Towards a better description of cardiovascular function in pulmonary hypertension
Kind, T.

2012

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)

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Download date: 05. Jun. 2022
Cardiac phase-dependent time normalization reduces load dependence of time-varying elastance

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Abstract

The time-varying elastance concept provides a comprehensive description of the intrinsic mechanical properties of the left ventricle that are assumed to be load independent. Based on pressure-volume measurements obtained with combined pressure conductance catheterization in six open-chest anesthetized sheep, we show that the time to reach end systole (defined as maximal elastance) is progressively prolonged for increasing ventricle pressures, which challenges the original (load-independent) time-varying elastance concept. Therefore, we developed a method that takes into account load dependency by normalization of time course of the four cardiac phases (isovolumic contraction, ejection, isovolumic relaxation, filling) individually. With this normalization, isophase lines are obtained that connect points in pressure-volume loops of different beats at the same relative time in each of the four cardiac phases, instead of isochrones which share points at the same time in a cardiac cycle. The results demonstrate that pressure curves can be predicted with higher accuracy if elastance curves are estimated using isophase lines instead of using isochrones [root-mean-square error (RMSE): 3.8 ± 1.0 vs. 14.0 ± 7.4 mmHg (p<0.001), and variance accounted for (VAF): 94.8 ± 1.3% vs. 78.6 ± 14.8% (p<0.001)]. Similar results were found when the intercept volume was assumed to be time-varying [(RMSE: 1.7 ± 0.3 vs. 13.4 ± 7.4 mmHg (p<0.001), and VAF: 97.4 ± 0.5% vs. 81.8 ± 15.5% (p<0.001)]. In conclusion, phase-dependent time normalization reduces cardiac load dependency of timing and increases accuracy in estimating time-varying elastance.

Key Words: ventricular loading ■ cardiac time course ■ isochrones ■ isophase lines
Time normalization improves estimation of elastance

Introduction

CARDIAC PUMP FUNCTION is essential to provide oxygen and nutrients to tissues. Changes, and especially a decrease, in pump function may be life threatening. Quantification of pump function in health and disease is, therefore, of great importance. Factors that affect pump function are heart rate, ventricular filling, conduction velocity, and myocardial contractility. Ventricular pressure-volume (P-V) loops provide a useful basis to describe pump function. Although the basic concepts were originally introduced by Roy\(^1\) and Frank\(^2\); it was Suga and Sagawa in the 1970s who introduced a quantitative description of pump function based on P-V loops, using the time-varying elastance \([E(t)]\), defined as: \(P(t)=E(t)\cdot[V(t)-V_0]\), where \(P(t)\) is ventricular pressure, \(V(t)\) is ventricular volume, and \(V_0\) a constant intercept volume\(^3,4\). \(E(t)\) as a measure for pump function, was shown to be practically independent of loading conditions in the physiological range and to be sensitive to inotropic interventions\(^4\). In particular, it was shown that the end-systolic P-V relation (ESPVR) is a sensitive and load-independent parameter of contractility.

A prerequisite for the elastance concept is that isochrone lines that connect equal time points in a P-V diagram of different beats (acquired under different loading conditions) can be described by linear relations. However, measurements in mice\(^5\), rats\(^6\) and dogs\(^7-9\) show that isochrones and also the ESPVR are generally nonlinear and that the degree of nonlinearity depends on the contractile state.

In addition, studies investigating the length-tension relationship of mammalian papillary muscle showed that the time-course of isometric and isotonic contraction vary significantly\(^10-16\). This indicates load dependence of the time course of contraction.

At the ventricular level, Hunter\(^17\) showed that, in ejecting beats with ejection fractions ranging between 30 to 50%, the systolic period is considerably prolonged compared with the first isovolumic beat after clamping at end-systolic volume. In the intact ventricle, this phenomenon has also been observed by Burkhoff et al.\(^18\). Thus not only are isochrones nonlinear, but also the cardiac timing appears load dependent.

