CAP.**

I. Introduction

LEFT ventricular ejection fraction (EF) – the ratio of the stroke volume (SV) to the left ventricular end-diastolic volume (EDV) – is perhaps the most clinically significant index of global ventricular function [1]. For example, epidemiological data have shown a powerful curvilinear relationship between EF and outcome in outpatients with heart failure [2]. Moreover, an EF of less than or equal to 30% has recently been recommended for determining which post-myocardial infarction patients should be implanted with a potentially life-saving, but very expensive, defibrillator [3].

Several methods are available for measuring EF or ventricular volume from which EF may be trivially computed. In clinical practice, EF is determined by imaging the left ventricular volume [4]. Perhaps, the most commonly used imaging method is trans-thoracic echocardiography, which is totally non-invasive. However, imaging methods generally share the major disadvantages of requiring a well-trained operator as well as bulky and expensive equipment. Thus, EF measurements are only obtained in the clinical setting and are usually made few and far between (*e.g.*, days to months). While a few methods have been introduced for continuous (*i.e.*, automatic) monitoring of left ventricular volume (*e.g.*, non-imaging nuclear monitoring [5], conductance catheter [6], and sonomicrometry [7]), these methods suffer from significant limitations (*e.g.*, high level of invasiveness) that have prevented them from replacing or even complementing imaging methods in clinical practice. A convenient method for continuous EF monitoring with a level of invasiveness suitable for clinical application is therefore needed to expand the measurement of this critical hemodynamic variable.

To this end, our overarching hypothesis is that EF may be continuously monitored by mathematical analysis of routinely measured blood pressure waveforms. Here, we specifically introduce a novel technique to estimate absolute EF by model-based analysis of only a central aortic pressure (CAP) waveform. We then demonstrate the validity of the technique with respect to five conscious dogs in which reference EF was independently measured before and after chronic pacing induced heart failure.

II. Model-Based Analysis Technique

Our technique for continuously monitoring EF is generally implemented according to the following three steps. First, a CAP waveform is measured and sampled using any of the available methods. Then, the parameters of a circulatory model are estimated to within a proportionality constant by fitting the model to the CAP samples. Finally, absolute EF is computed from the proportional left ventricular parameter estimates and the CAP samples.

The CAP samples are specifically fitted with the lumped parameter model of the left ventricle (lv) and arteries (a) shown in Fig. 1 in electrical analog form, where voltage is analogous to pressure (P), charge, to volume (V), and current to flow rate. This model may indeed be able to

Manuscript received April 3, 2006. This work was supported by the NHLBI Grant HL-55473 and an award from the AHA.

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provide a good approximation of CAP, as the confounding effects of wave reflections in the central aorta are relatively small [8]. For example, consistent with the model prediction, the diastolic intervals of experimental CAP waveforms have been shown to resemble pure exponential decays [9]. In particular, in the circulatory model, the left ventricle is represented with the well-known variable elastance (E or capacitance C = 1/E) model whose elastance oscillates over time (t) so as to drive the flow of blood [10]. The left ventricular outflow (aortic) valve is modeled by an ideal diode in order to ensure uni-directional blood flow. The arteries are represented with a Windkessel model accounting for the volume storage capacity of the large arteries and the resistance (R) to flow of the small arteries [8]. In addition to a capacitance, the left ventricle and large arteries are parameterized with an unstressed (0) volume (*i.e.*, zero-pressure filling volume). Key assumptions underlying the model are that its parameters are constant over each cardiac cycle (*e.g.*, C_a has been shown to be nearly constant over a wide pressure range and on the time scale of months to years [9][10]) and that aortic stenosis is absent (*i.e.*, $P(t)=P_{lv}(t)=P_a(t)$ during the systolic ejection phase). The dynamic equation governing the model during the systolic ejection phase is therefore given as follows:

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

where $\tau=R_aC_a$, while t = bs and t = es respectively denote the beginning and end of the systolic ejection phase.

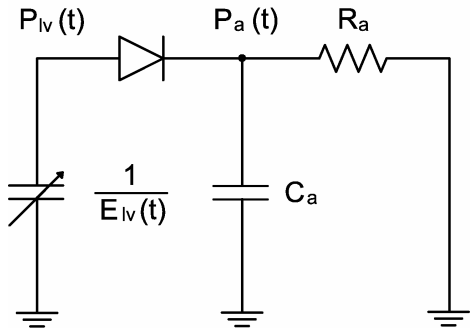

Fig. 1. Lumped parameter model of the left ventricle (lv) and arteries (a) in electrical analog form. P is pressure; E, elastance; C = 1/E, capacitance; R, resistance, and t, time.

