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Myocardial Contractility of the Canine Left Ventricle During Unsynchronized Dual Chamber Pacing

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Abstract

The influence of changes of left ventricular (LV) myocardial contractility on the decrease of cardiac output during atrial fibrillation was investigated in dogs using the slope (E_c) and the length intercept (L_0) of the LV end-systolic force-length relationship. The hearts of nine healthy adult mongrel dogs were instrumented with ultrasonic crystals and a micromanometer, after which pharmacologic autonomic blockade was instituted. The LV diameter and pressure data were recorded during inferior vena caval occlusion. Hemodynamic parameters were measured during pacing from the right atrial appendage at a pacing rate 30 beat/min greater than the natural heart rate using a cardiac stimulator (atrial pacing), and during simultaneous pacing from the right atrial appendage and right ventricular apex at the same rate (unsynchronized dual chamber pacing). Cardiac hemodynamics in the absence of synchronized left atrial contraction were simulated by unsynchronized pacing.

During atrial pacing, the cardiac output (1.68±0.25 vs 1.57±0.21 *l*/min, $p<0.005$) and E_c (110.1±58.5 vs 81.8±30.8 g/cm, $p<0.05$) were significantly greater than during normal sinus rhythm, whereas the stroke volume (12.4±2.4 vs 15.1±3.1 m*l*, $p<0.005$) and LV end-diastolic volume (16.6±2.7 vs 19.5±3.4 m*l*, $p<0.005$) were significantly smaller. L_0 did not change during pacing. During unsynchronized dual chamber pacing, cardiac output (1.46±0.17 vs 1.68±0.25 *l*/min, $p<0.005$), stroke volume (10.8±1.7 vs 12.4±2.4 m*l*, $p<0.005$), and LV end-diastolic volume (15.0±2.0 vs 16.6±2.7 m*l*, $p<0.05$) were significantly smaller than during atrial pacing. However, E_c and L_0 were similar during both types of pacing.

These findings suggest that the decrease of cardiac output and stroke volume during atrial fibrillation is chiefly due to the decrease of LV end-diastolic volume through loss of left atrial contraction, and is not due to a change of LV myocardial contractility.

Key Words

Atrial fibrillation, Cardiac pacing artificial (dual), Contractility (myocardial), Ultrasonic diagnosis, Active cross-bridge model

INTRODUCTION

During left ventricular (LV) diastole, left atrial booster pump function, *i.e.*, the atrial "kick", provides a valuable contribution to cardiac output. When atrial fibrillation occurs, cardiac output generally decreases by around 15 to 20% due to the loss of left atrial contraction[1,2]. In patients with hypertensive LV hypertrophy[3], acute myocardial infarction[4], hypertrophic cardiomyopathy[5], or chronic calcific constrictive pericarditis[6], a high LV end-diastolic pressure impedes the flow of blood

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Selected abbreviations and acronyms

E_c = slope of the left ventricular end-systolic force-length relationship
F_{es} = end-systolic circumferential force
L_{es} = end-systolic circumferential length
L_0 = length intercept of the ventricular end-systolic force-length relationship
LV = left ventricular
P_{es} = end-systolic pressure
V_0 = volume intercept of the left ventricular end-systolic pressure-volume relationship

from the left atrium to the left ventricle during left atrial contraction. In these patients, atrial contraction is of greater importance than normal for left ventricular filling. Thus, the onset of atrial fibrillation causes an immediate decline of cardiac output. Investigation of the atrial "kick" has already been approached from various angles. However, there have been no studies on whether a change in LV myocardial contractility is related to the decrease of cardiac output in patients with atrial fibrillation.

