Occurrence of Oxidative Stress During Reperfusion of the Human Heart

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We have investigated the relation between occurrence of myocardial oxidative stress and functional recovery during postischemic reperfusion in 20 selected patients subjected to aortocoronary bypass grafting. Patients were selected for having normal percent ejection fraction and left ventricular end-diastolic pressure before the operation. Occurrence of oxidative stress was assessed by measuring the formation and release of oxidized glutathione (GSSG) in the coronary sinus immediately before aortic cross-clamp, 1, 5, 10, and 20 minutes after removal of aortic cross-clamp, and 10 and 20 minutes after the end of cardiopulmonary bypass. Reduced glutathione (GSH), lactate, and creatine phosphokinase release were also monitored with the same timing. Standard hemodynamic measurements were recorded by means of a triple-lumen thermodilution pulmonary artery catheter before sternotomy, 15 minutes after the end of cardiopulmonary bypass, and during the 24 hours after termination of cardiopulmonary bypass. Reperfusion in patients after a short period of ischemia (less than 30 minutes; group 1) resulted in a small and transient release in the coronary sinus of GSSG and GSH and in a progressive improvement of hemodynamic parameters reaching a stable state 4 hours after the operation. In patients with a period of ischemia longer than 30 minutes (group 2), reperfusion induced a marked and sustained release of lactate, GSH, and GSSG; the arterio-coronary sinus difference for GSSG was still negative after the end of cardiopulmonary bypass. The arterio-coronary sinus difference for creatine phosphokinase also remained negative for as long as 20 minutes after cardiopulmonary bypass, and the rate of functional recovery was significantly delayed, reaching the values of group 1 only 12 hours after the operation. In these patients there was a positive correlation (r=0.88, p<0.01) between the duration of ischemia and the myocardial arteriovenous difference for GSSG. In addition, there was a negative correlation between the arterio-coronary sinus difference for GSSG and cardiac index measured 2, 4, and 6 hours after the operation. These data suggest for the first time that, depending on the severity of the ischemic period, oxidative stress occurs during reperfusion of patients with coronary artery disease who are subjected to heart surgery and that it may be linked with a delay in postoperative recovery of cardiac function. (Circulation 1990;81:201–211)

The availability of techniques such as surgical reperfusion, angioplasty, and thrombolysis for the restoration of blood flow to the ischemic myocardium has revived interest in the molecular events occurring during reperfusion.1–5 It is clear that reperfusion occupies a central role in tissue protection because without it no recovery is possible at all.6 Readmission of coronary flow, however, is not necessarily beneficial, and it has been reported that it can accelerate the rate of development of necrosis.7–9 The mechanism leading to cell death on reperfusion is unknown.

Recently, it has been suggested that reactive oxygen intermediates (oxygen-derived free radicals) play an important role in reperfusion damage. Oxygen free radicals may be generated within the myocardial cell from the mitochondria and from the cytosol,10,11 or they may be generated outside the myocytes from activated neutrophils,12–15 from the arachidonic acid cascade,16 or, in some species, from endothelial xanthine oxidase.17–19

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Supported by the Italian C.N.R. Grant 87.01485.04.

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Received January 3, 1989; revision accepted September 13, 1989.
All the evidence for an involvement of oxygen toxicity in myocardial damage has been derived from studies in animals in which agents known to eliminate or reduce oxygen free radicals have reduced myocardial injury in the setting of ischemia and reperfusion.

No data are available to support the hypothesis that myocardial oxidative damage occurs also in humans. There are three main reasons for this: 1) difficulties in following the molecular changes occurring during early phases of reperfusion, 2) the impossibility of standardizing the onset, severity, and duration of ischemia and reperfusion, and 3) the lack of reliable indexes capable of detecting the occurrence of an oxidative stress in humans.

We have attempted to overcome these problems by measuring the arteriocoronary sinus oxygen difference for reduced glutathione (GSH) and oxidized glutathione (GSSG) in 20 patients with coronary artery disease who were subjected to different periods of total and global ischemia followed by reperfusion during aortic coronary bypass grafting. It is known that GSH, as a cosubstrate of glutathione peroxidase, plays an essential protective role against oxygen reactive species. This protective mechanism results in increased formation of GSSG that is actively transported across the cell membrane so that its intracellular concentration is kept low. Thus, the increased formation and release (either active or passive) of GSSG from the cell reflects glutathione peroxidase activity and indicates an inability of the cell to produce reducing equivalents for GSH resynthesis, so that it may be considered a sensitive and specific index of myocardial oxidative stress.

