Revascularization of hibernating myocardium

Rate of metabolic and functional recovery and occurrence of oxidative stress

C. Ceconi1, G. La Canna1, O. Alfieri2, A. Carg noni3, G. Coletti4, S. Curello1, M. Zogno4, G. Parrinello5, S. H. Rahimtoola6 and R. Ferrari3,7

1Cattedra di Cardiologia Spedali Civili, Brescia, Italy; 2Divisione di Cardiochirurgia, Ospedale S. Raffaele, Milano, Italy; 3Centro di Fisiopatologia Cardiovascolare, Fondazione ’’S. Maugeri’’ IRCCS, Gussago (Brescia), Italy; 4Il Divisione di Cardiochirurgia Spedali Civili, Brescia, Italy; 5Dipartimento di Statistica, Università di Brescia, Italy; 6Griffith Center, Division of Cardiology, University of Southern California, Los Angeles, USA; 7Cattedra di Cardiologia, Università di Ferrara, Italy

Background Left ventricular (LV) dysfunction due to coronary artery disease (CAD) may improve after revascularization in patients with hibernating myocardium (HM).

Methods and Results We compared the rate of metabolic (arterial–great cardiac vein differences of lactate, glucose and pyruvate) and functional (intra-operative transesophageal and epicardial echocardiography) recovery and occurrence of oxidative stress (myocardial release of oxidized glutathione (GSSG)) early after surgical revascularization, in patients with CAD, LV dysfunction and HM (n=16) vs those with preserved LV function (n=15). By comparing the two groups, we observed that, after de-clamping, in patients with HM (a) the kinetic of lactate production was converted to extraction (P<0.01 at 1, 5, 10 and 20 min after revascularization), (b) myocardial extraction of pyruvate increased (P<0.01 during the first 5 min after revascularization), (c) GSSG release was less and of shorter duration (P<0.01 at all times), (d) segmental wall motion score improved from 2.4±0.3 to 1.7±0.5 (P<0.01) as did the thickening of the akinetic territories corresponding to the antero-distal septum and to the distal anterior wall regions (to 36±23%, and to 36±13%, respectively). There was a correlation between the rate of recovery of metabolic and functional indices.

Conclusions The contractile and metabolic recovery of HM is more rapid than that of non-HM, and it is not accompanied by oxidative stress.


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Key Words: Left ventricular dysfunction, coronary artery disease, hibernating myocardium, metabolic and contractile recovery, oxidative stress.

Introduction

Left ventricular (LV) dysfunction due to coronary artery disease (CAD) may improve or even normalize in some patients after revascularization[1,2]. Ischaemic myocardium that recovers contractile function after revascularization has been termed ‘hibernated myocardium’ (HM) and can be predicted by the presence of viable dysfunctional myocardium.[3,4]. The behavior of functional and metabolic recovery of HM early after revascularization is not known.

Such knowledge is important for the quantification of the actual operative risk[5].

The specific goals of this study were to determine:

- the rate of metabolic and contractile recovery of HM early after surgery;
- whether oxidative stress occurs during revascularization of HM and influences the rate of metabolic and contractile recovery;
- the tolerance of HM to surgically induced ischemia.
Therefore, we have compared early recovery of LV function, restoration of carbohydrate metabolism and occurrence of oxidative stress, between 16 patients with CAD and LV dysfunction and HM and 15 with preserved LV function.

Methods

Patients population

All patients gave informed consent. The study was approved by the local Hospital Joint Ethics Committee on Clinical Investigations. We considered two groups of patients: Group A (control) consisted of 15 CAD patients with preserved LV function, scheduled for elective multiple coronary artery bypass surgery (CABG) on the basis of persistent angina despite optimized treatment. All had a diseased left anterior descending coronary artery (LAD) that needed and received a graft. None had previous myocardial infarction (MI); Group B consisted of 16 CAD patients selected according to the following inclusion criteria: (a) segmental akinesia of the LV for at least 1 month before CABG, detected by serial echocardiograms (hypokinesis was not considered a criterion for entry into the study), (b) no LV aneurysm or extensive scar involving $>60\%$ of the LV (established as previously described$^{[6]}$), (c) presence of viable myocardium in at least two of the akinetic segments subtended by the LAD (viability was determined by positive echo–dobutamine test), (d) narrowing ($>75\%$) of the LAD subtending the akinetic areas suitable for revascularization.

