Oxygen wastage of stunned myocardium in vivo is due to an increased oxygen cost of contractility and a decreased myofibrillar efficiency

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Abstract

Objective: We investigated whether an increased oxygen cost of contractility and/or a decreased myofibrillar efficiency contribute to oxygen wastage of stunned myocardium. Because Ca\textsuperscript{2+}-sensitizers may increase myofibrillar Ca\textsuperscript{2+}-sensitivity without increasing cross-bridge cycling, we also investigated whether EMD 60263 restores myofibrillar efficiency and/or the oxygen cost of contractility.

Methods: Regional fiber stress and strain were calculated from mesomyocardially implanted ultrasound crystals and left ventricular pressure in anesthetized pigs (n = 18). Regional myocardial oxygen consumption (MVO\textsubscript{2}) was measured before contractility (end-systolic elastance, E\textsubscript{es}) and total myofibrillar work (stress–strain area, SSA) were determined from stress–strain relationships. Atrial pacing ates three heart rates and two doses of dobutamine were used to vary SSA and E\textsubscript{es}, respectively. After stunning (two times 10-min ischemia, followed by 30-min reperfusion), measurements were repeated following infusion of saline (n = 8) or EMD 60263 (1.5 mg kg\textsuperscript{-1} i.v., n = 10). Linear regression was performed using: MVO\textsubscript{2} = a\cdot SSA + b\cdot E\textsubscript{es} + g\cdot HR\textsuperscript{-1} (a\textsuperscript{-1}, myofibrillar efficiency; b, oxygen cost of contractility; and g, basal metabolism/min). Results: Stunning decreased SSA by 57% and E\textsubscript{es} by 64%, without affecting MVO\textsubscript{2}, while increasing a by 71% and b by 134%, without affecting g. From the wasted oxygen, 72% was used for myofibrillar work and 18% for excitation–contraction coupling. EMD 60263 restored both a and b.

Conclusions: Oxygen wastage in stunning is predominantly caused by a decreased myofibrillar efficiency and to a lesser extent by an increased oxygen cost of contractility. Considering that EMD 60263 reversed both causes of oxygen wastage, it is most likely that this drug increases myofibrillar Ca\textsuperscript{2+}-sensitivity without increasing myofibrillar cross-bridge cycling.

Keywords: Stunning; e–c coupling; Oxygen consumption; Energy metabolism; Contractile apparatus

1. Introduction

Despite the decreased contractile function, myocardial oxygen consumption (MVO\textsubscript{2}) of stunned myocardium has been reported to be relatively high [1]. The underlying mechanism of this ‘oxygen wastage’ is presently unclear.

During physiological conditions, MVO\textsubscript{2} is used for basal metabolism, excitation–contraction coupling and myofibrillar work [2] (Fig. 1). Although contractility (E\textsubscript{es}, Figs. 1 and 2) is decreased in stunned myocardium [3], calcium transients remain unchanged [4,5]. Hence, while 80–90% of intracellular calcium is taken up by the sarcoplasmic reticulum (SR) [6,7] and at least 70% of VO\textsubscript{2} for excitation–contraction coupling is consumed by the SR Ca\textsuperscript{2+}-ATPase [8], unchanged calcium transients may imply an unchanged VO\textsubscript{2} for excitation–contraction coupling (\(\beta\cdot E_{es}\), Fig. 1). In accordance with these arguments, Ohgoshi et al. [9] observed in isolated stunned dog hearts that the oxygen cost of contractility (\(\beta\), Fig. 1), i.e. the amount of non-myofibrillar VO\textsubscript{2} used per unit of contractility, was increased. These authors also showed that the increase in \(\beta\) is not only due to a decreased myofibrillar...
can be determined in isolated hearts, the individual contribution of $\alpha$ and $\beta$ to total MVO$_2$ consumed during normal working conditions can only be determined in vivo. Moreover, as SSA is highly load-dependent and isolated hearts lack normal loading conditions, the change in the contributions of $\alpha$ and $\beta$ to total MVO$_2$ in stunning is presently unknown. Consequently, it remains unclear to what extent the oxygen wastage of in vivo stunned myocardium can be explained by VO for excitation–contraction coupling or by VO for myofibrillar work. The first aim was therefore to study the oxygen cost of contractility and myofibrillar efficiency of stunned myocardium in vivo.

