Predictability of $O_2$ Consumption from Contractility and Mechanical Energy of Absolute Arrhythmic Beats in Canine Heart

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Abstract: Left ventricular (LV) $O_2$ consumption ($V_{O_2}$) per minute is measurable for both regular and arrhythmic beats. LV $V_{O_2}$ per beat can then be obtained as $V_{O_2}$ per minute divided by heart rate per minute for regular beats, but not for arrhythmic beats. We have established that $V_{O_2}$ of a regular stable beat is predictable by $V_{O_2} = a \cdot PVA + b \cdot E_{max} + c$, where $PVA$ is the systolic pressure-volume area as a measure of the total mechanical energy of an individual contraction and $E_{max}$ is the end-systolic maximum elastance as an index of ventricular contractility of the contraction. Furthermore, $a$ is the $O_2$ cost of PVA, $b$ is the $O_2$ cost of $E_{max}$, and $c$ is the basal metabolic $V_{O_2}$ per beat. We considered it theoretically reasonable to expect that the same formula could also predict LV $V_{O_2}$ of individual arrhythmic beats from their respective $PVA$ and $E_{max}$ with the same $a$, $b$, and $c$. We therefore applied this formula to the $PVA - E_{max}$ data of individual arrhythmic beats under electrically induced atrial fibrillation (AF) in six canine in situ hearts. We found that the predicted $V_{O_2}$ of individual arrhythmic beats highly correlated linearly with either their $V_{O_2}$ ($r = 0.96 \pm 0.01$) or $E_{max}$ ($0.97 \pm 0.03$) while both also highly correlated linearly with each other ($0.88 \pm 0.04$). This suggests that the above formula may be used to predict LV $V_{O_2}$ of absolute arrhythmic beats from their $E_{max}$ and $PVA$ under AF. [The Japanese Journal of Physiology 55: 135–142, 2005]

Key words: cardiac function, mechanoenergetics, oxygen consumption, arrhythmia.

We have established that left ventricular (LV) $O_2$ consumption ($V_{O_2}$) is predictable by $V_{O_2} = a \cdot PVA + b \cdot E_{max} + c$ on a per-beat basis in regular stable beats [1–3]. Here, $PVA$ is the total mechanical energy generated by each LV contraction [1–3], and $E_{max}$ is the end-systolic maximum elastance or pressure/volume ratio as a load-independent measure of LV contractility of the respective beat [1–5]. Furthermore, $a$ is the $O_2$ cost of PVA, $b$ is the $O_2$ cost of $E_{max}$, and $c$ is the basal metabolic $V_{O_2}$ per beat [1–3, 6]. This formula proved to hold in regular stable beats under steady-state cardiac contractile (or $E_{max}$), loading (or $PVA$), and heart rate conditions where $V_{O_2}$ per beat is simply equal to $V_{O_2}$ per min divided by heart rate per min [1–3, 6]. Moreover, we have found $a$, $b$, and $c$ to be largely independent of $PVA$ and $E_{max}$ in both excised cross-circulated hearts and in situ hearts [1–3, 6], although $c$ per beat is inversely proportional to heart rate [7]. We have also confirmed that the same concept basically holds for the rhythmic-type arrhythmia such as bigeminy and paired pulse stimulation [1–3, 8].

However, $V_{O_2}$ of a random-type arrhythmic beat is no more predictable by simply dividing $V_{O_2}$ per min with the number of arrhythmic beats per min because both $PVA$ and $E_{max}$ change on a per-beat basis and hence $V_{O_2}$ of an individual arrhythmic beat is expected to vary among beats [9–12]. Despite this problem, there is a continuous need to better understand the energetic aspect of arrhythmic contractions [3–15].

Since the mechanoenergetical concepts of PVA and $E_{max}$...
E\text{max} are based on the time-varying elastance model of a contracting LV on a per-beat basis [1–5], it is theoretically reasonable to expect that the same mechanoenergetic relation among $PVA$, $E_{\text{max}}$, and $V_0$ on a per-beat basis established for regular stable beats would essentially hold in arrhythmic beats on a per-beat basis.

