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Effect of Chronic Cardiac Pacing on Cross-Bridge Activation Rate in the Human Left Ventricle

Koichi KONO
Kouichi TAKEDA
Toru TANIGUCHI
Shigeru YAGI

Abstract

Our active cross-bridge model has theoretically established that the cross-bridge activation rate constant of the left ventricular myocardium (K_a), which may correspond to the rate constant for the binding of Ca^{2+} with troponin C, can be approximately expressed as a simple formula : $K_a = 3/\text{electromechanical systole}$ (sec^{-1}). To determine whether this constant has the potential to be used as a clinical index of cardiac adrenergic tone, we investigated the chronic effect of cardiac pacing on the value of K_a in 15 subjects with a pacemaker in full pacing rhythm. The value of K_a (7.10 ± 0.50 vs 6.62 ± 0.39 sec^{-1}, $p < 0.05$) and that of K_a corrected for heart rate (K_{ac}) (7.63 ± 0.50 vs 6.60 ± 0.41 sec^{-1}, $p < 0.01$) were both decreased significantly at one month or more after permanent pacemaker implantation. Another eight subjects were investigated to evaluate the effect on K_{ac} of acute left bundle branch block due to intermittent right ventricular pacing. Intermittent pacing did not cause a significant change of the K_{ac} value (7.46 ± 0.43 vs 7.29 ± 0.39 sec^{-1}). The decrease of K_{ac} during chronic cardiac pacing might reflect reduced cardiac adrenergic activity, since acute left bundle branch block due to intermittent right ventricular pacing did not affect this parameter.

Key Words
active cross-bridge model, left bundle branch block, cardiac adrenergic activity

INTRODUCTION

Congestive heart failure is associated with excessive adrenergic stimulation, as manifested by increased central sympathetic outflow, elevation of the plasma norepinephrine level, depletion of myocardial catecholamine stores, and abnormalities of myocardial norepinephrine uptake and release[1,2]. Some investigators have found correlations between the changes in plasma catecholamine concentrations or excretion and the clinical status or left ventricular function of patients with congestive heart failure[3,4]. The circulating norepinephrine level is generally considered to be a marker of sympathetic activity. However, to assess accurately the myocardial catecholamine balance, blood collection from the coronary sinus is required. To investigate cardiac neural activity, several workers have performed direct determination of sympathetic nervous activity using microneurography[5,6], while others have examined the β-adrenergic receptor density of the myocardium[7] or assayed myocardial catecholamine levels by cardiac biopsy[8]. However, these techniques are not suitable for the evaluation of instantaneous cardiac adrenergic activity.

Our previous studies[9–13] suggested that the mechanical and energetic properties of cardiac contraction are both primarily characterized by at least four biochemical parameters related to cross-bridge activation and cycling : 1) the intracellular free Ca^{2+} concentration, 2) the rate of Ca^{2+} binding with troponin C, 3) the calcium affinity of troponin C, and

獨協医科大学 循環器内科 : 〒321-02 栃木県下都賀郡壬生町北小林 880
Department of Medicine, Division of Hypertension and Cardiorenal Disease, Dokkyo University School of Medicine: Kita-kobayashi 880, Mibu, Shimotsuga-gun, Tochigi 321-02
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4) the myosin ATPase activity. Although no definitive biological proof has yet been provided, the cross-bridge activation rate constant in our model (K_a) appears to correspond to the rate constant for the binding of Ca^{2+} with troponin C in the myocardium[12]. In our models the myocardial K_a value is estimated as three divided by the total contraction period (T_{sys}: the time from the mechanical onset of myocardial contraction to the end of contraction)[10]. The K_a value corrected for heart rate (K_{ac}) shows a very small mean variation (4.6%) in the normal human left ventricle and is independent of age or initial myocardial fiber length, but is increased by dobutamine infusion[14]. The approximate value of K_{ac} is readily estimated from the systolic time interval (QS_2 interval) and the heart rate. Accordingly, K_{ac} is a potentially useful index for the clinical assessment of instantaneous cardiac adrenergic activity.