Ca$^{2+}$-sensitizers restore the decreased myofibrillar Ca$^{2+}$-sensitivity of stunned myocardium [13]. These drugs decrease oxygen cost of contractility [14,15] and have therefore an energetic advantage over drugs that restore function by increasing Ca$^{2+}$ transients. However, if a decreased myofibrillar efficiency also contributes to the oxygen wastage of stunned myocardium, Ca$^{2+}$-sensitizers will only partly reverse the oxygen wastage, unless they also restore myofibrillar efficiency. This is not unlikely, as Ca$^{2+}$-sensitizers may act by slowing down the dissociation of the actin–myosin cross-bridges or even by increasing their force rather than by increasing the number of formed cross-bridges [13]. Some in vitro studies have shown an unchanged myofibrillar efficiency for Ca$^{2+}$-sensitizers [16,17], but these findings are constrained by the above-presented arguments. Consequently, we also investigated whether EMD 60263, which does not have a $\beta_2$-cyclic monophosphate (cAMP)-mediated effect [18,19], normalizes the increased oxygen cost of contractility and the myofibrillar efficiency in stunned myocardium.

2. Methods

All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals as published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.1. Instrumentation

Crossbred Yorkshire–Landrace pigs (29–43 kg, $n=18$) were anesthetized, intubated and ventilated with a mixture of oxygen and nitrogen, before instrumentation for infusion of 10–15 mg·kg$^{-1}$·h$^{-1}$ sodium pentobarbital, saline, EMD 60263 (courtesy of Prof. P. Schelling, E. Merck) and the negative chronotrope agent zatebradine (courtesy of Dr. J.W. Dammgen, Dr. Karl Thomae) and measurement of aortic blood pressure and left ventricular (LV) pressure (Braun Medical BV, The Netherlands) [20]. A balloon catheter was positioned in the inferior caval vein to transiently reduce left ventricular preload.

After a midsternal thoracotomy, electromagnetic flow
probes (Skalar, Delft, The Netherlands) were placed around the ascending aorta and the proximal part of the left anterior descending coronary artery (LADCA). Distal to the flow probe, the LADCA was dissected for placement of an atraumatic clamp. To obtain local coronary venous blood samples, a cannula was inserted into the great cardiac vein. Pacing leads were attached to the right atrium and connected to a pacing stimulator (Grass S9). Rectal temperature was kept between 37 and 38°C.

Segment areas and LV diameter were measured using ultrasonic crystals as described before [20]. Segment area crystals were implanted in the distribution area of the LADCA and left circumflex coronary artery (LCXCA) the LADCA region [20]. The energy consumption per ml crystals were implanted in the distribution area of the coronary venous oxygen content divided by the mass of ultrasonic crystals as described before [20]. Segment area calculated as the product of LADCA-flow and the arterial±temperature was kept between 37 and 38°C and connected to a pacing stimulator (Grass S9). Rectal area enclosed by the end-systolic and end-diastolic relation±contraction coupling and basal metabolism to the oxygen wastage of stunned myocardium was expressed as a percentage of the total oxygen wastage.

2.2. Experimental protocol

After 30–45 min of stabilization, heart rate (HR) was lowered below 70 beats·min⁻¹ by infusion of zatebradine. Then, either saline (control) or one out of two doses of dobutamine, increasing maximum LV pressure rise (LVdP/ dt_max) to approximately 3000 (low dose, 0.7–2.5 μg·kg⁻¹·min⁻¹) and 4000 mmHg·s⁻¹ (high dose, 1.1–5.5 μg·kg⁻¹·min⁻¹), was infused in random order. During each infusion measurements of hemodynamics and wall function were made and blood samples [20] were taken at HR’s of 70, 100 and 130 beats·min⁻¹ (in random order). With the ventilator turned off, LV preload was gradually reduced by inflating the balloon in the inferior caval vein [20]. Stunning was produced by two 10-min LADCA occlusions separated by 10 min of reperfusion [20]. Thirty min after the second occlusion, animals received either 1.5 mg·kg⁻¹ of EMD 60263 (n=10) or saline (n=8). Ten min later, in all animals the saline, low and high dose dobutamine infusions and measurements were repeated. In a time control group (n=3), all interventions described above with the same time protocol were performed, except that these hearts were not subjected to the occlusion intervention.