Therefore, this study aims at finding a load-independent description (in terms of the time course of contraction) of cardiac pump function. To this end, we introduce the term isophase line that connects points in P-V loops of different beats at the same relative time in each of the four cardiac phases (isovolumic contraction, ejection, isovolumic relaxation, and diastolic filling), in contrast to isochrone lines that mark points at the same time in a cardiac cycle. In fact, the concept of isophase lines is not completely new, since the ESPVR is an isophase line as well. The analysis reveals that this time normalization reduces the influence of loading on the time course in a P-V diagram, which allows better estimation of \(E(t)\), and is therefore a better method to derive a load-independent description of cardiac pump function.
Methods

Experimental setup

For this study, we used pressure and volume data that were earlier measured for a study of Staal et al.\textsuperscript{19}. Data were measured in six sheep (35.0-40.6 kg) during left heart conductance catheterization. During the procedure, preload was gradually reduced by balloon occlusion of the vena cava inferior. Heart rate was kept constant by pacing the right atrium (range 58-91 beats/min). In each sheep, 9-14 beats were recorded. Volume was calibrated by thermodilution in the pulmonary artery and parallel conductance was assessed by the hypertonic saline method\textsuperscript{20}. Left ventricular (LV) volume and pressure and an ECG lead were sampled at a frequency of 250 Hz using a Leycom Sigma 5 signal processor (CDLeycom, Zoetermeer, The Netherlands).

Time-normalization through isophase lines

We first divide each heartbeat in four cardiac phases: isovolumic contraction, ejection, isovolumic relaxation and diastolic filling. We assume that a corner point of the $P$-$V$ loop marks a phase transition between these periods (Figure 1; corner point detection is explained in the next paragraph). The upper right and left corner points of a $P$-$V$ loop mark the start and end of ejection, respectively. Equivalently, the lower left and right corner points mark the start and end of filling, respectively. To obtain isophase lines, pressure, $P(t)$ and $V(t)$ recordings are resampled for each of the four cardiac phases individually. The duration of the phases that will be resampled is determined by a reference beat, which is assumed here to be the first beat measured before loading conditions are altered. Missing data points are constructed by linear interpolation. After this time

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{p-v-loop.png}
\caption{Typical $P$-$V$ loops measured in a sheep (sheep 1 in Table 1). Dots at $P$-$V$ corner points indicate, in reversed clockwise order from right below, start of isovolumic contraction, ejection, isovolumic relaxation and filling phase. These points are also called isophase points since which mark the same relative time in each cardiac phase.}
\end{figure}
Time normalization improves estimation of elastance

normalization each phase of each beat contains the same number of data points and has the same duration in time, namely that of the corresponding phase of the reference beat (illustrated in Figure 2). The advantage of this normalization is that any sample point in a given beat corresponds to the same sample point in the reference beat. It should be noted that this time normalization does not affect the shape of the $P$-$V$ loops, since time is only a parameter. In contrast, the shape of isochrones is not necessarily the same as the shape of the isophase lines. For example, if pressure and volume are plotted both as a function of time and as a function of normalized time, isochrones turn from vertical lines into oblique lines, while the reverse holds for the isophase lines (Figure 2).

![Figure 2 - Pressure and volume as a function of original (A and C) and normalized time (B and D). Data are from sheep 1 and 7 beats (out of 14) are shown. The first beat (thick line) is measured before altering the preload and represents the reference beat. After resampling, each phase of each beat contains the same number of data points as the corresponding phase of the reference beat. $t = 0$ s corresponds to the moment of the R wave of the ECG. Note that, before normalization, isochrones are vertical and isophase lines are oblique, whereas, after normalization, the reverse holds true.](image-url)
Automatic corner point detection

