

# Mode of frequency distribution of external work efficiency of arrhythmic beats during atrial fibrillation remains normal in canine heart

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Received: 10 September 2008 / Accepted: 5 November 2008 / Published online: 12 December 2008  
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**Abstract** The external work (EW) efficiency of individual arrhythmic beats of the left ventricle (LV) cannot directly be obtained since LV O<sub>2</sub> consumption (VO<sub>2</sub>) of each beat cannot directly be measured under beat-to-beat varying contractile and loading conditions. We, however, have recently reported that VO<sub>2</sub> of each arrhythmic beat can reasonably be estimated by  $VO_2 = aPVA + bE_{max} + c$  even under varying PVA and E<sub>max</sub>. Here, PVA is the LV pressure–volume (*P–V*) area as a measure of the LV total mechanical energy, E<sub>max</sub> is the LV end-systolic elastance as an index of the LV contractility, *a* is a constant O<sub>2</sub> cost of PVA, *b* is a constant O<sub>2</sub> cost of E<sub>max</sub>, and *c* is the basal metabolic VO<sub>2</sub> of the beat, all on a per-beat basis. Using the above formula in this study, we calculated VO<sub>2</sub> of the individual arrhythmic beats from their measured PVA and E<sub>max</sub> during electrically induced atrial fibrillation (AF) in normal canine hearts. We then calculated their LV EW efficiency by dividing their measured EW with the estimated VO<sub>2</sub>. We found that the thus calculated EW efficiency of the arrhythmic beats had a rightward skewed distribution with a mode of 15% and a maximum of 18% around a mean of 13% on average in six hearts. This mode remained comparable to the efficiency (15%) at regular

tachycardia though 22% lower than mean arrhythmic tachycardia.

**Keywords** Arrhythmia · Cardiac efficiency · E<sub>max</sub> · Oxygen consumption · PVA

## Introduction

We have already established that left ventricular (LV) O<sub>2</sub> consumption (VO<sub>2</sub>) is reasonably predictable by  $VO_2 = aPVA + bE_{max} + c$  on a per-beat basis in regular beats [1, 2]. Here, PVA is the LV pressure–volume (*P–V*) area as a measure of the LV total mechanical energy [1], E<sub>max</sub> is the LV end-systolic elastance or *P–V* ratio as an index of contractility [3], *a* is a constant O<sub>2</sub> cost of PVA, *b* is a constant O<sub>2</sub> cost of E<sub>max</sub>, and *c* is the basal metabolic VO<sub>2</sub>, all per beat [1]. The above formula proved to hold in steady-state beats under stable LV contractile and loading conditions where VO<sub>2</sub> per beat is simply equal to VO<sub>2</sub> per min divided by the regular heart rate [1]. We previously extrapolated the above formula to individual arrhythmic beats and reported its feasibility to predict the respective VO<sub>2</sub> on a per-beat basis even under atrial fibrillation (AF) [4]. The purpose of the present study is to determine whether the EW efficiency of individual beat under AF is reasonably predictable from the measured EW and the predicted VO<sub>2</sub>/beat.

In the present study, we applied the above-established formula for the first time to estimate the external work (EW) efficiency of individual arrhythmic beats in six normal canine in situ LVs under electrically induced AF. We measured LV E<sub>max</sub> and PVA as well as EW of individual arrhythmic beats under AF. We then substituted these E<sub>max</sub> and PVA data into our VO<sub>2</sub> formula shown above with the

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physiologically normal representative  $a$  and  $b$  values and the  $c$  value as the basal metabolic  $VO_2$ . We then calculated the EW efficiency of each individual arrhythmic beat by dividing the measured EW with the estimated  $VO_2$  of the beat.

