Effect of milrinone and atrial pacing on stunned myocardium

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Abstract

Objective: Most mammalian cardiac muscles show a positive force-frequency relation, which is turned into a negative relation in failing hearts. Stunned myocardium shows similar defects as failing myocardium, it has a functional reserve recruitable by positive inotropic interventions, and possibly shows a disturbed response to increased heart rate. The present experiments compare in vivo the response of stunned and intact myocardium to atrial pacing before and during inotropic stimulation by milrinone.

Methods: In anaesthetised (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. Heart rate was raised by right atrial pacing after 90 min reperfusion before and during i.v. milrinone (105 µg/kg bolus + 8 µg/kg per min infusion). The ischaemic/reperfused area was sliced post mortem and stained by triphenyl tetrazolium chloride to exclude myocardial infarction. Data from ten experiments are presented.

Results: After 90 min LAD reperfusion, LAD blood flow and power were 110 and 36% of preischaemic control, respectively, indicating myocardial stunning. The power of the intact area was not changed (102% of control). Pacing from 87 to 164 per min increased the power of the intact area (+96%), the power of the stunned myocardium decreased (−64%). Milrinone increased the power of the stunned region to 72% of the pre-stunning level and the power of the intact area by +51%. Pacing from 111 to 164 per min during milrinone increased the power of the intact myocardium to the same level as before milrinone, the power of the stunned region did not change.

Conclusions: Stunned myocardium responds pathologically to atrial pacing with a negative staircase in contrast to the positive staircase of intact myocardium. Inotropic stimulation by the phosphodiesterase inhibitor milrinone recruited the functional reserve of stunned myocardium. Milrinone did not restore a positive staircase in stunned myocardium, but power was maintained during atrial pacing. The pathological staircase of stunned myocardium may arise from an impaired availability of cyclic AMP, but the data do not exclude defects in calcium handling, a dysfunction of the sarcoplasmic reticulum, or an impaired Ca-sensitivity of the myofilaments. © 1997 Elsevier Science B.V.

Keywords: Stunned myocardium; Staircase phenomenon; Milrinone; Anaesthetised pigs

1. Introduction

Since first described by Bowditch [3], it is well established that contractility of isolated myocardium is affected by the rate of contraction [1]. In most mammalian cardiac muscles including human and porcine hearts, myocardial force increases with increasing frequency of stimulation [1]. This positive force–frequency relation, however, is blunted or turned into a negative relation in different types of end-stage heart failure in man [12,21,23,30] and experimental heart failure in animals [8,27]. The defect seems to depend on several factors including an abnormal intracellular Ca²⁺ handling [21,22,25], a dysfunction of the sarcoplasmic reticulum [8,12], a reduced responsiveness of...
the myofilaments to Ca$^{2+}$ [22], and an impaired production of cAMP [21–23].

Stunned myocardium represents a specific type of ‘failing heart’. It is characterised by a prolonged postischaemic myocardial dysfunction at restored myocardial blood flow without irreversible myocardial damage by necrosis [14,29]. The presence of stunned myocardium is of importance at any occasion of myocardial ischaemia-reperfusion as in coronary angioplasty or surgical revascularisation, because it prevents a prompt functional improvement following restored normal blood flow. Similar to failing hearts, stunned myocardium presents a disturbed intracellular homeostasis of Ca$^{2+}$ [2,19], a dysfunction of the sarcoplasmic reticulum [14,20,26], and a reduced responsiveness of the myofilaments to Ca$^{2+}$ [5,9,15,18]. Regardless of the functional defect, stunned myocardium has a functional reserve, which may be recruited by a number of positive inotropic interventions depending on or independent of cAMP [29].

