Normal distribution of ventricular pressure-volume area of arrhythmic beats under atrial fibrillation in canine heart

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MANY GROUPS, including ours, investigated the statistical characteristics of cardiodynamic variables during ventricular arrhythmia under atrial fibrillation (AF) in basic and clinical studies (1–5, 7–13, 15, 23, 24). We previously found that Emax and Ea are the two major determinants of the total mechanical energy of LV contraction that is measurable as the systolic pressure-volume area (PVA; Fig. 1) (18, 19). The PVA is the sum of the LV external mechanical work (EW) and the elastic potential energy (PE; Fig. 1). Then we wondered whether normally or nonnormally the PVA determined by the combination of the nonnormally distributing Ea and the normally distributing Emax would distribute. If PVA distributes normally, its mean (SD) could fully characterize its distribution. However, if PVA distributes nonnormally, its mean (SD) alone could not fully characterize its distribution.

In the present study, we investigated the frequency distribution of PVA and compared it with that of other major cardiodynamic variables including Emax (16, 18, 19) and Ea (16, 21) during AF in the canine in situ ejecting heart. The present experimental data showed that PVA distributed much more normally than Ea and slightly more normally than Emax. The PVA is determined predominantly by Emax and Ea when the end-diastolic volume (EDV) of each arrhythmic beat is given (16, 18). Here, Emax is primarily determined by the preceding beat intervals (24), Ea is determined by the ventricular-aortic coupling in each arrhythmic beat (16), and EDV is determined by the beat intervals, Emax, and Ea of the preceding beats. We found the normal distribution of PVA to be attributable to the complexity of the PVA formula as a function of Emax and Ea. The present result indicates that the mean (SD) of PVA of arrhythmic beats of the ventricle could reasonably characterize the distribution of PVA in the same manner as Emax.

METHODS

Surgical preparation. We performed the canine experiments in conformity with the guiding principles for the care and use of animals in the field of physiological sciences of the Japan Physiological Society and the American Physiological Society. Six mongrel dogs (6–12 kg) were anesthetized with pentobarbital sodium (25 mg/kg iv) after premedication with ketamine hydrochloride (50 mg/kg im) and intubated in each experiment. The anesthesia was maintained by fentanyl (100 μg/h per dog iv) as usual in our laboratory (11, 12, 24). The chest of the dog was opened midsternally. A 3-F catheter-tipped micromanometer was inserted into the LV from the apex to measure the LV pressure (LVP). A 7-F eight-electrode conductance catheter (Webster Laboratories, Baldwin Park, CA) was introduced into the LV through an apical stab and placed along the ventricular long axis to measure LV volume (LVV) continuously. The method for

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measuring LVV with this catheter was described in detail previously (11, 12, 24).

Briefly, the catheter measured continuously the time-varying electrical conductance \( [G_i(t)] \) of the five segments \((i = 1 – 5)\) of blood in the LV cavity. The LV total blood volume was then continuously calculated from the five segmental \( G_i(t) \) \((i = 1 – 5)\) after calibration of blood conductivity in the sampling cuvette. Our custom-made signal conditioner-processor (SI Medicotech) was used to convert the segmental \( G_i(t) \) to LV conductance volume. The parallel conductance \( (G_p) \) due to the conductance of the LV wall and the surrounding tissues and fluid was obtained by the standard hypertonic saline-nea (rectangular area) within the P-V loop and the elastic PE (trian-

\[ PVA = t \] in PVA.

We calculated PVA of each contraction by summing all the PVA increments per 3 s from end diastole to end systole. Each 3-ms (\( \Delta t \)) PVA increment (\( \Delta PVA \)) corresponds to the narrow triangular area scanned by a line connecting the instantaneous P-V data point drawing the P-V loop and \( V_0 \) on the volume axis (16) (Fig. 1). We obtained EW by summing \( \Delta PVA \) from the onset of the present contraction to the onset of the next contraction (16). We obtained PE by subtracting EW from PVA (16).

