

## Effects of a Left Ventricular Assist Device with a Centrifugal Pump on Left Ventricular Diastolic Hemodynamics

Akira Saito, MD

The purpose of this investigation was to analyze how left ventricular assist device (LVAD) with a centrifugal pump alters left ventricular diastolic hemodynamics and energy by means of a left ventricular pressure volume relationship. Fifteen anesthetized normal pig hearts were studied after placement of an apical drainage LVAD with a centrifugal pump. Indices of the left ventricular isovolumic relaxation phase, left ventricular filling phase and general hemodynamic data were recorded with the LVAD in on and off situations. The pump assist rate was adjusted to 25%, 50% and 75%. Left ventricular stroke work, with a high correlation with oxygen consumption, decreased as the assist rate increased. Left ventricular relaxation delayed as the assist rate increased, but the atrioventricular pressure gradient increased in the left ventricular rapid filling phase. This finding clarifies left ventricular rapid filling. In this study, it was suggested that although left ventricular isovolumic relaxation was affected, 75% assistance is the most effective for the pump flow in terms of circulation support and restoration of cardiac function. (*Ann Thorac Cardiovasc Surg* 2002; 8: 275–80)

**Key words:** assisted circulation, centrifugal pump, left ventricular assist device (LVAD), diastolic function

### Introduction

Since the left ventricular assist device (LVAD) has been developed recently and is available for postcardiotomy cardiac support, mechanical therapy for end-stage heart failure, and bridge to heart transplantation; the survival rate of end-stage heart failure has improved.<sup>1-4)</sup>

LVAD restores native cardiac function by reduction of left ventricular stroke work and myocardial oxygen utilization.<sup>5)</sup> Some investigators have reported that chronic left ventricular unloading improved native cardiac function.<sup>6-9)</sup> A small number of patients recover enough left ventricular function to survive after being weaned from LVAD used as a bridge to recovery.<sup>10)</sup>

However, these studies did not assess left ventricular diastolic function. Left ventricular diastolic dysfunction affects left ventricular filling and consequently causes congestive heart failure.<sup>11,12)</sup> Left ventricular decompres-

sion limits left ventricular dilatation. The relationship between pump performance and the influence of left ventricular diastolic hemodynamics with LVADs with a centrifugal pump is not clear. To clarify this, is important for management of pump performance and restoring cardiac function.

The purpose of this investigation was to analyze how LVAD with a centrifugal pump changes left ventricular diastolic hemodynamics and energy by means of the left ventricular pressure volume relationship.

### Materials and Methods

This study was performed with 15 pigs, each weighing 45 to 55 kg. Each animal was anesthetized with an intravenous injection of 20 mg/kg sodium pentobarbital and ketamine chloride (1 mg/kg/hr), and vecuronium bromide (0.02 mg/kg/hr). After tracheostomy and intubation, controlled mechanical ventilation was established at 20-25 beats/min with a tidal volume of 10-15 ml/kg using volume controlled ventilation (Servo 900-E, Siemens-Elema Inc., Stockholm, Sweden). A venous line was inserted into the right carotid vein to monitor central venous pressure and injection. The left femoral artery was cannu-

*From Second Department of Surgery, Nihon University School of Medicine, Tokyo, Japan*

Received April 30, 2002; accepted for publication July 2, 2002. Address reprint requests to Akira Saito, MD: Second Department of Surgery, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi Itabashi-ku, Tokyo 173-8610, Japan.

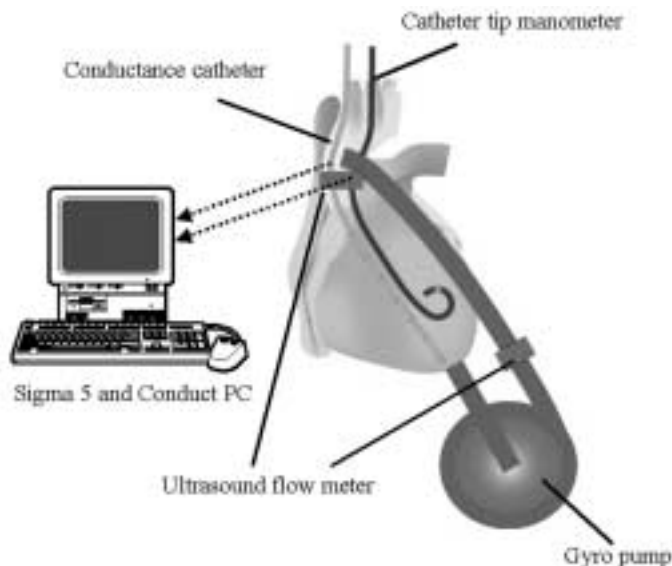


Fig. 1. In vivo experimental set-up.

