New Method to Determine Oxygen Cost for Contractility

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Abstract We developed a new method to determine the oxygen cost for myocardial contractility and applied it to epinephrine in the excised cross-circulated dog heart. We utilized the relation between myocardial oxygen consumption (V_{O_2}) and the systolic pressure-volume area (PVA) which represents the total mechanical energy generated by contraction. We first obtained a reference V_{O_2} -PVA relation in a baseline contractile state. Then, the end-diastolic and stroke volumes were fixed constant and a global index of ventricular contractility, E_{max} , was enhanced by infusing epinephrine. The V_{O_2} -PVA data point was shifted linearly right-upward with the increases in E_{max} . From the slopes of both the reference V_{O_2} -PVA relation line and the regression line of V_{O_2} on PVA during the gradually increased E_{max} , we calculated the oxygen cost for contractility, i.e., the ratio of the elevation of the V_{O_2} -PVA relation to enhanced E_{max} in each heart. The ratio was 0.00095 ± 0.00013 ml $O_2 \cdot$ ml $\cdot$ mmHg $^{-1} \cdot$ beat $^{-1} \cdot$ 100 g LV $^{-2}$. The result indicates that the oxygen cost for contractility can be reliably and efficiently determined by this new method.

Key words: heart, contractile state, E_{max} , pressure-volume area, excitation-contraction coupling.

A greater myocardial oxygen consumption (V_{O_2}) is required for the same level of mechanical work when the contractile state is enhanced (GRAHAM *et al.*, 1968). We have shown that the total mechanical energy generated by ventricular contraction, as quantified by the systolic pressure-volume (P - V) area (PVA), correlates closely and linearly with myocardial oxygen consumption (V_{O_2}) in a given contractile state in the left ventricle (LV) of the excised, cross-circulated dog heart (SUGA, 1979; SUGA *et al.*, 1981a). We have further demonstrated that, when the LV contractility is enhanced, the V_{O_2} -PVA relation shifts upward in a parallel manner (SUGA *et al.*, 1983). This upward shift is primarily attributable to an increase in V_{O_2} component for activation or excitation-contraction coupling associated with

enhancement of the contractile state because V_{O_2} for basal metabolism remains unchanged (KLOCKE *et al.*, 1966; GIBBS *et al.*, 1982; SUGA *et al.*, 1983; NOZAWA *et al.*, 1988).

The oxygen cost for contractility, i.e., the ratio of the elevation of the V_{O_2} -PVA relation to enhanced E_{max} , has been determined by two or more V_{O_2} -PVA regression lines for positive or negative inotropic interventions (SUGA *et al.*, 1983; BURKHOFF *et al.*, 1987). However, each regression line requires two (BURKHOFF *et al.*, 1987) or more V_{O_2} -PVA data points (SUGA *et al.*, 1983) to be obtained under different loading conditions in a stable contractile state.

In order to determine specifically and more efficiently the oxygen cost for contractility in a given heart, we devised a new method appropriate to the excised cross-circulated dog heart preparation.

MATERIALS AND METHODS

Surgical preparation. We made ten excised, cross-circulated dog heart preparations by the same method as described previously (SUGA *et al.*, 1983). In each experiment, two mongrel dogs (10–17 kg) were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) after premedication with ketamine hydrochloride (7 mg/kg, i.m.). Blood was heparinized (1,000 U/kg) in both dogs. The smaller dog of the two was used as a heart donor, and the larger dog as a supporter of the heart preparation.

The heart donor dog was thoracotomized midsternally under artificial ventilation and the heart-lung section was isolated from the systemic circulation. The left subclavian artery of the heart preparation was cannulated and connected to the common carotid arteries of the support dog. The right ventricle (RV) was cannulated via the right atrium and connected to the external jugular vein of the support dog. The bilateral pulmonary hili were ligated and the cross circulation was started. The supported beating heart was excised from the chest.

The left atrium was opened widely and a thin latex balloon with an unstressed volume greater than 50 ml was fitted into the LV chamber and the mouth of the balloon was fixed at the mitral annulus. The balloon was connected to the volume servo-pump which was described in detail elsewhere (SUGA *et al.*, 1983).

LV pressure was measured with a Konigsberg P-7 miniature pressure gauge placed inside the apical end of the balloon. The LV ECG was recorded and used to trigger the volume command signal of the servo-pump. Heart rate was fixed constant by left atrial pacing (170 ± 7 beats/min) in each heart.