2.3. Data acquisition and analysis

Hemodynamic and segment area signals were digitized and stored on disk for off-line analysis. Systolic area shortening (SAS, in %) was calculated as: [(end-diastolic area-end-systolic area)/end-diastolic area]*100%. Left ventricular wall stress (σ, in N·m⁻²) and strain (ε, dimensionless) were calculated off-line [20] and end-systolic stress-strain (σ=E(1−ε)) relationships were determined from the preload changes. The slope of this relationship, E, (end-systolic elastance), was calculated at a constant stress corresponding to a LV pressure of 50 mmHg at baseline and taken as a measure of contractility [20]. (Fig. 2). A pressure of 50 mmHg was chosen to include stunning-induced changes from convex to concave of the non-linear stress–strain relationships [3]. The area enclosed by the LV stress–strain loop during a single heartbeat was determined as an index for regional external myocardial work (EW, in J·m⁻³, Fig. 2) [21]. The stress–strain area (SSA), an index of total regional myocardial work, was calculated as the area enclosed by the end-systolic and end-diastolic relations and the systolic trajectory of the stress–strain loop [22]. Oxygen consumption of the LADCA region was calculated as the product of LADCA-flow and the arterial–coronary venous oxygen content divided by the mass of the LADCA region [20]. The energy consumption per ml of O₂ was set at 20 J; this equivalence is independent of the substrate [23].

2.4. Statistics

To assess the effect of the various interventions on global hemodynamics and regional contractile and energetic parameters, two general linear models (GLM) for repeated measures were applied (SPSS, version 9.0, SPSS Inc.). One GLM tested the effect of HR, dobutamine dose and stunning in the baseline and stunning data, the other GLM tested the effect of HR, dobutamine dose and EMD 60263 in the stunning data without or with subsequent infusion of EMD 60263.

To calculate the VO₂ for myofibrillar work, the VO₂ for excitation–contraction coupling and the VO₂ for basal metabolism, multiple linear regression was performed on the pooled LADCA data of all animals using: MVO₂=HR=α·SSA·HR+β·E(1−ε)·HR+γ. To this end, animals were encoded using dummy-variables. Subsequently, the two conditions of stunning and stunning after administration of EMD 60263 were encoded separately as dummy-variables, which were multiplied with SSA and E(1−ε) to create new dummies for differences in α and β, caused by stunning or stunning with EMD 60263. For each of these dummies, an F-test was performed to evaluate their individual contribution to the entire regression model. Two data points with high leverage values out of 305 data points were removed from the analysis.

The oxygen wastage in stunned myocardium was calculated by subtracting the predicted ‘normal’ MVO₂ from the ‘stunned’ MVO₂. The predicted ‘normal’ MVO₂ was calculated applying the baseline α, β and γ to the stunning SSA and E(1−ε). The ‘stunned’ MVO₂ was calculated applying the stunning α, β and γ to the stunning SSA and E(1−ε). The individual contribution of myofibrillar work, excitation–contraction coupling and basal metabolism to the oxygen wastage of stunned myocardium was expressed as a percentage of the total oxygen wastage.

P values below 0.05 were considered significant. Only significant changes are mentioned in the Results section, unless stated otherwise.
3. Results

3.1. Systemic hemodynamics (Table 1)

3.1.1. Before stunning

Raising HR from 70 to 130 beats·min⁻¹ significantly increased MAP and CO (both 21%), independent of the dobutamine dose, and decreased LVP_{ed} (44%), while LVP_{max}/d_{max} remained unchanged. Infusion of dobutamine increased LVP_{max}/d_{max} (164% for the highest dose) and CO (33%), while SVR decreased (13%).

3.1.2. After stunning

Induction of stunning decreased LVP_{max}/d_{max} (23%), thereby causing a 30% decrease in MAP and an 18% decrease in CO while LVP_{ed} increased (26%). Moreover, stunning decreased the positive effect of dobutamine on LVP_{max}/d_{max} to 122% at the highest dose.

3.1.3. Infusion of EMD 60263

EMD 60263 restored the effect of dobutamine on LVP_{max}/d_{max} to a maximum of 209% at the highest dose and reversed the positive effect of HR on CO to a decrease of 17%.

3.2. Regional contractile and energetic parameters

3.2.1. LADCA region (Table 2)

3.2.1.1. Before stunning SAS decreased significantly (32%), SSA (40%), EW (40%) and MVO₂ (39%) when HR was raised from 70 to 130 beats·min⁻¹. Dobutamine infusion increased SAS (30%), E_{es} (198%), EW (50%), and MVO₂ (65%). Dobutamine also augmented the HR-induced decreases in SSA (from 20% during control to 40% during the high dose of dobutamine).