lated with a pig tail catheter to monitor continuous aortic pressure (AoP). Left atrial pressure (LAP) was also monitored by an inserted cannula. A conductance catheter (2012-6-27-P, Alpha Medical Instruments Inc., CA, USA) was inserted through the aortic valve into the left ventricle with the catheter tip placed at the apex. A catheter tip manometer (811-195S/ANP534, Sentron Inc., Roden, Netherlands) was also inserted into the left ventricle (LV) to monitor continuous left ventricular pressure. The left ventricular pressure volume loop (P-V loop) was recorded by a Sigma-5 (CardioDynamics Inc., Zoetermeer, Netherlands). Hemodynamic data were calculated by analyzing the P-V loop with a Conduct PC (CardioDynamic Inc., Zoetermeer, Netherlands).

For hemodynamic data, mean AoP, mean LAP, left ventricular end-systolic pressure (LVESP), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic pressure (LVEDP), left ventricular end-diastolic volume (LVEDV) and left ventricular stroke work (LVSW) were calculated. As indices of left ventricular isovolumic relaxation, the time constant ( $\tau$ ) and maximum negative  $dP/dt$  ( $dP/dt$  min) were calculated. As indices of left ventricle filling, diastolic filling time (DFT), peak filling rate (PFR;  $dV/dt$  max) and time to PFR from the start of the filling phase (tPFR) were estimated. After anesthesia, a median sternotomy was performed. The animals were assisted by LVAD with a centrifugal pump (Gyro C1E3, Kyocera Inc., Kyoto, Japan). An inflow cannula (28 Fr, TF-028-L, Edwards Lifesciences Inc.; Irvine,

CA, USA) was inserted into the left ventricle through the apex, and an outflow cannula (5.2 mm, A211-52A, Stockert, Muenchen, Germany) was inserted into the ascending aorta. Then, ultrasonic flow transducers (T206, Transonic System, Inc., Ithaca, NY, USA) were placed into the ascending aorta and the outflow cannula to measure native heart flow and pump flow (Fig. 1). Initial baseline hemodynamic measurements were taken with the pump circuit clamped (control). The clamp then was removed and the pump activated. Motor speed was increased until the assist rate (pump flow/total flow; total flow = native flow + pump flow) was approximately 25%. A stabilization period of 30 minutes was allowed before each set of data recordings. The assist rate was increased to 50% and 75%.

The experimental results were expressed as mean  $\pm$  standard deviation. The paired *t* test and one factor ANOVA were applied to test statistical significance of differences in each assist rate group. When a value was determined to be significant by one factor ANOVA, the Scheffe method was used to further analyze the relationship.  $P < 0.05$  was considered significant. All animals received humane care in accordance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research, as well as with the "Guide for the Care and Use of Laboratory Animals", prepared by the Institute of Laboratory Animal Resources and published by the National Institute of Health (NIH publication 86-23, revised, 1996).

**Table 1. Results of hemodynamic measurements**

	Control	25%	50%	75%
mAoP (mmHg)	82.1±11.2	83.7±4.7	77.0±6.9	76.3±5.9
LVESP (mmHg)	110±12	101±15	96±13	87±18
LVEDP (mmHg)	5.9±2.9	5.0±3.9	6.0±3.4	4.3±1.2
LVESV (ml)	91±19	84±22	81±21	74±23
LVEDV (ml)	145±32	134±37	126±36	120±34
mLAP (mmHg)	5.1±1.9	5.6±0.6	5.6±1.1	6.0±1.9
SW (×10 <sup>-4</sup> J)	2,836±1,208	2,257±1,259	1,787±844	1,572±579

\*p<0.05, \*\*p<0.01

mAoP: mean aortic pressure, LVESP: left ventricular end systolic pressure, LVEDP: left ventricular end diastolic pressure, LVESV: left ventricular end systolic volume, LVEDV: left ventricular end diastolic volume, mLAP: mean left atrial pressures, SW: left ventricular stroke work