A roller pump (3R-SH, Junken) was placed in the middle of the arterial cross-circulation tube to maintain mean coronary perfusion pressure stable within ± 10 mmHg around a mean level of 107 ± 23 (S.D.) mmHg. Arterial blood pH, P_{O_2} , and P_{CO_2} were maintained within their physiological ranges by supplemental oxygen and intravenous sodium bicarbonate. The heart temperature was maintained at 35–37°C. After the experiment, the LV including the septum and the RV free

Fig. 1. Pressure-volume area (PVA) consists of external mechanical work (EW) and end-systolic elastic potential energy (PE) in the pressure-volume diagram. ED, end-diastolic P - V relation curve; ES, end-systolic P - V relation line; $E_{\max}$, means the slope of ES; TJ, P - V trajectory; V_{es} , end-systolic volume; V_{ed} , end-diastolic volume; SV, stroke volume; V_0 , volume-axis intercept of the ES.

wall were weighed. LV weight was 72 ± 10 g. RV weight was 26 ± 4 g.

Contractility index ($E_{\max}$). We assessed LV contractile state by $E_{\max}$ of individual contractions in the same way as before (SUGA and SAGAWA, 1974; SUGA *et al.*, 1983). Briefly, we computed $E_{\max}$ as the maximal value of instantaneous ratio of $P(t)/(V(t) - V_0)$ with the signal processing computer. $P(t)$ and $V(t)$ are instantaneous ventricular pressure and volume, respectively, in one contraction. V_0 is LV volume at which peak isovolumic pressure is 0. $E_{\max}$ is therefore the slope of the end-systolic P - V line, as shown in Fig. 1. $E_{\max}$ was normalized for 100 g LV, and its dimensions were mmHg/(ml/100 g LV).

Pressure-volume area (PVA). PVA is a specific area in the pressure-volume (P - V) diagram that is circumscribed by the end-systolic P - V line, the end-diastolic P - V curve, and the systolic segment of the P - V trajectory as schematically illustrated in Fig. 1. PVA consists of two elements: the external mechanical work (EW) performed by the LV, and the mechanical potential energy (PE) accumulated in the LV until the time of end-systole. PVA represents theoretically the total mechanical energy generated during one LV contraction (SUGA, 1979).

Cardiac C_2 consumption. We determined V_{O_2} per minute as the product of coronary flow and arteriovenous O_2 content difference with a signal processing computer (7T-18, NEC-Sanei). Total coronary flow (ml/min) was measured continuously with an electromagnetic flowmeter (MVF 2100, Nihon Kohden) by placing an in-line probe (FF-050T) in the coronary venous draining tube. Coronary arteriovenous O_2 content difference was measured with a continuous arteriovenous O_2 difference analyzer, either an A-VOX (SHEPHERD and BURGAR, 1977) or an Erma

PWA-200S (SUGA *et al.*, 1989). The bypassed venous blood was returned to the venous tube upstream of the flowmeter. V_{O_2} per beat (ml O_2 /beat) was obtained by dividing V_{O_2} per minute by heart rate in a steady state.

Experimental protocol. Reference run: At first, an experimental run was performed in a baseline contractile state without any intentional inotropic interventions in each heart. Different loading conditions were imposed on each LV, either isovolumic or ejecting or both (SUGA *et al.*, 1981b), to cover a wide range of PVA. We obtained $E_{\max}$, PVA, and V_{O_2} and subjected V_{O_2} and PVA data to regression analyses.

Enhancement run: After the reference run, end-diastolic ventricular volume (V_{ed}) was fixed to a low level so that end-systolic ventricular pressure of the pre-enhancement contraction was about 70 mmHg. Stroke volume (SV) was also kept constant in ejecting contractions. Next, contractile stage was enhanced by infusing epinephrine at stepwise increased infusion rates up to about 5 μ g/min into the femoral vein of the support dog. When the contractile state was stably enhanced at 3 min after increasing the infusion rate, $E_{\max}$, PVA, and V_{O_2} were measured. The regression line of these V_{O_2} -PVA data points provides the V_{O_2} -PVA relation at stepwise increased $E_{\max}$ levels as shown in Fig. 2. We call hereafter this regression line " V_{O_2} -PVA composite line." Both V_{ed} and SV were kept constant throughout the enhancement run.

