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**A METABOLIC PROTECTIVE STRATEGY COULD IMPROVE LONG-TERM
SURVIVAL IN PATIENTS WITH LV- DYSFUNCTION UNDERGOING CABG**

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ABSTRACT

Objective Adverse outcome after CABG is closely related to postoperative heart failure precipitated by ischemia and myocardial infarction. Restrictive use of inotropes is therefore desirable. Patients with preoperative left ventricular dysfunction are a high-risk group in this respect. To reduce myocardial oxygen expenditure we evolved a metabolic strategy for perioperative care.

Design Observational study on 104 consecutive patients with severe left ventricular dysfunction undergoing CABG. The metabolic strategy implied physiological measures to minimize myocardial oxygen expenditure including restrictive use of inotropes and specific measures such as extended CPB and metabolic support to facilitate myocardial recovery. Hemodynamic state was primarily assessed by mixed venous oxygen saturation (SvO₂). Follow-up averaged 9.7±1.4 years.

Results LVEF was 0.30 ± 0.05 (range 0.20-0.37) and 3.5 ± 1.3 vessels were bypassed. Inotropes were used in 6.7% for weaning from CPB. Increase of s-creatinine by ≥ 50% compared to preoperative values was observed in 2.9%. Logistic EuroSCORE was 8.3% whereas observed 30-day mortality was 1.0%. Crude 5-year survival was 89.4%.

Conclusions The metabolic strategy allowed restrictive use of inotropes and was associated with encouraging long-term survival. Renal function was well preserved suggesting that SvO₂ served as an adequate marker of circulation. Randomized trials with metabolic support are warranted.

Key words: left ventricular dysfunction, coronary artery bypass surgery, glutamate, glucose-insulin-potassium, inotropic agents

INTRODUCTION

Postoperative heart failure is a major cause of in-hospital mortality after coronary artery bypass grafting (CABG) and frequently precipitated by myocardial ischemia and infarction(1-3). Treatment of postoperative heart failure presents a therapeutic dilemma as inotropic agents not only aggravate ischemia and increase the size of evolving myocardial infarction, but also stimulate apoptotic processes that may have adverse long-term consequences(4, 5). Thus, restrictive use of inotropes would be particularly desirable in patients with limited cardiac reserve. On the other hand, patients with preoperatively compromised left ventricular function are particularly prone to require treatment for postoperative cardiac failure(6, 7). Accordingly, postoperative morbidity and mortality is more frequently encountered in patients with preoperatively compromised left ventricular function(8-31). Furthermore, long-term survival is markedly impaired(8, 9, 12, 14-17, 19, 26, 27, 29-39).

In an effort to reduce postoperative work-load on the myocardium and facilitate myocardial recovery we evolved a metabolic strategy for perioperative care and have previously reported encouraging results in treatment of severe heart failure at weaning from CPB(40). Here we report our short-term and long-term clinical experience in patients with preoperatively compromised left ventricular function undergoing CABG. An over-view of the literature with regard to short-term and long-term results is also given. Based on our results and the over-view we will provide an argument for the principles of our strategy and the need for adequately powered randomized clinical trials to determine the role of metabolic interventions in cardiac surgery.

METHODS

Patients

During a five-year period (1991-1995) when the metabolic strategy was introduced 775 consecutive patients operated for ischemic heart disease by two surgeons (RS, IV) were registered in a database. Left ventricular function was assessed by angiography or echocardiography. 104 patients presented with severely compromised left ventricular function (LVEF 0.20–0.37) before surgery. The records of the patients were investigated in detail according to a protocol and data retrieved and stored in a database. Data on late mortality were retrieved from the Swedish Civil Registry. Follow-up was 100% complete and averaged 9.7 ± 1.4 years. Demographic and intraoperative data are presented in table 2.