There are some questions open, however. The response of stunned myocardium to an increase in rate of contraction was not yet investigated. In analogy to other types of failing myocardium, a functional deterioration with increasing rate of contraction might be expected. The pathological force–frequency relation of myocardium from failing hearts, however, is normalised by isoprenaline [30] and by forskolin [23], which both increase myocardial cAMP by stimulating the adenylate cyclase. Similarly, inhibition of the breakdown of cAMP by the phosphodiesterase III by milrinone may improve resting performance of stunned myocardium and reverse a pathological response to increased heart rate.

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 inotropic stimulation by milrinone.

2. Methods

2.1. Animals and anaesthesia

The experiments were performed in 13 domestic pigs, body weight 30–45 kg, pretreated by azaperon i.m. (4 mg/kg Stresnil®, Janssen, Neuss, FRG), ketamine i.m. (5 mg/kg Ketanest®, Parke Davis, München, FRG), and atropine sulfate i.m. (25 μg/kg, Braun, Melsungen, FRG). Anaesthesia was induced by thiopental sodium i.v. (12.5 mg/kg Trapanal®, Byk-Gulden, Konstanz, FRG) and maintained by piritramide i.v. (30 μg/kg per min in Ringer’s solution 3 mg/ml Dipidolor®, Janssen, Neuss, FRG). The animals were paralyzed by pancuronium bromide i.v. (priming 0.1 mg/kg, sustaining dose 4 μg/kg per min in glucose 5%/Ringer’s solution (1:1) 80 mg/l Pancuronium Curamed®, Curamed, Karlsruhe, FRG) and ventilated with O$_2$/N$_2$O via an endotracheal tube. Arterial pCO$_2$, pO$_2$, base excess, and K$^+$ were checked every 30 min (GEMPremier 5300, Mallinckrodt Sensor Systems, Ann Arbor, MI). pCO$_2$ was adjusted to 3540 mmHg and pO$_2$ to 100–150 mmHg by ventilation, base excess was kept at ± 2 mmol/l by i.v. NaHCO$_3$ (1 Mol) or HC1 (0.4 Mol), and plasma K$^+$ at 4.5–5.5 mmol/l by i.v. K-Mg-aspartate (K$^+$ = 200 mmol/l, Mg$^{2+}$ = 75 mmol/l, Inzolen®, Köhler, Alsbach, FRG). Rectal temperature was monitored by a thermistor (9230-20, Ellab, Rødovre, Danmark) and kept at 36.5–38.5°C.

2.2. Preparation and instrumentation (Fig. 1a)

Jugular veins and a femoral artery were cannulated for application of drugs and fluids, monitoring of central venous pressure (CVP, P23ID, Spectramed, Oxnard), and blood sampling. The heart was exposed from a left side thoracotomy. Catheter tip manometers were advanced to the ascending aorta from a femoral artery (SPC 350, Millar, Houston, Texas) and to the left ventricle from the atrial appendage (SPR 524, Millar, Houston, Texas) to measure aortic pressure (AoP) and left ventricular enddiastolic pressure (LVedP) and dP/dt$_{\text{max}}$, respectively. Perivascular ultrasonic transit-time flowprobes (T206, Transonic, Ithaca) were placed at the ascending aorta, left descending (LAD), and circumflex (LCX) coronary artery to stroke

Fig. 1. Instrumentation of the animals (A) and experimental protocol (B).
volume (SV) and coronary blood flow (Q), respectively. 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. Two insulated wires were attached to the right atrial appendage for increasing heart rate (HR) by electrical stimulation. Respiratory pressure was measured (P23ID, Spectramed, Oxnard) to assign the cardiovascular variables to the respiratory phase. Chest and pericardium remained open during the experiment.