Oxygen cost for contractility. The oxygen cost for contractility was determined by the following method. PVA can be calculated as the sum of the areas for EW and PE (Fig. 1), and is expressed as

$$\begin{aligned} \text{PVA} &= \{(V_{es} - V_0)^2 E_{\max}\} / 2 + (V_{es} - V_0) \text{SV} \cdot E_{\max} \\ &= (V_{es} - V_0) \{(V_{es} - V_0) / 2 + \text{SV}\} E_{\max}, \end{aligned} \quad (1)$$

when V_{es} = end-systolic volume. In Eq. (1), end-diastolic pressure was neglected and hence a small area under the end-diastolic P - V curve, if any, was neglected. However, since we set the end-diastolic pressure close to 0, Eq. (1) was reasonable in this study. Equation (1) is converted to

$$E_{\max} = 2 \cdot \text{PVA} / [(V_{es} - V_0) \{(V_{es} - V_0) + 2 \cdot \text{SV}\}]. \quad (2)$$

When we replace $k = 2 / [(V_{es} - V_0) \{(V_{es} - V_0) + 2 \cdot \text{SV}\}]$, Eq. (2) can be expressed as

$$E_{\max} = k \cdot \text{PVA}. \quad (3)$$

In our previous study (SUGA *et al.*, 1985), we have shown that V_{O_2} is empirically formulated by

$$V_{O_2} = A \cdot \text{PVA} + B \cdot E_{\max} + C, \quad (4)$$

where A is the slope of the reference V_{O_2} -PVA relation in a constant contractile state, (as obtained in the reference run in each experiment), B is a coefficient of $E_{\max}$, and C is V_{O_2} for basal metabolism during one contraction cycle. The B in

Fig. 2. The steep diagonal solid line, called " V_{O_2} -PVA composite line," indicates schematically the linear regression line of V_{O_2} on PVA obtained during gradual increases in E_{max} in enhancement run. The lower solid line is the reference V_{O_2} -PVA regression line. The upper several dashed lines in parallel with the reference V_{O_2} -PVA regression lines are the hypothetical V_{O_2} -PVA relation lines passing through the V_{O_2} -PVA data points obtained in gradually enhanced E_{max} levels.

Eq. (4) represents the oxygen cost for contractility to be obtained in this study. We can reasonably regard A and C to be independent of contractility (SUGA *et al.*, 1983), and B to be independent of V_{ed} (YASUMURA *et al.*, 1989). Based on this preload-independent B , we assumed B to be also independent of PVA.

Combining Eqs. (3) and (4) yields

$$V_{O_2} = (A + B \cdot k)PVA + C. \quad (5)$$

The term $(A + B \cdot k)$ is considered to be equal to the slope (A^*) of the V_{O_2} -PVA composite line, i.e., the regression coefficient of the regression line of V_{O_2} on PVA obtained at various levels of E_{max} , shown in Fig. 2. $A^* = (A + B \cdot k)$ can be rearranged as

$$B = (A^* - A)/k, \quad (6)$$

where k is the empirical constant in each heart as defined above.

The B was determined from A^* , A , and k values in each heart using Eq. (6). The B values were finally normalized for 100 g LV by multiplying B by $100^2/\{LVW(LVW + RVW)\}$ (see APPENDIX). Dimensions of normalized B (B_n) were $\text{ml } O_2 \cdot \text{ml} \cdot \text{mmHg}^{-1} \cdot \text{beat}^{-1} \cdot 100 \text{ g LV}^{-2}$.

Basal metabolic V_{O_2} . Equations (4) and (5) also show that V_{O_2} for basal metabolism can be estimated from the V_{O_2} -axis intercept C by the present method without arresting cardiac contraction with KCl. This C value is also normalized for 100 g LV. Heart rate times C gave basal metabolic V_{O_2} per minute.

Statistics. Probability values smaller than 0.05 indicate statistical significance. Data are presented as mean $\pm$ S.D.

Table 1. Statistical data in individual hearts.