As the result, we found that the EW efficiency under AF varied around a mean of 13%, ranging between 5 and 18%, on average. The distribution of the EW efficiency tended to skew to the higher side with a mode of 15% on average. Although the mean efficiency under AF was significantly smaller than the efficiency under regular tachycardiac pacing, the mode efficiency was comparable to the efficiency of the regular beat and the maximum efficiency exceeded it in the respective hearts. We reasonably accounted for these statistical results by the ratio of the normally distributing EW of each beat under AF to the respective  $VO_2$  linearly correlating with EW, but always containing a considerable PVA-independent  $VO_2$  consisting of both basal metabolic  $VO_2$  and excitation–contraction coupling  $VO_2$ .

## 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 Physiological Society of Japan and the American Physiological Society. We anesthetized six adult mongrel dogs (mean  $\pm$  SD:  $8.6 \pm 1.0$  kg) with pentobarbital sodium (25 mg/kg, i.v.) after premedication with ketamine hydrochloride (50 mg/kg, i.m.) and intubated for artificial respiration in each experiment. We maintained the anesthesia by fentanyl (100  $\mu$ g/h per dog, i.v.) as usual in our laboratory [4].

After midsternal thoracotomy, we inserted a 3F catheter-tip micromanometer into the LV from the apex to measure the LV pressure ( $P$ ). We introduced a 7F eight-electrode conductance catheter (Webster Laboratories, Baldwin Park, CA, USA) into the LV through an apical stab and placed it along the ventricular long axis to measure instantaneous LV volume ( $V$ ) continuously. We described the method for measuring LVV with this catheter elsewhere [4].

Briefly, the catheter measured continuously the time-varying electrical conductance  $G(t)$  of the blood within the LV cavity of the beating heart [5, 6]. Our custom-made signal conditioner–processor (SI Medicotech Co., Ltd., Osaka, Japan) converted the  $G(t)$  to LV conductance volume after calibrating blood conductivity in the sampling cuvette. We obtained the parallel conductance  $G_p$  attributable to the conductance of the LV wall and the surrounding tissues and fluid by the standard hypertonic saline dilution

method. From this  $G_p$ , we calculated a constant offset volume ( $V_c$ ) and obtained the absolute LVV by subtracting  $V_c$  from the LV conductance volume [5, 6].

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. AF started and stopped the stimulation [5]. We maintained AF for 2 min and recorded LVP and LVV during the latter 1 min at sampling intervals of 3 ms in a computer (Fig. 1a). We also recorded LVP and LVV while pacing the left atrium at a constant rate for 2 min after we raised the regular pacing rate to approach the mean arrhythmic heart rate during AF until pulsus alternans barely started. As the result, the regularly paced tachycardiac heart rate (mean  $\pm$  SD:  $170 \pm 17$  beats/min) reached 78% on average of the mean arrhythmic heart rate ( $219 \pm 51$  beats/min) in the six hearts.

The LV, including the septum, weighed  $46.5 \pm 15.1$  g after each experiment. Using these LV weights, we normalized LV mechanoenergetic variables relative to 100 g in each LV.