We therefore investigated in the present study how $V_0$ of individual arrhythmic beats predicted from their $PVA$ and $E_{\text{max}}$ under atrial fibrillation (AF) behaved in canine in situ ejecting hearts, using $V_0$ per beat = $aPVA + bE_{\text{max}} + c$ with the empirically representative $a$, $b$, and $c$ values. We found that the predicted $V_0$ of individual arrhythmic beats highly correlated linearly with either their $PVA$ or $E_{\text{max}}$, both of which also highly correlated linearly with each other. We would expect that the LV $V_0$ of arrhythmic beat thus predicted may help better understand the energetic aspect of absolute arrhythmia under AF.

**METHODS**

**Surgical preparation.** We performed the canine experiments in conformity with the animal use guidelines set by the American Physiological Society and the Physiological Society of Japan. Six adult mongrel dogs (mean ± SD: 8.6 ± 1.0 kg) were anesthetized with pentobarbital sodium (25 mg/kg, I.V.) after premedication with ketamine hydrochloride (50 mg/kg, I.M.) and intubated in each experiment. The anesthesia was maintained by fentanyl (100 µg/h per dog, I.V.) as usual in our laboratory [9–12].

The chest of the dog was opened midsternally. A 3F catheter-tip micromanometer was inserted into the LV from the apex to measure the LV pressure (P). A 7F eight-electrode conductance catheter (Webster Laboratories, Baldwin Park, CA, USA) was introduced into the LV through an apical stab and placed along the ventricular long axis to measure LV volume (V) [16]. The method for measuring LVV with this catheter was described in detail previously [6, 9–12, 16].

Briefly, the catheter continuously measured the time-varying electrical conductance $G_i(t)$ of the five segments ($i = 1–5$) of blood in the LV cavity of the beating heart [16]. The LV total blood volume was then continuously calculated from the five segmental $G_i(t)$ signals ($i = 1–5$) after calibrating blood conductivity in the sampling cuvette [16]. Our custom-made signal conditioner商品 (SI Medicotech Co., Ltd., Osaka, Japan) was used to convert the segmental $G_i(t)$ to LV conductance volume [16]. 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 dilution method [16]. A constant offset volume ($V_0$) was calculated from the $G_p$. The absolute LVV was obtained by subtracting $V_0$ from the LV conductance volume converted from the segmental $G_i(t)$ [16].

We attached a pair of stimulation electrodes to the left atrial appendage. Suprathreshold electrical stimulation at 20 Hz via these electrodes induced and maintained AF, which started on and stopped off the stimulation [9–12]. We maintained AF for 2 min and recorded LVP and LVV during the latter 1 min at sampling intervals of 3 msec in a computer (Fig. 1A).

The LV, including the septum, weighed 46.5 ± 15.1 g at the end of each experiment.

**End-systolic elastance ($E_{\text{max}}$) and pressure-volume area (PVA).** We obtained LV $E_{\text{max}}$ and PVA of the individual arrhythmic beats for 1 min. The methods used to calculate them have been described elsewhere [6, 12]. Briefly, we first gradually clamped the inferior vena cava until LVV and LVP halved during regular beats before AF [6–12]. We obtained the LV P-V loops from these LVV and LVP and drew a straight line through their left-upper corners (i.e., end-systolic P-V points) to obtain its V-axis intercept as $V_0$ (Fig. 1B).

The $V_0$ means the unstressed LV volume at which peak systolic LVP was expected to be zero. We assumed this $V_0$ to remain unchanged in arrhythmic beats because no method was available to obtain it during arrhythmia [4, 5]. We then calculated by a computer the slope of the instantaneous P-V line connecting the $V_0$ and the instantaneous P-V data point at 3 ms intervals [1–3, 6, 12].

We obtained $E_{\text{max}}$ as the maximum slope of the instantaneous P-V line at end systole corresponding to the left upper corner of each P-V loop (Fig. 1B). We also calculated $PVA$ by a computer as the P-V area scanned by the instantaneous P-V line from end diastole to end systole [1–3, 6, 12] (shaded area in Fig. 1, C and D). We normalized both $E_{\text{max}}$ and $PVA$ per 100 g LV.

**$V_0$ prediction.** We predicted $V_0$ of each individual arrhythmic beat from its normalized $E_{\text{max}}$ and $PVA$ using the following established formula already shown in the Introduction [1–3].

\[ V_0 \text{ per beat} = aPVA + bE_{\text{max}} + c \]  

Here, $a$, $b$, and $c$ stand for the O\text{2} cost of PVA, the O\text{2} cost of $E_{\text{max}}$, and the basal metabolic $V_0$ per beat, respectively, as once mentioned in the Introduction. Since we did not obtain these values in the present study, we used their representative values obtained in our previous studies [1–3]. Namely, $a$ was $1.8 \times 10^{-5}$ ml O\text{2}/(mmHg ml), and $b$ was $2.0 \times 10^{-3}$ ml O\text{2}/(mmHg ml), both per beat and per 100 g LV.