2.3. Experimental protocol (Fig. 1b):

After assessment of control data, QLAD was slowly obstructed within 10 min until myocardial systolic shortening distal to the stenosis was reduced to 16 ± 2% of control. This hypoperfusion was maintained for 30 min followed by repeated LAD-occlusion/perfusion (five times 1 min occlusion interrupted by 1 min perfusion on the hypoperfusion level). The tourniquet was removed after the last occlusion and the LAD was reperfused freely. After 90 min, heart rate was increased to 140 and 165 per min by atrial pacing. Then milrinone (Corotrop®, Sanofi Winthrop, München, FRG) was given i.v. (105 μg/kg + 8 μg/kg per min) and atrial pacing was repeated during sustained infusion of milrinone. At the end of the experiments, the myocardial areas where the ultrasonic transducers were placed were cut in slices and stained with triphenyl tetrazolium chloride for exclusion of myocardial infarction [33].

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

The variables were recorded on multi-channel chart recorders (TA 5000, Gould, Valley View) 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 $R_{sys} = (AoPm − CVP)/CO$ and coronary flow resistance $R_{cor} = (AoPm − CVo)/QLAD$, $LCX (AoPm = aortic mean pressure)$; indices of global left ventricular power $POW_{LV} = CO · AoPej/t_{ej}$, and of regional myocardial power $POW_{LAD, LCX} = MSS_{LAD, LCX} · AoPej · HR/t_{ej}$ (AoPej = aortic mean pressure during ejection, t$_{ej}$ = duration of ejection = 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 90 min reperfusion as compared with pre-ischaemia. Thus, data from ten experiments are given as mean ± S.E.M. Significance of paired differences were evaluated at a level of $2P < 0.05$ by the distribution-free test of Dixon and Mood.

3. Results

3.1. Myocardial ischaemia-reperfusion (Table 1, Fig. 2)

After 90 min reperfusion following hypoperfusion and repetitive occlusion of the LAD, heart rate and central venous pressure were slightly increased, whereas aortic pressure, stroke volume, cardiac output, and left ventricular power index were reduced. Myocardial segment length at aortic valve opening was not affected for the LCX territory, whereas the length in the area exposed to ischaemia was significantly increased. The systolic shortening of the normally perfused LCX territory was slightly diminished, but the power index of this area was not significantly changed (Fig. 2). In contrast, the LAD region showed severely impaired systolic shortening and power at a restored LAD blood flow (Fig. 2).

3.2. Atrial simulation before milrinone (Table 1, Fig. 3 and Fig. 4)

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 without a change in systemic flow resistance. LCX and LAD blood flow did increase concomitantly with a reduced flow resistance. Myocardial segment length at aortic valve opening was diminished in both areas. Systolic shortening of the intact myocardium was reduced by about 20%, but the power index was elevated by about 90%. For the ischaemically injured area systolic shortening and power index were diminished, systolic shortening even completely vanished in seven experiments (and thus power index became zero). All variables returned to the prestimulation level after turning off atrial pacing.

3.3. Effects of milrinone (Table 2, Fig. 3 and Fig. 4)

Central venous pressure, aortic pressure, and systemic flow resistance were decreased following intravenous infusion of milrinone, stroke volume was not changed systematically, whereas heart rate, cardiac output, and left ventricular power were enhanced. LCX and LAD blood flow was increased in association with a reduced flow resistance. The myocardial segment length at aortic valve opening was diminished in both areas. Systolic shortening of the intact LCX region was not affected significantly, whereas systolic shortening the functionally impaired LAD area got larger by about 60%. The myocardial power became augmented by 50%
in the intact LCX area and was more than doubled in the injured LAD region.

3.4. Atrial stimulation during milrinone (Table 2, Fig. 3 and Fig. 4)

The effects resembled those of atrial pacing before milrinone concerning global ventricular function and coronary blood flow and flow resistance, the myocardial segments became shorter in both territories, and the power index of the intact myocardium did increase up to the same level as prior to milrinone. The power of the ischaemic-reperfused wall area, however, did not decrease with increasing heart rate as observed before milrinone, but was maintained. 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