We previously developed a theoretical model of myocardial contraction (the active cross-bridge model)[7], which is based on the assumption that the fundamental mechanical and energetic properties of myocardial/cardiac contraction are principally characterized by the binding between calcium (Ca^{2+}) and troponin C. To review this model briefly, the slope of the myocardial end-systolic force-length relation (E_c) is expressed as a product of the initial concentration of free Ca^{2+} released by the sarcoplasmic reticulum of a cardiac myocyte, the force generated by one active cross-bridge, the cross-sectional area of the myocardium and the affinity of Ca^{2+} for troponin C[8]. This model consistently predicts measured values of LV pressure, force, and time-varying myocardial elastance throughout systole in dogs[8]. In addition, the LV force-length relation obtained in normal dogs[9] shows a linear relationship with that obtained in humans[10], and the theoretical model accurately predicts measured values for the LV end-systolic pressure-volume, pressure-diameter, and stress-diameter relations[9]. These findings suggest that E_c is an appropriate index of LV myocardial contractility, and that the value of the length axis intercept of the myocardial end-systolic force-length relation (L_0) may provide a measure of the quantity of noncontractile and nonfunctional myocytes. In the present study, we simulated cardiac hemodynamics during atrial fibrillation by unsynchronized dual chamber pacing in dogs, and investigated whether changes of LV myocardial contractility influenced cardiac output by determining E_c and L_0.

METHODS

Animal model

Nine healthy adult mongrel dogs (11.8 ± 1.3 kg) were anesthetized with intravenous sodium pentobarbital (26 mg/kg) and instrumented as described elsewhere[9]. Positive pressure ventilation was provided via an endotracheal tube, thoracotomy was performed in the left fourth intercostal space, the pericardium was opened, and the heart was suspended in a pericardial cradle. A micromanometer-tipped catheter (MPC500, Millar Instruments, U.S.A.; **Fig. 1–upper**) was balanced in a constant-temperature water bath (37°C), after which it was inserted into the apex of the left ventricle and held in place by a purse-string suture. A 5F Swan-Ganz catheter was inserted into the right femoral vein and was advanced to the pulmonary artery for the infusion of drugs and fluid and for the measurement of cardiac output. Another catheter was inserted into the right femoral artery for blood gas analysis. An occluder was set around the inferior vena cava to vary the preload. A pair of ultrasonic crystals (4 mm diameter with a frequency of 5 MHz) was implanted in the endocardium to allow continuous measurement of the anteroposterior LV diameter (UDM-5C Ultrasonic Dimension System, MECC, Japan; **Fig. 1–lower**). The stability of the LV pressure-diameter loops obtained with this setup was tested with an oscilloscope at steady state and also during preload manipulation. Lead II of the surface electrocardiogram was recorded and the LV pressure and the LV anteroposterior diameter were measured. Data on these variables were simultaneously stored on a hard disk at 1-msec intervals using a computer (PC9801VX21, NEC, Japan). The digital data on the hard disk were then evaluated without filtering.

Experimental protocol

Beta-adrenergic and vagal blockade were achieved with intravenous propranolol (2 mg/kg) and atropine sulfate (0.2 mg/kg). Arterial blood gases were determined with an analyzer (Model ABL4, Radiometer, Denmark) while the dogs were being ventilated, and the arterial P_{O_2} and P_{CO_2} were

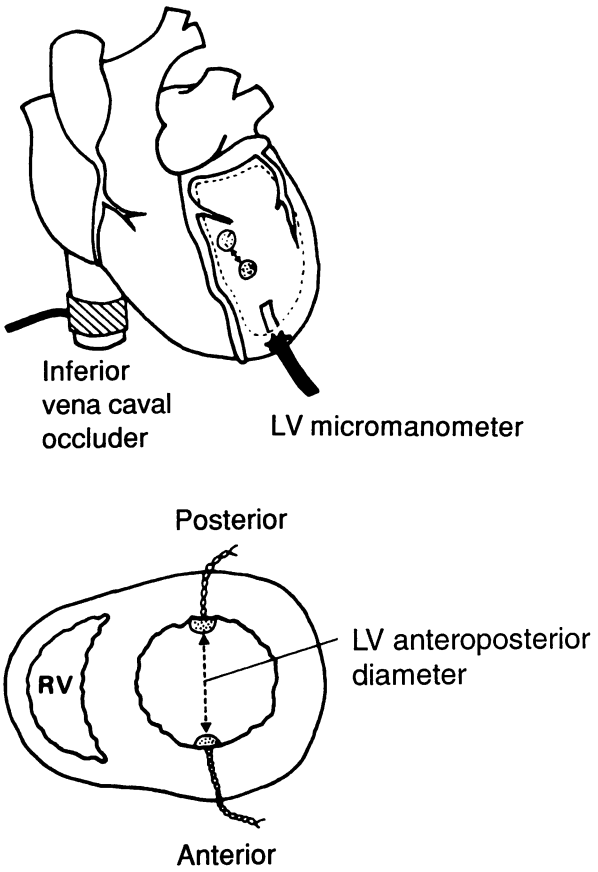

Fig. 1 Experimental setup

The micromanometer, the pair of ultrasonic crystals used for measuring the left ventricular diameter, and the occluder on the inferior vena cava used for preload reduction are shown. RV=right ventricle.

maintained above 90 mmHg and below 40 mmHg, respectively.