We further obtained the contractility index, \( E_{\text{max}} \), of each contraction as the slope of the ESPVR (Fig. 1) (16, 18, 19). We also obtained the effective \( E_a \) of each contraction as the slope of the line connecting the end-systolic P-V point on the left upper corner of the P-V loop and the EDV on the LVV axis (Fig. 1) (16, 18–21).

We know that PVA is formulated approximately by Eq. A10 as explained in the appendix. Equation A10 indicates that PVA is a complex function of \( E_{\text{max}} \), \( E_a \), and EDV.

Statistics. We performed the basic statistical analyses of PVA as well as \( E_{\text{max}} \), \( E_a \), beat interval (RR), EW, PE, EDV, and stroke volume (SV) of all the arrhythmic beats sampled in an arbitrary 1 min in each heart. We studied their frequency distributions and performed \( \chi^2 \) test of their normality, evaluating it by its \( P \) value (Table 1; see Figs. 4 and 5) (6, 17).

We also obtained two dimensionless measures of departure from the normality or Gaussianity of the frequency distributions, i.e., skewness and kurtosis, as in our previous study (Table 1; see Figs. 4 and 5) (11, 12). The normal distribution has zero skewness and zero kurtosis. A positive skewness indicates a leftward shift of the peak frequency, and a negative skewness indicates its rightward shift. A positive kurtosis indicates a sharper peak, and a negative kurtosis indicates a dull peak or even two separate peaks.

We analyzed correlations among \( E_{\text{max}} \), \( E_a \), EDV, and PVA and obtained their correlation coefficients \( (r) \) and coefficients of determinations \( (r^2); \) Table 2). We also obtained autocorrelation coefficients of EDV, \( E_{\text{max}} \), and PVA with a lag of only one beat interval, e.g., correlation coefficient between \( EDV_i \) and \( EDV_{i+1} \), where \( i \) was increased from 1 to the one beat before the last beat in the sampled 1 min (Table 3).

We compared the basic statistics of \( E_{\text{max}} \), \( E_a \), and EDV obtained by an individual with only one beat interval, e.g., correlation coefficient between \( EDV_i \) and \( EDV_{i+1} \), where \( i \) was increased from 1 to the one beat before the last beat in the sampled 1 min (Table 3).

We also compared the basic statistics between PVA calculated by Eq. A10 and the measured PVA (see Fig. 6).

We obtained moving-averaged PVA values by increasing the number of moving-averaged beats from 1 to 50 (see Fig. 7).

### Table 1. Basic statistics of PVA during atrial fibrillation in canine hearts

<table>
<thead>
<tr>
<th>Variables</th>
<th>Heart No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beats/min</td>
<td>181</td>
<td>183</td>
<td>298</td>
<td>174</td>
<td>265</td>
<td>217</td>
<td>220</td>
<td>(51)</td>
</tr>
<tr>
<td>Normality ( \chi^2 )</td>
<td>1.13</td>
<td>5.03</td>
<td>1.59</td>
<td>3.1</td>
<td>1.91</td>
<td>0.83</td>
<td>2.3</td>
<td>(1.6)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.999</td>
<td>0.162</td>
<td>0.904</td>
<td>0.425</td>
<td>0.772</td>
<td>0.999</td>
<td>0.710</td>
<td>(0.344)</td>
</tr>
<tr>
<td>Mean</td>
<td>432</td>
<td>503</td>
<td>175</td>
<td>218</td>
<td>353</td>
<td>953</td>
<td>439</td>
<td>(280)</td>
</tr>
<tr>
<td>SD</td>
<td>97</td>
<td>121</td>
<td>68</td>
<td>107</td>
<td>99</td>
<td>366</td>
<td>143</td>
<td>(110)</td>
</tr>
<tr>
<td>CV</td>
<td>0.22</td>
<td>0.24</td>
<td>0.39</td>
<td>0.49</td>
<td>0.28</td>
<td>0.39</td>
<td>0.34</td>
<td>(0.11)</td>
</tr>
<tr>
<td>Median</td>
<td>446</td>
<td>546</td>
<td>169</td>
<td>191</td>
<td>357</td>
<td>1007</td>
<td>453</td>
<td>(308)</td>
</tr>
<tr>
<td>Mode</td>
<td>477</td>
<td>529</td>
<td>265</td>
<td>321</td>
<td>437</td>
<td>1298</td>
<td>554</td>
<td>(377)</td>
</tr>
<tr>
<td>Skewness</td>
<td>-0.31</td>
<td>-0.54</td>
<td>0.7</td>
<td>0.61</td>
<td>0.03</td>
<td>0.07</td>
<td>0.09</td>
<td>(0.49)</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>-0.61</td>
<td>-0.81</td>
<td>0.33</td>
<td>0.76</td>
<td>0.14</td>
<td>0.56</td>
<td>-0.38</td>
<td>(0.49)</td>
</tr>
</tbody>
</table>

