Effects of Tachycardia on Regional Wall Motion in Acute Ischemic Canine Heart

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YAMAMOTO, Y., SAKUMA, M., HOZAWA, H., KOMAKI, K., TAKAHASHI, T., KUMASAKA, N., KAGAYA, Y., WATANABE, J. and SHIRATO, K. Effects of Tachycardia on Regional Wall Motion in Acute Ischemic Canine Heart. Tohoku J. Exp. Med., 2004, 203 (2), 111-121 —— Tachycardia accompanies the preload reduction. Our aim is to assess the effect of the heart rate change on wall motion in ischemic heart. In 8 dogs with occlusion of left anterior descending artery, we changed the heart rate (heart rate 90, 120, and 150 beats/minute) after using UL-FS49, a selective bradycardic agent, with atrial pacing. Preload was changed by inferior vena caval occlusion at a heart rate of 90 beats/minute. With either an increase in heart rate or an inferior vena caval occlusion, the end-diastolic length was decreased, but the end-diastolic length relationships between the non-ischemic and the ischemic region made different lines from those of the heart rate change and inferior vena caval occlusion. When increasing the heart rate, isovolumetric shortening was unchanged in the non-ischemic region with more expansion in the ischemic region. While inferior vena caval occlusion at a heart rate of 90 beats/minute, isovolumetric shortening was increased in the non-ischemic region, with more expansion in the ischemic region. Both in tachycardia and by the inferior vena caval occlusion, ejectional shortenings decreased in the non-ischemic and ischemic regions. Our results suggest that, in ischemic heart, tachycardia changes both in the end-diastolic length relationship between the non-ischemic and the ischemic region and at the isovolumetric contraction phase. The changes seem to be not only due to the inferior vena caval occlusion, but also due to tachycardia itself. ——— heart rate; preload; isovolumetric phase; ischemic region; UL-FS49

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In regional ischemic heart, the effects of changes in preload, afterload and contractile state on regional wall motion have been reported (Akaishi et al. 1985; Lew and Ban-Hayashi 1985; Lew et al. 1985; Noma et al. 1988a, b; Ishikawa et al. 1993; Sakuma et al. 1993). It has been shown that the degree of isovolumetric shortening in the non-ischemic region reflects the degree of paradoxical systolic expansion in the ischemic myocardium.

Tachycardia worsens systolic and diastolic function in depressed heart (Umana et al. 2003). But it has never been reported how tachycardia influences the regional wall motion during the isovolumetric contraction phase and ejection phase in regional ischemic heart. There are several reports which pointed out that tachycardia significantly increased the myocardial oxygen consumption and the myocardial viscosity (Templeton et al. 1975; Varma et al. 2000) in ischemic heart.

Therefore, we hypothesized that, in ischemic heart, tachycardia causes changes of the regional myocardial performance, which are different from the changes in preload by inferior vena caval (IVC) occlusion. In this study, we aimed to clarify how tachycardia worsens the myocardial dynamics in the ischemic heart through changes of the regional myocardial function.

**Materials and Methods**

**Experimental preparation**

Eight adult mongrel dogs weighing from 16.2 to 36.4 kg (average 25.2 kg) were anesthetized with intravenous sodium pentobarbital (30 mg/kg weight). Dogs were ventilated with a Harvard respirator through an endotracheal tube and a left thoracotomy was performed in the fifth intercostal space. Arterial blood gases were monitored intermittently and supplemental oxygen was given when necessary to maintain PaO₂ at 90 mmHg or more. The left ventricular pressure was recorded using a catheter-tipped micromanometer (Millar Instruments, Houston, TX, USA) with a fluid-filled lumen which was inserted into the left ventricle via the right carotid artery. Another catheter-tipped micromanometer was placed in the ascending aorta via the right femoral artery to measure the aortic pressure. Both left ventricular and aortic pressures were also measured with Statham P23Db pressure transducers. The zero point of the pressure signal from the micromanometer was corrected by the pressure wave recorded with the fluid-filled system in diastasis. The left anterior descending artery was dissected free near its origin through a small incision (about 10 mm) made in the pericardium and a snare was put around the vessel for later occlusion. Segment lengths of the left ventricular free wall were measured with an ultrasonic dimension system (Model 120; Triton Technology, San Diego, CA, USA). Two pairs of ultrasonic crystals (diameter=2 mm, 5 MHz) were implanted into the left ventricular free wall in the circumferential plane close to the endocardium through small incisions (less than 10 mm) in the pericardium (Shirato et al. 1978; Kanazawa et al. 1983). One pair of pacemaker leads was sutured on the right atrial appendage, and a pacemaker (MEP-2000, Baxter, IL, USA) was subsequently used to change the heart rate. Stroke volume was measured by an electromagnetic flow meter (Nihon-Kohden, MFV-3100, Tokyo), which was set around the ascending aorta through another incision (less than 25 mm) in the surrounding pericardium. All pericardial incisions were sutured loosely. A limb lead electrocardiogram was monitored throughout the experiment. A balloon catheter was positioned at IVC through the right femoral vein for transient occlusion. A polyethylene tube was inserted into the right femoral vein for drug infusion.
**Protocol**