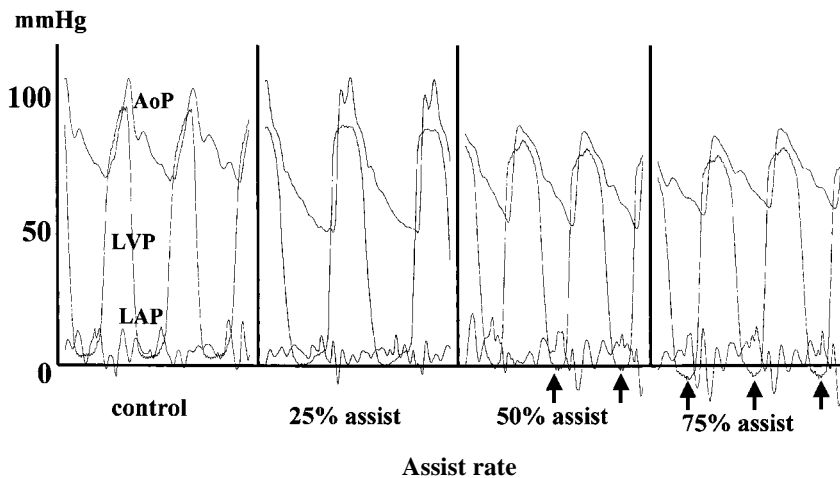
**Results**

**1. Hemodynamic data (Table 1)**

Mean AoP decreased as the assist rate increased, however, there was no significant difference in each assist rate group. LVESP decreased as the assist rate increased with a significant difference between control and 75% assist (110±12 versus 87±18 mmHg). LVESV, LVEDP and LVEDV decreased as the assist rate increased with no significant difference in each assist rate group. Regarding the mean LAP, there were no significant differences in each assist rate group. SW decreased as the assist rate increased with a significant difference between control and 75% assist (2,836±1,208 versus 1,572±579 ×10<sup>-4</sup> J). Pressure waveforms in aorta (Ao), LV and LA were shown in Fig. 2.

**2. Left ventricular isovolumic relaxation and filling (Table 2)**

Tau prolonged and dP/dt min increased as the assist rate increased with no significant difference in each assist rate group. As an index of left ventricular rapid filling, PFR increased as the assist rate increased with no significant difference. Time to PFR shortened as the assist rate increased with significant differences between the control and 25% assist (522±94 versus 423±49 msec), control and 50% assist (522±94 versus 361±72 msec), and control and 75% assist (522±94 versus 339±89 msec). DFT also shortened as the assist rate increased with significant differences between control and 25% assist (329±43 versus 261±23 msec), control and 50% assist (329±43 versus 235±34 msec), control and 75% assist (329±43 versus 210±39 msec). These findings suggested that an



**Fig. 2.** Pressure waveforms in Ao, LV and LA.

▲: In the left ventricular filling phase, negative left ventricular pressure was observed in the 50% assist group and 75% assist group, implying the atrioventricular pressure gradient increased with the assist rate.

Ao: aorta, LV: left ventricle, LA: Left atrium, AoP: aortic pressure, LVP: left ventricular pressure, LAP: left atrial pressure.

**Table 2. Indices of the left ventricular isovolumic relaxation phase and left ventricular filling phase**

	Control	25%	50%	75%
dP/dt (mmHg/sec)	-1,862±490	-1,555±328	-1,436±438	-1,308±356
Tau (msec)	27.0±4.6	29.4±6.3	31.9±6.8	32.6±6.8
PFR (ml/sec)	395±36	454±110	460±103	488±113
tPFR (msec)	522±94	423±49	361±72	339±89
DFT (msec)	329±43	261±23	235±34	210±39

\*\*p<0.01

dP/dt min: maximum negative dP/dt, Tau: time constant, PFR: peak filling rate, tPFR: time to peak filling rate, DFT: diastolic filling time

increased assist rate contributes to left ventricular filling. In the left ventricular filling phase, negative left ventricular pressure was observed in the 50% and 75% assist groups. Therefore, the atrioventricular pressure gradient increased as the assist rate increased (Fig. 2).