Methods

Patients

We studied 20 patients scheduled to have nonurgent aorticcoronary bypass grafting with reversed saphenous vein. All the patients gave informed consent to participate in this study, which had the approval of the local medical ethics committee. The patients have been retrospectively divided into two groups according to the duration of the cross-clamping period. Group 1 consists of eight patients with a cross-clamping period less than 30 minutes (25 ± 1.69 minutes, mean ± SEM); group 2 consists of 12 patients with a cross-clamping period longer than 30 minutes (55 ± 2.8 minutes).

Clinical data for all the patients are reported in Table 1. None had previous myocardial infarction, but all had angina on effort and were receiving either β-adrenergic receptor–blocking agents, nitrates, or calcium channel–blocking agents. All oral medications, with the exception of nitrates, were discontinued 4 days before surgery. Excluded from the study were patients with left ventricular end-diastolic pressure more than 15 mm Hg, ejection fraction less than 50%, atrioventricular conduction defects, or unstable angina. Those undergoing additional surgical procedures (e.g., valve replacement or aneurysmectomy) were also excluded.

Surgical Procedure

Phenobarbital (2.5 mg/kg) was administered 8 hours before surgery. After premedication with diazepam (0.25 mg/kg), morphine (0.15 mg/kg), and scopolamine (0.008 mg/kg), anesthesia was induced with fentanyl (0.05 mg/kg), and muscle relaxation was achieved with pancuronium (0.1 mg/kg). Ventilation was controlled with oxygen in air (50%).

Before sternotomy, an 18-gauge cannula was placed in the radial artery for arterial sampling. A triple-lumen thermodule pulmonary artery catheter was introduced through the left subclavian for hemodynamic measurements. After institution of cardiopulmonary bypass at a flow rate of 2.4 l/min/m², a coronary sinus catheter was advanced into the coronary sinus and used for coronary sinus sampling. The correct position of the catheter was repeatedly checked by comparison of PO₂ values of samples from coronary sinus and right atrium. The aorta was cross-clamped, and 11 St. Thomas Hospital Cardioplegic Solution containing (mmol/l) NaCl 110, KCl 16, MgCl₂ 16, CaCl₂ 1.2, and NaHCO₃ 10 was infused into the aortic root within 3 minutes at a flow sufficient to obtain an aortic pressure of 70–100 mm Hg. A second infusion of 300 ml was repeated after 30 minutes of clamping. At the same time, moderate hypothermia was induced to provide an esophageal temperature of 29 ± 1.3° C (mean ± SEM). Myocardial temperature was monitored by means of needle thermistor probes inserted in the midportion of the intraventricular septum and maintained below 15° C. After completion of all distal anastomoses, the aortic cross-clamp was removed, and the construction of the proximal anastomoses was begun after the patient was rewarmed. Reperfusion on cardiopulmonary bypass was continued for 30 minutes after removing the aortic cross-clamp, and the coronary sinus catheter was removed 20 minutes after the end of cardiopulmonary bypass.

Hemodynamic Measurements

Hemodynamic measurements included heart rate, mean aortic pressure, right atrial pressure, pulmonary capillary wedge pressure, and cardiac output (by thermodilution). Derived hemodynamic measurements included cardiac index, left ventricular stroke work index, and systemic vascular resistances calculated by standard formulas.

All measurements were recorded in the operating room before sternotomy, as well as 15 minutes after the end of cardiopulmonary bypass. The same measurements were also repeated after the operation in the intensive care room at 2, 4, 6, 9, 12, and 24 hours after termination of cardiopulmonary bypass.

Metabolic Measurements

Sampling for metabolic measurements was undertaken in the operative room and included myocardial
arteriovenous differences for GSH, GSSG, lactate, and creatine phosphokinase (CPK). For this purpose, 5 ml arterial and coronary sinus blood were simultaneously drawn 10 and 5 minutes before aortic cross-clamping, then at 1, 5, 10, and 20 minutes after removal of the aortic cross-clamp, and again 10 and 20 minutes after the end of cardiopulmonary bypass.

