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Cross-Bridge Activation Rate Constant Determined From Systolic Time Intervals in Patients With Systemic Lupus Erythematosus

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Abstract

Cardiac adrenergic activity was investigated in 38 patients with systemic lupus erythematosus (SLE) who were not receiving cardiovascular agents using a new index of the adrenergic tone of the working left ventricular (LV) myocardium and using the heart rate to represent sinus node adrenergic tone. According to the active cross-bridge model employed in this study, the cross-bridge activation rate constant (K_a) of the LV myocardium, corresponding to the rate constant for the binding of Ca^{2+} to troponin C, can be approximately expressed as K_a=3/electromechanical systole (sec^{-1}). The K_a value corrected for heart rate (K_{ac}) remains nearly constant in normal individuals, but is increased without change of the heart rate by dobutamine infusion. Fifty patients who fulfilled the American Rheumatism Association criteria for SLE underwent echocardiography, as well as simultaneous recording of the electrocardiogram, phonocardiogram, and carotid pulse wave tracing. K_{ac} was calculated from the interval between the onset of the QRS complex to the second heart sound (QS_2 interval) and the heart rate (HR) as follows: $K_{ac}=3/QS_2+0.0249\ (66-HR)$. The 38 SLE patients were divided into a normal K_{ac} group ($n=26$, $6.9<K_{ac}<8.3\ sec^{-1}$) and a high K_{ac} group ($n=12$, $K_{ac}\geqq 8.3\ sec^{-1}$). In the latter group, the heart rate was significantly higher (101.6 ± 4.8 vs 74.8 ± 2.2 bpm, $p<0.001$), the LV end-systolic dimension was significantly smaller (2.71 ± 0.19 vs 3.20 ± 0.10 cm, $p<0.05$), and the prednisolone dose was significantly larger (38.2 ± 6.9 vs 16.3 ± 3.6 mg/day, $p<0.05$) than in the normal K_{ac} group. These findings suggest that both the sinus node and the working LV myocardium may be in a hyperadrenergic state in a subgroup of SLE patients with more severe disease.

Key Words

active cross-bridge model, cardiac adrenergic nervous system, echocardiography, systemic lupus erythematosus

INTRODUCTION

The cardiac adrenergic system may be functionally divided into the adrenergic nerves supplying the sinus node and those supplying the working left ventricular (LV) myocardium. The heart rate reflects the adrenergic tone of the sinus node, but there has been no clinical parameter available to assess the adrenergic tone of the LV myocardium. We have proposed a new parameter of LV myocardial adrenergic activity, which is the rate constant (K_a) for the binding of Ca^{2+} to troponin C in our cross-bridge model[1]. A previous study[2] showed that the K_a value corrected for heart rate (K_{ac}) in resting hu-

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mans with no intervention remains constant between individuals, as well as being independent of age or individual myocardial fiber length. However, K_{ac} is significantly increased by the infusion of dobutamine, a selective β_1-adrenoreceptor agonist, despite the absence of change in heart rate. Thus, K_{ac} appears to be a potentially useful index for assessing the adrenergic tone of the working LV myocardium, although the K_a from which it is derived is not the experimentally determined kinetic constant for the binding of Ca^{2+} to troponin C and is completely dependent on our model.

Patients with systemic lupus erythematosus (SLE) often develop cardiac lesions considered to be due to immunological mechanisms involving immune complex deposition[3,4]. Cardiac lesions are not uncommonly the initial symptom of SLE and are also an important factor in making a final diagnosis of this disease. In addition, cardiac damage is often aggravated by infection, renal failure, respiratory failure, and hypertension, and thus becomes important in the treatment and prognosis of this disease. Patients with SLE also often develop neurological involvement that manifests as peripheral neuritis, psychosis, and seizures[5]. However, there have been no reports of cardiac sympathetic dysfunction associated with SLE.