In our previous study[14], the number of subjects undergoing chronic cardiac pacing was small. In addition, the acute effect on the K_{ac} value of complete left bundle branch block due to right ventricular pacing was not clarified. Therefore, the aims of the present study were to evaluate the acute effect of left bundle branch block due to right ventricular pacing on K_{ac} and to determine the chronic effect of cardiac pacing on K_{ac} in a larger subject group.

METHODS

1. Subjects

Test 1 Fifty-three patients with severe cardiac conduction disturbance but no other myocardial dysfunction underwent implantation of permanent pacemakers at our institution from June 1987 to February 1991. To evaluate the chronic effect of cardiac pacing on the cross-bridge activation rate constant of the left ventricular myocardium (K_a), subjects with the pacemaker working in full pacing rhythm were selected from among these 53 patients. Patients were excluded if they were receiving cardioactive agents before pacemaker implantation (*e.g.*, digitalis glycosides, catecholamines, atropine sulphate, xanthin derivatives, α- or β-adrenergic receptor antagonists) or if their echocardio-graphic images were too poor for the accurate measurement of left ventricular dimensions. Fifteen subjects were eligible for the study, including seven men and eight women with a mean age of 61.0 ± 11.2 years. Eight subjects had complete atrioventricular (AV) block, three had advanced AV block, two had second degree AV block, and two had sick sinus syndrome. The pacing modes used were DDD (dual-chamber universal) ($n=10$), VVI (ventricular-inhibited) ($n=3$), and VVIR (ventricular demand rate-responsive)($n=2$).

Test 2 To evaluate the acute effect of complete left bundle branch block on K_a, similar studies as in experiment 1 were performed on another eight subjects with a permanent or temporary pacemaker providing intermittent right ventricular stimulation. All patients were stimulated by VVI pacing. These patients included three men and five women with a mean age of 67.8 ± 9.5 years.

2. Experimental protocols and data collection

Test 1 While the patients rested in the supine position, the electrocardiogram, phonocardiogram, and M-mode echocardiogram (SSH-65A, Toshiba, Japan) were simultaneously recorded on a strip chart recorder (LSR-20B, Toshiba) at a paper speed of 50 mm/sec. Measurements of the left ventricular end-systolic and end-diastolic dimensions were made from an integrated assessment of M-mode and two-dimensional echocardiograms using the conventions recommended by the American Society of Echocardiography[15]. The heart rate was calculated as follows: (60/average R-R interval). The total electromechanical systolic time was measured from the onset of the QRS complex of the ECG to the first high frequency vibration of the aortic component of the second heart sound, *i.e.*, the QS_2 interval (**Fig. 1**). All data were obtained both before pacemaker implantation and at least one month after implantation.

Test 2 In this study, the QS_2 interval was measured 1) during sinus rhythm, and 2) within 5 beats of the onset of pacemaker rhythm. Before the pacemaker measurements, the heart was beating in normal sinus rhythm for at least 10 minutes.

3. Theoretical background and statistical analysis

A detailed description of our model has been published previously[9–13]. In brief, the following assumptions were adopted. 1) A cross-bridge is "activated" by the binding of one Ca^{2+} ion with the regulatory protein troponin C on the actin filament, and this process is represented by the proportionality constant K_a (sec^{-1}). Thus K_a is the cross-bridge acti-