For the measurement of total glutathione (GSH+GSSG), 1 ml fresh whole blood was added to 1 ml of 10 mM 5,5'-dithio-bis-(2-nitrobenzoic acid) (DTNB), 17.5 mM disodium ethylenediaminetetraacetic acid (EDTA), and 100 mM potassium phosphate, pH 7.5. The sample was gently mixed by tilting and was centrifuged for 6 minutes at 2,000g in a J6B centrifuge (Beckman Instrs, Inc, Fullerton, California). An aliquot (100 μl) of the DTNB-plasma solution was used for the determination of total glutathione with the Tietze method, which was modified by us. For the assay of GSSG, 1 ml fresh whole blood was added to 1 ml of 10 mM N-ethylmaleimide (NEM), 17.5 mM disodium EDTA, and 100 mM potassium phosphate, pH 6.5. The sample was mixed by tilting and centrifuged for 6 minutes at 2,000g. An aliquot (800 μl) of NEM-plasma solution was added to 100 μl trichloroacetic acid (20%) and 5 ml chloroform. After mixing by tilting, the organic phase was separated from the inorganic by centrifugation. Before the enzymatic assay, excess NEM was removed by extraction with diethyl ether. Hemolysis was not detected by procedures capable of revealing 0.2% free hemoglobin.

For lactate and CPK determination, 2 ml fresh whole blood was centrifuged immediately after sampling at 2,000g for 6 minutes. The extracted plasma was assayed on the same day for lactate as described by Noll and for CPK as described by Oliver.

**Statistical Analysis**

The data are expressed as mean±SEM of n experiments. For statistical evaluation of results, a multiple-group comparison was performed by analysis of variance followed by Student's t test for paired or unpaired data with Bonferroni's correction.

**Results**

Details of the patients are shown in Table 1. The two groups were comparable with respect to age, sex,
and preoperative hemodynamic findings, which were within normal range. The mean duration of cross-clamping was 55±2.8 minutes in group 2 and 25±1.6 minutes in group 1 (mean±SEM). The difference was mainly due to the higher number of distal anastomoses required in group 2. With the exception of patients 9 and 16, the anastomoses were constructed on the right coronary artery; the anatomy of left coronary artery between the two groups was similar.

No patient had electrocardiographic changes and enzyme elevation suggestive of a perioperative myocardial infarction or ischemia or postoperative low-output syndrome requiring inotropic agents.

**Metabolic Studies**

Figures 1 and 2 show mean values of myocardial arteriocoronary sinus difference for GSH (Figure 1A), GSSG (Figure 1B), lactate (Figure 2A), and CPK (Figure 2B) in the two groups. Tables 2 and 3 provide individual arterial and coronary sinus values of GSH and GSSG. As expected, before clamping in both groups there was almost no arteriocoronary sinus difference for GSSG and CPK and a positive difference for lactate. There was a small myocardial arteriovenous difference of GSH, which may be due to the activity of γ-glutamil transeptidase. In both groups, the arterial concentration of GSH remained constant during reperfusion (declamping), whereas the coronary sinus concentration increased above the arterial values and yielded a negative arteriocoronary sinus difference with a peak 1 minute after declamping. However, in group 1, the release of GSH into the coronary sinus had ended 20 minutes after removal of the clamps, whereas in group 2 the arteriocoronary sinus difference for GSH was still negative even at the end of cardiopulmonary bypass. In addition, GSH concentrations in the coronary sinus of the patients of group 2 were always significantly higher than those of patients of group 1 (Table 2).

Table 3 shows that before clamping, as one would expect, the level of GSSG was virtually zero in both arterial and coronary sinus blood. Reperfusion of patients of group 1 resulted in small and transient myocardial release of GSSG into the coronary sinus. On the contrary, in patients of group 2, myocardial

**Figure 1.** Bar graphs showing myocardial arteriocoronary sinus difference (A-V) for plasma-reduced glutathione (GSH) (panel A) and oxidized glutathione (GSSG) (panel B). The data are expressed as mean±SEM of the eight patients comprising group 1 (cross-clamping period <30 minutes) and the 12 patients comprising group 2 (cross-clamping period >30 minutes). Value of p relates to the significance of difference between the two groups.
production and release of GSSG was substantial and sustained; the arteriocoronary sinus difference was continuously negative during the 20 minutes of reperfusion and even after the end of cardiopulmonary bypass. During the early phases of reperfusion the arterial levels of GSSG were also increased. This could be the consequences of minor ischemia of other districts, such as lungs, in addition to the component generated from the myocardium.