Clinical management

On the day of surgery all patients were given their individual doses of betablockers and calcium-antagonists. After premedication with morphine hydrochloride and scopolamine, anesthesia was induced with thiopentone and fentanyl, and maintained with fentanyl and isoflurane. Pancuronium bromide was used for neuromuscular blockade. Cardiopulmonary bypass (CPB) was conducted with a membrane oxygenator and a roller pump generating non-pulsatile flow. Ringer's acetate and mannitol were used for priming the extracorporeal circuit. Moderate hemodilution (hematocrit 20 - 25%) and mild to moderate hypothermia (32-35 °C) were employed. Antegrade or combined antegrade and retrograde delivery of St. Thomas' cold crystalloid cardioplegic solution was used for myocardial protection. CPB was prolonged until recovery of left ventricular function was evident. Heparin was neutralized with protamine chloride. In the postoperative period rewarming was facilitated by radiant heat provided by thermal ceiling. Shed mediastinal blood was routinely retransfused after surgery. Ringer's acetate was used for volume substitution.

Definitions

Use of inotropes was defined as a continuous infusion of beta-receptor stimulants or a bolus or continuous infusion of phosphodiesterase inhibitors regardless of dose. Dosage presented was calculated as the average dose per hour during the first 6 hours from weaning or from 6 – 24 hours after weaning if the dose had been increased.

Complications presented refer to in-hospital events occurring at our institution. Intraoperative myocardial infarction was diagnosed by biochemical markers of myocardial injury or by findings at autopsy as previously reported(2, 41).

Postoperative renal failure is presented according to STS data base definition and furthermore the proportion of patients having an increase of s-creatinine of 50% or more compared to preoperative value is given(42).

Neurological injury in this study included the following cerebral complications: 1) stroke 2) depression of consciousness or confusion if associated with signs of cerebral injury on CT-scan or focal neurological deficit 3) transient ischemic attacks with focal neurological deficit. The majority of patients with suspected neurological injury were examined by a neurologist and by CT-scan. Cognitive dysfunction was not assessed.

Monitoring

Arterial, central venous and pulmonary artery pressures were monitored in all patients as well as ECG with ST-segment analysis. Pulmonary artery pressure and intermittent blood sampling for analysis of mixed venous oxygen saturation (SvO₂) was retrieved by either a Swan-Ganz catheter or an epidural catheter introduced during surgery through the right ventricular

outflow tract into the pulmonary artery. Transesophageal echocardiography was employed in the majority of patients. SvO₂ and urinary output served as the main guidelines for hemodynamic therapy.

Metabolic strategy

A variety of methods to protect the heart are available and complex procedures can be safely performed. However, efforts have mainly focused on myocardial preservation during the period of aortic cross clamping. Preoperative and postoperative ischemia remain major risk factors for perioperative myocardial infarction(3, 43). The metabolic strategy was evolved with the aim to reduce the consequences of myocardial ischemia during all phases of surgery and to facilitate metabolic and functional myocardial recovery after surgery(40, 44).

The metabolic strategy implied adherence to physiological principles to minimize myocardial and systemic oxygen expenditure and specific measures such as extended CPB and metabolic support to facilitate myocardial recovery in patients with inadequate hemodynamic state. Volume work by the heart rather than pressure work was promoted by after-load reduction when feasible. The adequacy of hemodynamic state was primarily assessed by measurement of SvO₂ and urinary output(45). Minimum accepted SvO₂ in relation to systolic blood pressure is given in table 1. A minimum urinary output of 1 ml/kg body weight and hour was considered desirable. Patients with severe heart failure were sedated and muscle relaxed during the first postoperative hours to reduce systemic metabolic demands. Low cardiac output was accepted if SvO₂ and urinary output were acceptable.

Inotropic drugs were used only if SvO₂ or urinary output suggested that cardiac output was inadequate despite correction of volume and treatment of other causes (table 1). A mechanical

assist device was preferred in favor of increasing the dose of inotropic drugs such as dobutamine above 5μ /kg/min.

Metabolic support

During the time frame of the study availability of glutamate solutions was restricted due to limited capacity of the local pharmacy to produce solutions. Hence, prophylactic glutamate infusion was reserved for patients with signs of severe myocardial ischemia or heart failure in the operating room before surgery. In these patients glutamate was infused intravenously preoperatively and after release of cross clamp to prevent heart failure at weaning from CPB. Intravenous glutamate was also instituted as treatment in patients with failure to wean from CPB at the first attempt.

High dose glucose-insulin-potassium (GIK) was added to intravenous glutamate infusion in patients with failure to wean from CPB at the first attempt. Details of treatment with intravenous glutamate and high-dose GIK have been reported previously(40, 46). Safety issues with regard to the metabolic treatments have been addressed(46, 47).