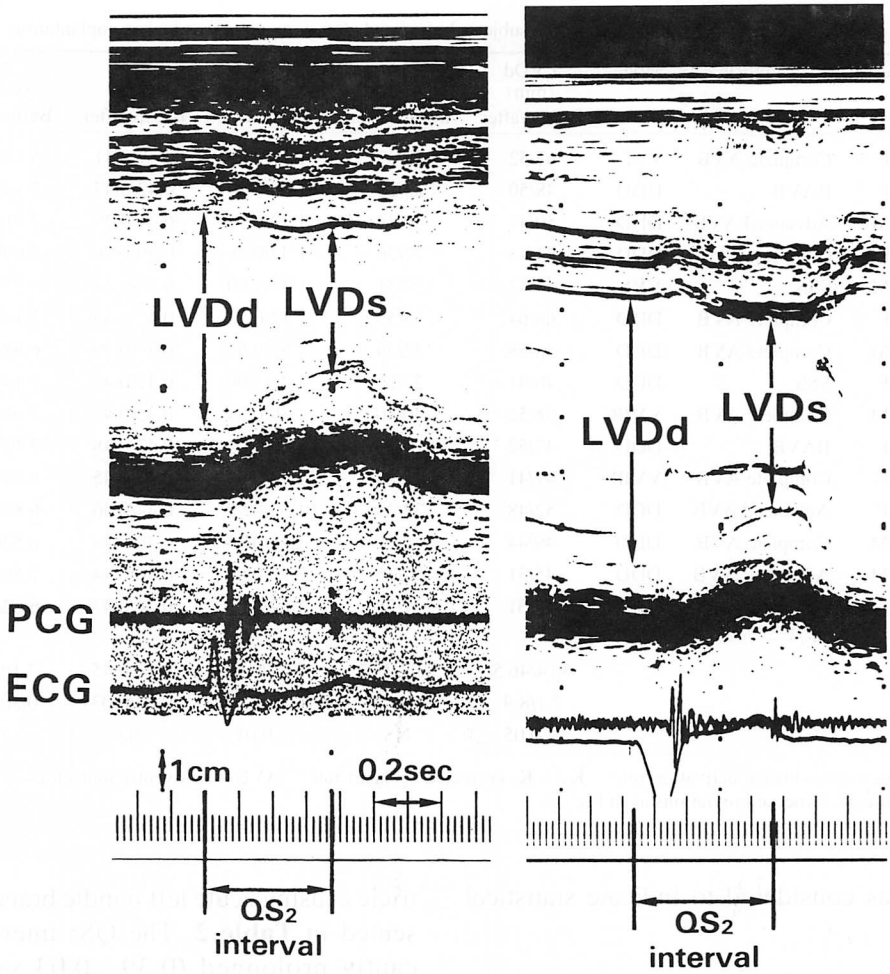

Fig. 1 Echocardiograms and phonocardiograms obtained (*left*) before permanent pacemaker implantation and (*right*) after implantation

LVDd=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; ECG=electrocardiogram; PCG=phonocardiogram; QS_2=total electromechanical systole

vation rate constant, which may be predicted by our model to correspond to the rate constant for the binding of Ca^{2+} with troponin C. 2) The active myocardial force at any given instant is related to the total number of activated cross-bridges at that time. 3) The myocardium continues to contract until almost all free Ca^{2+} (assumed to be 95% of the initial concentration) has become bound to troponin C at the end of systole. 4) The force at the end of systole remains linearly proportional to the muscle length over the entire tested range of force, according to the proportionality constant Ec (g/cm), which represents the end-systolic myocardial elastance.

On the basis of these assumptions, equation 1 was derived to describe the cross-bridge activation rate constant[10,12].

$$Ka = Tsys^{-1} \cdot \log_e (1-\alpha)^{-1} = 3/Tsys \quad (1)$$

where Tsys is the total contraction period (sec) and α is the Ca^{2+} affinity of troponin C (0.95). The value of α was obtained from studies of normal, open-chest, and autonomically blocked canine hearts[12]. The value of Tsys was estimated from the QS_2 interval in the present study[16]. In addition, the value of Ka corrected by the individual heart rate (Kac, 1/sec) can be calculated using equation 2[14].

$$Kac = Ka + 0.0249 \cdot (66 - HR) \quad (2)$$

where HR is heart rate and Kac is the predicted Ka value at a heart rate of 66 beats/min.