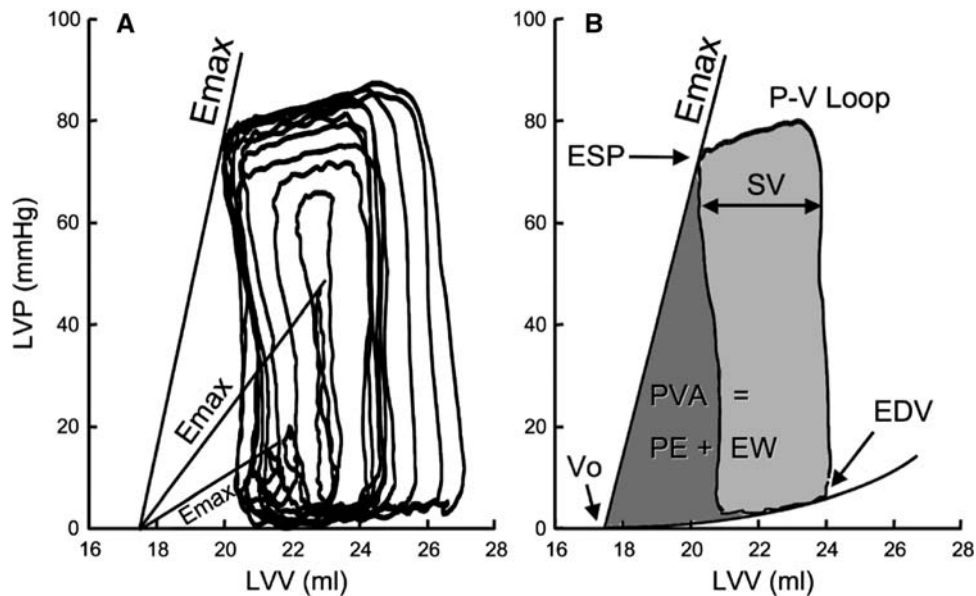
### Mechanoenergetic variables

We obtained such key mechanoenergetic variables as EW,  $E_{\max}$ , PVA, dead or unstressed volume ( $V_0$ ), mechanical potential energy (PE), stroke volume (SV), end-diastolic volume (EDV), and end-systolic pressure (ESP) of individual arrhythmic beats under electrically induced AF as well as regular stable tachycardiac beats in each LV. Figure 1 illustrates these variables under AF in the  $P$ – $V$  diagram. We have described in detail the methods to calculate EW,  $E_{\max}$ , and PVA elsewhere [7, 8]. Briefly, we first obtained  $V_0$  (Fig. 1) as the  $V$ -axis intercept of the straight line drawn through the end-systolic  $P$ – $V$  points of the shrinking  $P$ – $V$  loops while clamping the inferior vena cava during 10–20 regular beats, as described elsewhere [1, 3]. We then obtained LV  $E_{\max}$  as the slope of the line connecting  $V_0$  and the left-upper, end-systolic corner of each  $P$ – $V$  loop (Fig. 1).

We also calculated PVA as usual on a computer as the  $P$ – $V$  area scanned by the instantaneous  $P$ – $V$  line connecting the instantaneous  $P$ – $V$  point to  $V_0$  in each arrhythmic beat [7, 8]. This calculation also yielded EW and PE (shaded rectangular and triangular areas, respectively, in Fig. 1) as the two components of PVA. We normalized  $E_{\max}$ , PVA, EW, and PE relative to 100 g LV.

### $VO_2$ estimation

We estimated  $VO_2$  of each individual arrhythmic beat from the normalized  $E_{\max}$  and PVA by calculating it with the following equation:



**Fig. 1** **a** shows the left ventricular (LV) pressure (*P*)–volume (*V*) loops of 14 arbitrarily chosen continuous arrhythmic contractions under electrically maintained atrial fibrillation in a canine heart. **b** shows one of the *P*–*V* loops to explain abbreviations. In **a**, three *P*–*V* loops show their *E*<sub>max</sub> values as the slopes of the respective end-systolic *P*–*V* lines drawn from the common dead volume on the volume axis. In **b**, the area within the quasi-rectangular *P*–*V* loop, mostly shaded, is the external work (*EW*), and the quasi-triangular

area, also mostly shaded, under the *E*<sub>max</sub> line on the origin side of the *EW* area is the mechanical potential energy (*PE*). The systolic pressure–volume area (*PVA*) is the sum of these two areas, namely, *PVA* = *PE* + *EW*. The stroke volume (*SV*) is the width of the *P*–*V* loop; the end-systolic pressure (*ESP*) is the pressure at the left upper corner of the *P*–*V* loop; the end-diastolic volume (*EDV*) is the volume at the right lower corner of the *P*–*V* loop. *V*<sub>0</sub> is the dead volume at which end-systolic pressure is zero

$$VO_2 = aPVA + bE_{max} + c \quad (1)$$

where *a* = O<sub>2</sub> cost of *PVA*, *b* = O<sub>2</sub> cost of *E*<sub>max</sub>, and *c* = basal metabolic *VO*<sub>2</sub> of each beat, all normalized for 100 g LV. We already established the reasonable *VO*<sub>2</sub> predictability of this equation for a stable regular beat [1] and proposed the *VO*<sub>2</sub> per beat prediction method for each individual arrhythmic beat [4]. Although the *VO*<sub>2</sub> predictability for a stable regular beat is solid empirically [1], that of an arrhythmic beat is not yet so because no direct method is yet available to confirm it on a per-arrhythmic-beat basis.