## Discussion

Patients requiring a heart transplant due to end-stage heart failure have increased year by year, and donor shortages have become a serious problem.<sup>13,14</sup> Due to donor shortage, the mean waiting time for heart transplantation has been prolonged.<sup>14</sup> Thus, the role of long-term mechanical circulatory assistance has become more important and critical to save those patients who cannot benefit from heart transplantation.

Currently, LVAD has been developed and is available for postcardiotomy cardiac support, mechanical therapy for end-stage heart failure and as a bridge to heart transplantation, and the survival rate of end-stage heart failure has been improved.<sup>1-4</sup> In recent years, rotary blood pumps, such as axial flow pump and centrifugal pumps, have been developed worldwide by several groups for use as implantable VADs in the clinical field.<sup>15-18</sup> In particular, clinical trials of the Jarvik-2000 heart,<sup>19</sup> DeBakey VAD<sup>15,20</sup> and HeartMate II<sup>18</sup> began in Europe and the United States.

The advantages of the rotary blood pump are 1) no valves, 2) compact, 3) relatively good efficiency, 4) no need for a compliance chamber, 5) low cost.<sup>21</sup> However, the problem of long-term mechanical support remains.

LVAD reduces cardiac stroke work and myocardial oxygen consumption by left ventricular unloading and attempts to recover cardiac function.<sup>6-9</sup> Furthermore, assisting blood flow prevents systemic organ ischemia. A small number of patients recover enough left ventricular function to survive after being weaned from LVAD used

as a bridge to recovery.<sup>10</sup> However, these studies did not assess left ventricular diastolic function. Pulsatile pumps have valves and operate independently of LV pressure and contraction. In contrast, rotary pumps have no valves and operate in synchronicity with LV pressure and contraction, as there is continuous flow through the pump.<sup>22</sup>

Comparing the position of cannulation, LV cannulation has advantages of lower rates of thromboembolism and higher pump flow than LA cannulation.<sup>23,24</sup> Therefore, LV cannulation is better for long-term circulatory support and LV decompression. In this study, we chose LV cannulation, and during the experiment LVEDV decreased as the assist rate increased. This suggested that the efficacy of LV decompression was better as the assist rate increased. With apical drainage LVAD with a centrifugal pump, blood flows from the left atrium through the left ventricle to the pump. Therefore, pump flow is influenced by the pulsatility of the native heart and non-pulsatile flow of the centrifugal pump; the centrifugal pump drains blood not only in the systolic phase, but also in the diastolic phase.

Left ventricular diastolic dysfunction affects left ventricular filling and thus causes congestive heart failure.<sup>11,12</sup> Left ventricular decompression limits left ventricular dilatation. The relationship between pump performance and the influence on left ventricular diastolic hemodynamics when the LVAD is driven by a centrifugal pump is not clear, but this is important for management of pump performance and restoring cardiac function.

A diastolic function of the LV regulates the blood flow from the LA to the LV in the diastolic phase. Left ventricular diastolic function consists of relaxation and filling. The diastolic phase consists of an isovolumic relaxation phase and a filling phase in which blood flows from the LA to the LV. Left ventricular relaxation is a function which particularly expresses the characteristics of the left

ventricular isovolumic relaxation phase. Left ventricular relaxation is an active process which needs energy and reduces the strain in the systolic phase.<sup>25,26</sup> This process regulates the descending velocity of left ventricular pressure and left ventricular minimum pressure. Left ventricular filling is a passive process in which blood flows from the LA to the LV after mitral valve opening by a driving pressure which is produced by the atrioventricular pressure gradient.<sup>25</sup> The delay in left ventricular relaxation reduces the descending velocity of left ventricular pressure and affects the left ventricular filling.

In this study, LVESP decreased as the assist rate increased with a significant difference between control and 75% assist ( $110 \pm 12$  versus  $87 \pm 18$  mmHg). LVESV, LVEDP and LVEDV decreased as the assist rate increased with no significant difference among any assist rate group. The afterload of the left ventricle decreased because the LV has two outlets which are the ascending aorta and the inlet port of the pump. SW decreased as the assist rate increased with a significant difference between the control and 75% assist ( $2,836 \pm 1,208$  versus  $1,572 \pm 579 \times 10^{-4}$  J).