Regional myocardial performance is usually assessed by the systolic shortening of a given wall segment. Systolic shortening, however, does not only indicate the functional state, but is also affected by heart rate and afterload showing an inverse relation to these variables [17,10]. In contrast, myocardial oxygen consumption increases with heart rate and afterload [6] reflecting an increase in myocardial power. Therefore, in the present experiments an index of myocardial power was calculated from systolic shortening, ejection time, ejection pressure, and heart rate. For myocardium, this index increased indeed with increasing heart rate by

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Fig. 2. Myocardial systolic shortening and power index of the area of the left circumflex (LCX) and descending coronary artery (LAD), and LCX&LAD blood flow after LAD ischaemia and 90 min reperfusion. LAD area systolic shortening and power index were significantly reduced, the other variables were not different from pre-ischaemic values. Mean ± S.E.M. (n = 10).

atrial pacing, whereas systolic shortening showed the well known decrease. Thus, the used index seems more appropriate than systolic shortening to assess regional myocardial performance.

Fig. 3. Response of systolic shortening of intact ○ and stunned ● myocardium to increasing heart rate by electrical stimulation of the right atrium before and during inotropic stimulation by i.v. milrinone. Mean ± S.E.M. (n = 10), significance of differences is given in Table 1 and Table 2.

Following LAD hypoperfusion/occlusion and 90 min reperfusion, the LAD territory showed a 65% decreased systolic shortening and power index without signs of myocardial necrosis at restored LAD blood flow. This pattern corresponds to the generally accepted definition of ‘stunned myocardium’ [14,29]. It cannot be explained by an adequate increase in afterload or heart rate, because firstly, afterload was not increased as evidenced by the decreased aortic pressure and unchanged systemic flow resistance, and secondly, comparable changes did not occur in the untouched LCX area. On the other hand, the slightly reduced systolic shortening of the LCX myocardium was rather due to the increased heart rate than to an impaired myocardial performance, because the power index of the region was not changed as compared with control. Furthermore, the length of the myocardial segments at aortic valve opening was increased in the stunned region but unchanged in the intact area after 90 min reperfusion as against pre-ischaemia. This agrees well with the typical increase of the enddiastolic dimension of myocardium distal to a coronary artery stenosis [28]. Additionally, stunning of the LAD area affected also global left ventricular performance as reflected by the increased enddiastolic pressure, the reduced $dP/dt_{\text{max}}$, and the diminished stroke volume. The increase in heart rate, probably mediated by the baroreceptor reflex in consequence to the reduced stroke volume, did not completely compensate for stroke volume reduction so that cardiac output and power index were reduced, too.
Atrial pacing before milrinone, consistently decreased stroke volume and systolic shortening as repeatedly described [7,17,24,31]. This correlation is explained according to the Frank-Starling mechanism by a reduced diastolic filling of the ventricle with increasing heart rate as observed in man and animals [7,24]. In the present experiments, this is reflected in a decreased myocardial segment length during atrial pacing as described previously [17].

The rate of myocardial contraction affects myocardial contractility known as Bowditch effect or force–frequency relation [1,3]. In most mammals including man and pig, the force–frequency relation is positive, i.e. contractility increases with increasing heart rate [1]. In vivo, a positive force–frequency relation is reflected by an increase in dP/dt_{max} [27]. In the present experiments dP/dt_{max} did not change significantly with atrial pacing probably due to the functional deterioration of the stunned area. The power of the intact myocardium did increase with increasing heart rate, but the power of the ischaemically injured region approached zero.

The staircase phenomenon was not yet investigated for stunned myocardium as to our knowledge. A blunted or negative staircase phenomenon, however, is observed in heart failure of different causes [8,12,21,23,27,30]. This pathological response to an increase in rate of contraction is associated with an abnormal intracellular handling of calcium [21,22,25,30], a dysfunction of the sarcoplasmic reticulum [8,12], a reduced responsiveness of the myofilaments to Ca^{2+} [22], and a disturbed production of cAMP [21–23].

Similar to failing hearts, the impaired contractile function of stunned myocardium is also related to disturbed intracellular homeostasis of Ca^{2+} [2,19], to dysfunction of the sarcoplasmic reticulum [14,20,26], and a reduced responsiveness of the myofilaments to Ca^{2+} [5,9,15,18].