To fit the model to the CAP samples so as to estimate its parameters, Equation (1) is discretized by approximation of the integral via the trapezoidal formula as follows:

$$\frac{P(0)}{C_a E_{lv}(0)} - \frac{P(nT)}{C_a E_{lv}(nT)} = P(nT) - P(0) + \frac{T}{2\tau}\sum_{k=1}^{n}(P(kT) + P((k-1)T), \qquad 1 < n \le N. \tag{2}$$

Here, T is the sampling period, n = 0 corresponds to the first sample in the systolic ejection phase for which t > bs, and n = N corresponds to the last sample in the systolic ejection phase for which t ≤ es. The sampling period T and the CAP samples P(nT) for 0 ≤ n ≤ N are known (through measurement and sampling), while the proportional model parameters, τ and $C_aE_{lv}(nT)$ for 0 ≤ n ≤ N (with proportionality constant C_a), are unknown. It is evident that Equation (2) does not provide a basis for uniquely determining the unknown parameters from the known CAP samples, as it represents an underdetermined set of equations with N equations and N+2 unknowns.

Thus, a further assumption of the model of Fig. 1 is a specific parametric function that succinctly characterizes the temporal evolution of $E_{lv}(t)$ over each cardiac cycle so as to result in a solvable (*i.e.*, overdetermined) set of equations. This assumption is based on the compelling experimental and computational studies of Senzaki et al. [12] and Heldt et al. [13]. Senzaki et al. specifically showed that experimentally measured, time-varying ventricular elastance functions, normalized both in amplitude and time, are "remarkably consistent" in 87 patients despite extremely wide variations in their ventricular state. Heldt et al. subsequently demonstrated that these normalized experimental elastance data could be well represented, especially during the systolic ejection phase (*i.e.*, the higher normalized elastance range), with the following parametric raised cosine function:

$$\frac{E_{lv}(t)}{E_{\max}} = \begin{cases} \frac{E_{\min}}{E_{\max}} + \frac{E_{\max}-E_{\min}}{2E_{\max}}\left\{1-\cos\left(\frac{\pi t}{T_s}\right)\right\}, & 0 \le t < T_s \\ \frac{E_{\min}}{E_{\max}} + \frac{E_{\max}-E_{\min}}{2E_{\max}}\left\{1+\cos\left(\frac{2\pi(t-T_s)}{T_s}\right)\right\}, & T_s \le t < \frac{3}{2}T_s \\ \frac{E_{\min}}{E_{\max}}, & \frac{3}{2}T_s \le t, \end{cases} \tag{3}$$

where E_{max} and E_{min} are parameters respectively representing the maximum and minimum ventricular elastances over a cardiac cycle, and T_s is a parameter indicating the time duration to reach E_{max} from E_{min} (see Fig. 2). Substituting Equation (3) into Equation (2) reduces the number of unknown parameters to five (τ, C_aE_{max}, C_aE_{min}, $C_aE_{lv}(0)$, and T_s). Additionally, C_aE_{min} is assumed to be equal to $0.05\cdot C_aE_{max}$ so as to further reduce the number of unknown parameters to four. This assumption is based on the data in Fig. 2 and the fact that the estimation of C_aE_{min} is likely to be unreliable here, as it would essentially be based on an extrapolation. That is, C_aE_{min} is not directly "seen" by CAP.

The four unknown parameters are specifically estimated on a beat-to-beat basis in two steps. In the first step, τ is estimated from each diastolic interval of the CAP samples. More specifically, the model of Fig. 1 predicts that CAP should decay like a pure exponential during each diastolic interval with a time constant equal to τ. Thus, τ is determined by least squares fitting of a mono-exponential function to each diastolic CAP interval. Optimal fitting is

achieved analytically after log transformation of the diastolic CAP samples. In the second step, the estimated value of τ is plugged into Equation (2), and the three left ventricular parameters (C_aE_{max}, $C_aE_{lv}(0)$, and T_s) are estimated by least squares fitting of the resulting equation to each systolic ejection interval of the CAP samples. Optimal fitting is achieved via a two-dimensional numerical search, as the fitting equation here is linear in the parameter C_aE_{max}.