As the representative *a* and *b* values of canine LVs, we used *a* = 1.8 × 10<sup>-5</sup> ml O<sub>2</sub>/(mmHg ml) and *b* = 1.0 × 10<sup>-3</sup> ml O<sub>2</sub>/(mmHg/ml) [1, 9]. We could reasonably assume these *a* and *b* values to be independent of the LV loading and contractile conditions (1). As for the *c* value, we used *c* = 1.0 × RR/60,000 ml O<sub>2</sub>/beat, all per 100 g LV. Here, 1.0 is in ml O<sub>2</sub>/min, and both RR (ECG R-R interval) and 60,000 are in ms. Since these representative values have some variations even among normal canine hearts (1), the above calculated *VO*<sub>2</sub> values could serve as representatively estimated values in normal canine LVs.

#### External work (EW) efficiency

The EW efficiency is defined as *EW/VO*<sub>2</sub>. We obtained *EW* as the area within each arrhythmic *P*–*V* loop (Fig. 1b). We divided it by the above-estimated *VO*<sub>2</sub>. Namely,

$$EW/VO_2 = EW/(aPVA + bE_{max} + c) \quad (2)$$

*EW* in mmHg ml was converted to *EW* in joule (J), using 1 mmHg ml = 1.33 × 10<sup>-4</sup> J. *VO*<sub>2</sub> in ml O<sub>2</sub> was also converted to *VO*<sub>2</sub> in J by 1 ml O<sub>2</sub> = 20 J (1). Therefore, *EW/VO*<sub>2</sub> became dimensionless between 0 and 1 or percent between 0 and 100%.

#### Statistical analyses

We analyzed the basic statistics [10, 11] of the obtained mechanoenergetic variables of individual arrhythmic beats sampled for 1 min in each of the six hearts. We had shown that 1 min was long enough to obtain a large enough number of arrhythmic beats for statistical analyses since we had found both *E*<sub>max</sub> and *PVA* to distribute normally even within 1 min [8]. We used Microsoft Office 2004 Excel and SAS StatView 5.0 for the statistical analyses.

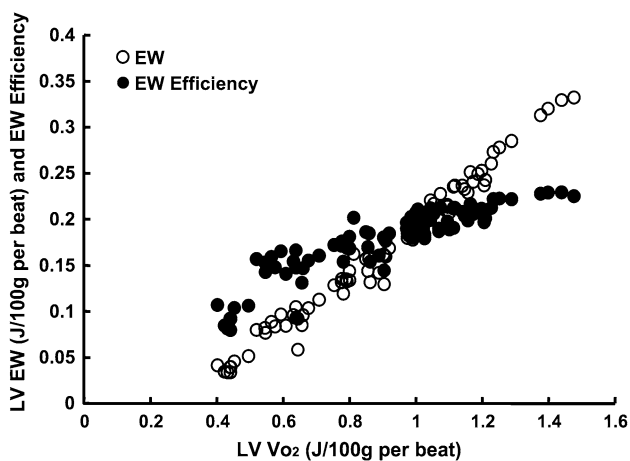
## Results

Figure 1 shows a representative set of continuous LV  $P$ – $V$  loops of arrhythmic beats under AF in one canine heart (Panel a) and a representative one of these loops (Panel b). The loops clearly show that their  $E_{\max}$  fluctuated among the arrhythmic beats, and their SV, EW, PE, PVA (=PE + EW), EDV, and ESP also fluctuated simultaneously. As for these fluctuations under AF, we have already analyzed them in detail [4, 5, 8, 12–15].