Normality \( \chi^2 \), \( \chi^2 \) of pressure-volume area (PVA) relative to its normal distribution; \( P \), \( P \) value of \( \chi^2 \); mean, mean of PVA in 1 min; SD, its standard deviation; CV, coefficient of variation (mean/SD); median, median of PVA in 1 min; mode, mode of PVA in 1 min; skewness, skewness of PVA distribution in 1 min; kurtosis, kurtosis of PVA in 1 min.
H1742

LEFT VENTRICULAR PVA DURING ARRHYTHMIA

Table 2. Correlation coefficients and coefficients of determination among \(E_{\text{max}}, E_a, \text{EDV}, \text{and PVA in canine hearts}\)

<table>
<thead>
<tr>
<th></th>
<th>EDV-PVA</th>
<th>(E_{\text{max}})-PVA</th>
<th>EDV-(E_a)</th>
<th>(E_a)-PVA</th>
<th>EDV-(E_{\text{max}})</th>
<th>(E_{\text{max}})-(E_a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(r)</td>
<td>0.925 (0.036)</td>
<td>0.881 (0.035)</td>
<td>-0.792 (0.015)</td>
<td>-0.714 (0.065)</td>
<td>0.700 (0.024)</td>
<td>-0.606 (0.129)</td>
</tr>
<tr>
<td>(r^2)</td>
<td>0.856 (0.066)</td>
<td>0.777 (0.062)</td>
<td>0.627 (0.023)</td>
<td>0.513 (0.092)</td>
<td>0.490 (0.034)</td>
<td>0.381 (0.157)</td>
</tr>
</tbody>
</table>

Values are means (SD); \(n = 6\). \(r\), Correlation coefficient; \(r^2\), coefficient of determination; EDV, end-diastolic volume; \(E_{\text{max}}\), left ventricular end-diastolic elastance; \(E_a\), left ventricular afterload elastance. All \(r\) values were significant \((P < 0.05)\).

RESULTS

Figure 2 shows a representative 3-s segment of the continuous traces of LVP and LVV during AF. It contains nine arrhythmic beats separated by various beat intervals and featured by all varying peak LVPs and end-diastolic and end-systolic LVVs. All six hearts showed similar arrhythmic beats during AF.

Figure 3 shows the same set of LV P-V loops of the four consecutive arrhythmic beats during AF and their PVA as well as \(E_{\text{max}}\) and \(E_a\) (16, 18–21). These correspond to the first four beats in Fig. 2. Figure 3A illustrates PVA of the arrhythmic beat with the highest contractility (largest \(E_{\text{max}}\)) and largest SV of the four beats. PVA consists of the sum of the rectangular (shaded) area within the P-V loop and the triangular (hatched) area between the ESPVR line and the EDPVR curve on the origin side of the P-V loop of this contraction. The former area represents EW performed by the LV during this contraction. The latter area represents PE that was generated by this contraction in the LV wall but was not converted to EW (18, 19). Figure 3B illustrates PVA of the arrhythmic beat with the lowest contractility (smallest \(E_{\text{max}}\)) and the smallest SV of the four beats. In this beat, EW was nearly zero.