Twelve patients had previous MI; four had angina, eight angina and dyspnea, the remaining four, only dyspnea (NYHA class II and III). These patients, in addition to the antischemic therapy, were receiving angiotensin-converting enzyme (ACE) inhibitors and, if necessary, diuretics.

History of acute MI or unstable angina within the previous 6 months of the study, concomitant pulmonary or valvular diseases, and ventricular tachy-arrhythmias, were exclusion criteria.

Echocardiography

All patients underwent complete M-mode and two-dimensional echocardiography$^{[7]}$. Regional wall motion was evaluated according to the 16–segment model recommended by the American Society of Echocardiography$^{[8]}$. The following scoring system was used: 1=normal ($\geq 5$ mm endocardial excursion, $\geq 25\%$ systolic thickening); 2=hypokinesia ($<5$ mm endocardial excursion, $<25\%$ systolic thickening); 3=akinesia (absence of endocardial excursion and wall thickening); 4=dyskinesia (paradoxical outward motion in systole). Ejection fraction (EF) was quantified as previously described$^{[6]}$.

Echo-dobutamine test (in Group B patients)

Dobutamine was infused at 5 and 10 $\mu$g·kg$^{-1}$ body weight·min$^{-1}$, each dosing lasting 5 min$^{[9]}$. Inotropic or $\beta$-adrenergic blocking agents were withdrawn at least 48 h before the test. The effects of dobutamine were evaluated only in the akinetic segments. There were no complications.

CABG and intra-operative echocardiography

All oral medications, with the exception of nitrates, were discontinued 4 days before surgery. Anesthesia and monitoring transesophageal echocardiography and haemodynamic measurements were performed as previously described$^{[6]}$. After cardiopulmonary bypass (CPB) at a flow rate of 2.4 l·min$^{-1}$·m$^{-2}$, a coronary sinus catheter was advanced into the great cardiac vein for blood sampling. The correct position of the catheter was repeatedly checked by fluoroscopy and comparison of PO$_2$ values of samples from the great cardiac vein and the right atrium.

All patients underwent CABG using the left internal mammary artery to the LAD and saphenous vein grafts. CABG was completed on CPB with mild hypothermia (30°C). The distal anastomoses were performed during a period of aortic cross-clamping, while the myocardium was protected using the anterograde St. Thomas Hospital Cardioplegic Solution. Aspartate/glutamate-enriched warm blood cardioplegia was injected throughout the aortic root for 2 min before release of the aortic cross-clamp at a fixed flow rate of 0.31 l·min$^{-1}$. Reperfusion on CPB was continued for 30 min after removal of the cross-clamp, and the coronary sinus catheter was removed 20 min after the end of CPB.

The epicardial echocardiographic examination was performed as previously described$^{[6]}$. M-mode recording was also performed to evaluate quantitatively systolic thickening, thus avoiding the effect of pericardiotomy. During echocardiographic recordings, no inotropics or vasodilators were administered and ventricular pacing was not used. The epicardial echocardiographic examination after CABG was obtained after removal of the arterial and venous cannula at least 20 min after CPB and 10 min after administration of protamine.

Haemodynamic measurements

These were recorded before sternotomy, 15 min after the end of CPB, and in the intensive care room at 2, 4, 6, 12 and 24 h after CPB. These parameters included left ventricular stroke work index (LVSWI), pulmonary capillary wedge pressure (PCWP), LVSWI/PCWP and systemic vascular resistances (SVR); calculations were performed using standard formulae$^{[8]}$.
**Myocardial Metabolism**

Arterial–great cardiac vein differences for lactate, glucose, pyruvate, oxidized glutathione (GSSG) (as an index of oxidative stress) and creatine phosphokinase (CPK) (as an index of membrane damage) were measured in 5 ml of arterial and venous blood simultaneously drawn 10 and 5 min before cross-clamping the aorta, and then at 1, 5, 10 and 20 min after removal of the aortic cross-clamp, and again 10 and 20 min after the end of CPB. Lactate, glucose, pyruvate and CPK were determined spectrophotometrically, as previously described [10]; GSSG was determined by the modified Tietze method, as previously described [10,11].

**Statistical analysis**

Differences among groups were evaluated either by the Student t- or the Kruskal–Wallis test, according to the distribution of the analysed variables. Correlation between different parameters was analysed either by the Pearson’s or by the Spearman’s coefficient. To evaluate possible differences of the trend of the curves relevant to the haemodynamic parameters or the metabolic variables related to carbohydrate metabolism between HM and control group patients (Group B vs Group A), a ‘linear mixed model for repeated measures’ was applied.