The present study examined the adrenergic tone of the LV myocardium in patients with SLE using K_{ac} as the index. The K_{ac} value was often found to be abnormally high in patients with SLE, suggesting that it may be a useful parameter for analysis of the pathogenesis, treatment, and prognosis of SLE.

MATERIALS AND METHODS

Subjects

Sixty-seven patients with SLE were examined by echocardiography at our institution from July 1983 to May 1992. Fifty of these 67 patients fulfilled four or more of the 1982 revised criteria of the American Rheumatism Association for the diagnosis of SLE[6]. Of the 67 patients, one patient with concomitant thyroid disease and two patients with congestive heart failure were excluded. Some patients were being treated with Ca^{2+} antagonists ($n=6$), α_1-adrenoreceptor blockers ($n=7$), β-adrenoreceptor blockers ($n=1$), and digitalis ($n=2$), but none were receiving β-adrenoreceptor agonists or xanthine derivatives. Fifty patients were in sinus rhythm. There were 6 men and 44 women, with a mean age of 34± 2 years.

Study protocol and data collection

Echocardiographic examination was performed with the patient resting in the supine position. M-mode echocardiograms were obtained by the routine procedure described elsewhere[7] using an SSH-65A echocardiograph (TOSHIBA), and were recorded at a paper speed of 50 mm/sec on an LSR-20B strip chart recorder (TOSHIBA). LV dimension measurements were obtained by aiming the beam just beyond the tip of the mitral valve leaflets. The electrocardiogram, phonocardiogram, and carotid pulse wave tracing were recorded simultaneously (**Figs. 1–A, B**). The interval from the onset of the QRS complex on the electrocardiogram to the aortic component of the second heart sound on the phonocardiogram (**Fig. 1–A**), representing the total electromechanical contraction period[8], was defined as the QS_2 interval. The LV ejection time (LVET) was defined as the interval from the beginning of the upstroke to the onset of the dicrotic notch on the carotid pulse wave tracing[9] (**Fig. 1–B**). Using the QS_2 interval and the LVET, the preejection period (PEP) was calculated as : $PEP = QS_2 - LVET$. Then the ratio of PEP to LVET (PEP/LVET ratio) was calculated. The LV end-systolic and end-diastolic dimensions, the thickness of the interventricular septum, and the LV posterior wall thickness were also measured by M-mode echocardiography. The LV end-diastolic and end-systolic points were defined as corresponding to the QRS onset[10,11] and the aortic component of the second heart sound[12], respectively.

Theoretical background and data analysis

Detailed descriptions of the models used in this study have been published previously[2,13,14]. In brief, the following assumptions are made.

1) A cross-bridge is "activated" by the binding of one Ca^{2+} ion to the regulatory protein troponin C on an actin filament, and this binding reaction is described by the proportionality constant K_a (sec^{-1}), which thus represents the cross-bridge activation rate constant.

2) The myocardial force at a given time is related to the total number of active cross-bridges at that time.

3) The myocardium continues to contract until almost all free Ca^{2+} (assumed to be 95% of the ini-

