Journal of Zhejiang University SCIENCE
ISSN 1009-3095
http://www.zju.edu.cn/jzus
E-mail: jzus@zju.edu.cn

Early association of electrocardiogram alteration with infarct size and cardiac function after myocardial infarction

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Received Sep. 30, 2003; revision accepted Nov. 25, 2003

Abstract: Objective: Myocardial infarction (MI) is the main cause of heart failure, but the relationship between the extent of MI and cardiac function has not been clearly determined. The present study was undertaken to investigate early changes in the electrocardiogram associated with infarct size and cardiac function after MI. Methods: MI was induced by ligating the left anterior descending coronary artery in rats. Electrocardiograms, echocardiographs and hemodynamic parameters were assessed and myocardial infarct size was measured from mid-transverse sections stained with Masson's trichrome. Results: The sum of pathological *Q* wave amplitudes was strongly correlated with myocardial infarct size ($r = 0.920$, $P < 0.0001$), left ventricular ejection fraction ($r = -0.868$, $P < 0.0001$) and left ventricular end diastolic pressure ($r = 0.835$, $P < 0.0004$). Furthermore, there was close relationship between MI size and cardiac function as assessed by left ventricular ejection fraction ($r = -0.913$, $P < 0.0001$) and left ventricular end diastolic pressure ($r = 0.893$, $P < 0.0001$). Conclusion: The sum of pathological *Q* wave amplitudes after MI can be used to estimate the extent of MI as well as cardiac function.

Key words: Electrocardiogram, Myocardial infarction, Cardiac function
Document code: A **CLC number:** R540.41

INTRODUCTION

In patients with congestive heart failure specific electrocardiogram (ECG) alterations, such as pathological *Q* waves or persistent ST segment elevations in MI-related leads, may be seen after transmural myocardial infarction (MI). Infarct expansion occurs within hours of myocyte injury, results in wall thinning and ventricular dilation, and causes the elevation of diastolic and systolic wall stresses (Warren *et al.*, 1988). Ventricular remodeling may continue for weeks or months until the distending forces are counterbalanced by the tensile strength of the collagen scar (Pfeffer and Braunwald, 1990). Evaluation of pathological *Q* waves on admission of patients with acute MI has prognostic importance. It is known that pathological *Q* waves on admission of patients with acute MI are associated with higher peak creatine kinase, higher prevalence of heart failure, and increased mortality in patients with anterior MI (Birnbaum *et al*., 1997). Generally, cardiac function can be assessed by echocardiography and by invasive methods such as radionuclide and cardiac catheterization, but these methods are not convenient, especially in emergency cases. The assessment of cardiac function with ECG in patients with congestive heart failure resulting from MI has received little attention.

Furthermore, scar size has been the exclusive criterion for the evaluation of animals with congestive heart failure after MI (Richer *et al*., 1999). Therefore, in the present study we tested the hypothesis that pathological *Q* waves in the ECG of rats after MI can predict infarct size and cardiac function.

MATERIAL AND METHOD

Animals

MI was induced in male Sprague-Dawley rats weighing 230 to 240 g by legating the left anterior descending coronary artery (Pfeffer *et al.*, 1985). Briefly, rats were anesthetized with 4% chloral hydrate, intubated, and ventilated with room air (rodent ventilator DH 140, Zhejiang Univ. Medical Instruments Inc., Hangzhou, China). A 2 cm incision was made between the third and fourth ribs and enlarged with an eye speculum (3.5×8.0 cm), the pericardium was cut, and the left anterior descending coronary artery was ligated with 5 sutures. The chest was closed, and the animals were allowed to recover. Thirty-five percent of the rats did not survive 24 hours after surgery. Sham-operated rats were treated identically, but the sutures were only passed under the artery and not tied; all of them survived 24 hours after surgery.

Rats were housed 5 per cage, fed *ad libitum* with standard diet and had free access to tap water. Room temperature was maintained at 21±1 °C with a 12 h light/dark cycle. All procedures were approved by Animals Research Committee of School of Medicine, Zhejiang University.

ECG

Two weeks after surgery, rats were anesthetized with a combination of ketamine (75 mg/kg) and diazepam (5 mg/kg) and placed supine with the limbs extended. ECG was recorded on a MedLab data acquisition system (Nanjing MedEase Co., Nanjing, China) (Chen *et al*., 2002). Needle electrodes were introduced subcutaneously into the front right and left feet, to record the standard lead I ECG. The precordial ECG was recorded using the electrode system provided by MedLab. The placements were similar to those previously described (Wexler *et al*., 1973). The exact placement procedure was as follows: the fourth interspace was identified and V1 and V2 were placed immediately to the right and left of the sternum in this interspace, V4 was placed in the mid-collarbone line and V6 in the mid-axillary line, in the same horizontal plane. The amplitude of the pathological *Q* wave was measured as the mean of 5 consecutive QRS complexes in each of the five leads; the sum of pathological *Q* wave amplitudes in the five leads ($\sum Q$ in mV) was then calculated for each rat.