After control data were recorded, the left anterior descending artery was completely occluded by tying a silk thread around the vessel. Hemodynamic data and the segment lengths became stable within 5 minutes after coronary occlusion in all the dogs and then the new stable state was confirmed. In all dogs, after coronary occlusion, systolic bulging appeared in the ischemic region. Ten minutes after coronary occlusion, UL-FS 49 (Karl Thomae, Biberach, the Federal Republic of Germany ([FRG]), 8 mg of a selective bradycardic agent (Kobinger and Lillie 1984; Dammenge et al. 1985; Guth et al. 1987; Indolfi et al. 1989) were administered intravenously, and an additional dose of the drug (2 mg/each) was infused until the heart rate decreased to under 90 beats/minute (total dose: 8–14 mg), if necessary. About ten minutes later, the hemodynamic and segment lengths were stable. Thereafter, the heart rate was randomly changed from 90 to 150 beats/minute every ten beats/minute by right atrial pacing. At each heart rate, IVC occlusion was performed transiently. The heart rate was changed to the next level after all the hemodynamic data had become stabilized. All the protocols were finished within 60 minutes. In the preliminary experiments we confirmed that UL-FS 49 maintained the bradycardic effect hemodynamically for at least two hours.

**Data analysis**

All data were recorded on an eight-channel recorder (Rectigraph 8K; San-Ei Instruments, Tokyo) and stored on magnetic tape (Model FE 3907W; Sony, Tokyo) for subsequent analysis. The recorded analogue data were digitized (MacLab 8; AD Instruments, Oxfordshire, UK) and analyzed by a personal computer (Centris 650; Apple Computer, Cupertino CA, USA). End-diastole was determined as the onset of a steep increment of the left ventricular pressure after atrial contraction. The timing of aortic valve opening was determined by transposing the aortic pressure at the onset of systole onto the left ventricular tracing. End-systole was determined as the timing of the aortic valve closure by transposing the aortic pressure of the dicrotic notch onto the left ventricular pressure tracing. The first derivatives of left ventricular pressure (dP/dt) were calculated as a running five-point, polyorthogonal transformation from the digitized left ventricular pressure.

![Fig. 1. A representative recording of ischemic and non-ischemic myocardial motion at heart rate 90 (shown as Base), 120 and 150 beats/minute in acute ischemia without controlled preload. ED, end diastole; AVO, the timing of aortic valve opening; ES, end systole; LVP, left ventricular pressure.](image-url)
pressure. The period from end-diastole to aortic valve opening was determined as the isovolumic contraction phase, and the period from aortic valve opening to end-systole as the ejection phase.

For comparison of the segment lengths in the ischemic and the non-ischemic regions, each measured value was normalized with the end-diastolic length of control being 10 mm (Shirato et al. 1978; Ishikawa et al. 1993). Total systolic shortening equals end-diastolic length minus end-systolic length. Isovolumetric shortening equals length at end-diastolic length minus the length at aortic valve opening. Ejectional shortening equals length at aortic valve opening minus end-systolic length. Stroke volume was calculated from the digitized aortic flow data using Simpson’s rule (Lax et al. 1976). All data were obtained in the end-expiratory phase. The time constant of left ventricular decline was calculated using the method by Weiss et al. (1976).

