# Myocardial Recovery During Mechanical Circulatory Support After Acute Myocardial Ischemia

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## Abstract

Irreversible myocardial failure due to severe ischemia is a challenging problem in clinical practice. The present study was performed to evaluate the potential benefit of mechanical circulatory support in a bovine model with prolonged, acute myocardial ischemia. Seven calves (74+6 kg) underwent 6 hours of regional ischemia by temporary (6h) ligation of the left circumflex coronary artery. Ventricular assist was started 10 minutes after occlusion of left circumflex coronary artery. Ventricular fibrillation occurred in all animals after a mean interval of 4.0±2.4 hours. Defibrillation was attempted immediately and every hour thereafter. Successful defibrillation was achieved in 6/7 animals after 4.1±2.5 hours of ventricular fibrillation during mechanical circulatory support. Weaning from biventricular assist was attempted after 24 hours and was successful in 5/6 animals. Hence timely mechanical circulatory support in acute, prolonged ischemia with subsequent "irreversible" cardiac failure allows not only maintainence of acceptable hemodynamics for bridging to heart transplantation but also significant myocardial recovery if coronary artery blood flow is restored within 6 hours.

## Introduction

Irreversible myocardial failure due to severe ischemia is a challenging problem in clinical practice. Since the introduction of percutaneous cardiopulmonary support (CPS), even desperately ill patients with sudden ischemic myocardial failure can be candidates for surgical revascularization of the myocardium. As percutaneous cardiopulmonary support cannot be used for prolonged periods if post-cardiotomy cardiac failure occurs, these patients are also potential candidates for mechanical circulatory support with pulsatile devices. In our hands[1], mechanical circulatory support with pulsatile devices for post-cardiotomy myocardial failure showed primary success in 16/20 cases (80%: weaned 14/20, transplanted 2/20). Thirty-day survival was 55% (11/20). Hence, myocardial recovery can be achieved with uni- and/or biventricular mechanical circulatory support in a significant number of cases.

The present study was performed to evaluate the potential benefit of mechanical circulatory support in prolonged, acute myocardial ischemia in a bovine model of regional ischemia and reperfusion.

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## Materials and Methods

### Animals

Seven calves with a mean bodyweight of 74±6 kg were studied. Following standardized premedication, general anesthesia was started with thiopental sodium and after

**Table 1**

| p<0.05=* | | BASELINE | ISCHEMIA 2 min | FIBRILLATION 1 hour | ASSIST 24 hours |
|---|---|---|---|---|---|
| aortic pressure | mmHg | 125±13 | 108±16 | 87±24 | 68±11 |
| Cardiac output | l/min | 4.7±0.5 | * 3.3±0.8 | * 0 | * 3.1±0.9 |
| VAD-flow | l/min | 0 | 0 | 3.9 | 0 |
| WTH ischemic | % | 14±10 | * -7±7 | 0 | * 26±15 |
| | | NS | * | NS | NS |
| WTH control | % | 17±9 | * 28±12 | 0 | * 18±12 |

endotracheal intubation and volume controlled ventilation with a positive end-expiratory pressure of 5 cm $H_2O$, was maintained with halothane and nitrous oxide. The left chest was entered through a left thoracotomy. Before instrumentation, heparin, 300 IU/kg bodyweight, was given intravenously.