Echocardiography

Following the ECG measurements, imaging was performed with a Sequoia model 512 clinical echocardiograph fitted with a 12 MHz sector-scanning probe (Acuson, Mountainview, CA). Left ventricular short-axis images were acquired at the level of the chordae tendineae; long-axis images were acquired perpendicular to the short-axis and were deemed appropriate when left ventricular length was maximum and both mitral and aortic valves were contained in the image. Endo- and epicardial borders were identified at end-diastole and end-systole using the leading-edge convention. Ventricular volumes were calculated using the area-length method, which had been validated in rodents (Hill *et al*., 2000).

Hemodynamics

After the echocardiographic measurements, the right carotid artery was cannulated with a BD Angiocatheter (20GA 1.1×48 mm, Italy) and advanced into the aorta for recording arterial pressure. The aortic catheter was then advanced into the left ventricle (LV) for recording systolic pressure (LVSP), end-diastolic pressure (LVEDP) and maximal rates of pressure development and decline (dP/dt_{max}). All pressure data were recorded on a MedLab system (Chen *et al*., 2002).

Cardiac histomorphometry

After measuring the cardiac hemodynamic parameters, the heart was arrested in diastole with 3 ml of 10% KCl injected into the femoral vein, the atria and great vessels were trimmed away, and the

LV was separated. A mid-transverse cross-section about 2 mm thick was cut through the LV, fixed in 10% formalin, then dehydrated and embedded in paraffin. One 4 μm section was obtained from this slice, stained with Masson's trichrome and mounted onto a glass slide for measurement of infarct size and left ventricular cavity area. The boundary lengths of the infarcted and non-infarcted endocardial and epicardial surfaces were traced with a planimeter digital image analyzer (Sony). Infarct size was expressed as the ratio of the sum of external and internal scar lengths to the sum of external and internal perimeters of the LV.

Statistical analysis

Data are expressed as $\bar{x} \pm$ SD. Comparisons between groups were made by the independent samples t test and a value of $P<0.05$ was accepted as statistically significant. Linear regression analysis was used to examine the correlations among $\sum Q$, MI size and cardiac function. Significance levels were determined using Pearson's r correlation coefficient.

RESULT

Histomorphometry and hemodynamics

As shown in Table 1, body weights and heart rates were similar between sham-operated and MI rats (rats with MI sizes less than 19.5% were excluded from analysis). At 2 weeks, when compared with sham-operated rats, MI induced significant increases in LV to body weight ratio ($P<0.05$) and left ventricular cavity area to body weight ratio ($P<0.01$); MI greater than 19.5% significantly lowered mean arterial pressure, LV systolic pressure, and $dP/dt_{max,}$ and elevated LVEDP ($P<0.01$).

Table 1 Histomorphometric and hemodynamic measurements

	Sham (n=8)	MI (n=9)
BW (g)	262±7	259±4
LVW/BW (mg/g)	2.07±0.09	2.18±0.05*
LVCA/BW (mm^2/g)	0.035±0.004	0.045±0.008**
MI size (%)		31.5±10.4
HR (bpm)	407±13	410±14
MAP (mm Hg)	121±3	114±5**
LVSP (mm Hg)	143±4	134±5**
LVEDP (mm Hg)	1.86±2.67	9.76±6.66**
dP/dt_{max} (mm Hg/s)	14003±386	13885±598**

Values are $\bar{x} \pm$ SD. In the MI group, rats with $\sum Q$ less than 0.63 mV were excluded from analysis. BW=body weight; LVW/BW= left ventricle to body weight ratio; LVCA/BW=left ventricular cavity area to body weight ratio; HR=heart rate; MAP=mean arterial pressure; LVSP=left ventricular systolic pressure; LVEDP =left ventricular end-diastolic pressure; dP/dt_{max}=maximum rate of LV pressure development and decline. *$P<0.05$, **$P<0.01$ vs Sham

Echocardiographic assessment of left ventricular geometry and function

Two weeks after MI, animals showed a progressive LV dilation. The echocardiographic images from sham-operated rats showed normal LV during systole and diastole, with almost complete LV emptying at systole while the images from MI rats showed a dilated and globular LV chamber both at diastole and systole (Fig.1). Left ventricular dimensions at end-diastole and left ventricular end-diastolic volume significantly increased in rats with MI. The mean LVEF and left ventricular fraction shortening (LVFS) in MI rats were significantly ($P<0.01$) reduced. MI also caused a dramatic decrease in early (E) wave velocity and an increase in atrial (A) wave velocity (Table 2).