We used these $a$ and $b$ values for the following reasons. Their variations had consistently been shown
relatively small among different normal canine hearts and largely independent of the contractile (or $E_{\text{max}}$) and loading (or $PVA$) conditions and heart rate [1–3, 6, 8]. This seems reasonable for the following reasons. Coefficient $a$ is inversely proportional to the contractile efficiency from $V_{O_2}$ to $PVA$ of ~25%, which seems in some degree common among different hearts [1–3]. Coefficient $b$ is proportional to the excitation–contraction coupling energy per unit increment in contractility in terms of $E_{\text{max}}$ in normal canine hearts, although it increases in various types of failing hearts [1–3]. Moreover, $b$ is independent of $E_{\text{max}}$ regardless of positive and negative inotropic agents [1–3].

As for $c$, the basal metabolic $V_{O_2}$ per min obtained in KCl-arrested canine hearts was 1.0 ml O$_2$ per min per 100 g on average [1–3, 17]. Therefore, $c$ of a regular stable beat is given as 1.0 ml O$_2$ per min divided by heart rate per min. However, $c$ of an arrhythmic beat must be given as 1.0 ml O$_2$ per min divided by its own instantaneous heart rate, which is equal to 60,000 ms divided by its beat interval ($RR$) in ms. Hence, $c = 1.0 \times 60,000 = RR/60,000$.

Therefore, we substituted such average $a$, $b$, and $c$ values into Eq. 1 and obtained

$$V_{O_2}\text{ per beat} = 1.8 \times 10^{-5} PVA + 2.0 \times 10^{-3} E_{\text{max}} + RR/60,000 \ (2)$$

as a representative formula to predict $V_{O_2}$ of each arrhythmic beat from its $PVA$, $E_{\text{max}}$, and $RR$.

**Statistical analyses.** We analyzed the basic statistics [18, 19] of the measured $E_{\text{max}}$ and $PVA$ and the predicted $V_{O_2}$ of individual arrhythmic beats sampled in 1 min in each of the six hearts. We considered that 1 min was long enough to obtain a sufficient number of arrhythmic beats for statistical analyses, since both $E_{\text{max}}$ and $PVA$ have been found to distribute normally within 1 min [11, 12].

We also analyzed correlations among the measured $E_{\text{max}}$ and $PVA$ and the predicted $V_{O_2}$ in each heart. We then performed regression analyses of $PVA$ on $E_{\text{max}}$ as well as of $V_{O_2}$ on each $PVA$ and $E_{\text{max}}$ in each heart. We
used Microsoft Office 2001 Excel and SAS StatView 5.0 for the statistical analyses.

RESULTS

End-systolic elastance ($E_{\text{max}}$)

Figure 1 representatively shows the variably oscillating LVP (thick) and LVV (thin) curves (Panel A) and the P-V loops (Panel B) of a series of 10 arrhythmic beats for an arbitrarily chosen 3 s in the posterior 1 min under electrically induced AF in a canine in situ ejecting heart. In Panel B, the larger-font $E_{\text{max}}$ shows the end-systolic maximum elastance of the strongest beat with the highest pressure, corresponding to the 2nd beat from the last in Panel A, and the smaller-font $E_{\text{max}}$ shows that of the weakest beat, corresponding to the last beat in Panel A. The $E_{\text{max}}$ as a contractility index of any other beat sampled for Panel B fell between those two extreme beats in this panel.

Pressure-volume area (PVA)

Figure 1, Panel C, representatively shows the PVA (shaded area) of the strongest beat in Panel B. This PVA consists of the quasi-square area within the tall and wide P-V loop (external work, EW) and the quasi-triangular area (potential energy, PE) on the origin side of the loop [1–3, 11]. Panel D shows the PVA of the weakest beat shown in Panel B. This PVA consists of no area (EW = 0) within the closed P-V loop and the small quasi-triangular area (PE) on the origin side of the short and slant P-V loop. The PVA of any other P-V loop in Panel B varied between these two extreme beats.