In group 1, there was a transient release of lactate and CPK into the coronary sinus immediately after declamping. Five minutes later, the negative arteriocoronary sinus difference for lactate was converted into a positive one, and the myocardial arteriovenous difference for CPK was not different from that obtained before clamping (Figures 2A and 2B). In group 2, the arteriocoronary sinus difference for lactate remained negative during the entire declamping period and returned to positive values after cardiopulmonary bypass.

The data on CPK release in group 2 were also quite different from those of group 1. During declamping, CPK concentration in the coronary sinus was always significantly higher in group 2 than in group 1. Furthermore, the maximum release of CPK in the coronary sinus in group 2 occurred 20 minutes after declamping and continued for as long as 20 minutes after the end of cardiopulmonary bypass.

**Hemodynamic Studies**

Mean hemodynamic parameters for both groups before and after cardiopulmonary bypass are reported in Table 4. Before the operation, hemodynamic variables between the two groups were not significantly different. In patients of group 1, there was a progressive increase of heart rate and cardiac output during the first 4 hours after the operation with a concomitant decrease of pulmonary capillary wedge pressure, right atrial pressure, and systemic vascular resistances. In the following 20 hours, there was no further improvement of hemodynamic parameters, which remained stable.

The patients of group 2 had an ultimate recovery of myocardial function similar to that in group 1; 24
hours after cardiopulmonary bypass, there was no significant difference between the values obtained in the two groups. The rate of recovery of patients of group 2, however, was significantly delayed with respect to that of group 1 and approached similar values only 12 hours after the operation. In particular, during the first 6 hours after cardiopulmonary bypass, the cardiac output and left ventricular stroke work index of group 2 was significantly lower than that of group 1, whereas pulmonary capillary wedge pressure, right atrial pressure, and systemic vascular resistance were significantly higher.

Correlations

Correlations between GSSG release and metabolic and hemodynamic parameters have been made. Because of the limited number of patients, association had to be strong to reach a level of significance. The data obtained immediately after declamping showed large variations, which may be due to difficulties in the accuracy of sampling. Consequently, the values obtained 5 and 20 minutes after declamping have been taken to represent events occurring during early and late reperfusion, respectively. Figure 3 shows the correlation between arteriocoronary sinus difference for GSSG and duration of clamping period. There was a clear difference between the two groups. When the ischemic period was less than 30 minutes, there was no significant correlation. When the ischemic period was longer than 30 minutes, GSSG release into the coronary sinus (negative arteriocoronary sinus difference) was positively correlated with the duration of ischemia.

Figure 4 shows the correlation between arteriocoronary sinus difference for GSSG and cardiac index measured at 2, 4, and 6 hours after the operation. Again, there was a clear difference between the two groups. No significant correlation was present in group 1, and a positive, inverse correlation was found for group 2. This was true for GSSG values obtained either 5 or 20 minutes after declamping. When cardiac index was measured after more than 6 hours from the end of the operation, it was not correlated with the arteriocoronary sinus difference for GSSG.

GSSG release was not significantly correlated with the other metabolic or hemodynamic parameters that have been measured in this study.

Discussion

Previous experimental studies have demonstrated that during severe ischemia there is a considerable reduction of tissue GSH/GSSG ratio.22,39–41 The reduced availability of cellular GSH becomes a rate-limiting factor for detoxification of oxygen metabolites, and the readmission of oxygen with reperfusion results in oxidative damage, evidenced by a further
### Table 3. Absolute Arterial and Coronary Sinus Plasma Values for Oxidized Glutathione

<table>
<thead>
<tr>
<th>Patient</th>
<th>GSSG before clamping (nmol/dl)</th>
<th>GSSG after cross-clamp removal (nmol/dl)</th>
<th>GSSG after cardiopulmonary bypass (nmol/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 min A</td>
<td>10 min A</td>
<td>1 min A</td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

GSSG, oxidized glutathione; A, arterial; CS, coronary sinus; group 1, patients with cross-clamping period of less than 30 minutes; group 2, patients with cross-clamping period of greater than 30 minutes.