Run 1 (sinus rhythm): In a steady state at least 10 min after the initiation of β-adrenergic and vagal blockade, the inferior vena cava was gradually occluded while data were collected from the ultrasonic crystals, micromanometer, and electrocardiogram. To eliminate the effect of changes in lung volume due to respiration, all data were recorded during 20 sec periods of apnea. Cardiac output was measured by the thermodilution method using the Swan-Ganz catheter (EH-11 cardiac output computer, Fukuda Denshi, Japan).

Run 2 (atrial pacing): After performing run 1, the pacing electrode was placed on the right atrial appendage, which was stimulated at a pacing rate 30 beat/min greater than the spontaneous heart rate using a cardiac stimulator (BC-03, Fukuda Denshi, Japan). Data were collected by the same procedure as before.

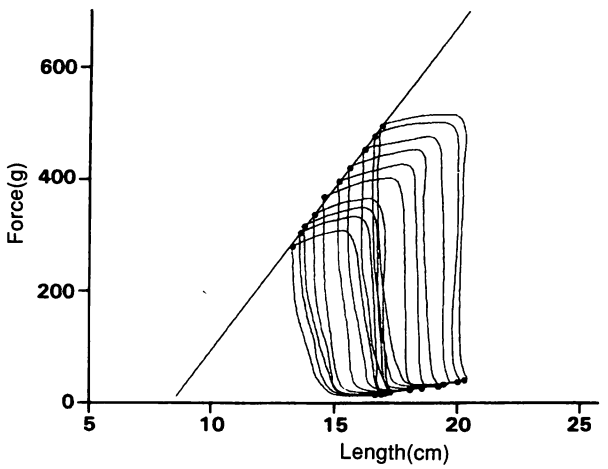

Fig. 2 Representative LV force-length loops obtained with the ultrasonic crystals in a single dog during inferior vena caval occlusion

The upper left corner of the loop represents the end-systolic point in each cardiac cycle. The straight line demonstrates the LV end-systolic force-length relationship obtained by linear regression analysis.

Run 3 (unsynchronized dual chamber pacing): After performing run 2, another pacing electrode was placed on the right ventricular apex. Then the right atrial appendage and right ventricular apex were simultaneously stimulated at a pacing rate 30 beat/min greater than the spontaneous heart rate and data were collected by the same procedure as before.

After the study, the positions of the ultrasonic crystals were examined at necropsy. In all dogs, no arrhythmias occurred during manipulation of preload, the micromanometer drift was less than 1.0 mmHg, and the ultrasonic crystals were positioned appropriately.

Theoretical background

Instantaneous LV pressure (P; mmHg) and myocardial length (L; cm) data recorded from several cardiac cycles during the manipulation of preload were used for the construction of LV force-length loops. LV circumferential force (F; g) was calculated from the equation $F=P\times L\times 1/2\times a\times \pi$, where 1 is the height of a cylinder (1 cm) and a is a conversion factor of 0.735 $mmHg\cdot g^{-1}\cdot cm^2$ [7]. The circumferential myocardial length (L) for the cylindrical segment was estimated by the equation: $L=\pi\times D$, where D (cm) is the LV anteroposterior diameter obtained from the pair of ultrasonic crystals. The LV force-length relationship data for one representative dog are shown in **Fig. 2**.

End-systole was defined as the upper left corner of the LV force-length loop, *i.e.*, the point where the ratio of myocardial force to length [F/(L−L_o)] was maximal[11]. LV end-systolic circumferential force (F_{es}) was assumed to be linearly proportional to myocardial length. Thus, F_{es} was expressed by the following equation[9]:

$$F_{es}=E_c(L_{es}-L_o)$$

where E_c (g/cm) denotes the slope of the LV end-systolic force-length relation (an index of the inotropic state of LV myocardium) and L_o (cm) is the basal myocardial length. End-systolic circumferential force (F_{es}) and length (L_{es}) data were used to obtain the values of E_c and L_o.