Corner points are detected for all four quadrants in a PV-loop, with the origin equal to the centroid of a PV-loop \([P_{\text{cent}}, V_{\text{cent}}]\). To this end, pressure and volume are normalized for their dimension, and, subsequently, the distance \(d(t)\) of each point in a given quadrant to the centroid is determined by:

\[
d(t_i) = \sqrt{\left(\frac{V(t_i) - V_{\text{cent}}}{\Delta V}\right)^2 + \left(\frac{P(t_i) - P_{\text{cent}}}{\Delta P}\right)^2}
\]

where \(\Delta V = V_{\text{max}} - V_{\text{min}}\) and \(\Delta P = P_{\text{max}} - P_{\text{min}}\).

Next, a corner point is obtained when the distance between the normalized PV-coordinates and the centroid is maximal, denoted as \(\max_{t_i} d(t_i)\).

Estimation of time-varying elastance

\(E(t)\) is estimated for two different formulations and computed both from the original and from the time-normalized data. First, the conventional \(E(t)\) model with constant intercept \(V_0\) is used. \(V_0\) is obtained by linear regression of ESPVR, followed by extrapolation to determine the intercept with the volume axis. Subsequently, \(E(t)\) is estimated from linear regression of all isochrones, through \(V_0\). Note that ESPVR is defined by the upper left corner points of the \(P-V\) loops and that it does not necessarily coincide with an isochrone. Second, a modified \(E(t)\) model is used in which the volume intercept \(V_0(t)\) is allowed to vary with time. This formulation was previously explained in a theoretical study by Drzewiecki et al.\(^{21}\) and later also suggested by Segers et al.\(^{22}\) and Claessens et al.\(^{5}\) Again, unconstrained linear regression was applied to isochrones to obtain elastance. For time-normalized data, the isophase lines are analyzed in the same way as the isochrones. Again, a constant intercept volume and a time varying intercept volume are used for the description.

P-V loops and denormalization

With the elastance estimated from isochrones/isophase lines, the (constant or time-varying) intercept volume and measured volume, pressure curves can be predicted using the elastance formulations, as discussed in the previous paragraph. Subsequently, these curves can be transformed back to original time. Since the absolute durations of all cardiac phase are known in advance (i.e. from start and end points of corner points, see Figure 1 and Figure 2), the curves can be easily “denormalized” to these periods by resampling.
Data analysis

**Linearity of the isochrone and isophase lines**
To investigate whether time normalization enhances or attenuates nonlinearity of isochrones, we compare the root-mean-square error (RMSE) of fitted isochrones and isophase lines by linear regression. The RMSE is defined as:

$$
\text{RMSE} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (P_{\text{meas}}(t_i) - P_{\text{est}}(t_i))^2}
$$

where $N$ is the total number of samples in a pressure curve and $P_{\text{meas}}(t_i)$ and $P_{\text{est}}(t_i)$ are the measured and estimated pressures, respectively. Note that $t_i$ represents either original or normalized time. We additionally assessed the “variance accounted for” (VAF) to evaluate the percentage of accounted variance for linearity, defined as:

$$
\text{VAF} = 1 - \frac{\frac{1}{N} \sum_{i=1}^{N} ||P_{\text{meas}}(t_i) - P_{\text{est}}(t_i)||_2^2}{\frac{1}{N} \sum_{i=1}^{N} ||P_{\text{meas}}(t_i)||_2^2} \cdot 100\
$$

In this expression, a VAF of 100% indicates a zero prediction error of pressure. For other predictions the VAF will be lower. Thus the more non-linear the isochrones/isophase lines are, the lower the VAF of fitted isochrones/isophase lines.