Exp. No.	A (ml O ₂ / (mmHg·ml))	r_1	Range of $E_{\max}$ (mmHg/ (ml/100 g LV))	A^* (ml O ₂ / (mmHg·ml))	r_2	B_n (ml O ₂ ·ml·mmHg ⁻¹ · beat ⁻¹ ·100 g LV ⁻²)	BM V_{O_2} (ml O ₂ ·min ⁻¹ · 100 g LV ⁻¹)
1	2.18	0.98	20.3-60.7	13.70	0.99	0.00111	2.96
2	1.34	0.99	5.8-11.9	2.96	0.99	0.00111	2.48
3	1.88	0.99	7.4-34.4	6.50	0.99	0.00103	3.19
4	1.81	0.94	5.7-9.3	3.70	0.97	0.00089	3.96
5	1.21	0.98	7.4-28.2	4.30	0.99	0.00074	2.16
6	1.69	0.98	13.4-26.3	12.74	0.97	0.00093	3.35
7	1.76	0.98	11.7-31.2	12.84	0.99	0.00086	2.65
8	1.98	0.98	18.1-48.5	29.18	0.99	0.00083	2.83
9	1.74	0.99	7.4-23.0	3.22	0.98	0.00082	1.93
10	2.05	0.97	9.1-20.0	3.90	0.99	0.00114	3.25
Mean	1.76			9.30		0.00095	2.88
±S.D.	±0.28			±7.81		±0.00013	±0.57

Exp. No., experiment number; A , slope of the reference regression line of V_{O_2} on PVA in reference run; r_1 , correlation coefficient between V_{O_2} and PVA in reference run. Range of $E_{\max}$: operating range of $E_{\max}$ in enhancement run, which was normalized for 100 g LV. A^* , slope of the composite regression line of V_{O_2} on PVA in enhancement run; r_2 , correlation coefficient between V_{O_2} and PVA in enhancement run; B_n , the oxygen cost for contractility, normalized for 100 g LV; BM V_{O_2} , basal metabolic V_{O_2} per minute.

RESULTS

Table 1 summarizes the slopes (A in Eqs. (4)–(6)) of the reference V_{O_2} -PVA regression lines, the ranges of $E_{\max}$, the slopes (A^* in Eq. (6)) of the V_{O_2} -PVA composite lines in the enhancement runs, the B_n values as the oxygen cost for contractility, and basal metabolic V_{O_2} in all experiments.

Reference run

The mean $E_{\max}$ value in the reference run was 10.2 ± 4.0 mmHg/(ml/100 g LV). V_{O_2} increased linearly with increases in PVA in any LV. The mean A value was $(1.76 \pm 0.28) \times 10^{-5}$ ml O_2 /(mmHg · ml), as shown in Table 1. The V_{O_2} intercept of the reference V_{O_2} -PVA regression line ($B \cdot E_{\max} + C$ in Eq. (4)) was 0.024 ± 0.005 ml $O_2 \cdot \text{beat}^{-1}$. The correlation coefficient (r_1) between V_{O_2} and PVA was almost unity, indicating the high linearity of the reference V_{O_2} -PVA regression line. These slope and V_{O_2} intercept values are comparable to the corresponding values in the baseline contractile state in our previous studies (SUGA *et al.*, 1983, 1988a, b, c; FUTAKI *et al.*, 1988; WU *et al.*, 1989).

Enhancement run

Figure 3 shows a representative set of tracings in the enhancement run. With

Fig. 3. Representative tracings of left ventricular pressure (LVP), left ventricular volume (LVV), epicardial electrocardiograph (ECG), coronary flow (CF), coronary arteriovenous oxygen content difference (AVOD), and left ventricular pressure-volume (P - V) trajectory from top down in enhancement run in one heart. With increases in the infusion rate of epinephrine in the order from Panel A to E, the slope of the end-systolic P - V line ($E_{\max}$) also increased.

Fig. 4. Representative V_{O_2} -PVA data in reference run (open circles) and in enhancement run (solid circles). The dashed line indicates the reference V_{O_2} -PVA regression line, whose slope is A . The steep solid line indicates the V_{O_2} -PVA composite line, whose slope is A^* .

increases in epinephrine, all $E_{\max}$, PVA, coronary flow, and arteriovenous O_2 content difference increased. As shown in Fig. 4, the V_{O_2} -PVA data point shifted linearly in a right-upward direction from the pre-enhancement point on or near the reference V_{O_2} -PVA relation with the increases in $E_{\max}$ in each heart. The mean A^* value of the V_{O_2} -PVA composite lines was $(9.30 \pm 7.81) \times 10^{-5}$ ml O_2 /(mmHg $\cdot$ ml), as shown in Table 1. The correlation coefficient (r_2) between V_{O_2} and PVA was almost unity, indicating the high linearity of the composite V_{O_2} -PVA regression line.

The mean value of the resultant normalized B (B_n) values was 0.00095 ± 0.00013 ml $O_2 \cdot$ ml $\cdot$ mmHg $^{-1} \cdot$ beat $^{-1} \cdot$ 100 g LV $^{-2}$, as shown in Table 1. There was no significant correlation ($r = -0.21$, $p > 0.5$) between A^* and B_n values.