## Pumping Systems

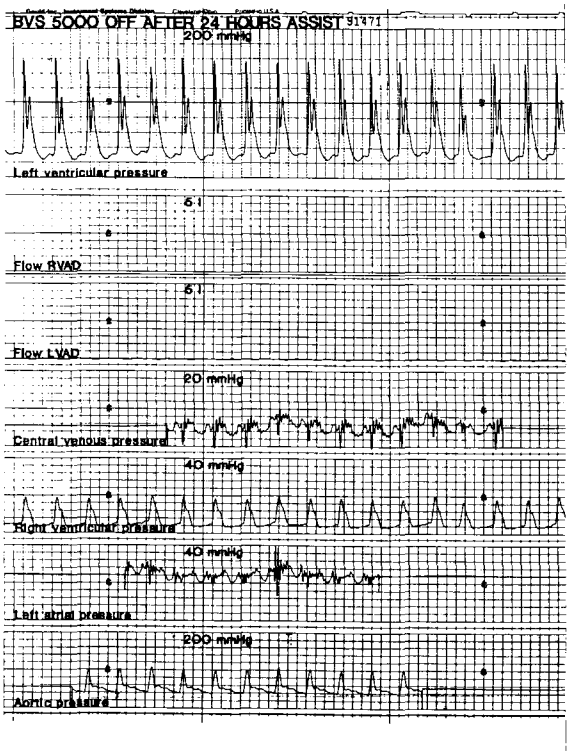
For mechanical circulatory support the ABIOMED BVS 5000[a] ventricular assist device (VAD) was used. As previously reported[2], each VAD contains two chambers: an artificial atrium (inflow bladder) which fills passively, and an air-actuated artificial ventricle (outflow bladder) which provides pulsatile blood return. After full systemic heparinization, right atrium and pulmonary artery as well as left atrium and aorta were cannulated and connected to the respective right and left ventricular assist device.

## Measurements

EKG, right atrial pressure, pulmonary artery pressure, left atrial pressure, left ventricular pressure (standard and microtip pressure transducer[b]), and aortic pressure were recorded continuously. Cardiac output was determined by thermodilution whereas VAD flows were measured by electromagnetic flow meters and recorded continuously. Pairs of ultrasonic crystals were implanted in the region perfused by the left anterior descending coronary artery (control region) and in the region perfused by the circumflex coronary artery for measuring left ventricular wall thickness[3,4]. When instrumentation was completed an interval of 10 minutes was allowed for stabilization of hemodynamic variables. After recording of baseline values, each animal underwent 6 hours of regional ischemia by temporary (6 hours) ligation of the left circumflex coronary artery. Hemodynamic variables were recorded after 2 minutes of ischemia. Mechanical circulatory support was started after a mean interval of 10 minutes following occlusion of left circumflex coronary artery. If ventricular fibrillation occurred, electrical and pharmacological defibrillation were attempted immediately and every hour thereafter. Weaning of the biventricular assist device was attempted after 24 hours of mechanical circulatory support. Positive inotropic support with dopamine (average dose: 10 ug/kg/min) was used during this procedure.

a ABIOMED Inc., Danvers, Mass.
b Millar Instruments Inc., Houston, Texas

**Figure 1**




Hemodynamic variables recorded after weaning from biventricular assist: significant recovery of myocardial function after severe ischemia injury.

## *Analyses*

Left ventricular wall thickness tracings were digitized manually. End-diastolic wall thickness was defined as the wall thickness at the time of end-diastolic pressure and end-systolic wall thickness at the time of end-systolic pressure. Systolic wall thickening was calculated as end-systolic minus end-diastolic wall thickness divided by end-systolic wall thickness multiplied by 100. A mean and standard deviation were derived for each parameter. Paired and unpaired Students t-tests were used where applicable to determine statistical significance of data ($P<0.05$).

## *Results*

Ventricular fibrillation occurred in all animals (7/7) after a mean interval of 4.0±2.4 (mean±standard error) hours following onset of ischemia. Defibrillation was attempted immediately and every hour thereafter. Success-

ful defibrillation was achieved in 6/7 animals after a mean interval of 4.1+2.5 (mean+standard error) hours of ventricular fibrillation during mechanical circulatory support. Weaning from mechanical circulatory support was attempted after 24 hours (18 hours of reperfusion) and was successful in 5/6 animals whereas support was terminated in the animal that could not be defibrillated after 24 hours. A recorder tracing after weaning from right and left ventricular assist device is shown in Figure 1.