Figure 4 shows a representative set of the frequency distributions of PVA and \(E_a\) in one heart (heart 1 in Table 1). PVA distributed much more normally than \(E_a\). We chose \(E_a\) to compare with PVA, because we had found \(E_a\) to have a considerable nonnormal distribution (11). The \(\chi^2\), its \(P\) value, skewness, and kurtosis quantify the difference of the frequency distribution between PVA and \(E_a\). The mean, median, and mode scattered less for PVA than for \(E_a\). The other hearts showed similar results (Table 1). For PVA, no \(P\) value of \(\chi^2\) test was <0.05; the smallest \(P\) value was 0.162. Neither skewness \((P > 0.661)\) nor kurtosis \((P > 0.116)\) was significantly different from 0.

Table 3. Autocorrelation coefficients of \(E_{\text{max}}, E_a, \text{EDV}, \text{and PVA between two adjacent arrhythmic beats in 1 min in six canine hearts}\)

<table>
<thead>
<tr>
<th></th>
<th>EDV</th>
<th>(E_{\text{max}})</th>
<th>(E_a)</th>
<th>PVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(r)</td>
<td>0.018 (0.160)*</td>
<td>0.165 (0.191)†</td>
<td>-0.065 (0.115)*</td>
<td>0.100 (0.130)*</td>
</tr>
</tbody>
</table>

Values are means (SD); \(n = 6\). \(r\), autocorrelation coefficient. Insignificant correlation of the respective variables between 2 adjacent beats \((P > 0.05)\); *in 5 hearts; †in 3 hearts.

![Fig. 2](image)

An arbitrarily chosen 3-s segment of the continuous traces of LV pressure (LVP, thick traces) and volume (LVV, thin traces) of several arrhythmic beats during electrically induced atrial fibrillation (AF) in a canine in situ heart.
Although we did not include end-systolic pressure (ESP) and end-systolic volume (ESV) in Fig. 5, their small \( \chi^2 \), skewness, and kurtosis were comparable to those of PVA and EDV and much smaller than those of \( E_a \).

Figure 6 compares means (SD) of \( \chi^2 \), its \( P \) value, skewness, and kurtosis of the various complex terms of Eq. A10 to determine PVA from EDV, \( E_{ma} \), and \( E_a \) (see APPENDIX) in all six hearts. Terms 1–7 (Fig. 6) are arranged in decreasing order of \( \chi^2 \) values from left to right. Term 8 is the PVA calculated by Eq. A10, and term 9 is the measured PVA.

The calculated PVA (term 8) had relatively small \( \chi^2 \) and large \( P \) (>0.155, all insignificant). However, its skewness and kurtosis were closest to zero. These statistical values were comparable to those of the measured PVA (term 9). The measured PVA data used here are the same as those used in Fig. 5.

The results in Fig. 6 indicate that \( E_{ma}^2 E_a \) (term 1) had the most nonnormal distribution with the largest \( \chi^2 \), the smallest \( P \) value (<0.05 only in 2 hearts), and the largest skewness and kurtosis. However, term 7 \( (E_{ma}^2 E_a + E_{ma} E_a^2/2)/(E_{ma}^2 + E_a^2) \) had the smallest \( \chi^2 \), the largest \( P \) value (>0.772), and small, but not the smallest, skewness and kurtosis, although it contains multiple \( E_a \) values.

Table 2 shows \( r \) and \( r^2 \) values among \( E_{ma} \), \( E_a \), and EDV in Eq. A10 and the calculated PVA. They were positively or negatively correlated significantly in all six hearts. The \( r^2 \) values indicate that the variation of any of \( E_{ma} \), \( E_a \), EDV, and PVA was attributable to those of the other three variables by 30–80%. This result indicates that \( E_{ma} \), \( E_a \), EDV, and PVA were variably, although not fully, independent of each other.