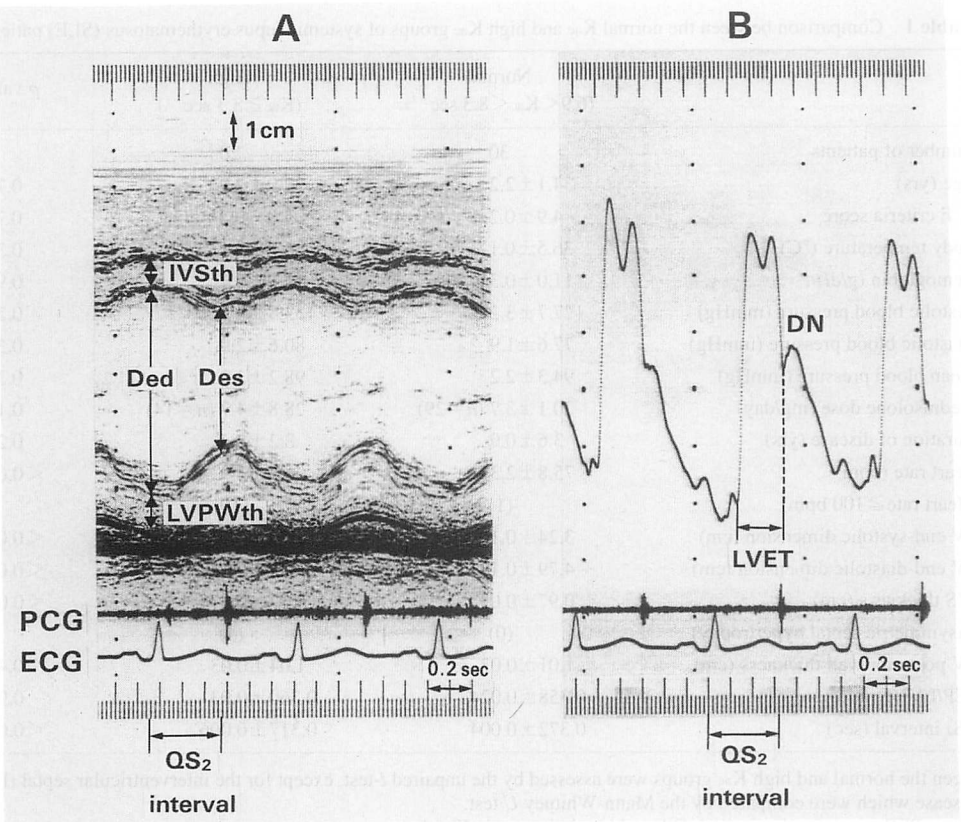

Fig. 1 Representative M-mode echocardiogram (*A*) and carotid pulse wave tracing (*B*)

Ded=end-diastolic dimension; Des=end-systolic dimension; ECG=electrocardiogram; IVS=interventricular septum; PCG=phonocardiogram; LVPW=left ventricular posterior wall; IVSth=thickness of the IVS; LVPWth=thickness of the LVPW; QS_2 interval=total electromechanical systole; DN=dicrotic notch; LVET =left ventricular ejection time.

tial calcium concentration) has become bound to troponin C at the end of systole.

4) The force at end-systole remains linearly proportional to the muscle length according to the proportionality constant E_c (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 (K_a) :

$$K_a = \log_e (1-\alpha)^{-1}/T_{sys} = 3/T_{sys} \quad [1]$$

where T_{sys} is the total contraction period [*i.e.*, the time from the onset of mechanical contraction to the end of contraction as defined by our model (sec)] and α is the Ca^{2+} affinity of troponin C. The value of α was determined to be 0.95 in normal, open-chest, autonomically blocked canine hearts[14], while T_{sys} was estimated from the QS_2 interval in the present study. The K_a value corrected for the heart rate (K_{ac}, 1/sec) was determined using equation [2][2] :

$$K_{ac} = K_a + 0.0249\ (66 - HR) \quad [2]$$

where HR denotes the heart rate (bpm). K_{ac} corresponds to the predicted K_a value at a heart rate of 66 bpm (the mean rate previously determined in 102 normal human volunteers).

Results are expressed as the mean±SEM. The statistical significance of differences between mean values was assessed by the unpaired *t*-test, or by the Mann-Whitney *U* test for interventricular septal thickness and disease duration.

RESULTS

The 50 SLE patients were divided into two groups on the basis of their K_{ac} values, *i.e.*, a normal K_{ac} group ($6.9 < K_{ac} < 8.3$ sec^{-1}; mean K_{ac} : 7.84±0.06 sec^{-1}) and a high K_{ac} group ($K_{ac} \geqq 8.3$ sec^{-1}; mean K_{ac} : 8.78±0.17 sec^{-1}) (**Table 1**). The K_{ac} value of 8.3 sec^{-1} was the upper limit of normal (mean+2SD) as previously determined in 102 healthy human subjects[2]. There were 30 patients in the normal K_{ac} group (3 men and 27 women) and 20 in the high K_{ac} group (3 men and 17 women).