**Time-varying elastance**
When $V_0$ or $V_0(t)$ are known (i.e. estimated by linear regression of the ESPVR) it is possible to apply the elastance models on a single pressure-volume loop. This results in a “single-beat” elastance curve $E_i(t)$ or $E_i(t_N)$, where $i$ is the beat number, and $E_i(t)$ and

### Table 1 - Characteristics of all sheep.

<table>
<thead>
<tr>
<th>Sheep No.</th>
<th>Cardiac cycles, no</th>
<th>Heart rate, beats/min</th>
<th>End-diastolic $P_{\text{LV}}$, mmHg</th>
<th>End-systolic $P_{\text{LV}}$, mmHg</th>
<th>End-diastolic $V_{\text{LV}}$, ml</th>
<th>Stroke volume, ml</th>
<th>Ejection Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>83.4 ± 0.3</td>
<td>13.5 ± 4.1</td>
<td>92.5 ± 9.5</td>
<td>66.6 ± 19.6</td>
<td>34.5 ± 10.8</td>
<td>0.52 ± 0.02</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>78.2 ± 1.1</td>
<td>10.7 ± 5.1</td>
<td>85.0 ± 11.8</td>
<td>60.6 ± 23.2</td>
<td>29.3 ± 11.7</td>
<td>0.48 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>57.8 ± 0.3</td>
<td>13.8 ± 2.3</td>
<td>75.7 ± 9.4</td>
<td>58.4 ± 13.4</td>
<td>26.9 ± 6.5</td>
<td>0.46 ± 0.01</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>90.8 ± 0.8</td>
<td>11.6 ± 1.3</td>
<td>77.1 ± 9.1</td>
<td>33.4 ± 11.5</td>
<td>13.3 ± 4.8</td>
<td>0.40 ± 0.04</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>84.9 ± 2.4</td>
<td>9.3 ± 4.0</td>
<td>90.1 ± 12.3</td>
<td>60.1 ± 19.5</td>
<td>26.3 ± 12.3</td>
<td>0.44 ± 0.07</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>67.5 ± 0.1</td>
<td>13.2 ± 4.1</td>
<td>81.9 ± 4.3</td>
<td>48.7 ± 10.3</td>
<td>20.9 ± 4.0</td>
<td>0.43 ± 0.02</td>
</tr>
</tbody>
</table>

Values are mean ± SD, with the average over all cardiac cycles. HR = heart rate; $P_{\text{LV}}$ = left ventricle pressure; $V_{\text{LV}}$ = left ventricular volume.
$E_i(t, N)$ are the estimates for isochrones and isophase lines, respectively. Obviously, the shapes of these “single-beat” elastance curves are slightly different from the elastance curve obtained by linear regression of all beats (as explained in the previous paragraph). The differences between these single-beat elastance curves and the “regressed” elastance curve can be expressed as a residual error and thus is a measure of accuracy. This can be understood to consider that the smaller the residual error the better the “regressed” elastance describes the pressure-volume relationship. In the following, we will only mention elastance if we consider the “regressed” elastance.

The effect of normalization on elastance is investigated by comparison of the residual error. The shapes of the elastance curves are qualitatively compared.

**Pressure predictions**

Predicted pressure curves from estimated elastance, intercept volume and measured volume curves are compared with measured pressure curves. Also here, RMSE and the VAF are used as an overall measure of the goodness of fit for a complete heart cycle.

**Results**

Table 1 summarizes the sheep hemodynamic data. The heart rate showed negligible variation within individual sheep, because hearts were paced at a constant rate.

**Normalization**

The effect of normalization is shown in Figure 2. Figure 2 A and C show the original $P-V$ measurements before normalization. This figure shows that a decrease in pre-load is reflected by a shortening of the ejection. On the other hand, the duration of the filling phase and to a lesser extend isovolumic relaxation, is reduced. Total total duration of the cardiac cycle is constant for all beats because the hearts were paced. The isovolumic contraction is hardly affected by preload. Note that the times of end-systole (i.e. isophase points) do not coincide with isochrone points, which lie on a vertical line before normalization. Figure 2 B and C show the same $P-V$ loops, but at a normalized time basis.