To study possible associations between the release of lactate, glucose, pyruvate, GSSG and CPK in the de-clamping and CPB period, and the trend of the haemodynamic parameters in the 24 h after surgery, the area under the curve (AUC, as a sensitive summary measure of the metabolic patterns) was calculated in the diagrams, time vs lactate, glucose, pyruvate, GSSG and CPK, and these values were used as covariates in the linear mixed model.

The statistical packages — SAS (SAS Institute Inc., Cary NC, USA) and S-plus (Mathsoft, Seattle WA, USA) — were used to perform the statistical analysis. P-values ≤ 0.05 were considered statistically significant.

**Results**

**Patient Characteristics**

The two groups of patients were comparable for age (54.9 ± 8.4 vs 58.5 ± 8.5 years in Groups A and B, respectively), sex (15 M in Group A and 15 M and one F in Group B), treatments (nitrates, β-blockers, ACE-inhibitors and diuretics were given to 13/12, 10/10, 11/13 and 11/13 patients in Group A/Group B, respectively), number of anastomoses (2.8 ± 0.4 in Group A vs 2.7 ± 0.7 in Group B) and mean duration of cross clamping (37.7 ± 10.2 in Group A vs 42.0 ± 11.2 min in Group B). LVEF was lower in Group B than in Group A (37.0 ± 7.3% vs 57.3 ± 4.7%, P<0.001); conversely, LV end diastolic pressure (LVEDP) and PCWP were higher (12.9 ± 2.5 vs 10.7 ± 2.7 mmHg, P<0.05; 11.7 ± 0.7 vs 8.9 ± 0.9 mmHg, P<0.05, respectively).

The evaluation of viable myocardium in Group B by echo–dobutamine was performed in 256 segments, 159 of which were akinetic at baseline. Systolic wall thickening and wall motion improved after dobutamine infusion in 97 akinetic segments, 43 of which were subtended by LAD territory (at least two segments for each patient). Wall motion score improved from 2.4 ± 0.2 to 1.9 ± 0.3 and to 1.9 ± 0.4 after the first and second dobutamine infusions, respectively (both, P<0.01).

**Operative course**

No patients showed electrocardiographic changes or enzyme elevation suggestive of peri-operative MI, and continuous intra-operative transesophageal echocardiography showed no occurrence of new wall motion abnormalities. No patients had a low output syndrome requiring inotropic agents. There were no substantial differences in the management of the two Groups of patients in the Intensive Care Unit after surgery.

**Recovery of contractile function**

**Intra-operative echocardiography**

To ensure that the pre-operative segmental wall motion reflected the chronic state of ventricular function, we compared the data obtained before revascularization by epicardial echocardiography with those obtained at baseline transthoracic echocardiography. There were no variations in regional wall motion in the 256 segments.

In Group B, the segmental wall motion score improved after CABG from 2.4 ± 0.3 to 1.7 ± 0.5 (P<0.01), while, in Group A, there was no segmental alteration of contraction. To further investigate the contractile recovery after CPB, segmental wall thickening was determined by M-mode epicardial echocardiography. The correlation between contractility and metabolic data was performed by studying in detail the territories subtended by the LAD draining into the great cardiac vein. These territories correspond to the anteroseptal and to the distal anterior wall (akinetic and vital, as per inclusion criteria), and are the ones evaluated in the study to guarantee the reproducibility of the results.

Figure 1 shows the individual and mean changes in segmental wall thickening determined by echo-epicardial measurements. Only two timing evaluations were performed: one at the pre-clamping timing and the other post-reperfusion (10 min after protamine injection). In patients with HM, these regions rapidly recovered their thickening to 36 ± 23% in the anteroseptal septum wall, and to 36 ± 13% in the distal anterior wall. The control group showed reduction in thickening compared to pre-operative values, from 50 ± 23% to 43 ± 19% (P<0.001) and from 40 ± 14% to 31 ± 8% (P<0.001),
respectively. This was probably due to a reduced contractility experienced by some patients, possibly as a result of the post-operative stunning.