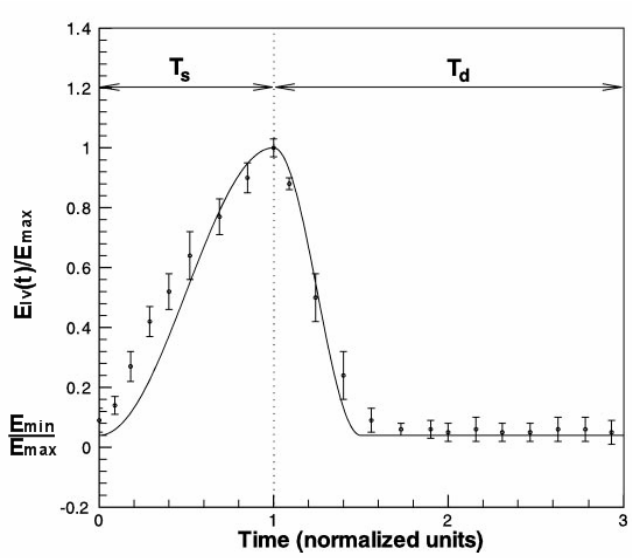

Fig. 2. Time-varying left ventricular elastance function $E_{lv}(t)$, normalized in time by T_s and in amplitude by E_{max}. The discrete-time data (dots with bars) represent group average experimental data from 87 human subjects with a wide variety of cardiac states [12], while the continuous-time function is a plot of the parametric raised cosine function given in Equation (3). Adapted from [13].

With the resulting proportional, parametric left ventricular elastance function estimate during the systolic ejection phase, $C_aE_{lv}(nT)$ for $0 \le n \le N$, and the CAP samples P(t), absolute EF is computed (through cancellation of the proportionality constant C_a) based on the following equation:

$$EF = \frac{\frac{SV}{C_a}}{\frac{EDV}{C_a}} = \frac{\frac{P(0)}{C_aE_{lv}(0)} - \frac{P(NT)}{C_aE_{lv}(NT)}}{\frac{P(0)}{C_aE_{lv}(0)} + \frac{V_{lv0}}{C_a}} \qquad (4)$$

Note that V_{lv0}/C_a in this equation, which represents proportional, unstressed ventricular volume, is not estimated from the CAP samples. However, this parameter is normally much smaller than EDV/C_a (*e.g.*, about a magnitude smaller) [14][15]. Thus, V_{lv0}/C_a may be assumed to be zero or, as done here, set equal to a nominal value reported in the literature so as to reduce any estimation bias.

Alternatively, V_{lv0}/C_a may be measured by first obtaining an independent measurement of EF via imaging and then finding the value of V_{lv0}/C_a that makes the EF estimated from the CAP samples equal to the independent EF measurement. In this case, the value determined for V_{lv0}/C_a may be utilized to compute subsequent EF estimates by CAP waveform analysis, and large changes in these EF estimates over time may, in turn, suggest when to re-image the heart. This alternative approach may be preferred in patients with dilated cardiomyopathy. It may also be possible that the ratio of SV to stressed EDV (*i.e.*, $V_{lv0}/C_a = 0$) could be a more valuable indicator of global ventricular function.

III. Methods

A. Experimental Procedures

The hemodynamic data utilized here to evaluate the model-based analysis technique were originally collected to address different specific aims, and much of the materials and methods are presented in detail elsewhere [16]. We briefly describe below the most basic aspects of the experimental procedures that were relevant to the present study. All procedures were reviewed and approved by the Wayne State University Animal Investigation Committee.

Five adult mongrel dogs (20-25 kg) of either gender were studied as follows. Chronic instrumentation was installed in each dog including a catheter in the aorta for CAP, an ultrasonic flow probe around the ascending aorta for SV, two pairs of sonomicrometry crystals on the opposite sides of the endocardium for left ventricular volume (via a geometric assumption), and three stainless steel electrodes on the right ventricular free wall for ventricular pacing. After recovery from the surgery, the hemodynamic data were continuously recorded and sampled at 300 Hz while the dog was standing quietly. Then, a chronic pacing protocol was initiated (to induce heart failure and thereby reduce EF) in which the ventricular pacing rate was set to 240-250 bpm for a period of three to four weeks. Finally, the hemodynamic data were again collected as described above.