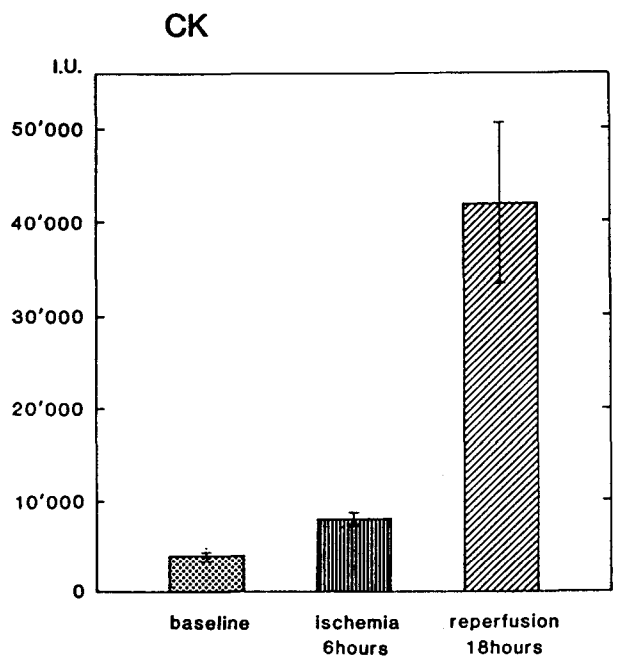
Creatinekinase (CK) levels moved from 408±138 I.U. before ischemia to 7994±2761 I.U. ($P<0.05$) after 6 hours of ischemia and reached 40297±9615 I.U. after 18 hours of reperfusion (Figure 2). Lactatedehydrogenase (LDH) moved from 1751±290 I.U. before ischemia to 4284±2230 I.U. ($P<0.05$) after 6 hours of ischemia and reached 10484±2188 after 18 hours of reperfusion (Figure 3). The main measured hemodynamic variables before, after 2 minutes of ischemia, after 1 hour of fibrillation, as well as after weaning from biventricular support (24 hours) are summarized in Table 1. After 2 minutes of ischemia, cardiac output dropped significantly from 4.7±0.5 l/min to 3.3±0.8 l/min. During ventricular fibrillation, left and right ventricular function was completely taken over by the respective assist devices (mean flow 3.9 l/min). After defibrillation and 18 hours of reperfusion, cardiac output returned in the weanable animals to 3.1±0.9 l/min.

Sonomicrometric assessment of systolic regional left ventricular wall thickening (WTH) is illustrated in Figure 4. Negative thickening of the ischemic left ventricular wall can be easily recognized after 2 minutes of ischemia whereas there is increased thickening for the control wall at this moment. After 18 hours of reperfusion, weaning from mechanical circulatory support, and dopaminergic stimulation, ischemic wall thickening returns to control values.

## Discussion

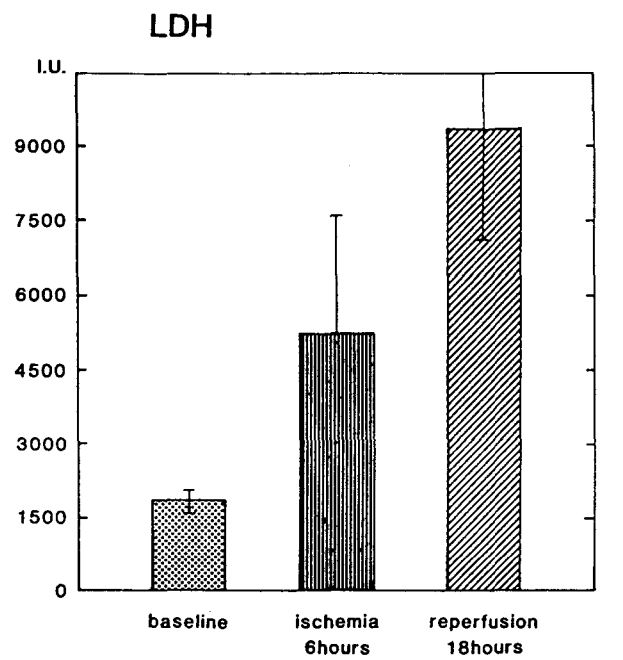
Myocardial recovery in acute, prolonged ischemia with subsequent "irreversible" cardiac failure can be achieved in a significant number of animals if acceptable hemodynamics are maintained and coronary artery blood flow is restored within 6 hours. Temporary coronary artery ligation was selected for creation of ischemia in the present study. There can be no doubt, that significant ischemia was provoked as CK-levels reached almost 20 fold baseline values after 6 hours of ischemia and 100 fold after 18 hours of reperfusion (Figure 2). Somewhat less dramatic but still 6 fold values were observed for LDH-levels after 18 hours of reperfusion (Figure 3). The severity of the ischemia provoked was further documented by the decrease in cardiac output (-30%). The sonomicrometric wall motion studies showed after 2 minutes of ischemia a negative wall thickening for the ischemic wall which indicates the bulging of this left ventricular wall region (Figure 4). On the other hand the control wall showed a significant increase in wall thickening representing the compensating activity of this intact left ventricular wall region. The fact that ventricular fibrillation occurred in all animals for a mean

