Effect of dopamine and atrial pacing on stunned myocardium

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Abstract

Objective: Post-ischaemic stunned myocardium shows an impaired function at restored coronary blood flow, but performance can be normalized by positive inotropic stimulation. The power of stunned myocardium, however, is not augmented with increasing heart rate by atrial pacing, which is in contrast to intact areas. This pathological response is mitigated by inhibiting the degradation of cyclic AMP. The present experiments studied the effect of stimulating cyclic AMP formation by dopamine on the response of stunned myocardium to atrial pacing.

Methods: In anaesthetized (piritramide) open chest pigs, heart rate, left ventricular and aortic pressure, left descending (LAD) and circumflex (LCX) coronary artery and aortic blood flow, myocardial systolic shortening in the LAD and LCX area were monitored, and myocardial power was calculated. The LAD region was subjected to ischaemia and reperfused for 2 h. Subsequently, heart rate was raised by right atrial pacing before and during intravenous infusion of dopamine (10 mg/kg per min). The ischaemic/reperfused area was sliced post mortem and stained by triphenyl tetrazolium chloride to exclude myocardial infarction. Data from 11 experiments are presented.

Results: After 2 h LAD reperfusion, LAD blood flow and power were 100% and 36% of pre-ischaemic control, respectively, indicating myocardial stunning. The power of the intact area was not changed significantly (111% of control). Increasing heart rate by +36 and +70 from 94 beats/min increased the power of the intact area to 161% and 183% of control; the power of the stunned myocardium decreased to 34% and 19% of pre-stunning control. Dopamine increased the power of the stunned region to 143% of the pre-stunning level and the power of the intact area to 206% of control. Increasing heart rate by +34 and +70 from 113 beats/min during dopamine, increased the power of the intact myocardium to 288% and 344% of control and the power of the stunned region to 177% and 174% of the pre-stunning level.

Conclusions: The data confirm the pathological response of stunned myocardium to atrial pacing and the recruitment of a functional reserve by catecholamines. The adverse effect of pacing on the function of stunned myocardium is abolished by positive inotropic stimulation. Physiologically increased heart rate by an increased activity of the sympathetic nervous system, is probably not accompanied by a reduced power of stunned myocardium, due to the associated positive inotropic stimulation.

Keywords: Stunned myocardium; Pacing; Dopamine; Anaesthetized pigs

1. Introduction

The heart has the intrinsic property to change contractility with the rate of contraction as first described by Bowditch [1]. The force of cardiac muscle from most mammals including man and pig rises with increasing rate of stimulation [2,3]. This positive force-frequency relation, however, is lost or turned into a negative relation in different types of end-stage heart failure in man [4–7] and in experimental heart failure in animals [3,8].

In a recent study, similar results were obtained with respect to the response of the power of intact and stunned myocardium to rising heart rate by atrial pacing [9]. The power of intact myocardium was found to increase with heart rate. Stunned myocardium, which is characterized by a prolonged postischaemic myocardial dysfunction at
restored myocardial blood flow without irreversible myocardial damage by necrosis [10,11], did not show this positive power-frequency relation, instead the power decreased with increasing heart rate. The pathological response of stunned myocardium, however, was ameliorated during positive inotropic stimulation with milrinone. According to the mode of action of milrinone, i.e. inhibition of the degradation of cAMP by phosphodiesterase III, this result suggests, that the myocardial response to atrial pacing depends on the cAMP pathway and that cAMP is still generated in stunned myocardium. Nevertheless, the formation of cAMP may be impaired as discussed for the pathological force-frequency relation of myocardium from failing hearts [5,6,12].

A well known feature of stunned myocardium is a functional reserve, which is recruitable by positive inotropic interventions including the application of catecholamines [11]. This shows, that the formation of cAMP can be stimulated in stunned myocardium. From these data was hypothesized, that catecholamines restore also a physiological response of stunned myocardium to atrial pacing. Therefore, the present experiments were designed to compare in an in vivo model the response of stunned and intact myocardial areas to an increase of heart rate by electrical stimulation before and during positive inotropic stimulation by dopamine.

2. Method

The present experiments are part of an animal experiments project approved by the Regierung von Oberbayern. The methods and the protocol of the present study are very similar to preceding experiments and have been described more detailed previously [9].