**Isochrones and isophase lines**

Figure 3 shows some examples of isochrone and isophase lines in a $P-V$ diagram obtained with the $P-V$ data from Figure 2. This figure illustrates that, although normalization affects the shape of pressure and volume individually, it does not affect the form of a $P-V$ loop because in a $P-V$ loop time is only a parameter. It appears that the largest difference in form between isochrones and isophase lines is found during the isovolumic relaxation.
Time normalization improves estimation of elastance

Figure 3 - Some examples of isochrones and isophase lines. Data are from sheep 1 and 7 beats (out of 14) are shown. Dots denote corresponding isochronal or isophasic points in the cardiac cycle. (A): original time; 6 isochrones are shown. Note that the points at the end of ejection are near, but not at, the left top corner. (B): normalized time: 6 isophase lines are shown. The figures illustrate that, although the time course (parameterization) differs, the shape of all P-V loops is equal.

Figure 4 - Examples of fitted isochrone and isophase lines using linear relations. The P-V loops and isochronal or isophasic points, denoted by dots, are the same as in Figure 3. Data are from sheep 1. Fitted linear isochrone and isophase lines are shown with \( V_0 \) constant (A and B) and for \( V(t) \) time-varying (C and D). Elastance (E) is equal to the tangent of a fitted linear isochrone or isophase line and the volume axes by definition and is shown in the panels. Note that the times of the isochrones and isophase lines are different.
phase. Moreover, the S-shaped isochrones during isovolumic relaxation change into almost straight isophase lines (Figure 3). Some examples of extrapolated isochrones and isophase lines are shown in Figure 4. The value of the fixed intercept \( V_0 \) is determined using the intercept of ESPVR and hence is equal for original time and normalized time (Table 2).

\[
\text{Table 2 - Estimation results for elastance formulations with } V_0 \text{ and } V_0(t) \text{ time-varying.}
\]

<table>
<thead>
<tr>
<th>Sheep No.</th>
<th>( V_0 ), ml</th>
<th>( E_{es} ), mmHg/ml</th>
<th>Mean ( V_0(t) ), ml</th>
<th>( E_{es} ), mmHg/ml</th>
<th>( V_0 ), ml</th>
<th>( E_{es} ), mmHg/ml</th>
<th>Mean ( V_0(t) ), ml</th>
<th>( E_{es} ), mmHg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-63</td>
<td>1.00 ± 0.04</td>
<td>-60</td>
<td>3.44 ± 1.16</td>
<td>-63</td>
<td>1.03 ± 0.01</td>
<td>-65</td>
<td>1.03 ± 0.01</td>
</tr>
<tr>
<td>2</td>
<td>-64</td>
<td>0.95 ± 0.05</td>
<td>-53</td>
<td>3.23 ± 1.49</td>
<td>-64</td>
<td>0.98 ± 0.03</td>
<td>-61</td>
<td>0.98 ± 0.03</td>
</tr>
<tr>
<td>3</td>
<td>-29</td>
<td>1.39 ± 0.06</td>
<td>-41</td>
<td>2.81 ± 0.38</td>
<td>-29</td>
<td>1.42 ± 0.03</td>
<td>-55</td>
<td>1.42 ± 0.03</td>
</tr>
<tr>
<td>4</td>
<td>-19</td>
<td>2.16 ± 0.05</td>
<td>-41</td>
<td>3.73 ± 0.42</td>
<td>-19</td>
<td>2.18 ± 0.04</td>
<td>-52</td>
<td>2.18 ± 0.04</td>
</tr>
<tr>
<td>5</td>
<td>-39</td>
<td>1.32 ± 0.06</td>
<td>-35</td>
<td>4.18 ± 1.11</td>
<td>-39</td>
<td>1.35 ± 0.04</td>
<td>-46</td>
<td>1.35 ± 0.04</td>
</tr>
<tr>
<td>6</td>
<td>-83</td>
<td>0.78 ± 0.01</td>
<td>-48</td>
<td>3.43 ± 0.15</td>
<td>-83</td>
<td>0.78 ± 0.01</td>
<td>-75</td>
<td>0.78 ± 0.01</td>
</tr>
<tr>
<td>mean</td>
<td>-49</td>
<td>1.27</td>
<td>-46</td>
<td>3.47</td>
<td>-49</td>
<td>1.29</td>
<td>-59</td>
<td>1.29</td>
</tr>
<tr>
<td>SD</td>
<td>25</td>
<td>0.5</td>
<td>9</td>
<td>0.46</td>
<td>25</td>
<td>0.5</td>
<td>10</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values are mean ± SD (ranges in parentheses), with the average over all cardiac cycles. Results are shown for original time and for normalized time. \( V_0 \) = constant intercept volume; \( V_0(t) \) = time-varying \( V_0 \); \( E_{es} \) = end-systolic elastance. \*Values of \( V_0 \) are equal for both original and normalized time, since these are computed using the end-systolic pressure-volume relationship in both situations. \( E_{es} \) is equal for the formulation with \( V_0 \) constant and for \( V_0(t) \) time-varying, if time is normalized since the end-systolic pressure-volume relationship is equal in both formulations.