The present experiments were not designed to elucidate the reason for the negative staircase phenomenon in stunned myocardium. The similarity of defects in stunned and failing hearts, however, suggest that inverse response of stunned myocardium to heart rate depends on the same abnormalities as in failing hearts.

### 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 ten anaesthetized pigs following 90 min LAD-reperfusion before milrinone i.v., during milrinone i.v., and during subsequent right atrial electrical stimulation (stim). 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 percentage of this length

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Milrinone 105 µg/kg + 8 µg/kg per min</th>
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<tbody>
<tr>
<td></td>
<td>Stimulation</td>
<td>Stimulation 1</td>
</tr>
<tr>
<td>Heart rate (per min)</td>
<td>91 ± 5</td>
<td>111 ± 5^a</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>6.5 ± 0.4</td>
<td>3.7 ± 0.4^a</td>
</tr>
<tr>
<td>Aortic mean pressure (mmHg)</td>
<td>86 ± 5</td>
<td>78 ± 3^a</td>
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<tr>
<td>LV enddiastolic pressure (mmHg)</td>
<td>14.5 ± 0.9</td>
<td>9.7 ± 0.5^a</td>
</tr>
<tr>
<td>dP/dt_{max} (mmHg/s)</td>
<td>1296 ± 127</td>
<td>1926 ± 198^a</td>
</tr>
<tr>
<td>LV stroke volume (ml/kg)</td>
<td>0.74 ± 0.05</td>
<td>0.78 ± 0.06</td>
</tr>
<tr>
<td>Cardiac output (ml/min per kg)</td>
<td>67 ± 4</td>
<td>87 ± 8^a</td>
</tr>
<tr>
<td>LV power index (% of control)</td>
<td>83 ± 6</td>
<td>120 ± 7^a</td>
</tr>
<tr>
<td>Systemic flow resistance (% of control)</td>
<td>105 ± 7</td>
<td>77 ± 5^a</td>
</tr>
</tbody>
</table>

| LCX                        |              |            |              |
| Blood flow (ml/min)        | 27 ± 4       | 36 ± 5^a   | 38 ± 4       | 43 ± 4^d   | 33 ± 4    |
| Flow resistance (% of control) | 98 ± 9       | 69 ± 5^a   | 62 ± 4^b   | 59 ± 3^c,d | 72 ± 9    |
| Myocardial segment length (% of control) | 99.1 ± 1.0  | 95.2 ± 1.0^a | 91.7 ± 1.4^b | 90.3 ± 1.3^c,d | 93.7 ± 1.1^e |
| Myocardial systolic shortening (%) | 17.6 ± 1.4  | 18.7 ± 1.5   | 16.0 ± 1.6^b | 14.8 ± 1.4^c,d | 17.5 ± 1.4^e |
| Myocardial power index (% of control) | 106 ± 6     | 153 ± 10^a | 182 ± 17^b   | 201 ± 20^c,d | 155 ± 12 |

| LAD                        |              |            |              |
| Blood flow (ml/min)        | 41 ± 4       | 50 ± 5^a   | 52 ± 5       | 56 ± 4^d   | 48 ± 4    |
| Flow resistance (% of control) | 84 ± 7       | 65 ± 5^a   | 63 ± 5      | 59 ± 5^a   | 67 ± 5    |
| Myocardial segment length (% of control) | 106.0 ± 1.7 | 102.1 ± 2.1^a | 99.2 ± 1.9^b | 97.6 ± 1.6^c,d | 100.2 ± 1.8^e |
| Myocardial systolic shortening (%) | 7.8 ± 1.6   | 12.3 ± 2.2^a | 8.4 ± 1.5^b  | 6.5 ± 1.4^c,d | 11.1 ± 1.9^e |
| Myocardial power index (% of control) | 34 ± 5     | 72 ± 11^a  | 70 ± 11     | 64 ± 12    | 72 ± 13   |