Data and statistical analysis

The digital data stored on the hard disk were processed using a computer system (PC9801VX21, NEC, Japan) and software developed at our laboratory. Results are expressed as the mean value±SD. Comparisons between mean values were assessed using the repeated measures ANOVA, and $p<0.05$ was considered statistically significant. Linear regression analysis by the least squares method was used to fit data to the LV F_{es}-L_{es} relationship.

RESULTS

The heart rate, LV end-systolic pressure (P_{es}), LV L_{es}, LV F_{es}, cardiac output, stroke volume, LV end-systolic volume, LV end-diastolic volume, E_c, and L_o during sinus rhythm, atrial pacing, and unsynchronized dual chamber pacing are presented in **Table 1**. Under all conditions, the heart rate was significantly changed by inferior vena caval (IVC) occlusion, although the extent was less than 10 beat/min.

The LV P_{es} and LV F_{es} before IVC occlusion showed no significant difference between sinus rhythm and atrial pacing (**Table 1**). The LV L_{es} was significantly smaller during atrial pacing than during sinus rhythm (7.80±1.30 vs 8.22±1.38 cm, $p<0.005$). Cardiac output was significantly greater during pacing than during sinus rhythm (1.68±0.25 vs 1.57±0.21 *l*/min, $p<0.005$). However, stroke volume (12.4±2.4 vs 15.1±3.1 m*l*, $p<0.005$) and LV end-diastolic volume (16.6±2.7 vs 19.5±3.4 m*l*, $p<0.005$) were significantly smaller during atrial pacing than during sinus rhythm. E_c was significantly greater during atrial pacing than during sinus rhythm (110.1±58.5 vs 81.8±30.8 g/cm, $p<0.05$), but L_o did not change.

LV P_{es} was significantly smaller during unsynchronized dual chamber pacing than during atrial pacing (108.7±11.7 vs 117.4±16.9 mmHg, $p<0.05$; **Table 1**). In contrast, LV L_{es} was similar during both atrial pacing and unsynchronized dual chamber pacing. However, LV F_{es} was significantly smaller during unsynchronized dual chamber pacing than during atrial pacing (179±28 vs 197±39 g, $p<0.05$). Cardiac output (1.46±0.17 vs 1.68±0.25 *l*/min, $p<0.005$), stroke volume (10.8±1.7 vs 12.4±2.4 m*l*, $p<0.005$), and LV end-diastolic volume (15.0±2.0 vs 16.6±2.7 m*l*, $p<0.05$) were all significantly smaller during unsynchronized dual chamber pacing than during atrial pacing. However, E_c and L_o were similar during both types of pacing.

DISCUSSION

Background of the model

We previously developed a theoretical model of myocardial contraction (the active cross-bridge model)[7] based on the assumption that the fundamental mechanical and energetic properties of myocardial/cardiac contraction are chiefly characterized by binding between Ca^{2+} and troponin C. A train of equations derived from this model can provide a good explanation for a large number of phenomena related to the mechanical, energetic, and biochemical properties of myocardial/cardiac contraction[7–13]. To the best of our knowledge, no other model has been developed in which one simple hypothesis provides a fairly consistent theoretical explanation for such a wide variety of properties of myocardial/cardiac contraction. Of course, the model has certain limitations and complete experimental proof is not yet available. However, the hypothesis that the basic properties of myocardial/cardiac contraction are mainly characterized by binding between Ca^{2+} and troponin C appears to be both reasonable and tenable. On this basis, the physiological significance of the mechanical parameter E_c can be clarified. E_c can be expressed as the product of the initial concentration [$\sigma(Ca^{2+}T)$] of free Ca^{2+} released by the sarcoplasmic reticulum of a cardiac myocyte, the force (f) generated by one active cross-bridge (which might reflect myosin ATPase activity), the cross-sectional area of the myocardium (S), and the affinity (α) of Ca^{2+} for troponin C[8]. In short, E_c can be expressed by the equation:

$$E_c=\sigma(Ca^{2+}T)\times f\times S\times\alpha$$

Table 1 Effect of atrial pacing and unsynchronized dual chamber pacing

	Sinus rhythm	Atrial pacing	Unsynchronized dual chamber pacing	*F* value
Heart rate (beat/min)	105.8±10.3	136.9±9.8**	136.5±8.6	763.9‡‡
P_{es} (mmHg)	117.0±15	117.4±16.9	108.7±11.7†	7.2‡
L_{es} (cm)	8.22±1.38	7.80±1.30**	7.69±1.36	16.1‡‡
F_{es} (g)	208±43	197±39	179±28†	9.0‡‡
Cardiac output (*l*/min)	1.57±0.21	1.68±0.25**	1.46±0.17††	22.9‡‡
Stroke volume (m*l*)	15.1±3.1	12.4±2.4**	10.8±1.7††	56.7‡‡
LVESV (m*l*)	4.4±1.9	4.2±1.7	4.3±1.7	2.1
LVEDV (m*l*)	19.5±3.4	16.6±2.7**	15.0±2.0†	62.5‡‡
E_c (g/cm)	81.8±30.8	110.1±58.5*	106.9±62.1	4.7‡
L_0 (cm)	5.47±1.68	5.67±1.89	5.60±1.89	0.8

Data presented are mean value±SD. *$p<0.05$, **$p<0.005$ vs sinus rhythm. †$p<0.05$, ††$p<0.005$ vs atrial pacing. ‡$p<0.05$, ‡‡$p<0.005$ for the *F* value.
LVESV=left ventricular end-systolic volume; LVEDV=left ventricular end-diastolic volume.

Previous studies have suggested that the E_c value is an appropriate index of the contractility of functioning LV myocardium (Hooke's law), and that the value of the length axis intercept of the myocardial end-systolic force-length relation (L_0) may provide a measure of the length of nonfunctioning myocardium.

Left ventricular force-length relationship during pacing

In the present study, cardiac output was significantly greater and stroke volume was significantly smaller during atrial pacing than during sinus rhythm (**Table 1**). During atrial pacing, atrioventricular coupling may have been almost the same as during sinus rhythm, so an increase of cardiac output would occur due to the increased heart rate (30 beat/min) resulting from pacing. The augmentation of cardiac output by the increase in heart rate apparently exceeded the reduction of cardiac output due to the decrease of stroke volume, with the latter change possibly being due to a decrease of the end-systolic and end-diastolic dimensions through the Bowditch effect[14]. E_c was significantly greater during atrial pacing than during sinus rhythm, but L_0 did not change with pacing. It has been reported that myocardial contractility increases with an increase of the heart rate[14], so E_c may have increased due to the increased heart rate during pacing.

Unsynchronized dual chamber pacing impedes the flow of blood from the left atrium to the left ventricle. In the present study, cardiac output and stroke volume were significantly smaller (13% decrease) during unsynchronized dual chamber pacing than during atrial pacing, but E_c and L_0 were similar during both types of pacing (**Table 1**). These findings suggest that the decrease of cardiac output and stroke volume was chiefly due to the decrease of LV end-diastolic volume through loss of left atrial contraction, and was not due to a change of LV myocardial contractility.

The left atrium has four functions : 1) it acts as a reservoir during LV systole, 2) passive emptying occurs during rapid ventricular filling, 3) it acts as a conduit from rapid ventricular filling to late ventricular filling, and 4) active emptying occurs during left atrial systole[15–19]. In patients with atrial fibrillation, cardiac output generally decreases by around 15 to 20% due to the loss of left atrial contraction[1,2]. On the other hand, during unsynchronized dual chamber pacing, the decrease of LV end-diastolic volume might be due to loss of the reservoir and active emptying functions of the left atrium. In addition, the reservoir deficit during LV systole might decrease passive emptying during rapid ventricular filling. Thus, during unsynchronized dual chamber pacing, the decrease of LV end-diastolic volume might be due to the loss of left atrial contraction, the reservoir deficit, and the decrease of passive emptying.