2.1. Animals and anaesthesia

The experiments were performed in 14 domestic pigs, body weight 33–44 kg, pretreated by azaperon i.m. (4 mg/kg Stresnil®, Janssen, Neuss, Germany), ketamine i.m. (5 mg/kg Ketanest®, Parke Davis, München, Germany), and atropine sulfate i.m. (25 µg/kg, Braun, Melsungen, Germany). Anaesthesia was induced by thiopental sodium i.v. and the LAD was reperfused freely. After 90 min (n = 7) or 165 min (n = 7), heart rate was increased stepwise by atrial pacing. Then dopamine (Dopamin Guilini®, Guilini Pharma, Hannover, Germany) was given intravenously (10 µg/kg per min) and atrial pacing was repeated during sustained infusion of dopamine. At the end of the experiments, the myocardial areas analyzed by sonomicrometry were sliced and stained with triphenyl tetrazolium chloride for exclusion of myocardial infarction [13].

2.2. Preparation and instrumentation

Jugular veins and a femoral artery were cannulated for application of drugs and fluids, monitoring of central venous pressure (CVP, P23ID, Spectramed, Oxnard, USA), and blood sampling. The heart was exposed from a left side thoracotomy. Catheter-tip manometers were placed in the ascending aorta (SPC 350, Millar, Houston, TX) and the left ventricle (SPR 524, Millar, Houston, TX; via left atrial appendage) to measure aortic pressure (AoP) and left ventricular end diastolic pressure (LVedP) and dP/dt max. Perivascular ultrasonic transit-time flowprobes (T206, Transonic, Ithaca, NY) were placed at the ascending aorta, left descending (LAD), and circumflex (LCX) coronary artery to monitor stroke volume (SV) and coronary blood flow (Q). A tourniquet was placed around the LAD distal to the flow probe for controlled reduction of QLAD. The systolic-diastolic changes in length of myocardial segments in the LAD and LCX territory were assessed by sonomicrometry. Wires were attached to the right atrial appendage for increasing heart rate (HR) by electrical stimulation.

2.3. Experimental protocol

After assessment of control data, QLAD was obstructed within 10 min until myocardial systolic shortening distal to the stenosis was reduced to 19 ± 1% of control. This hyperperfusion was maintained for 30 min followed by repeated LAD-occlusion/perfusion (5 × 1 min occlusion interrupted by 1 min perfusion at the hyperperfusion flow level). The tourniquet was removed after the last occlusion and the LAD was reperfused freely. After 90 min (n = 7) or 165 min (n = 7), heart rate was increased stepwise by atrial pacing. Then dopamine (Dopamin Guilini®, Guilini Pharma, Hannover, Germany) was given intravenously (10 µg/kg per min) and atrial pacing was repeated during sustained infusion of dopamine. At the end of the experiments, the myocardial areas analyzed by sonomicrometry were sliced and stained with triphenyl tetrazolium chloride for exclusion of myocardial infarction [13].

2.4. Data assessment, calculations, exclusion of experiments, statistics

All signals were recorded on multi-channel chart recorders (TA 5000, Gould, Valley View, USA) and read in the end-expiratory phase. The following calculations were performed: myocardial systolic shortening MSS = % change in segment length from opening to closure of the aortic valve; cardiac output CO = SV·HR; systemic flow resistance Rsys = (AoPm – CVP)/CO and coronary flow resistance Rlad,lcx = (AOPm – CVP)/QLAD,LCX (AoPm, aortic mean pressure); indices of global left ventricular power POWL = CO·AoPm/tej and of regional myocardial power POWL,LAD,LCX = MSSLAD,LCX·AoPm·tej/AoPm, aortic mean pressure during ejection; tej, duration of ejec-
tion i.e. from opening to closure of the aortic valve). Three experiments were excluded from evaluation: one experiment showed infarction in the LAD-area, and in two experiments myocardial function of the LAD-area was not reduced after reperfusion for 90 min and 165 min, respectively, as compared to pre-ischaemia. Thus, data from 11 experiments are presented. Data obtained after 90 min and 165 min reperfusion are pooled, because no significant differences were observed. Data during atrial pacing were grouped according to an increase in heart rate by about +35 and +70 beats/min, respectively. All data are given as mean ± SEM. The data were subjected to the Friedman two-way ANOVA and significance of differences between the steps of the experimental protocol was evaluated at a level of $P < 0.05$ by the Wilcoxon matched-pairs signed-ranks test using the statistic software SPSS® 6.1.2 for Windows®.