This result suggests that LVAD decreases the external stroke work of the LV and pressure volume area that has a high correlation with oxygen consumption.<sup>26</sup>

Regarding left ventricular isovolumic relaxation, Tau prolonged and  $dP/dt$  min increased as the assist rate increased with no significant difference in each assist rate group. However, these findings suggested that left ventricular isovolumic relaxation is prolonged as the assist rate increases. Suga et al. reported that myocardial oxygen consumption is predominantly determined by the total mechanical energy generated during systole, or the systolic pressure-volume area, and is independent of pressure-volume trajectory during diastole.<sup>27</sup> The relationship between the delay in left ventricular isovolumic relaxation and the reduction of LVS<sub>W</sub> seems to be independent. When LVESP decreased, Tau and  $dP/dt$  min increased,<sup>28</sup> suggesting that decreased LVESP prolonged Tau and increased  $dP/dt$  min.

Concerning left ventricular filling, PFR increased as the assist rate increased with no significant difference. Time to PFR shortened as the assist rate increased with significant differences between the control and 25% assist ( $522 \pm 94$  versus  $423 \pm 49$  msec), control and 50% assist ( $522 \pm 94$  versus  $361 \pm 72$  msec), and control and 75% assist ( $522 \pm 94$  versus  $339 \pm 89$  msec). DFT also shortened as the assist rate increased with significant differences

between the control and 25% assist ( $329 \pm 43$  versus  $261 \pm 23$  msec), control and 50% assist ( $329 \pm 43$  versus  $235 \pm 34$  msec), and control and 75% assist ( $329 \pm 43$  versus  $210 \pm 39$  msec). In the left ventricular filling phase, negative left ventricular pressure was observed in the 50% assist group and 75% assist group, implying the atrioventricular pressure gradient increased with the assist rate (Fig. 2). These findings suggested that the increased atrioventricular pressure gradient in the diastolic phase, which becomes the driving pressure of left ventricular filling, contributes to left ventricular rapid filling. Theoretically, when LVAD is driven with full bypass, the mitral valve is open continuously. When the isovolumic phase does not exist, then the LV becomes a simple conduit in which blood simply flows. According to this theory, although left ventricular isovolumic relaxation is affected, the 75% assist is the most effective for pump flow for circulation support and restoration of cardiac function.

Left ventricular diastolic function involves many processes; each process is not completely independent and they all have some correlation with each other. Thus, when analyzing left ventricular diastolic function, it is better to use several indices and do multiple analysis. Because we used a normal heart model in this study, the same results would not be expected in a fatal heart failure model. Studies to compare the position of the drainage cannula with a heart failure model and chronic experiments are necessary as the next step.

## Conclusion

We analyzed the relationship between pump flow and left ventricular diastolic function of native hearts. In this study, left ventricular relaxation was delayed as the assist rate increased, but the atrioventricular pressure gradient in the left ventricular rapid filling phase increased. This phenomenon contributes to left ventricular rapid filling. Although left ventricular isovolumic relaxation was affected, the 75% assist was the most effective for pump flow for circulation support and restoration of cardiac function.

## Acknowledgments

I acknowledge honorary professor Yukiyasu Sezai, chief professor Nanao Negishi, associate professor Motomi Shiono and members of the VAD study group in Nihon University School of Medicine, second department of surgery, for help with this manuscript.