**Haemodynamic measurements**

In the control group, the recovery of the haemodynamic parameters was not immediate (Table 1). CI and LVSWI decreased after surgery and remained low for the following 12 h. At 24 h, CI returned to the pre-CPB values, i.e. the recovery to a normal haemodynamic pattern occurred between 12 and 24 h after surgery. Surprisingly, the rate of haemodynamic recovery of Group B patients was faster than that of Group A. During the 24 h after surgery, CI and LVSWI increased progressively from 3.3 ± 0.5 to 4.6 ± 0.8 l.min⁻¹.m⁻² and from 38 ± 11 to 48 ± 18 g.m⁻¹.m⁻². The linear mixed model for repeated measures showed a statistically significant difference in the trend between the two groups for these two parameters (both, *P*<0.01). At 24 h, CI and LVSWI were significantly higher in Group B vs Group A (*P*<0.05), while there was no difference in SVR. LVSWI/PCWP (a systolic index of contractility) of patients with HM was also higher than that of the control group at 2, 4, 6, 12 and 24 h, but, due to the large standard deviation, the difference was statistically significant only at 4 and 6 h.

**Recovery of myocardial metabolism**

**Carbohydrates**

Before clamping, arterial concentrations of lactate (148.5 ± 64.2 µmol.dl⁻¹ in Group A and 195.7 ± 88.9 µmol.dl⁻¹ in Group B), glucose (588 ± 125 µmol.dl⁻¹ and 571 ± 150 µmol.dl⁻¹, respectively) and pyruvate (5.5 ± 1.7 µmol.dl⁻¹ and 5.2 ± 0.7 µmol.dl⁻¹, respectively) were within normal fasting values in both groups. Figure 2 shows that, as expected, there was a positive myocardial A-V difference for glucose and pyruvate in both groups. Five patients in the control group released lactate into the great cardiac vein, while, in the remaining 10, the lactate myocardial A-V difference was negligible, i.e. overall balance was negative (Fig. 2(A)). Conversely, none of the patients with HM showed lactate release into the great cardiac vein. After de-clamping, there was lactate production in both groups, suggesting occurrence of anaerobic metabolism. However, the kinetic of lactate release was different: in the control group, it continued for the entire de-clamping period, while in patients with HM, lactate production was converted to extraction within 5 min after revascularization, suggesting an early recovery of aerobic metabolism (*P*<0.01 vs Group A at 1, 5, 10 and 20 min).

Accordingly, the myocardial A-V difference for glucose was higher in Group B patients than in Group A, but, due to the high variability within groups, it was not statistically different (Fig. 2(B)). The myocardial A-V difference for pyruvate was higher in patients with HM than in the control group (*P*<0.01), only during the first 5 min of de-clamping (Fig. 2(C)). At the end of CPB, there was no difference in carbohydrate metabolism between the two groups.

There was a correlation between recovery of CI (*P*<0.01), LVSWI (*P*<0.01), LVSWI/PCWP (*P*<0.05), and lactate metabolism. There was also a correlation between recovery of CI (*P*<0.01), LVSWI/PCWP (*P*<0.05), SVR (*P*<0.05) and myocardial A-V difference.
Table 1  Haemodynamic changes during the 24 h after CABG

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before CPB</th>
<th>After CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
<td>2 h</td>
</tr>
<tr>
<td>Group A</td>
<td>Patients with normal LV function (control group) (n=15)</td>
<td></td>
</tr>
<tr>
<td>HR (beats·min⁻¹)</td>
<td>67 ± 7</td>
<td>91 ± 6*</td>
</tr>
<tr>
<td>CI (l·min⁻¹·m⁻²)</td>
<td>42 ± 1.1</td>
<td>3.4 ± 1.7</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93 ± 4</td>
<td>76 ± 3*</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>8.9 ± 0.9</td>
<td>9.8 ± 0.7</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7.8 ± 1.0</td>
<td>6.6 ± 1.4</td>
</tr>
<tr>
<td>SVR (dyne·s⁻¹·cm⁻²)</td>
<td>1530 ± 566</td>
<td>1115 ± 400⁰</td>
</tr>
<tr>
<td>LVSWI (g·m⁻¹·m⁻²)</td>
<td>44 ± 12</td>
<td>33 ± 13</td>
</tr>
<tr>
<td>LVSWI/PCWP (g·m⁻¹·mmHg⁻¹)</td>
<td>4.9 ± 1.6</td>
<td>3.4 ± 2.7</td>
</tr>
</tbody>
</table>