Figure 2 plots LV EW (open circles) and its efficiency (solid circles) against the predicted LV  $VO_2$  of arrhythmic beats for 30 s in one canine heart. The EW –  $VO_2$  data fell fairly linearly with an extrapolated  $VO_2$  intercept of  $\sim 0.3$  J/100 g per beat. Since the mean arrhythmic heart rate was  $\sim 200$  beats/min, this extrapolated  $VO_2$  intercept per beat corresponds to  $\sim 60$  J/100 g per min. Although this  $VO_2$  intercept was about three times a representative basal metabolic rate of 1 ml  $O_2$ /min or 20 J/100 g/min under KCl arrest, we consider it physiologically reasonable because it was comparable to a representative PVA-independent  $VO_2$  of 0.3 J/100 g per regular beat in a relatively low  $E_{\max}$  (1), consisting of both basal metabolic  $VO_2$  and excitation–contraction coupling  $VO_2$ . Similar EW –  $VO_2$  relations were observed in all the other hearts.

The EW efficiency corresponds to the slope of the line connecting the respective EW –  $VO_2$  data (open circle) to the origin, but not to the positive  $VO_2$  intercept, indicating the PVA-independent  $VO_2$ . As the result, the EW efficiency tended to saturate as  $VO_2$  increased. Similar EW efficiency- $VO_2$  relations were observed in all the other hearts.

Figure 3 shows the frequency distribution histogram of the EW efficiency of the same data used in Fig. 2. The histogram obviously appeared to skew rightward as



**Fig. 2** Scattergram of left ventricular (LV) external work (EW) (open circles) and work efficiency (solid squares, dimensionless) on the ordinate against LV  $O_2$  consumption ( $VO_2$ ) on the abscissa in one canine heart under electrically induced atrial fibrillation

compared to the normal distribution curve, although  $\chi^2$  was not statistically significant ( $P > 0.05$ ). Similar distributions of the EW efficiency were observed in all the other hearts.

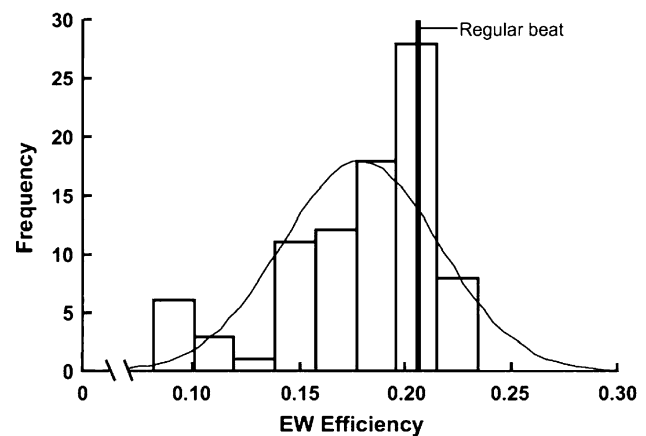
Figure 3 evidently shows that the mode EW efficiency of the arrhythmic beats was comparable to the constant EW efficiency of the regular beats and the maximum EW efficiency was variably greater than the stable EW efficiency of the regular beats ( $P < 0.01$ , paired  $t$  test).

Table 1 compares the EW efficiency data of the arrhythmic beats under AF and regular beats in each of the six hearts. Paired comparisons between them also showed that the maximum efficiency was significantly greater than the efficiency of regular beats in every heart as well as on average and the mode efficiency was comparable to the regular beat efficiency.

However, the mean efficiency was significantly smaller than the regular beat efficiency in every heart as well as on average (Fig. 3; Table 1).

## Discussion

This is the first study to have revealed the statistical characteristics of the distribution of EW efficiency of individual arrhythmic beats under electrically induced AF in non-failing hearts, though canine hearts. The mode EW efficiency (15% on average) of the LV arrhythmic beats under electrically induced AF was comparable to the mean EW efficiency (15%) of the regular beats in the six normal canine in situ hearts (Table 1). Moreover, the maximum EW efficiency (18% on average) under AF was greater than the mean EW efficiency of the regular beats in these hearts (Table 1).