3. Results

3.1. Myocardial ischaemia-reperfusion (Table 1)

After 124 ± 12 min reperfusion following hypoperfusion and repetitive occlusion of the LAD, haemodynamic data and data from the non-touched LCX area showed no striking differences were observed. Data during atrial pacing were grouped according to an increase in heart rate by about +35 and +70 beats/min, respectively. All data are given as mean ± SEM. The data were subjected to the Friedman two-way ANOVA and significance of differences between the steps of the experimental protocol was evaluated at a level of $P < 0.05$ by the Wilcoxon matched-pairs signed-ranks test using the statistic software SPSS® 6.1.2 for Windows®.

3.2. Atrial stimulation before dopamine (Table 1)

Electrical stimulation of the right atrium reduced stroke volume. Cardiac output and left ventricular power, however, were enhanced, accompanied by a slight increase in aortic mean pressure at a slightly reduced systemic vascular resistance. LCX and LAD blood flow did increase concomitantly with a reduced coronary vascular resistance. Myocardial segment length at aortic valve opening was diminished in both areas. Systolic shortening of the intact LAD myocardium was reduced by about –30% by increasing heart rate by 70 beats/min, but the power index was elevated by about +70%. For the ischaemically injured LAD area, however, systolic shortening and power index were diminished by –80 ± 9% and –56 ± 22%, respectively, with increasing heart rate by about 70 beats/min. All variables returned to the pre-stimulation level after turning off atrial pacing.

3.3. Effects of dopamine (Table 2)

Heart rate, left ventricular $dP/dt\text{max}$, stroke volume, cardiac output and left ventricular power index were signifi-

### Table 1

<table>
<thead>
<tr>
<th>Control</th>
<th>Reperfusion</th>
<th>Stim. 1</th>
<th>Stim. 2</th>
<th>Stim. off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>81 ± 4</td>
<td>94 ± 6</td>
<td>+36 ± 2</td>
<td>+70 ± 4</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>6.1 ± 0.6</td>
<td>7.5 ± 0.5</td>
<td>7.2 ± 0.6</td>
<td>7.6 ± 0.9</td>
</tr>
<tr>
<td>Aortic mean pressure (mmHg)</td>
<td>110 ± 3</td>
<td>94 ± 4</td>
<td>101 ± 5</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>LV end diastolic pressure (mmHg)</td>
<td>15.3 ± 1.1</td>
<td>18.7 ± 1.7</td>
<td>15.4 ± 2.0</td>
<td>15.4 ± 3.2</td>
</tr>
<tr>
<td>LV$\Phi$/d$t\text{max}$ (mmHg/s)</td>
<td>1656 ± 101</td>
<td>1368 ± 128</td>
<td>1408 ± 131</td>
<td>1393 ± 106</td>
</tr>
<tr>
<td>Stroke volume (ml/kg)</td>
<td>1.25 ± 0.08</td>
<td>0.98 ± 0.08</td>
<td>0.81 ± 0.03</td>
<td>0.58 ± 0.04</td>
</tr>
<tr>
<td>Cardiac output (ml/min per kg)</td>
<td>100 ± 8</td>
<td>90 ± 7</td>
<td>105 ± 7</td>
<td>95 ± 7</td>
</tr>
<tr>
<td>LV power index (%)</td>
<td>100</td>
<td>92 ± 11</td>
<td>129 ± 13</td>
<td>132 ± 16</td>
</tr>
<tr>
<td>Systemic flow resistance (%)</td>
<td>100</td>
<td>95 ± 7</td>
<td>91 ± 9</td>
<td>90 ± 8</td>
</tr>
<tr>
<td>LCX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood flow (ml/min)</td>
<td>31 ± 4</td>
<td>31 ± 5</td>
<td>38 ± 6</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>Flow resistance (%)</td>
<td>100</td>
<td>88 ± 6</td>
<td>76 ± 5</td>
<td>68 ± 5</td>
</tr>
<tr>
<td>Myocardial segment length (%)</td>
<td>100</td>
<td>97.7 ± 4</td>
<td>95.3 ± 2</td>
<td>88.5 ± 16</td>
</tr>
<tr>
<td>Myocardial systolic shortening (%)</td>
<td>24.0 ± 2.0</td>
<td>23.2 ± 2.2</td>
<td>20.0 ± 2.0</td>
<td>16.3 ± 1.7</td>
</tr>
<tr>
<td>Myocardial power index (%)</td>
<td>100</td>
<td>111 ± 10</td>
<td>161 ± 13</td>
<td>183 ± 14</td>
</tr>
<tr>
<td>LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood flow (ml/min)</td>
<td>36 ± 6</td>
<td>37 ± 7</td>
<td>43 ± 8</td>
<td>41 ± 7</td>
</tr>
<tr>
<td>Flow resistance (%)</td>
<td>100</td>
<td>87 ± 7</td>
<td>83 ± 7</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>Myocardial segment length (%)</td>
<td>100</td>
<td>105.4 ± 1.8</td>
<td>105.2 ± 1.8</td>
<td>101.1 ± 1.9</td>
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<tr>
<td>Myocardial systolic shortening (%)</td>
<td>22.7 ± 1.6</td>
<td>7.1 ± 0.8</td>
<td>3.8 ± 0.2</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>Myocardial power index (%)</td>
<td>100</td>
<td>36 ± 3</td>
<td>34 ± 5</td>
<td>19 ± 6</td>
</tr>
</tbody>
</table>