We compared the data at heart rates of 90 (shown as Base), 120 and 150 beats/minute in acute ischemia without controlled preload, and also compared at three preload levels with a heart rate of 90 beats/minute (Fig. 1). The high preload level (High=Base) was the state before IVC occlusion. The mid preload level (Mid) was 2 mmHg lower, and the low preload level (Low) was 4 mmHg lower than the left ventricular end-diastolic pressure at the high preload level.

The animal study was approved by the committee of Tohoku University on research animal use.

All data were expressed as mean±S.E. and the differences in means were assessed by one-way repeated-measures analysis of variance (ANOVA) (Glantz and Slinker 1990). Simultaneous multiple comparisons between groups were made using the Scheffe’s method (Bancroft 1968). A $p$-value less than 0.05 was regarded as statistically significant. Linear relationships were fitted with a standard least squares linear regression analysis and 95% confidence intervals for all individuals were calculated (Altman et al. 2002). Most of the data were calculated by using STATVIEW 5.0 for

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**Table 1. Hemodynamic data from heart rate change and preload change at HR 90 (n=8)**

<table>
<thead>
<tr>
<th></th>
<th>AVOP (mmHg)</th>
<th>A VOP (mmHg s⁻¹)</th>
<th>Peak (+)</th>
<th>Peak (−)</th>
<th>DT/τ (ms)</th>
<th>τ (ms)</th>
<th>SV (ml)</th>
<th>CO (ml/min)</th>
<th>Double Product (mmHg bpm)</th>
<th>DOUBLE PRODUCT (mmHg bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>9.5±1.0</td>
<td>83±9</td>
<td>1640±52</td>
<td>−169±90</td>
<td>44±4</td>
<td>40±3</td>
<td>11.2±0.6</td>
<td>1151±115</td>
<td>18.6±3.4</td>
<td>11.4±3.4</td>
</tr>
<tr>
<td>HR 120</td>
<td>7.8±1.0</td>
<td>88±9</td>
<td>1244±57</td>
<td>−179±71</td>
<td>41±3</td>
<td>41±3</td>
<td>10.6±0.6</td>
<td>1351±135</td>
<td>17.6±1.7</td>
<td>12.5±1.5</td>
</tr>
<tr>
<td>HR 150</td>
<td>7.9±1.2</td>
<td>87±9</td>
<td>1669±70</td>
<td>−148±120</td>
<td>37±2</td>
<td>37±2</td>
<td>11.4±0.1</td>
<td>1541±154</td>
<td>16.5±1.6</td>
<td>11.6±1.6</td>
</tr>
<tr>
<td>Mid</td>
<td>7.0±0.9</td>
<td>82±3</td>
<td>1510±70</td>
<td>−148±101</td>
<td>37±2</td>
<td>37±2</td>
<td>11.4±0.1</td>
<td>1541±154</td>
<td>16.5±1.6</td>
<td>11.6±1.6</td>
</tr>
<tr>
<td>Low</td>
<td>5.5±0.9</td>
<td>74±3</td>
<td>1315±87</td>
<td>−139±131</td>
<td>37±2</td>
<td>37±2</td>
<td>11.4±0.1</td>
<td>1541±154</td>
<td>16.5±1.6</td>
<td>11.6±1.6</td>
</tr>
</tbody>
</table>

All values are mean±S.E. HR, heart rate; Base, HR 90 which is identical with preload High; LVEDP, left ventricular end-diastolic pressure; CO, cardiac output; Mid, mid preload level; Low, low preload level.

$^*p<0.05$ vs. previous value.
Macintosh (SAS Institute, Inc., Cary, NC, USA).

**Results**

**Hemodynamics**

When the heart rate increased from 90 to 150 beats/minute, left ventricular end-diastolic pressure was decreased. The isovolumetric contraction time was unchanged, although ejectional time and total systolic time decreased. Compared with 90 beats/minute, the time constant decreased at 120 beats/minute, but was unchanged at 150 beats/minute. With the increase in heart rate, diastolic time/time constant and stroke volume significantly decreased, but cardiac output did not change significantly. Double product increased.