3.2.1.2. After stunning

Stunning decreased SAS (89%) and E_{es} (60%), while it increased e_{ps} (13%). The decrease in E_{es} caused a reduction in SSA (57%) and EW (77%). The positive effect of dobutamine on E_{es} was increased due to LADCA stunning (to 371%). Stunung did not affect MVO₂. In the control group, however, E_{es}, SSA and MVO₂ were unaffected.

3.2.1.3. Infusion of EMD 60263

EMD 60263 increased SAS (267%) and EW (135%), and decreased e_{ps} (9%). Moreover, EMD 60263 induced a positive effect of HR on

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Table 1

Systemic hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Heart rate</th>
<th>Baseline (n=18)</th>
<th>Δ from control</th>
<th>Stunna (n=8)</th>
<th>Δ from control at baseline</th>
<th>Stunna+EMD 60263 (n=10)</th>
<th>Δ from control at baseline</th>
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<tr>
<td></td>
<td>(beats·min⁻¹)</td>
<td>Control</td>
<td>Dobutamine Low dose</td>
<td>Dobutamine High dose</td>
<td>Control</td>
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<td>MAP (mmHg)</td>
<td>70</td>
<td>82±3</td>
<td>10±3</td>
<td>12±3</td>
<td>-10±3</td>
<td>-6±6</td>
<td>-8±6</td>
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<td>-29±3</td>
<td>-16±3</td>
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<tr>
<td>Test 2:</td>
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<td>4±2</td>
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<td>LVP_{max}/d_{max} (mmHg·s⁻¹)</td>
<td>70</td>
<td>1310±90</td>
<td>1220±110</td>
<td>2150±120</td>
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<td>2430±140</td>
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<td>-1.8±06</td>
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<td>2.3±07</td>
<td>1.2±11</td>
<td>0.8±09</td>
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<td>CO (l·min⁻¹)</td>
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<td>-0.2±0.1</td>
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<td>-7±3</td>
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<tr>
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<td>-5±2</td>
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<td>-6±2</td>
<td>-9±3</td>
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<tr>
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<td>-5±2</td>
<td>-1±4</td>
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<td>-7±4</td>
</tr>
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</table>

* Values are mean±S.E.M.: MAP, mean arterial pressure; LVP_{max}/d_{max}, maximal left ventricular pressure rise; LVP_{ed}, left ventricular end-diastolic pressure; CO, cardiac output; SVR, systemic vascular resistance. Test 1, Effect of HR, dobutamine and stunning. Test 2, Effect of HR, dobutamine and EMD 60263 in stunning.

†, effect of HR P<0.05; †, effect of dobutamine P<0.05; †, effect of stunning P<0.05; †, effect EMD 60263 P<0.05; †, interaction between HR and dobutamine effect P<0.05; †, interaction between HR and stunning effect P<0.05; †, interaction between HR and EMD 60263 P<0.05; 1, interaction between dobutamine and stunning P<0.05; 2, interaction between dobutamine and EMD 60263 P<0.05; 3, interaction between stunning and EMD 60263 P<0.05.
E_s (16%) and enhanced the negative effect of HR on SAS (to 56%) and SSA (42%) and decreased the negative effect on EW (48%). EMD 60263 also decreased the effect of dobutamine on MVO_2 (now up to 23%).

3.2.2. LCXCA region (Table 3)

3.2.2.1. Before stunning  Increasing HR from 70 to 130 beats·min⁻¹ decreased SAS (43%). Dobutamine increased EW (47–74%) and SAS (42–78%). The increase in E_s was not significant (P=0.139).

3.2.2.2. After stunning  Induction of LADCA stunning did not decrease E_s of the LCXCA region. However, SSA and EW were significantly decreased (59 and 63%, respectively). In addition, stunning increased the positive effect of dobutamine on EW (to 143%).

3.2.2.3. Infusion of EMD 60263  Subsequent infusion of EMD 60263 increased SAS (33%) and σ_{es} (16%), and decreased ε_s (6%). Additionally, EMD 60263 decreased the negative effect of HR on SSA (to 38%) and EW (52%).