Table 1 Comparison between the normal Kac and high Kac groups of systemic lupus erythematosus (SLE) patients

	Normal ($6.9<Kac<8.3$ sec^{-1})	High ($Kac \geqq 8.3$ sec^{-1})	*p* value
Number of patients	30	20	
Age (yrs)	34.1±2.2	32.9±2.9	0.73
SLE criteria score	4.9±0.2	5.0±0.2	0.77
Body temperature (°C)	36.5±0.1	36.6±0.1	0.34
Hemoglobin (g/dl)	11.0±0.3	11.0±0.4	0.91
Systolic blood pressure (mmHg)	127.7±3.2	133.5±4.3	0.28
Diastolic blood pressure (mmHg)	77.6±1.9	80.6±2.9	0.38
Mean blood pressure (mmHg)	94.3±2.2	98.2±3.2	0.31
Prednisolone dose (mg/day)	20.1±3.7 ($n=29$)	28.8±4.7 ($n=14$)	0.17
Duration of disease (yrs)	3.6±0.9	8.2±2.3	0.22
Heart rate (bpm)	75.8±2.3	96.7±3.9	<0.001
(Heart rate ≧ 100 bpm)	(1)	(10)	
LV end-systolic dimension (cm)	3.24±0.10	2.79±0.16	<0.05
LV end-diastolic dimension (cm)	4.79±0.13	4.36±0.14	<0.05
IVS thickness (cm)	0.97±0.03	1.17±0.07	<0.05
(Asymmetric septal hypertrophy)	(0)	(4)	
LV posterior wall thickness (cm)	1.01±0.03	1.04±0.03	0.49
PEP/LVET ratio	0.358±0.024	0.360±0.031	0.97
QS_2 interval (sec)	0.372±0.004	0.317±0.006	<0.001

Differences between the normal and high Kac groups were assessed by the unpaired *t*-test, except for the interventricular septal (IVS) thickness and the duration of disease which were compared by the Mann-Whitney *U* test.
LV = left ventricle; PEP = pre-ejection period. Other abbreviations as in Fig. 1.

The age, SLE criteria score, body temperature, hemoglobin, systolic blood pressure, diastolic blood pressure, mean blood pressure, prednisolone dose (excluding seven patients receiving betamethasone or dexamethasone), disease duration, and PEP/LVET ratio were all similar in the normal Kac and high Kac groups. However, the heart rate was significantly higher in the high Kac group than in the normal Kac group (96.7±3.9 vs 75.8±2.3 bpm, $p<0.001$), and the QS_2 interval was significantly shorter in the high Kac group compared with the normal Kac group (0.317±0.006 vs 0.372±0.004 sec, $p<0.001$). Ten of the 20 patients in the high Kac group had sinus tachycardia (heart rate ≧ 100 bpm). In the high Kac group, the LV end-systolic dimension (2.79±0.16 vs 3.24±0.10 cm, $p<0.05$) and end-diastolic dimension (4.36±0.14 vs 4.79±0.13 cm, $p<0.05$) were both significantly smaller than in the normal Kac group. Although the interventricular septum was significantly thicker in the high Kac group than in the normal Kac group (1.17±0.07 vs 0.97±0.03 cm, $p<0.05$), the difference in LV posterior wall thickness was not significant. All four patients in the high Kac group with asymmetric septal hypertrophy (IVS thickness/LV posterior wall thickness ≧ 1.3) had a normal heart rate (>100 bpm).

The Kac value was not related to the presence of Raynaud's phenomenon or renal dysfunction (SLE criterion No. 7 of the American Rheumatism Association). However, the mean Kac value of the 34 SLE patients receiving prednisolone was significantly higher than that of the nine patients who were not receiving steroids (8.20±0.08 vs 7.78±0.12 sec^{-1}, $p<0.05$).