**Fig. 3** Frequency distribution histogram of external work (EW) efficiency of arrhythmic beats under atrial fibrillation in a canine heart skewed to the higher efficiency and exceeded the mean EW efficiency of regular beats

**Table 1** Comparison of external work efficiency between arrhythmic and regular beats under atrial fibrillation in six hearts

Heart	Arrhythmic				Regular
	Minimum	Mean	Mode	Maximum	
1 (relative)	0.045 (35%)	0.107 (83%)	0.120 (93%)	0.138 (107%)	0.129 (100%)
2 (relative)	0.068 (50%)	0.132 (98%)	0.145 (107%)	0.161 (119%)	0.135 (100%)
3 (relative)	0.065 (41%)	0.116 (73%)	0.125 (78%)	0.178 (111%)	0.160 (100%)
4 (relative)	0.037 (27%)	0.119 (87%)	0.145 (106%)	0.190 (139%)	0.137 (100%)
5 (relative)	0.036 (24%)	0.145 (96%)	0.155 (106%)	0.191 (127%)	0.151 (100%)
6 (relative)	0.081 (39%)	0.179 (87%)	0.205 (100%)	0.232 (113%)	0.206 (100%)
Efficiency mean	0.055	0.133	0.149	0.182	0.153
SD	0.019	0.026	0.030	0.032	0.028
Relative mean	36%	88%	99%	122%	100%
SD	11%	10%	12%	11%	0%
<i>P</i> for paired <i>t</i>	<0.0001	<0.05	>0.5 (ns)	<0.01	Control

Arrhythmic columns list minimum, mean, mode (i.e., most frequent), and maximum efficiencies of arrhythmic beats under atrial fibrillation in comparison with constant efficiency of regular beats in each of six left ventricles. Paired *t* tests were applied between each of minimum, mean, mode, and maximum efficiencies of arrhythmic beats and efficiency of regular beats in the respective hearts. *ns*: *P* > 0.05

As Fig. 2 indicates, EW can be expressed as a linear function as

$$EW = p VO_2 + q. \tag{3}$$

Here, *p* is the slope of the  $VO_2$ -EW relation (*p* > 0) and *q* is the extrapolated EW axis intercept of the relation (*q* < 0). So, the EW efficiency can be expressed as

$$EW/VO_2 = p + q/VO_2. \tag{4}$$

As seen in Fig. 2, the EW efficiency showed the hyperbolic relation. This hyperbolic relation means the higher EW efficiency at the beat consuming the more oxygen. The short RRs in both regular tachycardia and AF, both decreasing the contractile force and shortening the filling time, decrease PVA, EW, and  $VO_2$  per beat. Thus, this hyperbolic relation between  $VO_2$  and EW efficiency indicates that the shorter RR causes the lower EW efficiency and may account for the reason of the beneficial effect of the rate control therapy for patients suffering from AF [16, 17].

The mean EW efficiency (13%) of the arrhythmic beats was, however, significantly smaller than the stable EW efficiency (15%) of the regular beats (Table 1). This confirms the already known experimental and clinical findings [18–21].

These mean, mode, and maximum efficiencies of the arrhythmic beats were also within the normal working ranges found not only in our previous studies on normal canine hearts [1, 22, 23], but also in other studies [24].

There are some limitations in this study. We were unable to compare  $EW/VO_2$  at the same heart rate between the irregular beats under AF and the regular beats under the regular atrial pacing. The latter was 22% lower than the

former. This was simply because the LV started to have pulsus alternans already at a pacing rate before reaching the mean arrhythmic heart rate under AF. Therefore, we cannot yet state that the present results would hold if the pacing rate is matched with the mean arrhythmic heart rate under AF.

An obvious limitation of the present study existed in the LV volumetry with the conductance catheter. The LV conductance changed even in the isovolumic contraction and relaxation phases due to the deformation of the LV cavity, as seen in Fig. 1. Therefore, even when no SV and hence no EW is produced in a relatively weak contraction, the *P*-*V* loop is a slightly open loop, but not a vertical line with zero width. For this reason, the minimum EWs even of weak arrhythmic beats presumably without SV were not zero as shown in Figs. 1 and 2. Therefore, the minimum EW efficiency was not zero as shown by the leftmost slightly high histogram bar in Fig. 3.