Linearity of isochrones and isophase lines is also evaluated by the computed accounted variance for nonlinearity (VAF). Normalization results in a reduction of accounted variance for non-linearity during isovolumic relaxation from 10 to 5% when averaged for all sheep (\( p < 0.05 \); data not shown). Accounted variance for non-linearity around the ESPVR is reduced from 5 to 3% (\( p < 0.05 \); data not shown). Figure 4 also illustrates that the nonlinearity of isochrones is most pronounced during isovolumic relaxation.
Time normalization improves estimation of elastance

Time-varying elastance

Figure 6 displays elastance curves that are obtained by fitting linear isochrone and isophase points of one sheep. Examples are shown for $V_0$ constant ($A$ and $B$) and $V_0(t)$ time-varying ($C$, $D$, $E$, and $F$). The variation of $E(t)$, expressed as the residual error, is denoted with error bars (see methods for description). Observe that after time normalization, the residual error is considerably reduced, especially during isovolumic relaxation. Also, note from this figure that the end-systolic elastance is equal in the formulation with $V_0$ constant and with $V_0(t)$ time-varying, if time is normalized.

Pressure-volume loops

Figure 7 shows examples of reconstructed $P-V$ data for original time and time-normalized data. In these figures, pressure is predicted using the elastance curves from Figure 6 and
measured volume. Figure 8 shows the goodness of fit for all sheep evaluated using the RMSE and VAF. There is a significant difference in accuracy for normalized time vs. original time for the formulation with $V_0$ constant (VAF: $94.8 \pm 1.3$ vs. $78.6 \pm 14.8\%$, $p < 0.001$, and RMSE: $3.8 \pm 1.0$ versus $14.0 \pm 7.4$ mmHg, $p < 0.001$), and for the formulation with $V_0(t)$ time-varying (VAF: $97.4 \pm 0.5$ vs. $81.8 \pm 15.5\%$, $p < 0.001$, and RMSE: $1.7\pm0.3$ versus $13.4\pm7.4$ mmHg, $p < 0.001$).

Discussion

In this study we time-normalized pressure and volume data of the four cardiac phases individually. We showed that this normalization procedure increases the accuracy in estimating elastance and improves the analysis of ventricular pump function.

Load dependence

Several authors have reported various limitations of the conventional assumption of load-independence of elastance. It has been found that the load independence was violated, if loading conditions were strongly changed\(^2^4\). Also, nonlinearity of isochrones and especially the ESPVR became evident for large alterations of ventricle loading\(^8^,9\).