Association of ECG with MI size and cardiac function

The patterns of QRS complex of sham-operated rats were Rs or qRs in all precordial leads. The mid-

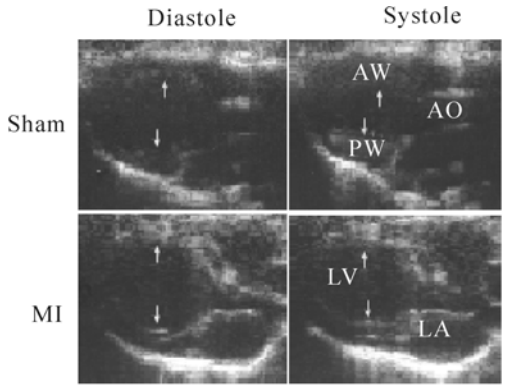

Fig.1 Long-axis echocardiographic images from a sham-operated (upper panels) and a MI (lower panels) rat (MI=myocardial infarction; AW=anterior wall; PW=posterior wall; AO=aorta; LV=left ventricle; LA=left atrium; Arrows indicate the endocardial surface of the anterior wall and the posterior wall of the LV)

Table 2 Echocardiograghic measurements

	Sham (n=8)	MI (n=9)
LVDd (mm)	5.96±0.33	7.26±0.65**
LVEDV (μl)	201±8	502±9**
LVEF (%)	62.9±3.4	41.2±4.8**
LVFS (%)	38.6±1.4	31.3±3.3**
E (cm/s)	56.9±5.3	102.8±6.6**
A (cm/s)	31.8±2.1	13.7±1.6**
E/A ratio	2.0±0.2	9.1±0.3**
EWD (m/s^2)	15.9±1.4	24.9±1.9**

Values are $\bar{x}$ ± SD. In the MI group, rats with $\sum Q$ less than 0.63 mV were excluded from analysis. LVDd=left ventricular dimension end diastole; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVFS=left ventricular fractional shortening; E=Early wave velocity; A=Atrial wave velocity; EWD=Early wave deceleration. *P<0.05, **P<0.01 vs Sham

transverse sections stained with Masson's trichrome from MI rats showed scars ranging from 0% to 51.7%, and the corresponding $\sum Q$ wave amplitudes varied from 0 mV to 4.21 mV. For example, a 16.8% scar corresponded to a $\sum Q$ of 0.56 mV, while a 37.0% scar produced a $\sum Q$ of 3.57 mV (Fig.2). The

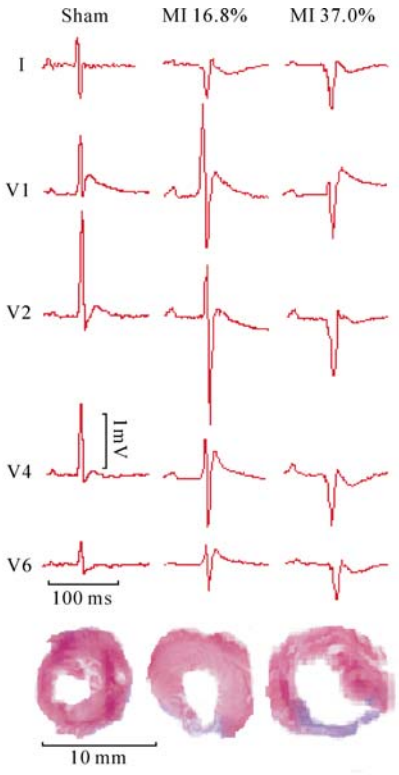

Fig.2 ECG QRS complexes on leads I, V1, V2, V4 and V6 and the corresponding mid-transverse sections stained with Masson's trichrome in sham-operated (left) and MI rats (middle and right) (The original magnification for the transverse sections was ×2.0)

correlation between $\sum Q$ and MI size was strongly positive (r=0.920, P<0.0001) (Fig.3). We determined the relationship between $\sum Q$ and cardiac function, and found strong correlations between $\sum Q$ and LVEF (r=–0.886, P<0.0001) and LVEDP (r=0.835, P<0.0004) (Fig.4). Furthermore, strong correlation existed between MI size and LVEF (r=–0.913, P<0.0001) and LVEDP (r=0.893, P<0.0001) (Fig.5).