Basic statistics

Table 1 lists the basic statistical results of the measured $E_{\text{max}}$ and PVA and the predicted $V_O^2$ by Eq. 2 of the individual arrhythmic beats in 1 min under AF. Their distribution ranges of the arrhythmic beats seem wide enough to cover their physiological ranges of regular beats under varied contractile and loading conditions. The mean, median, and mode of the respective variables were close to one another in each heart. Their skewness and kurtosis were relatively small. Their $\chi^2$ (chi-square) values were also small, and all their $p$ values were much greater than 0.05. These statistical results reasonably supported the normal distributions of the $E_{\text{max}}$ and PVA [10, 11], as well as the predicted $V_O^2$ under AF.

$E_{\text{max}}$–PVA relationship

Figure 2 shows a representative regression line of the PVA on the $E_{\text{max}}$ of individual arrhythmic beats under AF in one heart. They linearly and closely correlated with each other. The inset shows the regression equation of PVA on $E_{\text{max}}$ (i.e., of y on x, as usual), correlation

<table>
<thead>
<tr>
<th>$E_{\text{max}}$</th>
<th>PVA</th>
<th>$V_O^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>12.9 ± 3.9</td>
<td>903 ± 356</td>
</tr>
<tr>
<td>Median</td>
<td>12.8 ± 4.0</td>
<td>920 ± 408</td>
</tr>
<tr>
<td>Mode</td>
<td>13.3 ± 5.3</td>
<td>1,163 ± 499</td>
</tr>
<tr>
<td>Skewness</td>
<td>−0.64 ± 0.48</td>
<td>−0.38 ± 0.49</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>−0.08 ± 0.57</td>
<td>0.09 ± 0.49</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>3.202 ± 2.164</td>
<td>2.242 ± 1.552</td>
</tr>
<tr>
<td>$p$</td>
<td>0.544 ± 0.302</td>
<td>0.715 ± 0.339</td>
</tr>
</tbody>
</table>

Mean ± SD of all six hearts are listed. See text for details.

Table 1. Basic statistics of measured $E_{\text{max}}$ and PVA and predicted $V_O^2$ of individual arrhythmic beats under atrial fibrillation.

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Fig. 2. Linear and close correlation between left ventricular $E_{\text{max}}$ and PVA of arrhythmic beats under atrial fibrillation in a canine heart. The diagonal line is the regression line of PVA on $E_{\text{max}}$ (of y on x). The inset shows the regression equation, the correlation coefficient ($r$), its $p$, and the coefficient of determination ($r^2$).
Prediction of Cardiac $\text{O}_2$ Consumption of Arrhythmic Beats

Coefficient $r$, and coefficient of determination $r^2$. The $r$ was significant ($p < 0.001$). The $r^2$ indicates that as much as 84% of the variance of $\text{PVA}$ was attributable to that of $E_{\text{max}}$, while the other 16% ($1 - r^2 = 0.161$) was attributable to other factors.

All the other hearts showed similar results to this one. The left column of Table 2 lists $r$ and $r^2$ between $E_{\text{max}}$ and $\text{PVA}$ in all six hearts. All $r$ values were significant ($p < 0.001$). Mean $r^2$ indicates that as much as 78% on average of the variance of $\text{PVA}$ was attributable to the variance of $E_{\text{max}}$, while the other 22% was attributable to other factors. Table 2 (left column) also lists mean ± SD of the slope, the $\text{PVA}$-axis intercept, and their CV (coefficient of variation) values of the $E_{\text{max}}$-$\text{PVA}$ regression lines. These results indicate that both the slope and the intercept of the regression lines varied among the hearts.

$\text{PVA-VO}_2$ relationship

Figure 3 shows a representative regression line (solid diagonal) of the $\text{VO}_2$ on the $\text{PVA}$ (of $y$ on $x$) of the same set of the individual arrhythmic beats under AF in the same heart shown in Fig. 2. They linearly correlated significantly with a high correlation coefficient. The inset on the abscissa shows the regression equation, $r$, and $r^2$. The $r^2$ indicates that as much as 91% of the variance of $\text{VO}_2$ was attributable to that of $\text{PVA}$, while the other 9% was attributable to other factors.