Among the six patients receiving Ca^{2+} antagonists, three had a normal Kac value (7.88±0.18 sec^{-1}) and three had a high Kac value (8.45±0.05 sec^{-1}). Among the seven patients who were being treated with α_1-adrenoreceptor blockers, two were in the normal Kac group (7.82±0.25 sec^{-1}) and five were in the high Kac group (8.44±0.06 sec^{-1}). The only patient receiving a β-adrenoreceptor blocker was in the high Kac group (8.35 sec^{-1}), and both of the patients receiving digitalis were also in the high Kac group (9.10 and 8.35 sec^{-1}).

The 38 SLE patients not receiving Ca^{2+} antagonists, α_1- or β-adrenoreceptor blockers, or digitalis were also divided into a normal Kac group (mean Kac : 7.83±0.06 sec^{-1}) and a high Kac group (mean

Table 2 Comparison between the normal and high K_{ac} groups of SLE patients not receiving cardiovascular agents

	Normal ($6.9 < K_{ac} < 8.3$ sec^{-1})	High ($K_{ac} \geqq 8.3$ sec^{-1})	*p* value
Number of patients	26	12	
Age (yrs)	33.5±2.5	29.2±2.3	0.28
SLE criteria score	4.9±0.2	4.9±0.3	0.93
Body temperature (°C)	36.6±0.1	36.8±0.2	0.23
Hemoglobin (g/dl)	11.0±0.3	11.2±0.4	0.75
Systolic blood pressure (mmHg)	123.9±3.0	124.2±4.8	0.96
Diastolic blood pressure (mmHg)	76.4±2.0	73.8±1.9	0.43
Mean blood pressure (mmHg)	92.3±2.2	90.6±2.5	0.64
Prednisolone dose (mg/day)	16.3±3.6 (n=25)	38.2±6.9 (n=7)	<0.05
Duration of disease (yrs)	3.4±0.9	4.2±1.5	0.64
Heart rate (bpm)	74.8±2.2	101.6±4.8	<0.001
(Heart rate ≧ 100 bpm)	(0)	(7)	
LV end-systolic dimension (cm)	3.20±0.10	2.71±0.19	<0.05
LV end-diastolic dimension (cm)	4.73±0.13	4.31±0.17	0.08
IVS thickness (cm)	0.97±0.03	1.07±0.08	0.19
(Asymmetric septal hypertrophy)	(0)	(1)	
LV posterior wall thickness (cm)	1.03±0.03	0.99±0.04	0.50
PEP/LVET ratio	0.355±0.027	0.401±0.042	0.35
QS_2 interval (sec)	0.374±0.004	0.308±0.009	<0.001

Differences between the normal and high K_{ac} groups were assessed by the unpaired *t*-test, except for the interventricular septal (IVS) thickness which was compared by the Mann-Whitney *U* test.
Abbreviations as in Fig. 1, Table 1.

K_{ac} : 8.95±0.26 sec^{-1}) (**Table 2**). There were 26 patients in the normal K_{ac} group (3 men and 23 women) and 12 in the high K_{ac} group (one man and 11 women). The age, SLE criteria score, body temperature, hemoglobin, systolic blood pressure, diastolic blood pressure, mean blood pressure, duration of disease, interventricular septum thickness, and PEP/LVET ratio were all similar in the two groups. However, the heart rate was significantly higher in the high K_{ac} group than in the normal K_{ac} group (101.6±4.8 vs 74.8±2.2 bpm, $p<0.001$), and the QS_2 interval was significantly shorter in the high K_{ac} group compared with the normal K_{ac} group (0.308 ±0.009 vs 0.374±0.004 sec, $p<0.001$). Seven of the 12 patients in the high K_{ac} group had sinus tachycardia. Although the LV end-systolic dimension was significantly smaller in the high K_{ac} group than in the normal K_{ac} group (2.71±0.19 vs 3.20± 0.10 cm, $p<0.05$), the difference in LV end-diastolic dimension was not significant. The prednisolone dose (excluding six patients receiving betamethasone or dexamethasone) was significantly larger in the high K_{ac} group than in the normal K_{ac} group (38.2±6.9 vs 16.3±3.6 mg/day, $p<0.05$).