The mean value for the V_{O_2} intercept of the V_{O_2} -PVA composite line (C in Eqs. (4) and (5)) was 0.017 ± 0.003 ml $O_2 \cdot$ beat $^{-1} \cdot$ 100 g LV $^{-1}$. The mean value for basal metabolic V_{O_2} per minute was 2.88 ± 0.57 ml $O_2 \cdot$ min $^{-1} \cdot$ 100 g LV $^{-1}$.

DISCUSSION

We have shown in our previous studies (SUGA *et al.*, 1983; SUGA *et al.*, 1988a, b, c; FUTAKI *et al.*, 1988; WU *et al.*, 1989) that the V_{O_2} -PVA relation obtained in a given contractile state shifts up or down in a parallel manner with positive or negative inotropic interventions, respectively. The changes in the V_{O_2} intercept of the V_{O_2} -PVA relation (i.e., unloaded V_{O_2}) with changes in contractility are considered to be primarily due to the changes in the V_{O_2} component for excitation-contraction coupling, because the V_{O_2} component for basal metabolism is relatively constant despite inotropic interventions (GIBBS *et al.*, 1982; SUGA *et al.*, 1983; NOZAWA *et al.*, 1988). As an extension of these studies, we have demonstrated in the present study that the elevation of the V_{O_2} -PVA relation correlated linearly with contractility

over a wide range of $E_{\max}$ and the oxygen cost for contractility (B in Eq. (4)) could be reliably determined over the same wide range of $E_{\max}$.

In our previous studies (SUGA *et al.*, 1983; FUTAKI *et al.*, 1988; SUGA *et al.*, 1988a, b, c; WU *et al.*, 1989), we have discussed the oxygen cost for contractility with various inotropic interventions. The cost has been determined from the elevations of two parallel V_{O_2} -PVA relation lines in baseline and either enhanced or depressed contractile state. BURKHOFF *et al.* (1987) have confirmed the parallelism of the V_{O_2} -PVA relation lines obtained in several different contractile states and obtained a B value from them in a given heart, although they obtained only a set of one loaded and one unloaded data point in each contractile state.

To obtain a reliable B value, it is important to shorten the data measurement time because fixed magnitudes of a given inotropic intervention will not necessarily guarantee constant levels of contractility during a long measurement period. In this respect, the present method is much simpler and requires less time than the previous methods to determine a B value, because only several V_{O_2} -PVA data points are needed to cover a wide range of $E_{\max}$. This feature of time-saving is the main merit of the new method, particularly in comparison of B values for different inotropic agents in a given heart. In addition, we can compare B values at fixed V_{ed} and SV. This condition will minimize the complex effects on $E_{\max}$, PVA, and V_{O_2} of volume- or length-dependent factors such as length-dependent activation (TUCCI *et al.*, 1984) and the shortening deactivation and activation (HUNTER *et al.*, 1983).

The B values measured by the conventional method varied considerably among epinephrine (SUGA *et al.*, 1983), calcium (SUGA *et al.*, 1983), OPC-8212 (FUTAKI *et al.*, 1988), ouabain (WU *et al.*, 1989), decreased coronary perfusion pressure (SUGA *et al.*, 1988c), paired pulse pacing (SUGA *et al.*, 1988a), and cardiac cooling (SUGA *et al.*, 1988b) as well as among different hearts, ranging 10-fold between 0.0005 and 0.005 ml $O_2 \cdot ml \cdot mmHg^{-1} \cdot beat^{-1} \cdot 100 g LV^{-2}$. BURKHOFF *et al.* (1987) have also reported mean B value of 0.0036 ml $O_2 \cdot ml \cdot mmHg^{-1} \cdot beat^{-1} \cdot 100 g LV^{-2}$. The present B values were close to the lower end of this range except for the lowest B value for cooling (SUGA *et al.*, 1988b). Factors causing such a variation of the B values among different inotropic interventions can be studied more reliably and efficiently in the same groups of hearts by using the present method.