Statistics

The results are presented as percentages or mean \pm standard deviation. Long-term survival is given as crude 5-year survival and cumulative 10-year survival according to Kaplan-Meier analysis. Fisher's exact test was used for comparison of dichotomous variables and Mann-Whitney U test was used for comparison of continuous variables. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed with Statistica 7. 1, StatSoft Inc.,Tulsa, OK.

RESULTS

Demographics

The mean age was 65 ± 9 years, 20.2% of the patients had diabetes mellitus, 29.8% unstable angina. The mean left ventricular ejection fraction was 0.30 ± 0.05 (range 0.20-0.37). An average of 3.5 ± 1.3 vessels were bypassed and 6.7% of the patients also had a concomitant valve procedure. One third of the procedures were performed urgently or emergently.

Demographic and intraoperative data are given in table 2.

Outcome

Postoperative data are given in table 3. SvO₂ on arrival to ICU averaged 65.8 ± 7.4 %. Mean stay in the ICU was 1.9 ± 2.3 days. The incidence of postoperative renal failure according to STS definition was 1.0% and an increase of s-creatinine by 50% or more compared to preoperative values was found in 2.9%. One patient required dialysis.

Postoperatively 10.6% of the patients had signs of myocardial infarction. Of the patients with infarcts 18% were operated on ongoing infarction and 36% had chest pain or profound ST-changes on the ECG immediately before surgery despite 46% being on intravenous nitrates.

30-day mortality overall was 1.0% compared to expected mortality of 8.3% (95% confidence interval 5.8 – 10.8%) according to logistic EuroSCORE. Corresponding figures for the subgroups with LVEF ≤ 0.35 were 1.1% v 8.9% and for the subgroup with LVEF ≤ 0.30 1.5% v 10.9%.

Crude five-year survival overall was 89.4% and corresponding figures were 89.0% and 84.6% respectively for the subgroups with LVEF ≤ 0.35 and LVEF ≤ 0.30 .

Ten-year survival according to Kaplan-Meier is presented in figure 1.