B. Data Analysis

To benchmark technique performance, the mathematical analysis was applied to a 30 to 90 second segment of the measured and sampled CAP waveform from each dog in which the diastolic intervals visually resembled exponential decays. EF was computed for each beat in each analyzed segment with V_{lv0}/C_a set to 10 mmHg in accordance with data from the literature [9][10]. The beat-to-beat EF estimates were then averaged over each analyzed segment. For comparison, reference average EF over the same time segment was independently obtained by dividing the average SV via the aortic flow probe with the average EDV via sonomicrometry.

IV. Results

Fig. 3 shows examples of the analyzed CAP waveform segments from two of the studied dogs. Fig. 4 illustrates the average EF estimated by applying the technique to the CAP waveform segments plotted against reference EF from all five dogs. These results indicate that the technique, in general, agrees quite well with the much more invasive reference method. Moreover, this close agreement was obtained even though the analyzed CAP waveform segments did not always possess perfect exponential diastolic decays.

The technique did consistently overestimate EF following the chronic pacing, perhaps because of an increase in V_{lv0}/C_a due to ventricular dilatation. Importantly, however, the overestimation was small enough that the technique was still able to detect a significant reduction in EF caused by the chronic pacing.

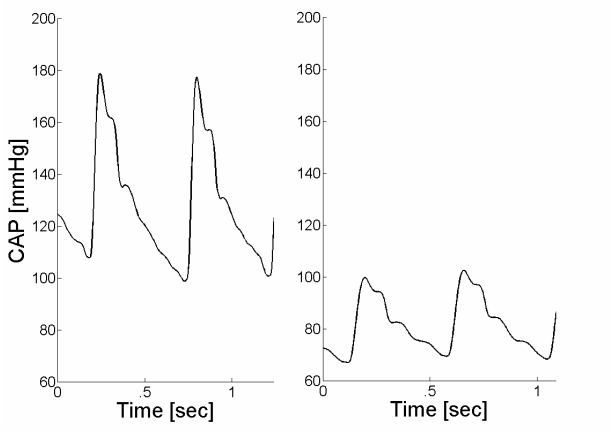

Fig. 3. Examples of the measured and analyzed central aortic pressure (CAP) waveform segments from two of the studied dogs.

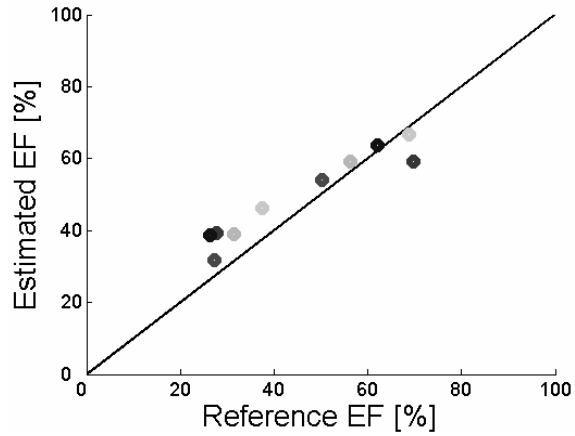

Fig. 4. Summary of the results for all five of the studied dogs in which absolute left ventricular ejection fraction (EF) estimated by applying the mathematical analysis technique to the measured central aortic pressure waveform segments is plotted against reference EF obtained from simultaneous aortic flow probe and sonomicrometry measurements.

V. Summary and Conclusions

In summary, we have introduced a novel technique for estimating the absolute EF by model-based analysis of only a CAP waveform. We have demonstrated the validity of the technique with respect to five conscious dogs in which reference EF was independently measured before and after chronic pacing induced heart failure. With further successful animal and human testing, the technique may potentially be utilized in lieu of, or at least as a complement to, imaging methods so as to permit continuous EF monitoring in research and clinical settings in which an aortic catheter is employed as well as for ambulatory EF monitoring in conjunction with recently developed implantable devices for measuring CAP [17]. Finally, we note that the clinical applicability of the technique may be further expanded, by future adaptation of the technique to more readily available peripheral arterial pressure waveforms.

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