Myocardial segment length refers to length at opening of the aortic valve, systolic shortening during ejection is given in % of this length. Mean ± SEM; significant differences at $P < 0.05$: ’reperfusion vs. control,’ ‘stim. 1 vs. reperfusion,’ ‘stim. 2 vs. 1,’ ‘stim. off vs. reperfusion. Data marked by an asterisk are based on only five experiments, because the signal in the other experiments was not to evaluate during atrial stimulation.
Table 2

Data on systemic haemodynamics, left circumflex (LCX) and anterior descending (LAD) coronary artery circulation, and left ventricular (LV) global and regional myocardial function from 11 anaesthetized pigs following 124 ± 12 min LAD-reperfusion before dopamine i.v., during dopamine i.v., and during subsequent right atrial electrical stimulation (stim.)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Dopamine (10 μg/kg per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stim. 1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>99 ± 6</td>
<td>+34 ± 2</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>6.9 ± 0.6</td>
<td>6.5 ± 0.6</td>
</tr>
<tr>
<td>Aortic mean pressure (mmHg)</td>
<td>91 ± 4</td>
<td>93 ± 3</td>
</tr>
<tr>
<td>LV end diastolic pressure (mmHg)</td>
<td>18.1 ± 1.0</td>
<td>16.5 ± 1.8</td>
</tr>
<tr>
<td>dP/dt max (mmHg/s)</td>
<td>1342 ± 115</td>
<td>3153 ± 374</td>
</tr>
<tr>
<td>LV stroke volume (ml/kg)</td>
<td>0.95 ± 0.07</td>
<td>1.20 ± 0.08*</td>
</tr>
<tr>
<td>Cardiac output (ml/min per kg)</td>
<td>88 ± 5</td>
<td>133 ± 7b</td>
</tr>
<tr>
<td>LV power index (% of control)</td>
<td>88 ± 10</td>
<td>182 ± 22d</td>
</tr>
<tr>
<td>Systemic flow resistance (% of control)</td>
<td>93 ± 8</td>
<td>63 ± 6e</td>
</tr>
<tr>
<td>LCX Blood flow (ml/min)</td>
<td>30 ± 4</td>
<td>38 ± 5c</td>
</tr>
<tr>
<td>Flow resistance (% of control)</td>
<td>86 ± 5</td>
<td>68 ± 4e</td>
</tr>
<tr>
<td>Myocardial segment length (% of control)</td>
<td>96.3 ± 1.1</td>
<td>94.5 ± 1.4</td>
</tr>
<tr>
<td>Myocardial systolic shortening (%)</td>
<td>22.9 ± 2.3</td>
<td>28.4 ± 2.9c</td>
</tr>
<tr>
<td>Myocardial power index (% of control)</td>
<td>112 ± 8</td>
<td>206 ± 17e</td>
</tr>
<tr>
<td>LAD Blood flow (ml/min)</td>
<td>35 ± 6</td>
<td>45 ± 7f</td>
</tr>
<tr>
<td>Flow resistance (% of control)</td>
<td>88 ± 7</td>
<td>66 ± 5g</td>
</tr>
<tr>
<td>Myocardial segment length (% of control)</td>
<td>104.4 ± 1.8</td>
<td>99.8 ± 1.5d</td>
</tr>
<tr>
<td>Myocardial systolic shortening (%)</td>
<td>7.0 ± 0.8</td>
<td>18.2 ± 1.7gh</td>
</tr>
<tr>
<td>Myocardial power index (% of control)</td>
<td>36.2 ± 2</td>
<td>143 ± 11h</td>
</tr>
</tbody>
</table>