DISCUSSION

A theoretical model of myocardial contraction (the active cross-bridge model)[13] was developed based on the assumption that the basic mechanical and energetic properties of myocardial/cardiac contraction are governed mainly by the binding of calcium (Ca^{2+}) to troponin C. A train of equations derived from this model and the cylinder model[15] have been shown to provide a consistent theoretical explanation of a variety of basic molecular biological, dynamic, and energetic properties of myocardial/cardiac contraction[2,13–18]. To briefly review this model, the parameter K_a (the reciprocal of the duration of myocardial contraction) corresponds to the kinetic constant of the chemical reaction between Ca^{2+} and troponin C. The slope of the myocardial 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 troponin C for Ca^{2+}[14]. Based on evidence that the model consistently predicts the measured values of LV pressure, force, and time-varying

myocardial elastance throughout systole in dogs[14], that the LV end-systolic force-length relation obtained in normal dogs[16] shows a straight-line relationship with that obtained in humans[18], and that the theoretical model accurately predicts the measured values for the LV end-systolic pressure-volume, pressure-diameter, and stress-diameter relations[16], it seems reasonable to conclude that this model is tenable.

We have previously found that the average variation of K_{ac} is very small (only 4.6%), and that the K_{ac} value in humans at rest without interventions appears to remain constant between individuals, as well as being independent of age or myocardial fiber length[2]. However, the K_{ac} value is significantly increased by dobutamine infusion (1.5 μg/kg/min), despite no change in the heart rate. These observations taken together with earlier clinical findings regarding the QS_2 interval suggest that the K_{ac} value may be a useful measure of both the adrenergic tone of the working LV myocardium and the cardiac reserve in patients with chronic myocardial dysfunction[2]. In our recent clinical study, the mean K_{ac} value at rest showed no significant difference between normal individuals and patients with mild to moderate heart failure. After walking for 6 minutes, however, the ratio of the increment in K_{ac} to the increment in heart rate with exercise was significantly greater in cardiac patients than in normal subjects[19]. This finding suggests that the increase in the rate of Ca^{2+} binding to troponin C at a given heart rate during exercise is greater in the presence of heart failure than in the healthy state. The binding of Ca^{2+} to troponin C is thought to be regulated by the cardiac adrenergic nervous system, the β_1-adrenoreceptors of the working LV myocardium, and cyclic AMP[20]. Thus, the above hypothesis is consistent with the well known hypersensitive response of LV adrenergic activity to even mild exercise in patients with moderate heart failure. It has been observed that the K_{ac} value is abnormally low in patients with a permanent pacemaker[2,21], and this may be explained by a decrease of LV adrenergic activity due to chronic pacemaker stimulation[2]. We have also found that the K_a value was not altered by regional myocardial ischemia in the β-blocked canine left ventricle[22].

The present study showed that the K_{ac} value of 20 SLE patients was above 8.3 sec^{-1} (**Table 1**), the upper limit determined in normal individuals, suggesting that LV myocardial adrenergic activity was abnormally high in these patients. Cardiac adrenergic stimulation of the sinus node also appeared to be abnormally increased in the high K_{ac} group, because the heart rate was significantly higher than in the normal K_{ac} group.

There was no significant difference between the normal and high K_{ac} groups with regard to factors such as age, SLE criteria score, body temperature, hemoglobin, blood pressure, prednisolone dose, and disease duration (**Table 1**), suggesting that a high K_{ac} value was not related to these parameters. However, the mean K_{ac} value of the 34 patients who required prednisolone therapy was significantly higher than that of nine patients who were not receiving steroids, suggesting that there may be some association between a high K_{ac} value and the severity of SLE.