Results were expressed as the mean ±SD. The statistical significance of differences between means was assessed using Student's paired *t*-test

Table 1 Clinical characteristics of the subjects before and after permanent pacemaker implantation

Patient No.	Age (yrs)	Sex	Diagnosis	Mode	LVDd (mm) Before/after	LVDs (mm) Before/after	RR (sec) Before/after	QS_2 (sec) Before/after	K_a (sec^{-1}) Before/after	K_{ac} (sec^{-1}) Before/after
1	75	F	Complete AVB	VVI	62/52	52/37	1.16/0.99	0.49/0.41	6.12/7.32	6.46/7.44
2	56	F	IIAVB	DDD	48/50	25/28	1.08/0.94	0.42/0.47	7.14/6.38	7.39/6.43
3	62	M	Advanced AVB	DDD	50/47	30/33	1.22/0.71	0.41/0.49	7.31/6.12	7.73/5.65
4	64	F	Complete AVB	DDD	44/43	27/26	1.33/0.86	0.39/0.46	7.69/6.52	8.21/6.42
5	52	M	SSS	VVI	48/43	27/31	1.41/1.00	0.36/0.44	8.33/6.82	8.90/6.79
6	41	F	Complete AVB	DDD	68/64	53/53	1.17/0.97	0.42/0.43	7.14/6.98	7.51/7.08
7	79	M	Complete AVB	DDD	50/58	32/39	1.51/0.99	0.43/0.49	6.98/6.12	7.63/6.24
8	49	F	SSS	DDD	46/41	27/20	1.27/1.00	0.42/0.44	7.14/6.82	7.61/6.97
9	80	M	Complete AVB	VVIR	58/52	40/40	1.39/0.84	0.43/0.41	6.98/7.32	7.55/6.60
10	52	F	IIAVB	DDD	47/52	21/39	1.69/1.01	0.42/0.48	7.14/6.25	7.89/6.42
11	58	F	Complete AVB	VVIR	47/41	27/29	1.68/0.95	0.44/0.45	6.82/6.67	7.57/6.74
12	62	F	Advanced AVB	DDD	52/48	32/23	1.62/0.98	0.44/0.46	6.82/6.52	7.54/6.64
13	61	M	Complete AVB	DDD	49/44	44/37	1.88/0.92	0.46/0.48	6.52/6.25	7.37/6.27
14	57	M	Advanced AVB	DDD	45/31	31/35	0.96/0.84	0.40/0.44	7.50/6.82	7.57/6.70
15	72	M	Complete AVB	VVI	42/31	31/28	1.62/1.05	0.44/0.47	6.82/6.38	7.54/6.60
Mean	61.3				50.4/46.5	33.2/33.2	1.39/0.94	0.42/0.45	7.10/6.62	7.63/6.60
SD	11.2				7.1/8.9	9.6/8.21	0.26/0.08	0.03/0.03	0.50/0.39	0.50/0.41
p value					<0.05	NS	<0.01	<0.05	<0.05	<0.01

RR=RR interval; K_a=cross-bridge activation rate; K_{ac}=K_a corrected by heart rate; AVB=atrioventricular block; SSS=sick sinus syndrome; NS=not significant. Other abbreviations as in Fig. 1.

and $p<0.05$ was considered to indicate statistical significance.

RESULTS

1. Effect of chronic cardiac pacing on K_{ac}

The clinical characteristics of the patients with permanent pacemakers in full pacing rhythm are summarized in **Table 1**. The left ventricular end-diastolic dimension decreased significantly from 50.4 $\pm$7.1 to 46.5$\pm$8.9 mm ($p<0.05$) after pacemaker implantation, whereas the left ventricular end-systolic dimension did not change significantly (33.2$\pm$ 9.6 mm vs 33.2$\pm$8.21 mm, p=ns). There was a significant prolongation of the QS_2 interval (from 0.42 $\pm$0.03 to 0.45$\pm$0.03 sec, $p<0.05$) after cardiac pacing for one month or more. The length of the RR interval (1.39$\pm$0.26 vs 0.94$\pm$0.08 sec, $p<0.01$) and the values of K_a (7.10$\pm$0.50 vs 6.62$\pm$0.39 sec^{-1}, $p<0.05$) and K_{ac} (7.63$\pm$0.50 vs 6.60$\pm$0.41 sec^{-1}, $p<0.01$) all decreased significantly after pacemaker implantation (**Fig. 2**).