## References

1. Hunt SA, Frazier OH, Myers TJ. Mechanical circulatory support and cardiac transplantation. *Circulation* 1998; **97**: 2079–90.
2. Mehta SM, Pae Jr WE, Rosenberg G, et al. The LionHeart LVD-2000: a completely implanted left ventricular assist device for chronic circulatory support. *Ann Thorac Surg* 2001; **71**: S156–61.
3. McCarthy PM. HeartMate implantable left ventricular assist device: bridge to transplant and future applications. *Ann Thorac Surg* 1995; **59**: S46–51.
4. Minami K. Surgical treatments for endstage heart failure due to dilated cardiomyopathy. *Asian Cardiovasc Thorac Ann* 2001; **9**: 159–65.
5. Goldstein AH, Pacella JJ, Clark RE. Predictable reduction in left ventricular stroke work and oxygen utilization with an implantable centrifugal pump. *Ann Thorac Surg* 1994; **58**: 1018–24.
6. Frazier OH, Benedict CR, Radovancevic B, et al. Improved left ventricular function after chronic left ventricular unloading. *Ann Thorac Surg* 1996; **62**: 675–82.
7. Nakatani T, Sasako Y, Kumon K, et al. Long-term circulatory support to promote recovery from profound heart failure. *ASAIO J* 1995; **41**: M526–30.
8. Levin HR, Oz MC, Chen JM, Packer M, Rose EA, Burkhoff D. Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. *Circulation* 1995; **91**: 2717–20.
9. Mueller J, Wallukat G, Weng YG, et al. Weaning from mechanical cardiac support in patients with idiopathic dilated cardiomyopathy. *Circulation* 1997; **96**: 542–9.
10. Hetzer R, Mueller JH, Weng YG, Meyer R, Dandel M. Bridging-to-recovery. *Ann Thorac Surg* 2001; **71**: S109–13.
11. Lenihan DJ, Gerson MC, Hoit BD, Walsh RA. Mechanisms, diagnosis, and treatment of diastolic heart failure. *Am Heart J* 1995; **130**: 153–66.
12. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995; **26**: 1565–74.
13. Hosenpud JD, Bennet LE, Keck BM, Fiore B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official report–1999. *J Heart Lung Transplant* 1999; **18**: 611–26.
14. Minami K, Arusoglu L, El-Banayosy A, et al. Bridge for heart transplantation by different types of ventricular assist device. In: Akutsu T, Koyanagi H, eds.; Heart Replacement–Artificial Heart 6. Tokyo: Springer-Verlag, 1998; pp 81–90.
15. Wieselthaler GM, Schima H, Hiesmayr M, et al. First clinical experience with the DeBakey VAD continuous-axial-flow pump for bridge to transplantation. *Circulation* 2000; **101**: 356–9.
16. Macris MP, Parnis SM, Frazier OH, Fuqua Jr JM, Jarvik RK. Development of an implantable ventricular assist system. *Ann Thorac Surg* 1997; **63**: 367–70.
17. Curtis JJ. Centrifugal mechanical assist for postcardiotomy ventricular failure. *Semin Thorac Cardiovasc Surg* 1994; **6**: 140–6.
18. Griffith BP, Kormos RL, Borovetz HS, et al. HeartMate II left ventricular assist system: from concept to first clinical use. *Ann Thorac Surg* 2001; **71**: S116–20.
19. Frazier OH, Myers TJ, Jarvik RK, et al. Research and development of an implantable, axial flow left ventricular assist device: The Jarvik 2000 Heart. *Ann Thorac Surg* 2001; **71**: S125–32.
20. Noon GP, Morley DL, Irwin S, Abdelsayed SV, Benkowski RJ, Lynch BE. Clinical experience with the MicroMed DeBakey ventricular assist device. *Ann Thorac Surg* 2001; **71**: S133–8.
21. Nojiri C, Kijima T, Maekawa J, et al. More than 1 year continuous operation of a centrifugal pump with a magnetically suspended impeller. *ASAIO J* 1997; **43**: M548–52.
22. Akimoto T, Yamazaki K, Litwak P, et al. Relationship of blood pressure and pump flow in an implantable centrifugal blood pump during hypertension. *ASAIO J* 2000; **46**: 596–9.
23. Lohmann DP, Swartz MT, Pennington DG, McBride LR, Reedy JE, Miller L. Left ventricular versus left atrial cannulation for the Thoratec ventricular assist system. *ASAIO Trans* 1990; **36**: M545–8.
24. Holman WL, Bourge RC, Murrah CP, et al. Left atrial or ventricular cannulation beyond 30 days for a Thoratec ventricular assist system. *ASAIO J* 1995; **41**: M517–22.
25. Yasumura Y, Nozawa T, Futaki S, Tanaka N, Suga H. Time-invariant oxygen cost of mechanical energy in dog left ventricle: consistency and inconsistency of time varying elastance model with myocardial energetics. *Circ Res* 1989; **64**: 764–78.
26. Suga H, Yasumura Y, Nozawa T, Futaki S, Igarashi Y, Goto Y. Prospective prediction of O<sub>2</sub> consumption from pressure-volume area in dog heart. *Am J Physiol* 1987; **252**: H1258–64.
27. Suga H, Goto Y, Yamada O, Igarashi Y. Independence of myocardial oxygen consumption from pressure-volume trajectory during diastole in canine left ventricle. *Circ Res* 1984; **55**: 734–9.
28. Gilbert JC, Glantz SA. Determinants of left ventricular filling and of the diastolic pressure-volume relation. *Circ Res* 1989; **64**: 827–52.