The high K_{ac} group had a significantly higher heart rate, significantly greater interventricular septal thickness, and significantly smaller LV end-systolic and end-diastolic dimensions than the normal K_{ac} group (**Table 1**). The increased heart rate may reflect stimulation by cardiac adrenergic drive and is clearly regulated by the autonomic nervous system acting on the sinus node. Asymmetric septal hypertrophy is common in patients with borderline hypertension and is probably associated with abnormal LV adrenergic activity[23]. However, this abnormality was not directly related to blood pressure in our SLE patients. On the other hand, the decrease of LV end-systolic and end-diastolic dimensions may be due to the Bowditch effect, *i.e.*, the increase of myocardial contractility associated with an increased heart rate[24]. The same effect of an increased heart rate has been observed in patients with a permanent pacemaker, since the LV end-systolic and end-diastolic dimensions both progressively decrease in proportion to the increase of the pacing rate without any change in blood pressure[2].

The cardiac adrenergic system is functionally divided into adrenergic nerves supplying the sinus node and those supplying the working LV myocardium. Among the 20 SLE patients in the high K_{ac} group, 10 had sinus tachycardia (heart rate≧ 100 bpm) and 10 did not, and it seems likely that adrenergic stimulation of the sinus node was increased in the former 10 patients (**Table 1**). In contrast, the adrenergic activity of the LV myocardium was increased, but that of the sinus node was not necessarily high, in the patients who had high K_{ac}

values and a normal heart rate (<100 bpm). Thus, the sinus node and the LV myocardium might be under independent regulation by the adrenergic system.

Ca^{2+} antagonists, α_1- or β-adrenoreceptor blockers, and digitalis were administered to some of our patients. It has been reported that Ca^{2+} antagonists do not alter the total contraction period in humans[25–27], while addition of Ca^{2+} increased the maximal force but did not change the total contraction period in an animal study[28]. Thus, Ca^{2+} antagonists may be unlikely to influence the K_{ac} value, while α_1- and β-adrenoreceptor blockers would be expected to reduce it. Since the K_{ac} value was abnormally high in six of the eight patients on α_1- or β-adrenoreceptor blockers, the actual values for these six patients may have been even higher before treatment. Both of the patients receiving digitalis also had high K_{ac} values. Digitalis is reported to shorten the QS_2 interval[29–32], so it might well have influenced the K_{ac} value in these two patients who were receiving a dose of 0.25 mg/day.

In the present study, 12 patients who were being treated with Ca^{2+} antagonists, α_1-adrenoreceptor blockers, and β-adrenoreceptor blockers had a history of hypertension. The 38 patients who were not receiving these cardiovascular agents or digitalis were divided into a normal K_{ac} group and a high K_{ac} group (**Table 2**). Although the heart rate was significantly higher and the LV end-systolic dimension was significantly smaller in the high K_{ac} group, the difference in interventricular septal thickness was not significant. These findings suggest that asymmetric septal hypertrophy may be associated with a history of hypertension. The prednisolone dose was significantly larger in the high K_{ac} group than in the normal K_{ac} group, suggesting that the high K_{ac} group had more severe SLE.

SLE is a chronic inflammatory disease which affects many organs of the body. Cardiac lesions are common in SLE and influence the prognosis. The results of the present study suggest that the hyperadrenergic state of the sinus node and working LV myocardium in some SLE patients could be normalized by treatment with β-adrenoreceptor blockers. If the K_{ac} value is normalized and cardiac complications are decreased by β-blocker therapy, it could be concluded that there is an association between a cardiac hyperadrenergic state and the cardiac complications of SLE. In addition, the large proportion of SLE patients with a high K_{ac} value suggests that this parameter may provide a useful indicator for investigation of the pathogenesis, treatment, and prognosis of this disease.

Limitations

The K_a value was estimated from the QS_2 interval in the present study. It should be emphasized that the K_a value was thus not an actual observed value for the kinetic constant of the binding of Ca^{2+} to troponin C, and was derived from the equations of our model.