In the literature, however, load dependence of the duration of the different phases of contraction received less attention than other features of the cardiac cycle. Experiments in isolated cardiac muscle demonstrated that the time to reach end systole from start of contraction varies between afterloaded isotonic and isometric twitches\(^1^1^,1^3^,2^5^,2^8\). Elzinga and Westerhof\(^1^4\) studied isolated cat trabecula under conditions closely resembling muscle fibers in the LV wall and did the same observation. More specifically, they observed that a small amount of shortening, i.e. a high level of end-systolic pressure, lengthens the duration of ejection. At the ventricular level, it was Hunter\(^1^7\) who reported a significant prolongation of the systolic duration in ejecting beats with ejection fractions ranging between 30 and 50% compared with isovolumic beats. Later studies in isolated heart also showed that the time constant of relaxation was decreased in ejecting beats so that, despite the marked lengthening of the duration of systole, the overall duration of isovolumic and ejecting beats is approximately equal\(^1^8\). These phenomena are explained by the fact that ejection not only exerts negative inotropic effects on LV pressure (and thus also end-systolic elastance), but also exerts positive inotropic effects: excess end-systolic pressure and prolonged duration of systole. Hence, the net effect of ejection on end-systolic pressure and systolic duration is a balance between two opposing factors\(^1^7\).
Time normalization improves estimation of elastance

Figure 6 - Elastance curves and time-varying intercept volumes corresponding to sheep 1 (as in Figure 1 and 4). Elastance curves are estimated for original (A and C) and normalized time (B and D). (A and B): estimated elastance curves when isochrones and isophase lines are fitted by linear regression with $V_0$ constant. In this case, $V_0$ is determined using the end-systolic P-V relationship. (C and D): estimated elastance curves when $V_0(t)$ is time-varying. The magnified inset in (C) displays the upper part of the elastance curve (from 0.2 to 0.4 s) since the maximum elastance is significantly larger than if time is normalized (D). The residual error of estimated elastance curves is indicated with error bars. Note that, after normalization, the residual error decreases, especially during isovolumic relaxation. (E and F): the time course of $V_0(t)$, with average values and range given inside these panels.
Difference between afterload and preload interventions?

In our data of the intact heart, we demonstrated a prolongation of the systolic duration in ejecting beats for increasing ventricular pressures, whereas the duration of diastole is decreased. It should be realized that these data are obtained by interventions in ventricular preload. On the contrary, the experiments described in the previous paragraph were all studies with afterload interventions. To our knowledge, no studies have compared the effects of interventions of these different loading conditions on cardiac timing. Baan et al.\(^2\) compared the effect of changes in preload and afterload on end-systolic elastance and observed no statistical significant differences between these intervention. However, the time course of cardiac contraction was not taken into account. From our data, it appears that the impact of ejection on the time course corresponds to afterload intervened experiments, but it is not known whether the time course is primarily affected by changes in preload or that it is predominated by afterload effects. We assume that the same mechanisms as described in the previous paragraph play a role in the systolic duration.

**Figure 7 -** Examples of reconstructed P-V loops (data from sheep 1). Pressure curves are predicted using the estimated elastance curves from Figure 6, intercept volume and measured volume. Dashed lines: reconstructed P-V data; thin lines: measured P-V data. (A and C): original time; (B and D): normalized time; (A and B): \(V_0\) constant; (C and D): \(V(t)\) time-varying.
Normalization

Conventionally, elastance is estimated from isochrones. In our study, we estimate elastance from isophase lines that are obtained after time normalization of pressure and volume data. The advantage of isophase lines is that clear landmarks in a cardiac cycle, such as start of filling, start-ejection, and end systole, are on one isophase line and are independent of the duration of a cardiac phase. Note that the time normalization is a generalization of what is in fact common practice for the ESPVR. This measure of contractility is defined by the upper left corner points of the P-V loops and not by an isochrone.