In Fig. 3, the dotted diagonal lines show the theoretical $\text{PVA-VO}_2$ relations (Eq. 2, inset at the top) at different $E_{\text{max}}$ values of, e.g., 5, 10, 15, and 20 mmHg/ml 100 g LV. The $\text{PVA-VO}_2$ regression line (solid) is steeper than those theoretical (dotted) lines with the slope corresponding to the $\text{O}_2$ cost of $\text{PVA}$ ($1.8 \times 10^{-5}$). The regression line intersected those dotted $E_{\text{max}}$ lines at increasing $\text{PVA}$ and $\text{VO}_2$ with increasing $E_{\text{max}}$.

All the other hearts showed similar results to this one. The middle column of Table 2 lists $r$ and $r^2$ between $\text{VO}_2$ and $\text{PVA}$ in all six hearts. All $r$ values were significant ($p < 0.001$). Mean $r^2$ indicates that as much as 93% on average of the variance of $\text{VO}_2$ was attributable to the variance of $\text{PVA}$, while the other 7% was attributable to other factors. Table 2 (middle column) also lists mean ± SD of the slope, the $\text{VO}_2$-axis intercept, and their CV (coefficient of variation) values of the $\text{PVA-VO}_2$ regression lines. The mean slope value ($4.0 \times 10^{-3}$) was twice as great as the $\text{O}_2$ cost of $\text{PVA}$ ($1.8 \times 10^{-5}$) used in Eq. 2, supporting $E_{\text{max}}$ to be a significant determinant of $\text{VO}_2$ beside $\text{PVA}$.

$E_{\text{max}}$-$\text{VO}_2$ relationship

Figure 4 shows a representative regression line (solid diagonal) of the $\text{VO}_2$ on the $E_{\text{max}}$ (of $y$ on $x$) of the same set of the individual arrhythmic beats under AF in the same heart shown in Figs. 2 and 3. They linearly correlated significantly with a high correlation coefficient. The inset on the abscissa shows the regression equation, $r$, and $r^2$. The $r^2$ indicates that as much as 98% of the variance of $\text{VO}_2$ was attributable to that of $\text{PVA}$, while; the other 2% was attributable to other factors.

In Fig. 4, the dotted diagonal lines show the theoretical $E_{\text{max}}$-$\text{VO}_2$ relations (Eq. 2, inset at the top) at different $\text{PVA}$ values of 500, 1,000, and 1,500 mmHg/ml 100 g LV. The $E_{\text{max}}$-$\text{VO}_2$ regression line (solid) is 40% steeper than those theoretical lines with the slope corresponding to the $\text{O}_2$ cost of $E_{\text{max}}$ ($2.0 \times 10^{-3}$). The regression line intersected the dotted lines at increasing $E_{\text{max}}$ and $\text{VO}_2$ with increasing $\text{PVA}$.

All the other hearts showed similar results to this one. The right column of Table 2 lists $r$ and $r^2$ between
$V_O_2$ and $E_{\text{max}}$ in all six hearts. All $r$ values were significant ($p < 0.001$). Mean $r_2$ indicates that as much as 95% on average of the variance of $V_O_2$ was attributable to the variance of $E_{\text{max}}$ while the other 5% was attributable to other factors. Table 2 (right column) also lists mean ± SD of the slope, the $V_O_2$-axis intercept, and their CV (coefficient of variation) values of the $E_{\text{max}}$–$V_O_2$ regression lines. This slope value ($3.8 \times 10^{-3}$) is twice greater than the $O_2$ cost of $E_{\text{max}}$ ($2.0 \times 10^{-3}$) used in Eq. 2, supporting $PVA$ to be a significant determinant of $V_O_2$.

The $r$ and $r^2$ values between $E_{\text{max}}$–$PVA$, and $V_O_2$ in Table 2 evidently indicate that all these three mechanismoenergetic variables correlated closely and linearly with one another under AF.

## DISCUSSION

We newly found in the present study that the predicted $V_O_2$ of individual arrhythmic beats under AF closely, positively, and linearly correlated ($r = 0.823$–0.992) with either their measured $E_{\text{max}}$ or their $PVA$ values within the full working ranges in all six canine hearts (Table 2, Figs. 3 and 4). We consider that this close correlation of $V_O_2$ with either $E_{\text{max}}$ or $PVA$ derives from the close correlation between $E_{\text{max}}$ and $PVA$ (Table 2, Fig. 2). If this $E_{\text{max}}$–$PVA$ correlation were poor, the close correlation of $V_O_2$ with either $E_{\text{max}}$ or $PVA$ could not exist, and the $V_O_2$–$E_{\text{max}}$ and $V_O_2$–$PVA$ data would scatter. Even if this should happen, however, the predicted $V_O_2$ per arrhythmic beat would remain theoretically reasonable because the prediction equation, Eq. 2, uniquely predicts $V_O_2$ from a set of $E_{\text{max}}$–$PVA$, and RR of each individual arrhythmic beat.