To evaluate the effect of this volume error, we zeroed the efficiency values of the leftmost histogram bar and reanalyzed the frequency distribution. As the result, the minimum EW efficiency could be zero, and the mean value would decrease in Table 1. Although this correction could increase the absolute value of the negative skewness and the positive kurtosis and augment the non-normality, the mode and maximum values in Table 1 remained unchanged.

Another limitation is that the present study was performed in normal, but not failing hearts. Therefore, the present finding cannot simply be extrapolated to variably failing hearts.

Taken together, only the mode, but not the mean, minimum, and maximum of the left ventricular EW efficiency

of arrhythmic beats under AF remained comparable to the stable efficiency at the regular tachycardia, which was, however, slightly lower than the mean arrhythmic tachycardia in the normal canine hearts. We reasonably accounted for these statistical findings mentioned above by the ratio of the normally distributing EW of each beat under AF to the respective  $\text{VO}_2$  linearly correlating with EW, but always containing a considerable PVA-independent  $\text{VO}_2$  consisting of both basal metabolic  $\text{VO}_2$  and excitation-contraction coupling  $\text{VO}_2$ . These cardiac energetic properties should be recognized to elucidate the mechanisms of the decreased cardiac performance under AF.

**Acknowledgments** We appreciated Hiroki Yamaguchi, MD, PhD, for his surgical contribution to this series of experiments in Okayama University. This work was partly supported by Scientific Research Grants nos. 13558113, 13770350, 13878185, 13878192, 14380405, 15650095, 15659186, 16659057, 17390230, 17390231, 18650125, and 20300162 from the Ministry of Education, Culture, Sports, Science and Technology, and Cardiovascular Diseases Research Grants (11C-1, 14A-1) from the Ministry of Health, Labor, and Welfare, both of Japan.