Percentage of control refers to the data prior to LAD-Ischaemia, myocardial segment length is the length at opening of the aortic valve, systolic shortening during ejection is given in % of this length. Mean ± SEM; significant differences at 2P < 0.05; *dopamine vs. before, Stim. 1 vs. dopamine, Stim. 2 vs. 1, Stim. off vs. dopamine.

cantly increased, following intravenous infusion of dopamine; systemic vascular resistance was reduced, whereas central venous pressure, aortic mean pressure, and left ventricular end diastolic pressure were not affected systematically. LCX and LAD blood flow was increased in association with a reduced coronary vascular resistance. The myocardial segment length at aortic valve opening was not changed significantly in the LCX area, but was diminished in the LAD region. Systolic shortening of the intact LCX and the injured LAD region was increased to 121 ± 3% and 265 ± 14%, respectively, of the value before dopamine. The myocardial power was almost doubled in the intact LCX area and became about fourfold in the injured LAD region by dopamine.

3.4. Atrial stimulation during dopamine (Table 2, Figs. 1 and 2)

The effects resembled those of atrial pacing before dopamine concerning global ventricular function and coronary blood flow and flow resistance. The myocardial segments became shorter in both territories. The power index of the intact myocardium did increase steeper than before dopamine. The most striking difference, however, showed the power of the ischaemia-reperfused wall area in response to atrial pacing: it did not decrease in contrast to the response before dopamine, but did initially increase (heart rate +34 beats/min) and was then maintained with increasing heart rate by +70 beats/min. The effects of atrial pacing were reversible after turning off stimulation.

3.5. Myocardial staining with triphenyl tetrazolium chloride (TTC)

TTC staining of the LCX territory gave no indication of myocardial infarction in any experiment, staining of the LAD territory revealed myocardial infarction in one experiment, which was excluded from further evaluation.

4. Discussion

4.1. Regional myocardial performance

Systolic shortening or thickening of a ventricular wall segment is often used to assess regional myocardial performance. As discussed recently [9], the amount of myocardial contraction, however, does not only reflect the functional state of the heart muscle, but is also inversely related to the heart rate. Myocardial power is a more appropriate measure to study the effect of atrial pacing on myocardial performance, because myocardial oxygen consumption increases with heart rate [14]. An index of regional myocardial power can be calculated from systolic
shortening of a given wall segment, ejection time, ejection pressure, and heart rate and this index shows a positive correlation to heart rate during atrial pacing [9]. This index was also used in the present experiments to assess the effects of the experimental interventions on the performance of given myocardial areas.

4.2. LAD hypoperfusion/occlusion and reperfusion

Two hours after the hypoperfusion/occlusion procedure, LAD blood flow was not different from the control level, but the afflicted myocardium still showed a severely impaired systolic shortening and power. LAD segment length at aortic valve opening was increased as typically seen for the end diastolic dimension of myocardium with impaired performance distal to a coronary artery stenosis [15]. The slightly impaired global left ventricular function, shown by the changes in left ventricular end diastolic pressure, dP/dtmax, and stroke volume, does not reflect global myocardial failure, e.g. due to the type or duration of anaesthesia, because the performance of the untouched LCX area was not affected significantly. It is explained by the limited contribution of the injured LAD area to ventricular performance. The increase in heart rate, probably mediated by a decreased activation of the baroreceptor reflex in consequence to the reduced stroke volume, did not completely compensate for stroke volume reduction involving a diminished cardiac output.