**Figure 2**




Plasma CK-levels before, after 6 hours of ischemia and after 18 hours of reperfusion: severe myocardial injury.

**Figure 3**




Plasma LDH levels before, after 6 hours of ischemia and after 18 hours of reperfusion: sever myocardial injury.

duration of 4.0±2.4 hours clearly demonstrates the severity of ischemic myocardial injury. There can be no doubt, that the natural history leads inevitably to death after prolonged ventricular fibrillation. In the present set-up, ventricular fibrillation lasted for several hours despite the fact that pharmacologic and electrical defibrillation were attempted repeatedly. Hence, in the absence of mechanical circulatory support, myocardial failure would have been irreversible. Interestingly, ventricular fibrillation occurred not only during ischemia but also during reperfusion. This latter finding should be remembered by the invasive cardiologist as well as the cardiovascular surgeon planning revascularization procedures in the setting of acute myocardial infarction. Adequate mechanical circulatory support over 24 hours allowed sufficient myocardial recovery in a significant number of animals enabling weaning from the biventricular assist devices. In the presence of significant myocardial recovery as documented by the wall thickening studies (Table 1, Figure 4), mechanical circulatory support with removable assist devices[5] appears to be more appropriate than implantation of total artificial hearts requiring finally transplantation. Hence, we conclude that timely mechanical circulatory support in acute ischemia with subsequent "irreversible" heart failure allows not only the maintenance of acceptable hemodynamics for bridging to heart transplantation but also substantial myocardial recovery if coronary artery blood flow is restored within 6 hours.

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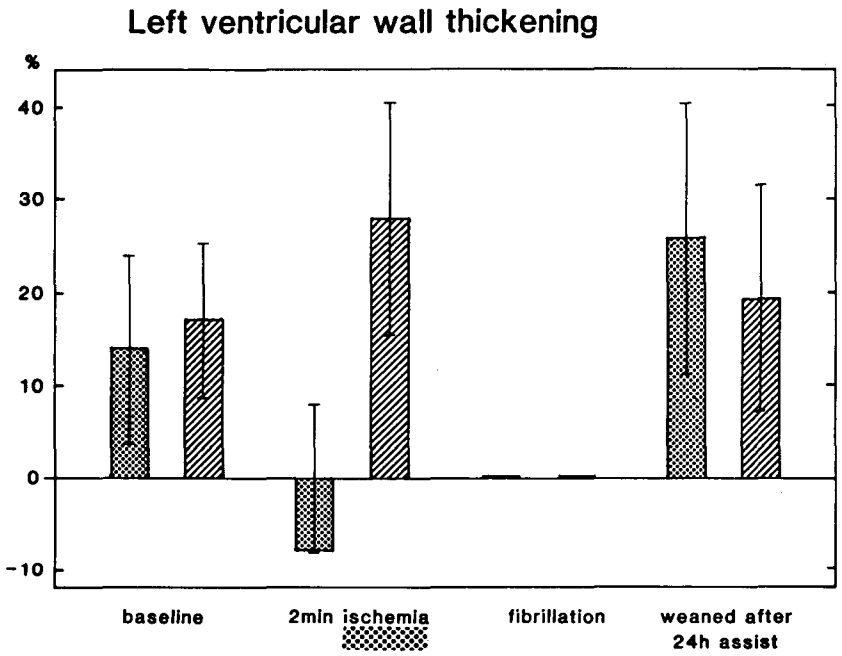
**Figure 4**




Myocardial thickening of ischemic and control left ventricular wall before, after 2 minutes of ischemia, after 1 hour of ventricular fibrillation and after weaning from biventricular assist (positive inotropic support with dopamine).