3.3. Myofibrillar work, excitation–contraction coupling and basal metabolism

3.3.1. Normal myocardium  Before stunning, the regression MVO_2·HR=α·SAS·HR+β·E_s·HR+γ yielded an α of 4.68±0.97 (dimensionless, Fig. 3, top panel) with β 6.87±1.26·10⁻³ (dimensionless, Fig. 3, middle panel) and γ 5.60±1.68·10⁻⁵ (J·m⁻³·min⁻¹, Fig. 3, bottom panel), with r²=0.70 for the total regression (P<0.001). The three additional control experiments yielded an α of 3.36±0.50, with β 3.14±1.36·10⁻³ and γ 3.86±1.79·10⁻⁵, with r²=0.81 for the total regression (P<0.001). These α, β and γ were not significantly different from baseline α, β and γ mentioned above (P=0.488, P=0.144 and P=0.748, respectively).

3.3.2. Stunned myocardium  After stunning, α (71%, P<0.001) and β (134%, P=0.019) increased while γ remained unchanged (P=0.969,
Fig. 3). Applying the baseline α, β and γ to the SSA and $E_s$ of stunned myocardium, a ‘normal’ MVO$_2$ was predicted that was significantly lower than the measured ‘stunned’ MVO$_2$. For example, $101 \pm 4$ J.m$^{-3}$ .beat$^{-1}$ was predicted for a HR of 100 beats.min$^{-1}$ without dobutamine, compared to the measured MVO$_2$ of 137.54 J.m$^{-3}$ .beat$^{-1}$. From the difference between predicted ‘normal’ and predicted ‘stunned’ MVO$_2$, the ‘wasted’ MVO$_2$ was for $72\%$ myofibrillar VO$_2$, for 18% excitation–contraction coupling VO$_2$ and for 10% basal metabolism VO$_2$. In the three control experiments neither α (by $-2\%$, $P=0.227$), β (by $31\%$, $P=0.738$) nor γ (by $18\%$, $P=0.832$) changed significantly.

3.3.3. Infusion of EMD 60263

Compared to baseline, stunning with subsequent infusion of EMD 60263 yielded an unchanged α ($P=0.173$), β ($P=0.235$) and γ ($P=0.127$, Fig. 3). Compared to stunning alone, α and β were decreased ($P<0.001$ and $P=0.015$, respectively), while γ was unaltered ($P=0.349$).

4. Discussion

The major findings of the present study are that, in regionally stunned myocardium in vivo: (i) the oxygen cost of contractility is increased; (ii) the myofibrillar efficiency is decreased; (iii) the relative contribution of both factors is such that oxygen wastage of stunned myocardium is caused mainly by an increased VO$_2$ for myofibrillar work and to a minor extent by an increased VO$_2$ for excitation–contraction coupling; and (iv) infusion of a cAMP-independent Ca$^{2+}$-sensitizer EMD 60263 reversed both these changes.

Oxygen wastage of stunned myocardium may be caused by disturbances in energy generation or in energy consumption. Although an existing anaerobic metabolism has been denied by several studies [24], and energy generation is therefore thought to be constant per ml of O$_2$, independent of the substrate [23], a decreased efficiency of the mitochondria could also explain part of the inefficient oxygen consumption of stunned myocardium. This could interfere with our results, as we did not directly measure ATP production. However, the efficiency of the mitochondrial ATP production is undiminished in stunned myocardium [25]. We may therefore assume that oxygen consumption adequately reflects ATP production, both in the normal and in the stunned myocardium.

The increased oxygen cost of contractility in stunned myocardium is in accordance with observations in isolated dog hearts [9], but the interpretation of the subcellular processes underlying this observation are not obvious. The VO$_2$ consumed per unit of contractility (β) may be increased because of a decreased myofibrillar Ca$^{2+}$-sen-
EMD 60263, at a dose restoring systolic shortening in stunned myocardium [26], reversed the increased oxygen cost of contractility in this study. Likewise, oxygen cost of contractility decreased in excised cross-circulated dog hearts and in human hearts in vivo with MCI-154 [14,15], but was unchanged in excised cross-circulated dog hearts with DPI 201-106 [27], pimobendan [28] and EMD 53998 [29], which is the racemic mixture of the Ca\(^{2+}\)-sensitizer EMD 57033 and the phosphodiesterase inhibitor EMD 57439. The unchanged oxygen cost of contractility for pimobendan and EMD 53998 may be explained by their combination of adenosine cAMP-mediated and Ca\(^{2+}\)-sensitizing effects [15]. However, DPI 201-106 is not cAMP-dependent and the unchanged oxygen cost of contractility for this drug remains unexplained.