Table 3 shows the autocorrelation coefficients (\( r \)) of EDV, \( E_{ma} \), \( E_a \), and PVA with a lag of only one beat. Most \( r \) values were insignificant. Therefore, these variables changed on a per-arrhythmic-beat basis, rather randomly, independent of their respective values of the last beat in most of the six hearts.

Figure 7 shows that the percent coefficient of variation (CV) of moving-averaged PVA decreased with an increasing number of moving-averaged beats in the six hearts. The percent CV of ~35% on average of raw PVA values during AF decreased rapidly to ~10% and further to ~5% as a result of an increase in the number of moving-averaged beats to 20 and 40 beats, respectively.

**DISCUSSION**

The present results have evidently shown for the first time the normality or Gaussianity of the frequency distribution of PVA of arrhythmic beats in canine LVs under electrically induced AF (Figs. 4 and 5). This normality existed despite the significantly nonnormal or non-Gaussian frequency distribution of \( E_a \) of the same arrhythmic beats. Here, \( E_a \) is one of the major determinants of PVA. Because PVA is a measure of the total mechanical energy of each ventricular contraction (18, 19), its normal distribution indicates that the ventricular total mechanical energy of each arrhythmic beat distributes normally during AF, despite the considerably nonnormally distributed \( E_a \) (11, 12, 24).

The present results have also shown that although \( E_a \) (Fig. 4) and \( E_{ma} E_a^2 \) (Fig. 6) in the formula (Eq. A10) to calculate PVA distributed nonnormally, the other terms of the formula distributed normally to the comparable extent of the calculated PVA as well as the measured PVA. Of these, \( E_{ma} \) and EDV have been determined by the onset of each contraction as the results of the cardiodynamic variables of the preceding arrhyth-
mic beats (22, 24). \( \text{Ea} \) is defined as ESP/SV in each contraction, where ESP and SV are determined as the result of the ventricular-aortic interaction during each contraction (14, 16, 21).

Therefore, PVA is determined as the consequence of a complex interaction of various cardiodynamic variables with normal or nonnormal frequency distributions (3, 4, 7, 9–13, 24). The normal distribution of PVA, therefore, seems principally attributable to the central limit theorem or the law of large numbers (6). This theorem assumes all the component variables to be mutually independent. However, the component variables, i.e., EDV, \( \text{Emax} \), and \( \text{Ea} \), of PVA correlated mutually by 30–80% in terms of \( r^2 \) (Table 2). This may partly account for some, although not significant, residual variation of PVA, despite its virtually zero skewness and kurtosis (Table 1, Fig. 6). The present study for the first time revealed the normal or Gaussian frequency distribution of PVA during AF and its underlying mechanism, although in the LV of normal canine hearts.

The present study has also shown that the mean of PVA per beat during AF could be estimated reliably with a reasonably small (10–5%) CV of the mean by averaging PVA values of 20–40 beats, respectively (Fig. 7). This indicates that the mean (SD) of PVA of only 20–40 beats could give us a reasonably reliable estimation of the frequency distribution of PVA of arrhythmic beats during AF, at least in normal canine hearts. This suggests that only 7–15 s are necessary to estimate reasonable mean (SD) of PVA under AF. This rather rapid convergence of the SD of moving-averaged PVA seems partly attributable to the largely insignificant autocorrelation of PVA between the present and preceding beats as the result of the similarly insignificant autocorrelation of the components (EDV, \( \text{Emax} \), and \( \text{Ea} \)) of PVA (Table 3).