### Table 4. Hemodynamic Changes During the 24 Hours After Myocardial Surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Before CPB</th>
<th>After CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.25 hr</td>
<td>2 hr</td>
</tr>
<tr>
<td>Group 1</td>
<td>HR (beats/min)</td>
<td>72±7</td>
</tr>
<tr>
<td></td>
<td>CI (l/min/m²)</td>
<td>2.69±0.24</td>
</tr>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>81±4</td>
</tr>
<tr>
<td></td>
<td>PCWP (mm Hg)</td>
<td>12±1.7</td>
</tr>
<tr>
<td></td>
<td>RAP (mm Hg)</td>
<td>8.6±1</td>
</tr>
<tr>
<td></td>
<td>SVR (dyne·sec·cm⁻¹)</td>
<td>1,275±174</td>
</tr>
<tr>
<td></td>
<td>LVSWI (g/m²)</td>
<td>45.9±3.3</td>
</tr>
<tr>
<td>Group 2</td>
<td>HR (beats/min)</td>
<td>75±6</td>
</tr>
<tr>
<td></td>
<td>CI (l/min/m²)</td>
<td>2.66±0.21</td>
</tr>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>84±5</td>
</tr>
<tr>
<td></td>
<td>PCWP (mm Hg)</td>
<td>9.1±0.9</td>
</tr>
<tr>
<td></td>
<td>RAP (mm Hg)</td>
<td>6.3±1.2</td>
</tr>
<tr>
<td></td>
<td>SVR (dyne·sec·cm⁻¹)</td>
<td>1,483±164</td>
</tr>
<tr>
<td></td>
<td>LVSWI (g/m²)</td>
<td>42.4±6.9</td>
</tr>
</tbody>
</table>

Data are reported as mean±SEM. Measurements were recorded either in operating room (before cardiopulmonary bypass [CPB]) and 0.25 hour after CPB or in intensive care room (all the remaining determinations).

Group 1, eight patients with cross-clamping period less than 30 minutes; group 2, 12 patients with cross-clamping period greater than 30 minutes. 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 compared with group 1.
†<p><0.01 compared with group 1.
decrease of GSH/GSSG ratio with concomitant production of GSSG, which is released in the venous effluent.40,41 These alterations of glutathione status reflect an important cellular oxidative stress and are correlated with the loss of cellular function and integrity.

The results obtained in the present study show that, as in animal models, reperfusion of patients with coronary artery disease results in oxidative stress, depending on the severity of the ischemic period. When clamping was contained within 30 minutes, reperfusion resulted only in a small and transient release of GSSG, which was not correlated with the duration of ischemia. It is likely that, during this relatively short period of ischemia, the combination of cardioplegia with hypothermia maintained structural integrity and the defense mechanisms of the myocytes against oxygen toxicity. The small release of GSSG probably reflects minor cellular damage or short and transient production during the metabolism of early phases of reperfusion. The transient release of GSH and of CPK, as in the absence of intermittent coronary perfusion, probably represent a washout process and not a reperfusion-induced further release of these compounds. In accordance with this explanation, the myocardial arteriovenous

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**Figure 3.** Plots of relation between oxidized glutathione (GSSG) release (negative arteriocoronary sinus difference) after 5 and 20 minutes of declamping and the duration of clamping period. Group 1, eight patients with cross-clamping period less than 30 minutes; group 2, 12 patients with cross-clamping period greater than 30 minutes.

**Figure 4.** Plots of relation between oxidized glutathione (GSSG) release (negative arteriocoronary sinus difference) after 5 and 20 minutes of declamping and cardiac index (C.I.) measured at 2, 4, and 6 hours after cardiopulmonary bypass (C.P.B.). Group 1, eight patients with cross-clamping period less than 30 minutes; group 2, 12 patients with cross-clamping period greater than 30 minutes.
difference for lactate was negative only during the first minutes of reperfusion. Thereafter, it was converted into a positive one. This finding indicated that the readmission of oxygen restored oxidative metabolism, which, in turn, was linked with a prompt recovery of myocardial function.