The present results agree very well with previous data [9], which proves the high reproducibility of the model. The observed function-flow pattern in the absence of myocardial infarction (TTC staining) in the LAD area following ischaemia corresponds to the generally accepted definition of ‘stunned myocardium’ [11].

4.3. Atrial pacing before dopamine

It is well established that increasing heart rate reduces stroke volume and myocardial systolic shortening [9,16–18] as observed in the present experiments. This inverse relation is explained by the Frank–Starling mechanism by a reduced ventricular filling with increasing heart rate [17]. Accordingly, myocardial segment length and left ventricular end diastolic pressure decreased during atrial pacing in the present experiments as described previously [9,16].

In contrast to the reduction in systolic shortening or stroke volume, the power of intact myocardium increased with increasing heart rate as reported recently [9]. Myocardium from most mammals including man and pig shows an increase in myocardial force with increasing rate of contraction [2]. In vivo, this positive force-frequency relation is reflected by an increase in dP/dtmax [3]. In the present experiments dP/dtmax did not change significantly with atrial pacing. This is explained, however, by the functional deterioration of the stunned area: the power of the ischaemically injured region did further decrease with pacing.

The reason for this pathological response of stunned myocardium to pacing is yet unknown, but it resembles the disturbed force-frequency relation of myocardium from failing hearts. A blunted or negative staircase phenomenon

![Fig. 1. Response of the power index of intact myocardium to right atrial pacing (p) before and during i.v. dopamine. Mean ± SEM (n = 11) of intrinsic and paced heart rate, and of change in power index as compared to the value at the intrinsic (i) heart rate. Significance of differences is given in Tables 1 and 2.](http://example.com/fig1)

![Fig. 2. Response of the power index of stunned myocardium to right atrial pacing (p) before and during i.v. dopamine. Mean ± SEM (n = 11) of intrinsic and paced heart rate, and of change in power index as compared to the value at the intrinsic (i) heart rate. Significance of differences is given in Tables 1 and 2.](http://example.com/fig2)
is observed in different types of heart failure [3,4,6–8,12], which is discussed as a result from an abnormal intracellular handling of calcium [4,7,12], a dysfunction of the sarcoplasmic reticulum [8], a reduced Ca\(^{2+}\)-responsiveness of the myofilaments [12], and a disturbed production of cAMP [6,12].

Similar to failing hearts, the impaired contractile function of stunned myocardium is related to a disturbed intracellular homeostasis of Ca\(^{2+}\) [19,20], a dysfunction of the sarcoplasmic reticulum [21–23], and a reduced responsiveness of the myofilaments to Ca\(^{2+}\) [24–27]. Additionally, there may be an impaired production of cAMP in stunned myocardium in analogy to failing hearts. To our knowledge, this question was not investigated as yet.

4.4. The effects of dopamine

The changes of the haemodynamic variables and the function of the intact myocardial regions following dopamine need no discussion: they demonstrate the generally known pharmacological profile of the drug. The enhanced overall left ventricular performance during dopamine resulted not only from an increase in systolic shortening and power of the intact myocardium, but the function of the ischaemically injured areas was also improved confirming the repeatedly described recruitment of a functional reserve by catecholamines [28–31].

The effects of atrial pacing during dopamine were very similar to those observed before dopamine with respect to haemodynamics and the response of intact myocardium. The increase in regional myocardial power by a given increase in heart rate, however, was greater during than before dopamine. Obviously, the positive inotropic stimulation with dopamine enhances the power frequency relation as described for the effect of \(\beta\)-adrenergic stimulation on the cardiac force frequency relation in conscious animals [3]. In analogy to these results [3], the positive power frequency relation is possibly also an adaptation to exercise and this per se important mechanism is amplified by the concomitant positive inotropic effect of the sympathetic nervous system.

The response of the stunned myocardium to atrial pacing during dopamine was significantly different from the response before inotropic stimulation: the power of the ischaemically injured area did not deteriorate with increasing heart rate, but showed an increase at moderately elevated heart rates (+35 beats/min) and than remained constant with a further increased pacing rate (+70 beats/min). Certainly, dopamine did not restore a physiological power frequency relation of the stunned areas, but the pathological response was significantly mitigated.