Although we analyzed neither LV myocardial \( \text{Ca}^{2+} \) handling nor cross-bridge cycling in the present study, we know that an increased EDV increases \( \text{Ca}^{2+} \) handling and cross-bridge cycling according to the Starling law of the heart (16, 18). An increased \( \text{Emax} \) manifests an LV contractility enhanced with increased \( \text{Ca}^{2+} \) handling and recruitability of cross-bridge cycling (16, 18). Here, myocardial \( \text{Ca}^{2+} \) handling is determined by its restitution and potentiation over the last two preceding beats (24), whereas cross-bridge cycling is primarily determined by EDV, \( \text{Emax} \), and \( \text{Ea} \) (16, 18). \( \text{Ea} \) can directly and simply be related to neither myocardial \( \text{Ca}^{2+} \) handling nor cross-bridge cycling, because it is defined as ESP/SV (11, 21), where ESP and SV are determined by EDV, \( \text{Emax} \), and total peripheral resistance (16, 21). These cardiac system-element interrelations suggest that PVA of an arrhythmic beat is determined in a complex manner by not only element, but also system, factors. Although we do not know the statistical characteristics of all the system-element factors involved in PVA determination, we could speculate that the central limit theorem may serve for the normal distribution of PVA.
An obvious limitation of the present study is the use of normal canine hearts with electrically induced AF. It is possible that statistical characteristics of PVA during AF in human diseased hearts are different from those we have found in the present study (1–4, 10). This warrants future studies to investigate the statistical characteristics of PVA in various pathological hearts under artificial or spontaneous AF. Their statistical characteristics may reflect the pathophysiological conditions of the heart.

One more limitation of the present study is the assumption of a constant \( V_0 \) under arrhythmia with a widely varying \( E_{\text{max}} \). Fortunately, our previous studies showed that changes in \( V_0 \), if any, with a varying \( E_{\text{max}} \) would be relatively small, e.g., a few milliliters within a physiologically working range of \( E_{\text{max}} \) (16, 20). Any change in \( E_{\text{max}} \) affects PVA via PE (Figs. 1 and 3, Eqs. A1 and A3 in APPENDIX). For example, even a 2-ml decrease in \( V_0 \) with an increase in \( E_{\text{max}} \) from 2.5 to 10 mmHg/ml could increase PE only by an additional triangular area bound by the end-systolic P-V point and the new 2-ml base on the volume axis in the P-V diagram, though not shown graphically. When the end-systolic pressure increases representatively from 50 to 100 mmHg with the increased \( E_{\text{max}} \) (Figs. 2 and 3), the decreased \( V_0 \) with the increased \( E_{\text{max}} \) would increase PVA by only 50–100 mmHg/ml. This increase in PVA seems too small to deviate the frequency distribution of PVA from normality (e.g., Fig. 4A).

We therefore conclude that the total mechanical energy generated by arrhythmic beats during AF can reliably be characterized by the mean (SD) of PVA in the normal canine LV. The normal distribution of PVA during AF seems theoretically attributable to the complexity of the PVA formula as a function of \( E_a \), \( E_{\text{max}} \), and EDV of individual arrhythmic beats.

**APPENDIX**

Figure 1 helps in our understanding of the following relations of PVA to the other cardiodynamic variables, including \( E_a \) and \( E_{\text{max}} \), in the LV P-V diagram (16).

First, by definition,
Substituting Eqs. A8 and A9 into Eq. A7 yields

\[ PE = (ESV - V_0)/2 = (EDV - V_0)^2 E_{a}E_{a} / 2 (E_{a} + E_{o})^2 \]  

Substituting Eqs. A8 and A9 into Eq. A1 yields

\[ PVA = EW + PE = (EDV - V_0)^2 E_{a}E_{a} / 2 (E_{a} + E_{o})^2 \]  

Equation A10 indicates that PVA is a complex function of \( E_{a} \), \( E_{o} \), and EDV, all of which change beat-by-beat with variable magnitudes of SD, skewness, and kurtosis (Fig. 5). The complexity of the PVA equation (Eq. A10) includes additions, multiplications, squares, and divisions of \( E_{a} \), \( E_{o} \), and EDV.

**REFERENCES**