On the contrary, reperfusion of group 2 led to an important and sustained release of GSSG that was still continuing at the end of cardiopulmonary bypass. These data are similar to the effects of reperfusion after prolonged ischemia in the isolated heart and imply oxidative damage.22,39,41

The presence of high values of GSSG in the coronary effluent for as long as 40 minutes after reperfusion indicates that in these patients the activity of glutathione peroxidase was substantially increased; this increase led to an enhanced tissue content of GSSG, which, in turn, was excreted from the cell in an attempt to keep the intracellular concentration low.

Several factors could account for the more pronounced GSSG release in the patients of group 2. For instance, it could be related to the greater extension of coronary artery disease of these patients. However, with the exception of patients 9 and 16 in group 2, the extra anastomoses were constructed on the right coronary artery, which drains only partially into the coronary sinus. None of the patients required urgent cardiac surgery for evolving myocardial infarction or unstable angina, and any cardiovascular therapy that could affect the measurements was stopped several days before the operation. Therefore, it is unlikely that in these patients preexisting regional ischemia could account for the occurrence of oxidative stress, which, most likely, was dependent on events occurring within the cardiac surgical procedure.

In this regard, the longer pump time of group 2 could be another possible factor accounting for the differences in GSSG release. However, it should be recalled that, since the aerobic pump time in the two groups was identical, the overall prolongation of pump time in group 2 was due exclusively to the longer length of clamping or, in other words, of the induced period of ischemia. This confirms, as suggested from the animal studies, the critical role of severity of the ischemic period on the occurrence of oxidative stress during reperfusion. 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 ischemic period required to complete surgical procedure. The relation between duration of ischemia and release of GSSG in the coronary sinus of patients of group 2 supports the hypothesis that the severity of ischemia is an important determinant of myocardial oxidative damage.

It is not possible to determine from our data whether oxidative stress occurred during ischemia and was only brought to light by reperfusion or whether it was due to reperfusion itself. During heart surgery, myocardial oxygen tension has been shown to fall to very low levels during ischemia and to revert rapidly to normal levels with release of the aortic cross-clamp.42 Often there is a brief period of extremely elevated oxygen tension levels early during reperfusion,43 which could be responsible for oxidative stress, particularly if the preceding period of clamping has been prolonged enough to cause alterations of the myocardial defense mechanisms against oxygen free radicals. The substantial and sustained release of the GSSG for as long as 40 minutes after declamping in group 2 supports the concept of a reperfusion-mediated component of oxidative stress.

In group 2, the arteriovenous difference for lactate was still negative at the end of the declamping period despite the readmission of oxygen and the presumed restoration of oxidative phosphorylation. These results are not new during reperfusion in humans,44 and there is not a simple explanation because tissue measurements of substrates and enzymatic activities are not immediately available in clinical studies. Nevertheless, free radicals directly, or GSSG indirectly, are known to inhibit the activity of pyruvate decarboxylase, the key enzyme of oxidative use of lactate.45

There was an inverse relation between the evidence of oxidative stress after declamping and the recovery of cardiac index in group 2. These findings are consistent with animal studies, which have suggested a causative role for oxygen free radicals in the poor recovery during early phases of reperfusion and a protective role for antioxidants against myocardial "stunning."46,47

The behavior of the right atrial pressure, pulmonary capillary wedge pressure, and left ventricular stroke work index in the patients of group 2 also suggest the presence of myocardial injury, as did the data on CPK release. Although, from our study, one cannot be sure that such injury was due to oxidative stress, the relation between GSSG release and cardiac index in the patients of group 2 seems to indicate a link between the two events.

We believe that data of this study represent an insight to the pathophysiology of reperfusion of the human heart. They suggest that, depending on the severity of the ischemic period, oxidative stress occurs during reperfusion of patients with coronary artery disease who have been subjected to heart surgery. This concept might be of importance with respect to other techniques for restoration of blood flow to the myocardium, such as angioplasty and thrombolysis. The data also provide a rationale for the additional use of agents against oxygen toxicity in the standard cardioplegic solution.

Acknowledgments

We thank Roberta Bonetti and Ornella Del Cielo for secretarial assistance in preparing the manuscript.

KEY WORDS • free radicals • reperfusion • ischemia
Occurrence of oxidative stress during reperfusion of the human heart.
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*Circulation.* 1990;81:201-211
doi: 10.1161/01.CIR.81.1.201

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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