In our previous study, equation [2] was developed from the K_a and heart rate data of 102 normal subjects without heart disease, and the range of the heart rates measured was 45 to 90 bpm[2]. Thus, it might not necessarily be appropriate to estimate the K_{ac} value from equation [2] in patients with sinus tachycardia (heart rate $\geqq 100$ bpm). However, we have previously found that the K_a value of patients with a permanent pacemaker set at 110 bpm was in agreement with the value extrapolated from the heart rate range of 50 to 90 bpm (Fig. 5 in reference 3). Thus, it seems that estimation of the K_{ac} value in patients with sinus tachycardia by using equation [2] is reasonable.

The K_a value is affected by body temperature[33], serum catecholamine levels[2,20], cyclic AMP levels[20], phosphodiesterase inhibitor administration[20], and thyroid function[34]. Moreover, it might be affected by circulating antibodies, increased activity of the renin-angiotensin system, or abnormalities of the acid-base balance. In the present study, none of the patients were receiving β-adrenoreceptor agonists or xanthine derivatives, and patients with thyroid disease were excluded. However, it cannot be completely ruled out that the K_a value was affected by the serum norepinephrine level and/or circulating antibodies in our SLE patients.

要　約

全身性エリテマトーデスにおける Systolic Time Intervals からの連結橋活性化速度定数 (K_{ac})

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背景：心臓の交感神経系は機能的に洞結節を支配する交感神経と左室作業心筋を支配する交感神経に分けられる．心拍数は洞結節の交感神経緊張を反映するが，臨床的に左室作業心筋の交感神経緊張は今まで評価できなかった．全身性エリテマトーデス (SLE) では末梢神経炎，精神症状，痙攣発作などの神経障害が報告されているが，心臓の自律神経活動の障害についての報告はない．今回われわれは，50 人の SLE 患者における心臓交感神経の活動性を，左室作業心筋の交感神経緊張を評価する新しい指標 (K_{ac}) を用いて調べた．われわれの活性連結橋モデルでは，左室心筋の連結橋活性化定数 (K_a) は Ca^{2+} とトロポニン C との結合反応速度定数に対応し，K_a＝3/全収縮時間で近似される．心拍数で補正された K_a(K_{ac}) は健常者ではほとんど一定値であるが，dobutamine 静注によって心拍数の変化はないにもかかわらず増加する．また，K_a は心筋内 cyclic AMP によって調節されているらしい．したがって，K_{ac} は左室作業心筋への交感神経活動変化を反映する指標として有用であることが示唆された．

方法：アメリカリウマチ協会の診断基準を満たす 50 人の SLE 患者に心エコー図検査を行った．このさい，心電図，心音図，頸動脈波を同時に記録した．K_{ac} は Q-II$_a$ 時間 (QS_2 時間) と心拍数 (HR) により以下の式で計算した．

$$K_{ac}=3/QS_2+0.0249\,(66-HR)$$

結果：心血管作動薬を投与されていない 50 人中 38 人の SLE 患者を，正常 K_{ac} 群 (26 例，$6.9<K_{ac}<8.3\ sec^{-1}$) と異常高値 K_{ac} 群 (12 例，$K_{ac}\geqq 8.3\ sec^{-1}$) に分けた．異常高値 K_{ac} 群では正常 K_{ac} 群に比べ有意に心拍数が増加し (101.6±4.8 vs 74.8±2.2 bpm, $p<0.001$)，左室収縮末期径が小さく (2.71±0.19 vs 3.20±0.10 cm, $p<0.05$), prednisolone 投与量が多かった (38.2±6.9 vs 16.3±3.6 mg/day, $p<0.05$).

結論：健常者に比べ SLE 患者では，その多くが洞結節と左室作業心筋への交感神経活動が過緊張状態にあることが示唆された．このような患者には多量の prednisolone 投与を必要とし，SLE 活動性が高かったことが示唆された．これらの結果と SLE 治療との関連は興味深いと思われた．

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