Group B=Patients with LV dysfunction (hibernating myocardium) (n=16)

| HR (beats·min⁻¹) | 65 ± 2     | 102 ± 3*   | 104 ± 4*   | 107 ± 3*   | 102 ± 3*   | 101 ± 3    | 96 ± 2*   |
| CI (l·min⁻¹·m⁻²) | 33 ± 0.6*  | 3.6 ± 1.6  | 3.7 ± 0.7  | 4.2 ± 1.1* | 3.8 ± 0.8* | 4.1 ± 0.7**| 4.6 ± 0.8**|
| MAP (mmHg)   | 84 ± 4     | 78 ± 4     | 88 ± 3     | 82 ± 2     | 78 ± 3     | 74 ± 3**   | 77 ± 2    |
| PCWP (mmHg)  | 11.7 ± 0.7*| 10.7 ± 1.1 | 9.9 ± 1.0  | 10.2 ± 0.8 | 10.2 ± 0.9 | 11.4 ± 0.9 | 9.6 ± 1.0 |
| RAP (mmHg)   | 84 ± 0.9   | 6.8 ± 0.9* | 7.9 ± 0.8  | 7.7 ± 0.8  | 7.9 ± 0.7  | 8.3 ± 0.5  | 7.7 ± 0.5 |
| SVR (dyne·s⁻¹·cm⁻²) | 1395 ± 354 | 1163 ± 496 | 1243 ± 516 | 988 ± 247⁰ | 901 ± 252⁰ | 827 ± 209⁰ | 906 ± 193⁰ |
| LVSWI (g·m⁻¹·m⁻²) | 38 ± 11    | 37 ± 15    | 41 ± 15    | 43 ± 11*   | 38 ± 12*   | 40 ± 15*   | 48 ± 18*   |
| LVSWI/PCWP (g·m⁻¹·mmHg⁻¹) | 3.3 ± 1.9  | 3.5 ± 2.5  | 4.1 ± 4.3  | 4.2 ± 2.2* | 3.7 ± 1.7* | 3.5 ± 2.6  | 5.0 ± 3.2  |

Data are reported as mean ± SD. Measurements were recorded either in operating room (before and 15 min after CPB) or in the intensive care room (all the remaining determinations). CABG=coronary artery bypass surgery; CPB=cardio-pulmonary bypass; HR=heart rate; CI=cardiac index; MAP=mean aortic pressure; PCWP=pulmonary capillary wedge pressure; RAP=right atrial pressure; SVR=systemic vascular resistances; LVSWI=left ventricular stroke work index.

*P<0.05, **P<0.01: differences between groups at each point; *P<0.05: difference of each group from baseline.
for glucose, suggesting that the early recovery of the aerobic metabolism is linked to the recovery of function.

**Occurrence of oxidative stress and CPK release**

Before clamping, there was no myocardial A-V difference for GSSG or CPK in either group (Figs 3(A) and 3(B)). After de-clamping, arterial concentration of GSSG remained constant, whereas that in the great cardiac vein increased above the arterial values, thus resulting in a negative myocardial A-V difference with a peak 1 min after de-clamping in both groups. However, in patients with HM, GSSG release was less and of shorter duration than that in Group A (P<0.01 at all times), as a result of a wash-out instead of continuous GSSG production. In contrast, in Group A patients, GSSG release continued for the whole observation period, probably as an expression of ongoing oxidative stress.

Figure 3(B) also shows the release of CPK into the great cardiac vein. Since none of these patients had a clinically detectable intra- or peri-operative MI, a negative myocardial A-V difference of CPK release is likely to reflect minor membrane damages due to reperfusion.

Surprisingly, in patients with HM, CPK release was less than that of the control group (P<0.01). However, due to the high variability of the data, the trend between the two groups was not statistically significant.

At the end of CPB, in Group A, but not in Group B, there was still a myocardial production and release of GSSG, while the myocardial A-V difference for CPK between groups was similar.

There was a correlation between the occurrence of oxidative stress and recovery of haemodynamic function in terms of CI (P<0.05), LVSWI (P<0.01) and SVR (P<0.05). CPK release was also correlated to CI (P<0.01) and LVSWI/PCWP (P<0.05).
Discussion

Contractile recovery of hibernating myocardium

This is still a controversial issue\[^{12}\]. In a model of short-term hibernation in isolated rabbit heart, cardiac function recovered almost completely within minutes\[^{13}\], while in anaesthetized pigs submitted to short-term hibernation, no recovery occurred within the first 30 min\[^{14}\] or even at 2 h after reperfusion\[^{15}\]. In other studies, in conscious dogs and in anaesthetized pigs, full functional recovery was observed only after 7 days\[^{16-18}\].