On the other hand, when preload decreased from High (=Base) to Low, left ventricular end-diastolic pressure and time constant decreased, and diastolic time/time constant increased. Stroke volume, cardiac output, and double product, also decreased. Throughout our protocol, the diastolic time/time constant was over 3.5 in all dogs.

**Regional myocardial motion**

When the heart rate increased from 90 to 150 beats/minute, the end-diastolic lengths in both the non-ischemic and ischemic regions were decreased. Isovolumetric shortening in the non-ischemic region was unchanged, whereas isovolumetric expansion slightly increased in the ischemic region. Ejectional shortenings decreased in both the non-ischemic and ischemic regions.

<table>
<thead>
<tr>
<th>Table 2. Time phase of heart rate change and preload change at HR 90 (n=8)</th>
</tr>
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<tbody>
<tr>
<td>Base</td>
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<tr>
<td>HR 120</td>
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<tr>
<td>HR 150</td>
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<tr>
<td>Mid</td>
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<td>Low</td>
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All values are mean±S.E. Sys. T., total systolic time; Iso. T., Isovolumetric contraction time; Ej. T., Ejectional time; other abbreviations are the same as in Table 1.

* p<0.05 vs. Base.

<table>
<thead>
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<th>Table 3. Regional myocardial function from heart rate change and preload change at HR 90 (n=8)</th>
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<tr>
<td>EDL</td>
</tr>
<tr>
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<tr>
<td>NIR (mm)</td>
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<tr>
<td>Base</td>
</tr>
<tr>
<td>HR 120</td>
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<tr>
<td>HR 150</td>
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<tr>
<td>Mid</td>
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<tr>
<td>Low</td>
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</tbody>
</table>

All values are mean±S.E. EDL, end-diastolic length; ΔL(Iso.), Isovolumetric shortening; ΔL(Ej.), Ejectional shortening; NIR, non-ischemic region; IR, ischemic region; other abbreviations are the same as in Table 1.

* p<0.05 vs. Base. † p<0.05 vs. previous value.
On the other hand, when preload decreased from High (=Base) to Low, end-diastolic lengths in both the non-ischemic and ischemic regions were decreased. Isovolumetric shortening in the non-ischemic region increased, whereas isovolumetric expansion increased more in the ischemic region. Ejectional shortening decreased in both the non-ischemic and ischemic regions.

In a representative relationship of the end-diastolic length between the non-ischemic and ischemic region in one dog, the points in heart rate change differed from those in preload change (Fig. 2A). A negative correlation between the non-ischemic and ischemic isovolumetric shortenings existed in the preload change, but not in the increase in heart rate (B). In each panel, the solid line is a regression line and the broken lines are 95% confidence intervals for all data from the preload change. EDL, end diastolic length; ΔL(Iso.), isovolumetric shortening; NIR, non-ischemic region; IR, ischemic region; ○, preload change at heart rate 90 bpm; ⋄, increase in heart rate; 120, heart rate 120 bpm; 150, heart rate 150 bpm.

Fig. 2. A representative relationship between the non-ischemic and the ischemic lengths in end-diastole (A) and isovolumetric shortenings (B). The end-diastolic relationship in the heart rate change differed from that in the preload change (A). A negative correlation between the non-ischemic and the ischemic isovolumetric shortenings existed in the preload change, but not in the increase in heart rate (B). In each panel, the solid line is a regression line and the broken lines are 95% confidence intervals for all data from the preload change. EDL, end diastolic length; ΔL(Iso.), isovolumetric shortening; NIR, non-ischemic region; IR, ischemic region; ○, preload change at heart rate 90 bpm; ⋄, increase in heart rate; 120, heart rate 120 bpm; 150, heart rate 150 bpm.

Fig. 3. Summarized data from eight dogs: end-diastolic length (EDL) relationship between the non-ischemic and ischemic regions in the heart rate change was different from that in the preload change (A). Isovolumetric shortening between the non-ischemic and ischemic regions had a negative correlation in the preload change, while in the heart rate increase, isovolumetric shortening in the ischemic region was more negative, but unchanged in the non-ischemic region ΔL (Iso) (B). Stars indicate the “Base” point of both the non-ischemic and ischemic region. Other abbreviations are the same as in Fig. 2.
expansions existed in the preload change, but not in the increase in heart rate, resulting from the greater expansion in the ischemic region and unchanged shortening in the non-ischemic region (Fig. 2B). In the other remaining seven dogs, the point at a heart rate of 150 bpm was out of the range of 95% confidence intervals of the two relations mentioned above. These probabilities are less than 0.0001.