In recent experiments [9], the decrease in power of stunned myocardium during pacing was attenuated by milrinone, but did not increase as in the present study. This difference in response to pacing during milrinone and dopamine probably resulted from a non-equivalent dosage of the drugs. The inotropic effect of the used dopamine dosage was significantly stronger than that of milrinone in the preceding experiments. This is evidenced by a greater increase in dP/dtmax, and in the power index of the left ventricle, but above all by the power of the intact areas following dopamine as compared to milrinone [9]. The present experiments give no information, however, whether or not the effects of inotropic equipotent amounts of milrinone and dopamine are different in quantity with respect to the response of stunned myocardium to increasing heart rate by pacing.

Both drugs increase myocardial cAMP either by stimulating cAMP formation by the adenylate cyclase (dopamine) or by inhibiting cAMP degradation by the phosphodiesterase III (milrinone). Thus, the data are compatible with an impaired formation of cAMP in stunned myocardium. The improved performance following milrinone shows that cAMP is still generated in stunned myocardium, but the rate of formation may be subnormal. Stimulation of the adenylate cyclase and inhibition of the phosphodiesterase III results in physiological levels of cAMP and restores a normal myocardial power. Accepting an analogy of the force frequency and power frequency relation, a defect in cAMP production is also supported by the observation that inhibition of the adenylate cyclase turns the positive force-frequency relation into a negative one in guinea-pig hearts [32].

The data do not exclude a defect more distal in the signal transduction pathway of cAMP or an impaired Ca\(^{2+}\)-sensitivity of the myofilaments as discussed by several authors [24–26]. \(\beta\)-Adrenergic stimulation increases myocardial Ca\(^{2+}\)-transients [33–35] and enhanced Ca\(^{2+}\)-transients can be assumed to compensate for a reduced responsiveness of the myofilaments to Ca\(^{2+}\) resulting in a normal contraction.

4.5. Conclusions

The present experiments confirm the pathological response of stunned myocardium to an increase in heart rate by electrical stimulation. Possibly, the cAMP system is involved in the normal response to pacing and this pathway is disturbed in stunned myocardium. Other defects are not excluded or supported by the present experiments, e.g. an impaired Ca\(^{2+}\)-responsiveness of the myofilaments, and may also contribute to the functional impairment of stunned myocardium. Possibly, a physiological increase in heart rate by an increased activity of the sympathetic nervous system is not accompanied by a reduction in the power of stunned myocardium, because the chronotropic action of the sympathetic nervous system is associated with a positive inotropic stimulation of the myocardium.

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analysis by Mrs. S. Dom, and the safe quantitative evaluation of the chart records by Mrs. U. Ettner.

References


Appendix A. Conference discussion

Dr T. Ferguson (St. Louis, MO, USA): Are your assumptions, drawn from your experimental data, chemically shown by other experiments? I mean you’ve talked about reduced cyclic AMP and so on, have you actually done measurements in the regard?

Dr Schad: No, we did not measure directly cyclic AMP. But there might be also an impairment or reduced activity of the adenylate cyclase.
or in the further pathway of signal transduction of cyclic AMP, but we did not measure in this model cyclic AMP.

**Dr Ferguson:** One is always looking for a transfer of good experimental data to the clinical situation. I’d ask you how these data could be taken to the clinical setting?

**Dr Schad:** That’s the problem of stunned myocardium and adrenergic stimulation as shown by the group of Heusch. It is possible to recruit an inotropic reserve or functional reserve in stunned myocardium. But if you do this, the energy storage goes down, ATP goes not down, and I think it’s a method for stimulation.

**Dr H.D. Schulte (Dusseldorf, Germany):** Why did you choose dopamine? And do you have any experience using dobutamine in those experiments?

**Dr Schad:** Since a number of other studies on stunned myocardium and the inotropic reserve were done with dopamine, therefore we used also dopamine to compare, for the possibility of comparison with other studies, but we did not use as yet dobutamine.

**Dr Ferguson:** That would make a nice extension for your model, to see what ones are most effective.