In patients, the recovery of contractile function can be rapid, subacute or chronic\[^{6,19-22}\]. This is not unexpected because differences in methods to assess the presence and extent of viability, severity and duration of flow reduction, and variables correlated to the revascularization procedures, can all affect recovery.

We observed that the contractile recovery of patients with LV dysfunction is more rapid than those with preserved LV function. An early recovery can be expected only in the absence of gross morphological alterations, in particular in the absence of loss of myofibrils. It follows that the selection procedure to assess viability used in our study, i.e. the echo-dobutamine test, might have strongly influenced the results. In fact, echo-dobutamine has a higher specificity for functional recovery than scintigraphic PET techniques, as it provides information on presence and functional behavior of the myocytes\[^{6,7,23,24}\]. For the above reasons, our data cannot be fully extrapolated to patients selected according to other methodologies, who might show delayed recovery despite presence of viability.

The duration of hibernation and the severity of myocardial blood flow reduction are also important factors in determining the rate of recovery. We have no information on the severity of flow reduction and on the actual duration of hibernation except that LV dysfunction was present for at least 1 month (inclusion criterion).

There are other variables that could have influenced the rate of recovery in our patients. The most obvious ones are the duration of the clamping period and the cardioprotective precautions (e.g. warm reperfusion) which, however, were comparable between the two groups.
groups. The reduction in systemic vascular resistance induced by surgery and the consequent release of endogenous catecholamines might also be relevant. However, there was no difference in systemic resistances between the two groups over the 24 h after surgery and the same improvement in contractile recovery was still detectable 3 months after revascularization in both groups (data not shown), when peripheral resistances and endogenous catecholamines should have returned to pre-operative values.

**Metabolic recovery and oxidative stress of hibernating myocardium**

In HM, there is a faster recovery of aerobic carbohydrate metabolism linked to an early recovery of haemodynamic parameters. We did not measure lipid metabolism since high doses of heparin are routinely used during surgical procedures, yielding unrealistically high levels of free fatty acids. We did not measure the coronary flow either, thus, the metabolic data are qualitative and not quantitative.

The metabolic profile of the control group, showing no lactate utilization or even a small production before clamping and a clear release during de-clamping, is in agreement with previous observations, representing the usual response of myocardium to surgically-induced ischemia.

In contrast, HM before clamping does not release lactate but might utilize this substrate which is immediately burnt, having only three carbon atoms. During de-clamping, HM released less lactate than normal and avidly utilized both glucose and pyruvate, myocardial A-V differences for pyruvate being maximum during the first 5 min. These data indicate that viable myocardium on reperfusion retains the activity of pyruvate dehydrogenase, the key enzyme for the oxidative utilization of carbohydrates. This enzyme is inhibited by oxidative stress which did not occur, or occurred to a significantly less extent in patients with HM.

Experimental studies have shown that on reperfusion after ischemia, there is an increase of tissue content and release of GSSG. The same occurs in CAD patients with preserved LV function subjected to CABG. In these patients, the degree of GSSG release is related to the duration of the clamping period and is considered predictive for post-surgical stunning.

Our data confirm and go beyond this finding: the degree of oxidative stress on revascularization after CABG correlates with the rate of haemodynamic recovery, independent of the baseline LV function. It is well known that oxygen free radicals exert a negative inotropic effect by: (a) alteration of calcium fluxes and calcium binding to the myofilaments, (b) inhibition of aerobic metabolism and (c) promotion of membrane damage. The data obtained in patients with HM show that oxidative stress and CPK release on reperfusion are negligible, aerobic metabolism recovers early, and mechanical function returns to normal within 6 h. Accordingly, there was a statistically significant correlation between GSSG and lactate release (r=0.70; P=0.0001), suggesting that the more the oxidative stress, the higher the anaerobic metabolism.

It could be argued that some patients with HM experienced MI, i.e. the fibrotic tissue possibly releases less CPK and lactate. However, the studied territories recovered both metabolism and contraction on reperfusion as a sign of viability and of no real transmural MI. Equally, the severity of the ischemic period could have influenced these results. During heart surgery, total and global ischemia is induced in the arrested, bloodless and cooled heart. Under these conditions, the severity of ischemia is mainly determined by the duration of the period required to complete the surgical procedures, which was similar or slightly longer in patients with HM, if compared to control. Another possible explanation for the reduced CPK release of hibernating myocardium are morphological changes reported in hibernating myocardium, suggesting that the total number of myocytes is reduced together with a reduction in the myofibrillar content of these myocytes.

**References**