EMD 60263 also restored the decreased myofibrillar efficiency of the stunned myocardium, which supports the hypothesis that EMD 60263 may slow down the dissociation of the actin–myosin cross-bridges or increase their force rather than increase the number of cross-bridges formed, as has been shown for other Ca\(^{2+}\)-sensitizing drugs [13]. An increased efficiency between force production and Ca\(^{2+}\)-ATPase activity has also been shown for EMD 53998 [30], but not for EMD 57033 alone [16,17]. As far as we know, a restored myofibrillar efficiency caused by EMD 60263 has not been reported before for this drug. It is clear that a drug showing increased myofibrillar efficiency has energetic advantages over drugs that do not increase myofibrillar efficiency.

Fig. 3. Coefficients of the regression equation as described in Fig. 1. Top panel, α; middle panel, β; and bottom panel, γ. * P<0.05 vs. normal myocardium.

5. Limitations

In this study, we calculated regional stress applying an adaptation from the validated method of Goto et al. [21] as described before [20]. In our formula we used global LV pressure, as pressure is the same for the whole ventricle and actually drops to zero at the epicardium in open-chest pigs, and regional wall thickness, calculated from area changes assuming a constant regional volume. In addition, we calculated regional curvature of the LADCA region from the regional posterior–anterior diameter, assuming a local spherical geometry. This assumption may underestimate regional stress in an absolute sense as the actual regional longitudinal wall radius may be larger than the measured transversal one. However, as we studied regional stress in the same way for all animals in all conditions, we think that the relative changes in stress and energetics, on which our conclusions are based, will not be seriously affected by this assumption. Subsequently, we used the posterior–anterior diameter to calculate regional stress in the LCXCA region, which may not be completely correct, as the diameter may increase after stunning the LADCA-perfused territory, due to stretch of the LADCA region. However, as LADCA stunning increased the diameter by only 4.8% (data not shown) and stunning did not affect $E_{cs}$. 

sitivity, causing the myocardium to generate less force at maintained Ca\(^{2+}\) transients, but also because of a decreased efficiency of the SR Ca\(^{2+}\)-uptake, causing the SR to consume more oxygen for unchanged Ca\(^{2+}\) transients, or both. In addition, an energetically unfavorable redistribution of calcium cycling towards sarcolemmal calcium cycling and the existence of futile cycles may also contribute [10].

However, the extensive mathematical modeling underlying these latter two hypotheses rely upon the in-vitro finding that the efficiency of the myofibrils remains unchanged [10]. The present study provides evidence that in stunned myocardium, myofibrillar inefficiency is the major cause of the oxygen wastage, despite the increase of the oxygen cost of contractility. This is plausible because myofibrillar ATP consumption per cardiac cycle is 60–70% of total energy consumption, while E–C coupling comprises only 20–30%. In contrast to earlier studies we determined the relative contribution of myofibrillar efficiency at normal working conditions. The decreased myofibrillar efficiency implies that myofibrillar ATP utilization is less reduced than the generation of force, which is consistent with the in vitro findings of Bezstarosti et al. [18].

$\text{EMD 60263}$
and σ_{es} of the LCXCA region, the error introduced was probably small.

Myofibrillar efficiency and oxygen cost of contractility were estimated in vivo and we were therefore unable to change contractility and myocardial work completely independent of each other. However, in the statistical analysis, the correlation coefficient between SSA and \( E_{es} \) was only 0.20, which does not pose problems of multicollinearity [31].

Dobutamine was used to increase excitation–contraction coupling. However, dobutamine decreases the \( \text{Ca}^{2+} \)-sensitivity of the myofibrils [32,33] and this may influence the values of α and β. To evaluate this effect, we performed a sub-analysis after excluding the dobutamine data from the regression. Although β could not be accurately determined due to the smaller changes in \( E_{es} \), α remained unchanged at 3.367±1.192 for normal myocardium, while it was still increased to 6.569±2.107 for stunned myocardium. Therefore, the decreased myofibrillar efficiency in myocardial stunning appears to be independent of dobutamine infusion.

6. Conclusion

In this study, regionally stunned myocardium in vivo showed both a decrease in myofibrillar efficiency and an increase in oxygen cost of contractility. Although both changes contributed to the relatively high oxygen consumption, this ‘oxygen wastage’ was mainly caused by the decreased myofibrillar efficiency. EMD 60263, a cAMP-independent \( \text{Ca}^{2+} \)-sensitizing drug, reversed both these effects. Therefore, this drug does not only increase myofibrillar \( \text{Ca}^{2+} \)-sensitivity, but probably without increasing myofibrillar cross-bridge cycling.

References

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