As a whole, the end-diastolic length relationship between the non-ischemic and ischemic region in the heart rate change was different from that in the preload change (Fig. 3A). Isovolumetric shortening between the non-ischemic and the ischemic region had a negative correlation with the preload change, while with the heart rate increase, isovolumetric shortening in the ischemic region was more negative but unchanged in the non-ischemic region (Fig. 3B).

In the left ventricular end-diastolic pressure-length relationships of the non-ischemic region (Fig. 4A) and the ischemic region (Fig. 4B), the point at a heart rate of 150 bpm was out of the range of 95% confidence intervals of the data from preload change. The same results were obtained from other seven dogs, both in the non-ischemic and the ischemic region (both,

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Fig. 4. A representative end-diastolic pressure-length relationship in the non-ischemic region (A) and in the ischemic region (B). A positive correlation existed in the preload change (open circles and triangles). However, when the heart rate increased, it was shifted upward to the left as compared with that in the preload change (closed circles and triangles). Solid lines indicate the regression line preload change at a heart rate of 90 bpm. Broken lines indicate 95% confidence intervals for all data from the preload change. EDP, end diastolic pressure; Other abbreviations are the same as in Fig. 2.

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Fig. 5. End-diastolic pressure-length relationship in the non-ischemic region and in the ischemic region. A positive correlation existed when the preload decreased. However, when the heart rate increased, it was shifted upward to the left as compared with that in the preload change. Circles indicate the relationship of the non-ischemic region, and triangles indicate the relationship of the ischemic region. Arrows with solid lines indicate the changes when the preload increased at a heart rate of 90 bpm. Arrows with broken lines indicate the changes when the heart rate increased. + and ★ indicate the “Base” point of both the non-ischemic and ischemic region, respectively. Other abbreviations are the same as in Fig. 4.
p<0.0001). When the heart rate increased, the end-diastolic pressure-length relationship was shifted upward to the left compared to that in the preload change (Fig. 5).

**DISCUSSION**

*End-diastolic relationships*

Our study showed that when the heart rate was increased in acute ischemic canine heart, the end-diastolic pressure-length relation shifted upward to the left from that in the preload change by IVC occlusion (Figs. 4 and 5), and the end-diastolic length in both the ischemic and non-ischemic regions decreased, but the end-diastolic length relationship between the non-ischemic and ischemic regions was different from that in the preload reduction (Figs. 2 and 3).

There were several possible reasons to explain the changes in these end-diastolic relationships. The first reason could be the effects of the relaxation phase, including incomplete relaxation. In the present study, when the heart rate increased, peak (−) dP/dt became less negative, but the time constant, the most sophisticated index in the relaxation phase, was shortened at the heart rate of 120 beats/minute, and was not changed significantly between 150 and 90 (Base) beats/minute. This means that the relaxation itself was not impaired by tachycardia. On the other hand, Weisfeldt et al. (1978) reported that incomplete relaxation was not caused in non-ischemic heart if the diastolic time/time constant was over 3.5. However, this issue was not examined in regional ischemic heart. In our study, the diastolic time/time constant was more than 3.5 in all the protocols, but was gradually shortened by the heart rate increase. Therefore, we cannot exclude the possibility that incomplete relaxation occurred in the ischemic heart, even if the diastolic time/time constant was more than 3.5.

The second reason is the viscous effect which is enhanced by an increase in myocardial velocity. Hashiguchi et al. (1988) demonstrated the possibility of an increase in the viscosity in ischemic heart. Thus, the viscous effect may play an important role when the heart rate is increased (Templeton et al. 1975).