As for the V_{O_2} intercept (C) of the V_{O_2} -PVA composite line, there is a scatter of basal metabolic V_{O_2} among different hearts in the present study as well as in the literature. The mean value for basal metabolic V_{O_2} in the present results was double the values directly determined under KCl arrest in blood-perfused dog hearts (GIBBS *et al.*, 1982; SUGA *et al.*, 1983; NOZAWA *et al.*, 1988). Because the present basal metabolic V_{O_2} was determined by extrapolation from beating LV data, it contains V_{O_2} for electrical activation of the frequency equal to heart rate. KLOCKE *et al.* (1966) have shown V_{O_2} for electrical activation to be 0.0004 ml $O_2 \cdot 100 g^{-1}$ per stimulation. This times heart rate yields only 0.068 ± 0.0028 ml $O_2 \cdot min^{-1} \cdot 100 g^{-1}$, which is only about 2% of the value for basal metabolism. Therefore, the V_{O_2} for electrical activation cannot yet account for the discrepancy in basal metabolic V_{O_2} .

between the present and KCl-arrest methods. Although the mechanism for this discrepancy remains to be revealed, the unloaded beating heart with zero $E_{\max}$ seems to have a higher basal metabolic V_{O_2} than an arrested heart.

In conclusion, we devised a new method to determine the oxygen cost for contractility and applied it to gradually increased epinephrine in excised cross-circulated dog hearts. The study showed feasibility of the new method.

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APPENDIX

To normalize the B value in Eqs. (4)–(6) for 100 g LV, the following procedure was performed.

V_{O_2} in Eq. (4) can be divided into LV and RV components as

$$V_{O_2} = \{V_{O_2(PVA-L)} + V_{O_2(INT-L)} + V_{O_2(INT-R)}\}, \quad (7)$$

where $V_{O_2(PVA-L)}$ is V_{O_2} component for LV mechanical activity in terms of PVA, $V_{O_2(INT-L)}$ and $V_{O_2(INT-R)}$ are V_{O_2} components for LV and RV non-mechanical activity mainly consisting of both excitation-contraction coupling and basal metabolism. V_{O_2} component for RV mechanical activity was neglected because RV was always collapsed by continuous hydrostatic drainage of the coronary venous blood.

Likewise, C in Eq. (4) can be divided into LV and RV components as

$$C = C_L + C_R, \quad (8)$$

where C_L and C_R are V_{O_2} components for LV and RV basal metabolism, respectively. Equations (4), (7), and (8) lead to

$$V_{O_2(PVA-L)} + V_{O_2(INT-L)} + V_{O_2(INT-R)} = A \cdot PVA + B \cdot E_{\max} + C_L + C_R.$$

Rearranging it yields

$$B = \{V_{O_2(PVA-L)} + V_{O_2(INT-L)} + V_{O_2(INT-R)} - A \cdot PVA - (C_L + C_R)\} / E_{\max}.$$

Because $V_{O_2(PVA-L)}$ is equal to $A \cdot PVA$, B is reduced to:

$$B = \{(V_{O_2(INT-L)} - C_L) + (V_{O_2(INT-R)} - C_R)\} / E_{\max}. \quad (9)$$

Both the ratio between $V_{O_2(INT-L)}$ and $V_{O_2(INT-R)}$ and the ratio C_L and C_R are considered to be proportional to the ratio between LV weight (LVW) and RV weight (RVW). This leads to

$$(V_{O_2(INT-R)} - C_R) = (V_{O_2(INT-L)} - C_L) RVW / LVW. \quad (10)$$

Substituting Eq. (10) into Eq. (9) reduces Eq. (9) to

$$B = (V_{O_2(INT-L)} - C_L)(1 + RVW / LVW) / E_{\max}. \quad (11)$$

Rearranging Eq. (11) yields

$$(V_{O_2(INT-L)} - C_L) / E_{\max} = B / (1 + RVW / LVW). \quad (12)$$

The left side of Eq. (12) means the oxygen cost for contractility and hence the denominator of the right side of Eq. (12) is a correction factor of B for LV alone.

$(V_{O_2(INT-L)} - C_L)$ can be normalized for 100 g LV by multiplying it by 100/LVW. $E_{\max}$ can also be normalized for 100 g LV by multiplying it by LVW/100. Therefore, we can finally obtain the normalized B value (B_n) for 100 g LV by multiplying Eq. (12) by $(100/LVW)/(LVW/100)$.

$$\begin{aligned} B_n &= \{(V_{O_2(INT-L)} - C_L)(100/LVW)\} / \{E_{\max}(LVW/100)\} \\ &= B(100/LVW) / \{(1 + RVW/LVW)(LVW/100)\} \\ &= B \cdot 100^2 / \{LVW(LVW + RVW)\}. \end{aligned} \quad (13)$$