2. Effect of acute left bundle branch block on K_{ac}

The results of temporary pacing of the right ventricle causing acute left bundle branch block are presented in **Table 2**. The QS_2 interval was significantly prolonged (0.39$\pm$0.03 sec during sinus rhythm vs 0.42$\pm$0.03 sec during pacing, $p<0.01$), and the K_a value was significantly decreased (7.71 $\pm$0.63 sec^{-1} vs 7.25$\pm$0.60 sec^{-1}, $p<0.01$). However, the K_{ac} value did not change significantly during temporary pacing (7.46$\pm$0.43 sec^{-1} vs 7.29$\pm$ 0.39 sec^{-1}) (**Fig. 3**).

DISCUSSION

The basis of myocardial contraction is the chemical reaction between free Ca^{2+} and the regulatory protein troponin C on myocardial actin filaments, which leads to the functional "activation" of cross-bridges. Using our active cross-bridge model[10] and the cylinder model[9], we have found that many properties of cardiac contraction can be expressed mathematically. Several indices for the evaluation of cardiac performance, *e.g.*, the QS_2 interval, V_{max}, dp/dt_{max}, and E_{max}, appear to be primarily characterized by one or two of our model parameters[10], namely E_c and K_a. E_c appears to be related to the initial Ca^{2+} concentration available for cross-bridge activation and/or to the myosin ATPase activity in-

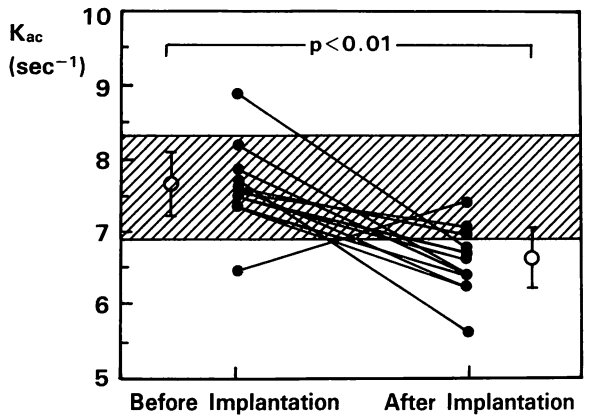

Fig. 2 Changes in Kac after permanent pacemaker implantation (mean ± SD)

The shaded area indicates the mean ± 2SD of Kac in 102 normal individuals.

volved in cross-bridge cycling, while Ka appears to correspond to the forward rate constant of the chemical reaction involved in the binding of Ca^{2+} to troponin C[12].

The systolic time intervals provide one of the oldest noninvasive cardiovascular parameters for the evaluation of left ventricular performance. The three systolic time intervals most commonly employed are the preejection period (PEP), the left ventricular ejection time (LVET), and electromechanical systole (the QS_2 interval)[17,18]. The QS_2 interval is constant for any individual and it shortens as the heart rate spontaneously increases[17,19]. Since positive inotropic agents generally shorten both LVET and PEP, the QS_2 interval is the most useful of the systolic time intervals for judging the effects of positive inotropic stimulation[17,19]. Earlier reports have shown that positive inotropic agents (*e.g.*, epinephrine or digitalis glycosides) shorten the QS_2 interval in a dose-related manner[20,21]. Lewis *et al*[22] found a strong correlation between urinary catecholamine excretion and the QS_2 interval in acute myocardial infarction. In addition, there is a correlation between clinical symptoms and the QS_2 interval in congestive heart failure[23] or acute myocardial infarction[24], while patients with sustained acute myocardial infarction have been shown to have increased adrenergic activity[22]. These observations suggest that shortening of the QS_2 interval may indicate cardiac adrenergic hyperactivity in patients with coronary artery disease[25–27] or congestive heart failure. This is also theoretically consistent with our hypothesis regarding the clinical implications of