The third reason is the influence of the ischemic zone size. It was reported that the ischemic zone size was unchanged in the ischemic heart even if preload, afterload, or contractility was altered (Buda et al. 1988; Kavanaugh et al. 1988). But Shell and Sobel examined myocardial CPK in acute ischemic canine heart and showed that an increase in the heart rate caused a worsening of the ischemic zone size during 60 to 90 and 120 to 180 beats/minute (Shell and Sobel 1973). The result suggested that an increase in the heart rate would expand the ischemic area. It is well known that the double product reflects the myocardial oxygen consumption (Tanaka et al. 1990), and that the double product is remarkably increased when the heart rate is increased. The increase of the double product may result in the expansion of the ischemic area. Thus, expansion of the ischemia into the border zone remains as one possibility.

*Regional wall motion in the isovolumetric phase*

The present study showed that, during the isovolumetric contraction phase in acute ischemic canine heart, the expansion in the ischemic region increased without changes in the shortening of the non-ischemic region when the heart rate increased. These results seem to differ from those of the previous reports (Akaishi et al. 1985; Lew et al. 1985; Noma et al. 1988a, b; Ishikawa et al. 1993; Sakuma et al. 1993) which showed that the increase of the isovolumetric shortening in the non-ischemic region reflected the increase of the isovolumetric bulging in the ischemic region, both in the preload change and in the afterload change. The changes of the end-diastolic relations between the non-ischemic and ischemic regions partly affected the relationship between these two regions in the isovolumetric phase. When the heart rate increased, the end-diastolic length (preload) were decreased but, at least, the left ventricular pressure at the timing of aortic
valve opening (afterload) was not decreased. On the basis of previously reported data on the effect of preload and afterload (Lew and Ban-Hayashi 1985; Ishikawa et al. 1993; Sakuma et al. 1993), tachycardia may precede the increase of the shortening in the non-ischemic region during the isovolumetric shortening phase. However, differing from this estimation, the shortening of the non-ischemic region showed no significant change with the increase in heart rate. This means that the increase in the heart rate itself was another independent determinant of the regional shortening. On the other hand, the increase in the bulging in the ischemic region with the increase in heart rate can be partly explained by the reduction of the end-diastolic length (Ishikawa et al. 1993). In the isovolumetric contraction phase, the increment of the shortening in the non-ischemic region has been explained by the augmentation of bulging in the ischemic region that is increased when the preload is decreased or the afterload increased (Lew and Ban-Hayashi 1985; Noma et al. 1988a; Ishikawa et al. 1993; Sakuma et al. 1993). But when the heart rate increased, the increase of the bulging in the ischemic region was not accompanied by shortening in the non-ischemic region. Thus, regional wall motion in both the non-ischemic and ischemic regions in the isovolumetric contraction phase could not be explained by the model of a simple serial interaction between the non-ischemic and the ischemic regions. This suggests the presence of another factor, i.e., the deformation of the left ventricle, or the involvement of the right ventricle. Unfortunately, this phenomenon could not be fully explained by the results of the present study, and further investigation will be needed.

Ejectional shortening in the non-ischemic region

When the heart rate increased, ejectional shortening in the non-ischemic region was decreased. This could be explained by the Frank-Staring mechanism, namely the decrease in the end-diastolic length and the shortening of the ejection time. In a human study, Petretta et al. (2002) reported that pacing tachycardia after left ventricular volume expansion improved the ejection fraction in normal human heart, but reduced it in patients with dilated cardiomyopathy heart.

Clinical implications and study limitations

The present study showed that tachycardia worsens the myocardial dynamics in the ischemic heart through changes in the regional myocardial function. The results suggested that the treatment of tachycardia has clinical importance in acute myocardial ischemia.

In the present study design, we did not determine the effect of β-adrenergic stimulation during preload change. This may affect the regional wall motion of both non-ischemic and ischemic region in ischemic heart. Therefore, future study will be needed to analyze this effect.

Conclusions

In ischemic heart, the change in heart rate was a determinant factor for the regional myocardial wall motion that differed from the preload change by IVC occlusion. Among heart rates of 90, 120 and 150 beats/minute, 90 seemed to be the most suitable heart rate for the ischemic heart, at least in terms of the regional wall motion.

Acknowledgments

In this study, UL-FS 49 was provided by Karl Thomae (Biberach, FRG). This material was one of the key factors to complete this study.

References