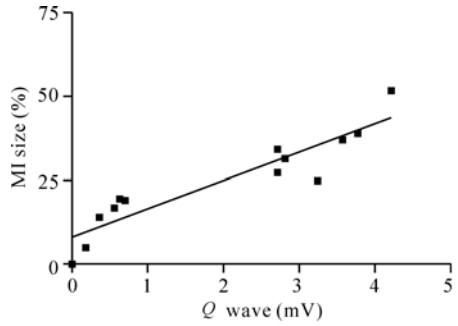

Fig.3 Linear regression curve showing correlation between $\sum Q$ (mV) and MI size (%). The linear regression equation is Y =8.4295X+8.0892, r=0.920, P<0.0001

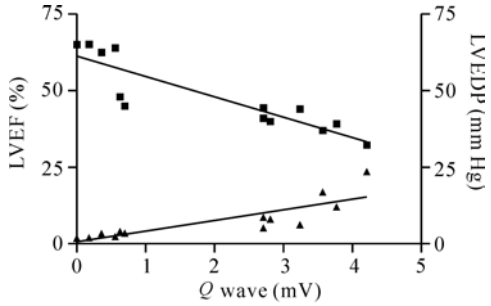

Fig.4 Linear regression curves showing correlations between $\sum Q$ (mV) and cardiac function as assessed by LVEF (%) (■) (r =–0.886, P<0.0001) and LVEDP (mm Hg) (▲) (r = 0.835, P<0.0004)

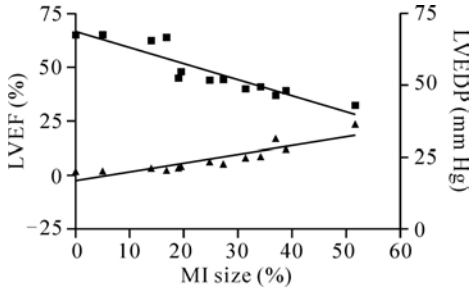

Fig.5 Linear regression curves showing correlations between MI size (%) and cardiac function as assessed by LVEF (%) (■) (r =–0.913, P<0.0001) and LVEDP (mm Hg) (▲) (r = 0.893, P<0.0001)

DISCUSSION AND CONCLUSION

Cardiac remodeling is generally accepted as the major determinant of the clinical course of heart failure, manifested as changes in size, shape and function of the heart resulting from cardiac load and/or injury. In post-infarction models, the process of LV remodeling begins rapidly and continues to progress (Korup *et al*., 1997). The acute loss of myocardium results in an abrupt increase in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote non-infarcted myocardium. Myocyte necrosis and the resultant increase in load trigger a cascade of intracellular signaling processes that initiate and subsequently modulate reparative changes, which include dilatation, hypertrophy, and the formation of a discrete collagen scar. Human and animal studies on the effects of myocardial infarction on ventricular architecture revealed that the injured ventricle progressively enlarged with time and that this alteration was paralleled by a corresponding decline in cardiac performance (Pfeffer *et al*., 1988; Warren *et al*., 1988)

The present study showed that 2 weeks after MI rats with more than 0.63 mV of total pathological Q waves (corresponding to more than 19.5% MI) showed dramatic decrease in LVEF and dramatic increase in LVEDP, $\sum Q$ closely correlated with MI size as well as LVEDP and LVEF. The mid-transverse sections stained with Masson's trichrome revealed that MI scars had clearly formed in the infarct region; that the left ventricular anterior and lateral wall bordering the scar zone had become thinner, and the left ventricular cavity area to body weight ratio was greater than in sham-operated rats. Echocardiographic images also showed that left ventricular volumes at diastole and systole were larger and LVEF and LVFS were lower compared with sham-operated rats.

The present study showed the sum of pathological Q waves closely correlated with infarct size as well as LVEF and LVEDP, so measurement of $\sum Q$ in an individual rat at 2 weeks can estimate MI size and the degree of heart failure. This method of post-infarction assessment of MI size and cardiac function by the sum of pathological Q waves is simpler than echocardiography and safer than cardiac catheterization. However, further work is required before this method applied to patients, since the human thorax and heart position differ from those of the rat.

The sum of pathological Q wave amplitudes is positively correlated with myocardial infarction size and cardiac function, and can be used to evaluate cardiac function after myocardial infarction.

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