The close $E_{\text{max}}$–$PVA$ correlation derives from the simultaneous close correlations of $PVA$ with both EDV and ESP, as explained in the Appendix. If the latter two correlations were poor, the $PVA$–$E_{\text{max}}$ correlation would also be poor, and the scatter of the predicted $V_O_2$ in Figs. 3 and 4 would be much greater than in the present.

![Fig. 4. Linear regression of left ventricular $V_O_2$ on $E_{\text{max}}$ (of $y$ on $x$) of the same set of arrhythmic beats under atrial fibrillation in the same canine heart shown in Figs. 2 and 3. The solid diagonal line is the linear regression line. The inset above the abscissa shows this regression equation, the correlation coefficient ($r$), its $p$, and the coefficient of determination ($r^2$). The top inset equation indicates the $E_{\text{max}}$–$PVA$–$V_O_2$ relation (Eq. 2) used for the present $V_O_2$ prediction. The dashed diagonal lines are a representative set of the predictable $V_O_2$–$E_{\text{max}}$ relations (part of Eq. 2) at the three different $PVA$ levels ($500$–$1,500$ mmHg ml per $100$ g) shown on the respective lines.](image)
results. There is no guarantee that the same close mechanoenergetic correlation as shown in Figs. 2–4 holds in arrhythmias of other types than the absolute arrhythmia under AF.

Summing up the predicted \( V_{O_2} \) of all arrhythmic beats in 1 min by Eq. 2 yields \( V_{O_2} \) per min as follows.

\[
V_{O_2} \text{ per min} = 1.8 \times 10^{-5} \sum PV A + 2.0 \times 10^{-3} \sum E_{\text{max}} + 1.0 \quad (3)
\]

where \( \sum \) stands for summing up the respective variable values of all the arrhythmic beats in 1 min. If an actually measured \( V_{O_2} \) per min was obtained in the same heart from which the arrhythmic \( E_{\text{max}} \) and \( PV A \) were measured and substituted into Eq. 3, one could compare the calculated \( V_{O_2} \) per min with the actually measured \( V_{O_2} \) per minute under the same arrhythmia in the same heart. This comparison will yield one correction factor \( k \) as their ratio.

\[
k = \frac{\text{actually measured } V_{O_2} \text{ per min}}{(1.8 \times 10^{-5} \sum PV A + 2.0 \times 10^{-3} \sum E_{\text{max}} + RR/60,000)} \quad (4)
\]

Once \( k \) is obtained, the \( V_{O_2} \) of each arrhythmic beat could be more reliably predicted by

\[
V_{O_2} \text{ per beat} = k \left( 1.8 \times 10^{-5} \sum PV A + 2.0 \times 10^{-3} E_{\text{max}} + RR/60,000 \right) \quad (5)
\]

However, \( a, b, \) and \( c \) in Eq. 1 vary independently among different hearts [1–3]. To take these inter-heart variations into consideration, one should obtain \( \sum PV A - \sum E_{\text{max}} - V_{O_2} \) (per min) data of arrhythmic beats under three different sets of contractile (or \( E_{\text{max}} \)) and loading (or \( PV A \)) conditions in the same heart and substitute them into the following general equation.

\[
V_{O_2} \text{ per min} = g \sum PV A + h \sum E_{\text{max}} + m \quad (6)
\]

Here, \( g = O_2 \) cost of PVA, \( h = O_2 \) cost of \( E_{\text{max}} \), and \( m = \) basal metabolic \( V_{O_2} \) per min. By solving this set of three simultaneous equations of Eq. 6, one can obtain the most reliable set of \( g, h, \) and \( m \) values for the given heart. Using these \( g, h, \) and \( m \) instead of \( a, b, \) and \( c \) in Eq. 1, one could predict the most reliable \( V_{O_2} \) of individual arrhythmic beats under AF in the heart in which \( g, h, \) and \( m \) were determined as follows.