Mean ± S.E.M.; significant differences at 2P<0.05.

a Milrinone vs. before.

b Stim 1 vs. milrinone.

c Stim 2 vs. 1.

d Stim 2 vs. milrinone.

e Stim off vs. milrinone.
The effects of milrinone on the myocardial, coronary, and haemodynamic variables agree with the well known pharmacological properties of the drug [16]: according to the positive chronotropic and vasodilatory action of milrinone, heart rate increased, central venous pressure decreased, and systemic and coronary flow resistance declined; preload was reduced as shown by the diminished left ventricular enddiastolic pressure and myocardial segment length at aortic valve opening; positive inotropy is evidenced by the increase in dP/dtmax and cardiac output was augmented.

The function of the stunned LAD area and the intact LCX region show, that the improved overall left ventricular performance during milrinone resulted from an increase in systolic shortening of the ischaemically injured myocardium. A characteristic feature of stunned myocardium is a functional reserve, which is recruitable by positive inotropic interventions [29] including inhibition of the breakdown of cAMP by blocking the phosphodiesterase III [32]. In a dog model similar to the present study, milrinone restored nearly pre-ischaemic values of systolic wall thickening of stunned myocardial areas [32]. Furthermore, stunned myocardium probably benefits even more than intact myocardium by milrinone [4].

The effects of atrial pacing during milrinone were very similar to those observed before. The most striking difference was seen for the power index of the stunned myocardium: the power of the ischaemically injured area was not affected significantly by increasing heart rate in contrast to the severe impairment prior to the positive inotropic stimulation. Thus, milrinone significantly attenuated the pathological response of the stunned myocardium although it was not converted into the positive staircase of intact myocardium. Possibly, a positive staircase may be achieved by a higher dosage of milrinone, which was not tested in the present experiments.

Comparable studies on stunned myocardium are not available. The pathological force–frequency relation of myocardium from failing hearts, however, is normalised by isoprenaline [30] and by forskolin [23]. Both drugs increase myocardial cAMP by stimulation of the adenylate cyclase and thus cAMP synthesis. Milrinone inhibits the cAMP degrading phosphodiesterase III resulting also in an increase in cAMP. The improved performance of stunned myocardium following milrinone shows, that cAMP is still generated in stunned myocardium, but the rate may be subnormal. A defect in cAMP generation is supported by the observation, that inhibition of the adenylate cyclase turns the positive force–frequency relation of guinea-pig hearts into a negative one [11]. On the other hand, the production of cAMP may be normal, but elevated levels of cAMP are necessary to compensate for defects in Ca2+ handling or responsiveness of the myofilaments. The present experiments give no conclusive evidence, however, for the perturbations underlying the impaired performance and the inversed staircase phenomenon in stunned myocardium. Recent in vivo studies in model similar to the presented one, however, did not show an attenuated response of stunned myocardium to intracoronary infusion of calcium [13].

In summary, the present experiments clearly demonstrate that stunned myocardium has lost the physiological response to an increase in heart rate by atrial pacing. This may be of significance following myocardial revascularisation, because an increase in heart rate further deteriorates the performance of stunned myocardium or curtails the beneficial effect of inotropic stimulation associated with tachycardia, whereas bradycardic interventions improve its performance. Inotropic stimulation by the phosphodiesterase inhibitor milrinone improves systolic shortening and power of stunned myocardial areas, which contributes to the improvement in global ventricular function. The negative staircase of stunned myocardium was not reversed to a positive one as present in intact myocardium, but performance was maintained and did not deteriorate during atrial pacing. The pathological response of stunned myocardium to heart rate may arise from an impaired availability of cyclic AMP, but the data do not exclude defects in calcium handling, a dysfunction of the sarcoplasmic reticulum, or an impaired Ca-sensitivity of the myofilaments.

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References