Table 2 Effect of right ventricular pacing on Kac

Patient No.	RR (sec) NSR/pace	QS_2 (sec) NSR/pace	Ka (sec^{-1}) NSR/pace	Kac (sec^{-1}) NSR/pace
1	0.83/0.97	0.39/0.40	7.69/7.50	7.54/7.59
2	1.15/0.98	0.40/0.41	7.50/7.32	7.84/7.44
3	0.82/0.81	0.39/0.42	7.69/7.14	7.52/6.94
4	0.68/1.10	0.39/0.42	7.69/7.14	7.14/7.41
5	0.50/0.85	0.36/0.41	8.33/7.32	6.99/7.20
6	1.15/1.18	0.44/0.49	6.82/6.12	7.17/6.49
7	1.04/1.19	0.42/0.42	7.14/7.14	7.21/7.54
8	0.69/0.65	0.34/0.36	8.82/8.33	8.30/7.68
Mean	0.86/0.97	0.39/0.42	7.71/7.25	7.46/7.29
SD	0.23/0.18	0.03/0.03	0.63/0.60	0.43/0.39
p value	NS	<0.01	<0.01	NS

All patients were stimulated by VVI pacing.
NSR=normal sinus rhythm; pace=during pacing. Other abbreviations as in Fig. 1 and Table 1.

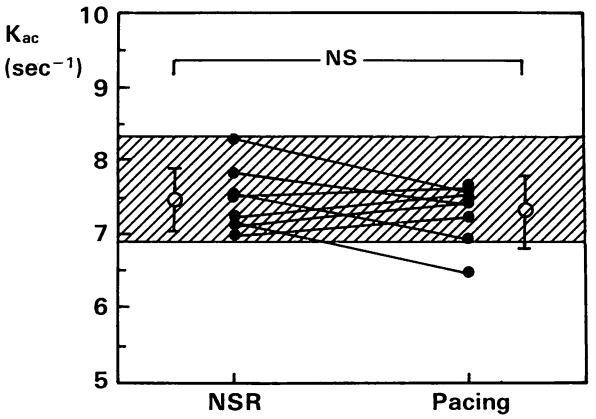

Fig. 3 Effect of acute left bundle branch block due to right ventricular pacing on Kac (mean ± SD)

The shaded area indicates the mean ± 2SD of Kac in 102 normal individuals.
NS=not significant; NSR=normal sinus rhythm

Kac, *i.e.*, that Kac is an index of cardiac adrenergic tone.

In our previous study[14], the Ka value corrected for heart rate (Kac) showed a very small mean variation (4.6%) in normal human hearts and was independent of the age or the initial myocardial fiber length of the subjects, but was increased by dobutamine infusion. Accordingly, the Kac value for normal human left ventricular myocardiums appears to remain constant from one individual to another. In addition, our findings suggested that the Kac value had the potential for use as a measure of cardiac adrenergic activity and cardiac reserve in patients with myocar-

dial dysfunction[14].

Cardiodynamic abnormalities often occur in patients with sinus node dysfunction or advanced atrioventricular block, *e.g.*, an increase of left ventricular end-diastolic pressure or pulmonary vascular resistance and a decline of cardiac output. These abnormalities may result from chronic bradycardia or from the loss of sequential atrioventricular contraction, with the absence of atrioventricular synchrony being especially important. Most investigators have found that the cardiac output is approximately 15–40% greater during atrioventricular synchrony when compared to during atrioventricular asynchrony[28-30]. Asynchronous atrial and ventricular contraction causes elevation of the atrial pressure, which leads to an increase in atrial natriuretic peptide (ANP) release[31]. Circulating ANP released by the atrium acts on the kidneys, the peripheral circulation, and the endocrine system to maintain an optimal circulating blood volume and atrial pressure. In fact, increased ANP levels have been found in patients with atrioventricular block[31] or congestive heart failure[32]. These observations suggest that patients with severe cardiac conduction disturbance may possibly develop adrenergic hyperactivity along with worsening of their hemodynamics.