We showed that normalization improves the uniqueness of the elastance since the variation is decreased (Figure 5 A and B and Figure 6 A and B), and show less variation compared with each other. In addition, normalization results in isophase lines that are straighter than isochrones (accounted variance for nonlinearity during isovolumic relaxation decreases from 10% for isochrones to 5% for isophase lines when averaged for all sheep, p < 0.05). Nonlinearity of the isochrones around the ESPVR, however, is less prominent in our data (accounted variance for non-linearity decreases from 5% for isochrones to 3% for isophase lines when averaged for all sheep, p < 0.05).

Our time-normalization process differs from that of Senzaki et al.30, since they normalized elastance curves for a whole cycle (both by peak and time to peak amplitude) and neglected the variation in timing of individual cardiac phases.

Figure 8 - Goodness of fit of predicted pressure curves evaluated using the root-mean-square-error (A) and the variance accounted for (B). Pressure is predicted using estimated elastance curves and intercept volume ($V_0$ constant or $V_0(t)$ time-varying) and measured volume. *p < 0.001 using a paired t-test after logarithm transformation.
Time varying $V_0(t)$

As already reported by previous authors\textsuperscript{5,21,22}, estimated linear isochrones (and we showed also isophase lines) do not intersect the volume axis at one point. The assumption of a constant $V_0$ will lead to over- or underestimation of elastance, depending on the moment in the cardiac cycle (Figure 4). Therefore, we also studied the effect of normalization on estimation of elastance when $V_0(t)$ is time-varying. It appears that, for normalized data, the variation of estimated elastance curves with $V_0(t)$ time-varying is much smaller compared with elastance curves when nonnormalized data is used (Figure 5 C and D, and Figure 6 C and D). Also, with these elastance curves, pressure curves can be predicted with higher accuracy (Figure 8). From these results, we can conclude that, also when $V_0(t)$ is time varying, a less load-dependent elastance curve will be obtained when $P$-$V$ data is normalized.

The time-varying $V_0(t)$ is first explained in a theoretical study of Drzewiecki et al.\textsuperscript{21} In their study, they modeled (nonlinear) isochrones by adding a passive and an active component. The passive component represents the elastic structure of the heart, which results in the passive function isochrone (passive $P$-$V$ relation) with a resting volume $V_{0,\text{rest}}$ at zero pressure. The active component is associated with the ability of the contractile units to develop pressure, resulting in active function isochrones with a common intercept volume, $V_a$ (i.e. the functional dead volume, occurring at negative pressures). Because it is assumed that the active intercept volume $V_a$ is smaller than the resting volume, the passive and active isochrones intercept all at $V_a$ but at negative pressures. This results in an apparent time-varying $V_0(t)$.

Limitations of this study

Interpretations of estimated values of $V_0(t)$ (Figure 6 E F) should be made with caution, since these values are computed by linear extrapolation outside the operating volume. In particular, this also explains the large variation of maximum elastance when time is nonnormalized (Figure 6C). It should also be realized that the slow rise of the elastance during ejection corresponds to the relative negative values of $V_0(t)$. The errors introduced by the linearization of isochrones and isophase lines require a separate study.

For the normalization procedure, we distinguished four cardiac phases. This choice has been suggested by Wiggers\textsuperscript{31} in the early 1920s and proved to be successful to most physiologists. We assumed that corner points in a $P$-$V$ loop mark the phase transitions. Although this assumption is often made in physiology, corner points would not necessary coincide with valve closures. This observation is material for further study.
Conclusions

Time normalization of the four cardiac phases reduces cardiac load dependency of timing, linearizes isophase lines, and increases accuracy in estimating $E(t)$.

Acknowledgements

Sources of funding

T. Kind was financially supported by the Netherlands Organisation for Scientific Research (NWO), Toptalent grant, project number 021.001.120. J.W. Lankhaar was financially supported by the Netherlands Heart Foundation, grant NHS2003B274. A. Vonk-Noordegraaf was financially supported by the NWO, Vidi grant, project number 91.796.306.

References

Chapter 6


Time normalization improves estimation of elastance