Park *et al.*[20] reported that the volume intercept (V_0) of the LV end-systolic pressure-volume relation was significantly increased during ventricular pacing when compared with atrial pacing, although

the slope (E_{max}) of the LV end-systolic pressure-volume relation showed no significant change. In their study, the value of V_0 was extrapolated from a linear approximation of the LV end-systolic pressure-volume relationship. However, this relationship is actually non-linear, so their extrapolated V_0 might have been incorrect. Thus, if LV pressure was significantly different during atrial pacing and ventricular pacing, the value of V_0 might be influenced. On the other hand, the LV end-systolic force-length relationship is far more linear[10] than the LV end-systolic pressure-volume relationship, which might explain why our results were different from theirs.

Limitations

The limitations of our model due to the assumption of thin-shell cylindrical geometry for the left ventricle, the neglect of various forces acting on the LV wall during systole, and the assumption of linearity for the myocardial end-systolic force-length relationship have all been discussed previously[7,9,11]. Since measurement of the actual myocardial developed force appears to be impossible at present, these values were calculated using thin-shell cylindrical LV geometry. The values calculated for myocardial force, length, E_c, and L_0 in the present study were completely dependent on the model. Some investigators might question the validity of using thin-shell cylindrical geometry and might be curious as to how E_c and L_0 vary with other assumptions (*e.g.*, thick-shell cylindrical, spheroidal, or ellipsoidal geometry). A complete answer must await the results of further investigations, but it has been shown that thin-shell cylindrical geometry can provide an excellent prediction of LV pressure development through almost all of systole[8], as well as predicting the measured relationship between end-systolic pressure and length in the canine left ventricle[9].

In the present study, cardiac hemodynamics in the absence of synchronized left atrial contraction were simulated by unsynchronized dual chamber pacing. However, in patients with atrial fibrillation, the RR interval of the electrocardiogram changes at every beat and the cardiac conduction pathway is completely different from that during unsynchronized dual chamber pacing. Thus, unsynchronized dual chamber pacing cannot exactly simulate cardiac hemodynamics during atrial fibrillation.

CONCLUSION

When cardiac contraction occurred without the atrial "kick", the decrease of cardiac output (stroke volume) was not due to a change of LV myocardial contractility. This finding confirms previous knowledge that the decrease of cardiac output and stroke volume in atrial fibrillation is chiefly due to the loss of left atrial contraction.

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要　約

非同期心房心室ペーシングにおけるイヌ左室心筋収縮性の検討

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心房細動において，左室心筋収縮性の変化が心拍出量低下に影響しているか否かを，機能心筋の収縮性を表す左室収縮末期力–長さ関係の傾き (E_c) と無機能心筋の長さを表す同切片 (L_0) を用いて検討した．

雑種成犬9頭を静脈麻酔下に開胸し，左室内にマイクロマノメーターを挿入，左室前壁ならびに後壁の心内膜面に超音波クリスタルを装着し，propranolol と atropine にて自律神経を遮断した．下大静脈結紮法にて左室圧を下降させ，左室短軸内径と左室圧を記録した．心臓電気刺激器を用いて，洞調律よりも 30 beat/min だけ多いペーシングレートで右心耳を刺激し，データを記録した (心房ペーシング)．次に右心耳と右室心尖部を，同じペーシングレートで同時刺激することで左房収縮のない心血行動態を模擬し，データを記録した (非同期心房心室ペーシング)．

心房ペーシングは洞調律に比べ，有意に心拍出量 (1.68±0.25 vs 1.57±0.21 *l*/min, $p<0.005$) と E_c (110.1±58.5 vs 81.8±30.8 g/cm, $p<0.05$) を増加させ，1 回拍出量 (12.4±2.4 vs 15.1±3.1 m*l*, $p<0.005$) と左室拡張末期容量 (16.6±2.7 vs 19.5±3.4 m*l*, $p<0.005$) を減少させたが，L_0 は変化しなかった．また非同期心房心室ペーシングでは心房ペーシングに比べ，心拍出量 (1.46±0.17 vs 1.68±0.25 *l*/min, $p<0.005$)，1 回拍出量 (10.8±1.7 vs 12.4±2.4 m*l*, $p<0.005$)，左室拡張末期容量 (15.0±2.0 vs 16.6±2.7 m*l*, $p<0.05$) を有意に減少させたが，E_c と L_0 は変化しなかった．

心房細動における心拍出量と 1 回拍出量の減少は，主に左房収縮の消失による左室拡張末期容量の減少に起因しており，左室心筋収縮性とは無関係であると考えられた．

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