In the present study, the mean K_{ac} value before pacemaker implantation was 7.63 ± 0.50 sec^{-1}, which is within the limit determined for normal individuals. This observation suggests that the cardiac adrenergic activity of our patients was relatively normal before pacemaker implantation and that their conduction disturbance was not so severe as to produce marked cardiodynamic abnormalities. However, the mean K_{ac} value decreased significantly after permanent pacemaker implantation (after: 6.60 ± 0.41 vs before: 7.63 ± 0.50 sec^{-1}, $p < 0.01$), and the K_{ac} values of 12 of the 15 pacemaker patients were lower than the mean -2SD for normal individuals (6.90 sec^{-1}). These findings suggest that adrenergic activity is depressed in hearts chronically stimulated by a permanent pacemaker.

Right ventricular pacing produces complete left bundle branch block. Since this bundle branch block is usually associated with delayed activation of the left ventricle, prolongation of the QS_2 interval might occur and could then influence the value of K_{ac}. However, we found no significant difference in the K_{ac} value between normal sinus rhythm and pacing rhythm associated with bundle branch block (7.46 ± 0.43 vs 7.29 ± 0.39 sec^{-1}). This indicates that the bundle branch block induced by right ventricular pacing would be unlikely to affect the value of K_{ac} in patients with a permanent pacemaker, so that the reduction of K_{ac} detected in this group would appear to be related to a decrease of cardiac adrenergic activity. As the heart is continually stimulated by a permanent pacemaker, the natural cardiac adrenergic activity may decline in such patients[14].

Although the K_a value was estimated from the QS_2 interval in the present experiments, it should be noted that the K_a values obtained were not actual observed values for the kinetic constant of the binding between Ca^{2+} and troponin C, and were instead completely derived from our model.

要　約

ヒトの左室心筋連結橋活性化速度に及ぼす長期心臓ペーシングの影響

高野　幸一　竹田　幸一　谷口　泰　八木　繁

左室心筋の連結橋活性化速度定数 (K_a) およびその心拍補正値 (K_{ac}) に対する心臓ペーシングの影響について検討を行った．永久ペースメーカー植込患者15例を対象に，植込術前および慢性期（植込後1ヵ月以上）においてMモード心エコー図の計測，K_a，K_{ac}の測定 ($K_a = 3/QS_2$, $K_{ac} = K_a + 0.0249 \cdot (66 - HR)$) を行い，長期ペーシングの影響を調べた．また$K_{ac}$に対する一時的右室ペーシングによる左脚ブロックの影響を調べるため，他の8例に対し洞結節時および右室ペーシング時においてK_{ac}の測定を行い，比較した．永久ペースメーカー植込前後においてK_a (7.09 vs 6.62 sec^{-1}, $p<0.05$)，K_{ac} (7.63 vs 6.60 sec^{-1}, $p<0.01$) は有意な低下を示した．また左室拡張末期径に有意な縮小を認めた (50.4 vs 46.5 mm, $p<0.05$)．一方，一時的右室ペーシングにおいてはK_{ac}には有意な変化は認められなかった．

Kacは左室心筋への交感神経活性の指標であると予測され，われわれはすでに正常心での値がほぼ一定 (6.9<Kac<8.3) であることを報告している．右室ペーシングでは急性期にはKacに有意な変化を認めないが，慢性期には正常値を逸脱する著明な低下を認めた．これは長期間のペーシングによる心臓交感神経活性の低下によるものと推測された．

以上，Kacは右室ペーシングによる左脚ブロックには影響されず，Kacの変化から，永久ペースメーカー植込後，慢性期において左室心筋への交感神経活性の低下が示唆された．

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