## References

- Suga H (1990) Ventricular energetics. *Physiol Rev* 70:247–277
- Sagawa K, Maughan L, Suga H, Sunagawa K (1988) Cardiac contraction and the pressure–volume relationship. Oxford Univ Press, New York, pp 232–298
- Suga H, Sagawa K, Shoukas AA (1973) Load independence of the instantaneous pressure–volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res* 32:314–322
- Shimizu J, Mohri S, Iribe G, Ito H, Morita T, Yamaguchi H, Sano S, Suga H (2005) Predictability of  $\text{O}_2$  consumption from contractility and mechanical energy of absolute arrhythmic beats in canine heart. *Jpn J Physiol* 55:135–142. doi:10.2170/jjphysiol.R2099
- Yamaguchi H, Takaki M, Ito H, Tachibana H, Lee S, Suga H (1997) Pressure–interval relationship characterizes left ventricular irregular beat contractilities and their mean level during atrial fibrillation. *Jpn J Physiol* 47:101–110. doi:10.2170/jjphysiol.47.101
- Baan J, van der Velde ET, de Bruin HG, Smeenk GJ, Koops J, van Dijk AD, Temmerman D, Senden J, Buis B (1984) Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation* 70:812–823
- Suga H, Hisano R, Ninomiya I (1982) Digital on-line computation of a predictor of cardiac oxygen consumption. Left ventricular systolic pressure volume area. *Jpn Heart J* 23:749–758
- Morita T, Araki J, Oshima Y, Mitani H, Iribe G, Mohri S, Shimizu J, Sano S, Kajiya F, Suga H (2002) Frequency distribution, variance, and moving average of left ventricular rhythm and contractility during atrial fibrillation in dog. *Jpn J Physiol* 52:41–49. doi:10.2170/jjphysiol.52.41
- Ohgoshi Y, Goto Y, Futaki S, Yaku H, Kawaguchi O, Suga H (1990) New method to determine oxygen cost for contractility. *Jpn J Physiol* 40:127–138. doi:10.2170/jjphysiol.40.127
- Snedecor G, Cochran W (1971) Statistical methods, 6th edn. Ames, Iowa, Iowa State Univ Press
- Glantz S. (1981) Primer of biostatistics. McGraw-Hill Book Co. New York, pp 217–221, 284–292
- Mohri S, Shimizu J, Iribe G, Ito H, Morita T, Yamaguchi H, Sano S, Suga H (2005) Normal distribution of ventricular pressure–volume area (PVA) of arrhythmic beats under atrial fibrillation in canine heart. *Am J Physiol Heart Circ Physiol* 288:H1740–H1746. doi:10.1152/ajpheart.00584.2004
- Mitani H, Yamaguchi H, Morita T, Oshima Y, Shimizu J, Ito H, Araki J, Takaki M, Sano S, Suga H (2000) Effective arterial elastance of irregular beats during atrial fibrillation in canine left ventricle. *Jpn J Physiol* 50:77–89. doi:10.2170/jjphysiol.50.77
- Shimizu J, Mohri S, Ito H, Yamaguchi H, Sano S, Takaki M, Suga H (2006) High mechanical efficiency of left ventricular arrhythmic contractions during atrial fibrillation. *J Physiol Sci* 56:269–274. doi:10.2170/physiolsci.RP004206
- Mohri S, Shimizu J, Ito H, Yamaguchi H, Sano S, Takaki M, Suga H (2005) Variable unstressed volume keeps normal distributions of canine left ventricular contractility and total mechanical energy under atrial fibrillation. *Jpn J Physiol* 55:255–264. doi:10.2170/jjphysiol.RP000405
- Savelieva I, Camm AJ (2004) Atrial fibrillation and heart failure: natural history and pharmacological treatment. *Europace* 5:S5–S19. doi:10.1016/j.eupc.2004.07.003
- The Atrial fibrillation follow-up investigation of rhythm management (AFFIRM) investigators (2002) A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 347:1825–1833
- Brookes CI, White PA, Staples M, Oldershaw PJ, Redington AN, Collins PD, Noble MI (1998) Myocardial contractility is not constant during spontaneous atrial fibrillation in patients. *Circulation* 98:1762–1768
- Kerr AJ, Simmonds MB, Stewart RA (1998) Influence of heart rate on stroke volume variability in atrial fibrillation in patients with normal and impaired left ventricular function. *Am J Cardiol* 82:1496–1500. doi:10.1016/S0002-9149(98)00693-6
- Muntinga HJ, Gosselink AT, Blanksma PK, De Kam PJ, Van Der Wall EE, Crijns HJ (1999) Left ventricular beat to beat performance in atrial fibrillation: dependence on contractility, preload, and afterload. *Heart* 82:575–580
- Yamada H, Mowrey KA, Popovic ZB, Kowalewski WJ, Martin DO, Thomas JD, Wallick DW (2004) Coupled pacing improves cardiac efficiency during acute atrial fibrillation with or without cardiac dysfunction. *Am J Physiol Heart Circ Physiol* 287:H2016–H2022. doi:10.1152/ajpheart.00347.2004
- Suga H, Igarashi Y, Yamada O, Goto Y (1985) Mechanical efficiency of the left ventricle as a function of preload, afterload, and contractility. *Heart Vessels* 1:3–8. doi:10.1007/BF02066480
- Nozawa T, Yasumura Y, Futaki S, Tanaka N, Uenishi M, Suga H (1988) Efficiencies from consumed  $\text{O}_2$  and pressure–volume area to work of in situ dog heart. *Jpn J Physiol* 38:713–728. doi:10.2170/jjphysiol.38.713
- Gibbs CL, Barclay CJ (1995) Cardiac efficiency. *Cardiovasc Res* 30:627–634
- Sunagawa K, Maughan WL, Burkhoff D, Sagawa K (1983) Left ventricular interaction with arterial load studied in isolated canine heart. *Am J Physiol* 245:H773–H780