\[
V_{O_2} \text{ per beat} = g \sum PV A + h \sum E_{\text{max}} + m (RR/60,000) \quad (7)
\]

However, since we did not measure \( V_{O_2} \) per min in any of the present six canine hearts, we obtained neither a particular \( k \) value nor a particular set of \( g, h, \) and \( m \) values in the present study. Therefore, future studies to test the feasibility of the proposed Eqs. 5 and/ or 7 are warranted in canine hearts under various types of arrhythmia. An important point to be studied is whether the same \( k \) value or set of \( g, h, \) and \( m \) values is obtained from both regular and arrhythmic beats in each given heart.

One limitation of the present study is that no direct evidence yet exists for the validity of Eq. 1 in individual arrhythmic beats, since the time resolution of \( V_{O_2} \) measurement as coronary flow times coronary arteriovenous \( O_2 \) content difference is not short enough to detect its beat-by-beat changes. In contrast, the heat measurement seems to have a reasonably high time resolution, which is enough to measure the beat-by-beat changes in myocardial or cardiac energetics [20, 21]. Therefore, the present proposed formula remains to be validated on a per-beat basis by the myothermal method.

In conclusion, the present study suggests that LV \( V_{O_2} \) of each arrhythmic beat under electrically induced AF in normal canine hearts seems reasonably predictable from its \( E_{\text{max}} \) and \( PV A \) using the already established formula once \( V_{O_2} \) per min is obtained in the same canine heart. Even without the measured \( V_{O_2} \) per min, the formula may be used to predict the relative changes in \( V_{O_2} \) of individual arrhythmic beats. Therefore, we would expect that the LV \( V_{O_2} \) of arrhythmic beats thus predicted may help better understand the energetic aspect of absolute arrhythmia under atrial fibrillation.

**APPENDIX**

Following are the equations of PVA as a function of various cardiodynamic variables, such as \( E_{\text{max}} \), EDV, and ESP [12].

First, by definition [1–3],

\[
PVA = EW+PE \quad (8)
\]

These EW and PE are formulated respectively as follows [12].

\[
EW = SV \times ESP = (EDV - ESV) \times ESP \quad (9)
\]

\[
PE = (ESV - V_O) \times ESP/2 \quad (10)
\]

Here, we assumed that the P-V loop and hence EW area is rectangular with perpendicular (i.e., isovolumic during both contraction and relaxation) and horizontal (i.e., isobaric during both ejection and filling) P-V trajectories and the PE area is triangular. We further assumed that LVP during ejection was constant at ESP and the end-diastolic P–V relation was virtually zero below ESV. These assumptions will little affect the magnitude of PVA unless either aortic stenosis or regurgitation exists.

Substituting Eqs. 9 and 10 into Eq. 8 yields

\[
PVA = ESP (EDV - ESV/2 - V_O/2) \quad (11)
\]
Since
\[ \text{ESV} = \text{ESP}/E_{\text{max}} + V_o \]  
(12)
its substitution into Eq. 11 yields
\[ \text{PVA} = \text{ESP} [(\text{EDV} - \text{ESP}/(2E_{\text{max}}) - V_o)] \]  
(13)
This indicates that PVA is an increasing function of not only \(E_{\text{max}}\) (as already shown in Fig. 2), but also ESP and EDV. However, the high correlation between PVA and \(E_{\text{max}}\) could not have been achieved unless both ESP and EDV correlated positively and closely with PVA.

In fact, our additional analyses showed positive significant correlations of PVA with ESP and EDV (\(r = 0.873 \pm 0.078\) and \(0.925 \pm 0.033\), respectively, both \(p < 0.001\)) in the same six canine hearts. Simultaneously, the correlation between ESP and EDV was also high (0.660 \(\pm 0.157\), \(p < 0.001\)). Figure 1B visually supports these tendencies, where a greater PVA was accompanied by a higher ESP and a larger EDV.

This work was partly supported by Scientific Research Grants (13558113, 13770350, 13878192, 14380405, 15650095, 15659186, and 16659057) from the Ministry of Education, Culture, Sports, Science and Technology, and Cardiovascular Diseases Research Grants (11C-1, 14A-1, 13558113, 13770350, 13878185, 13878192, 14380405) from the Ministry of Health, Labour and Welfare, both of Japan.

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