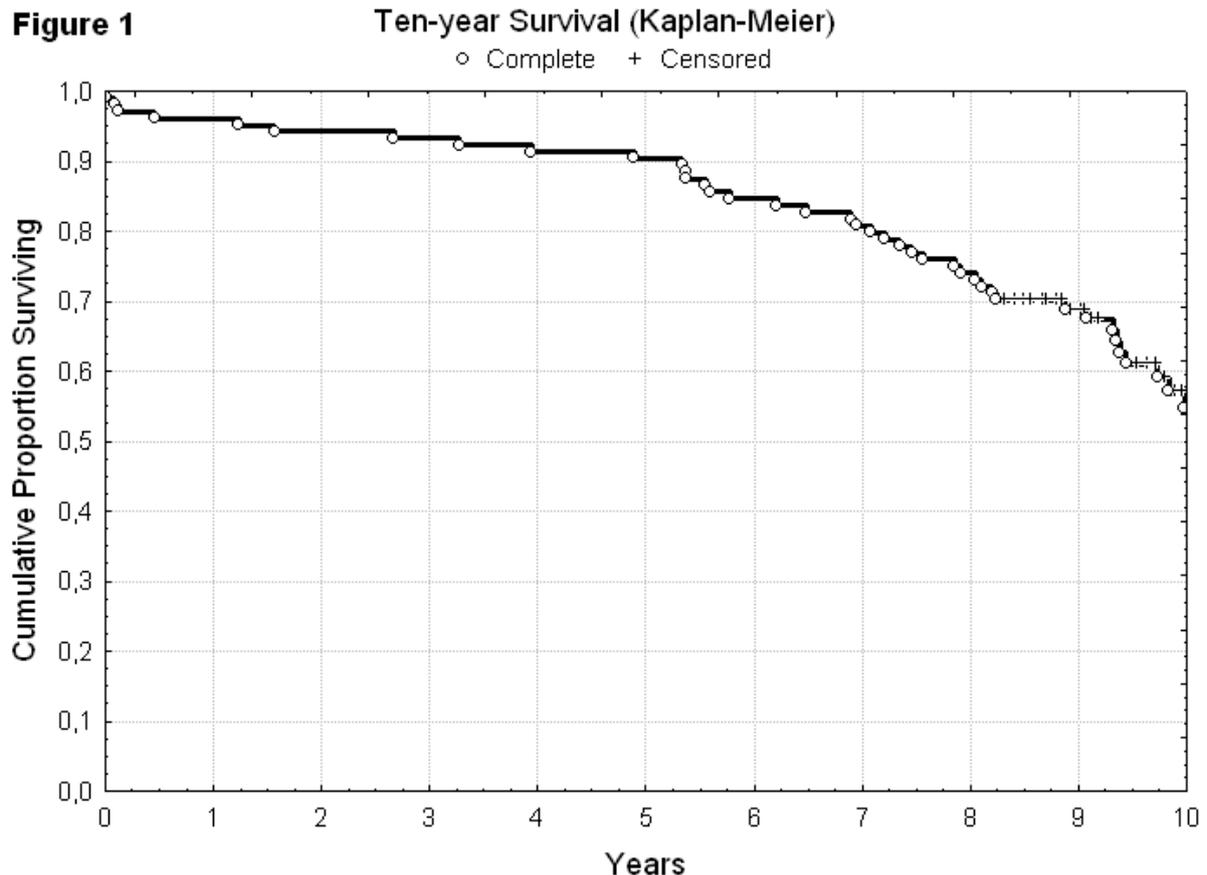


Figure 1. Cumulative 10-year survival (Kaplan-Meier) after CABG in patients with preoperative left ventricular ejection fraction < 0.40 managed according to the metabolic strategy.

Metabolic support

Glutamate was initiated in 24.0% of the patients to prevent heart failure and in 15.4% for treatment of heart failure at weaning from CPB. 67% of the patients treated with glutamate also received high-dose GIK. Patients treated with glutamate had an average LVEF of 0.27 ± 0.05 . Logistic EuroSCORE was 15.1% whereas observed 30-day mortality was 2.4%. Five-year survival in patients treated with glutamate was 82.9%.

High-dose GIK was used in 27.9% of the cases for treatment of heart failure at weaning from CPB. No side effects of the infusions were observed. 93% of these patients also received glutamate infusion. Patients treated with high-dose GIK had an average LVEF of 0.26 ± 0.05 . Logistic EuroSCORE was 17.4% whereas observed 30-day mortality was 3.4%. Five-year survival in patients treated with high-dose GIK was 82.8%.

Use of intravenous glutamate increased from 28.6% during the first half to 43.4% during the second half of the period studied ($p=0.18$) and corresponding figures for high-dose GIK was 10.7% v 34.7% ($p=0.025$). Overall intravenous metabolic support was given to 41.3% of the patients (table 3).

Pharmacological circulatory support

Use of inotropes for weaning decreased from 17.9% during the first half to 2.6% during the second half of the period studied ($p=0.015$). Patients treated with inotropes for weaning from CPB had an average LVEF of 0.30 ± 0.04 . Logistic EuroSCORE was 19.0% whereas observed 30-day mortality was 14.3%. Five-year survival in patients treated with inotropes was 53.9%.

In the ICU low dose inotropes or phosphodiesterase inhibitors were used to enhance urinary output in a total of 37.3% of the patients. The average doses when used were for dobutamine $2.2 \pm 1.1 \mu\text{g/kg}$ and min ($n=30$), dopamine $1.6 \pm 1.1 \mu\text{g/kg}$ and min ($n=6$) and for epinephrine $28 \pm 27 \text{ ng/kg}$ and min ($n=5$).

Overall nitroprusside was used in 53.8% of the patients and vasoconstrictors in 21.4%. Of the patients that received high-dose GIK 51.7% required angiotensin or norepinephrine to counteract vasodilatation.

Mechanical circulatory support

Extended reperfusion time on CPB to allow the heart to recover was a key issue in the strategy. In patients that could be weaned at the first attempt CPB time and aortic cross clamp time were 81 ± 27 minutes and 40 ± 19 minutes respectively. In patients with difficulty to wean at the first attempt (n=32) CPB time averaged 127 ± 62 minutes while cross clamp time was 45 ± 28 minutes. 94% of the patients with initial weaning difficulties were treated with metabolic support and 78% could be weaned from CPB without inotropes.

Mechanical circulatory support with intra-aortic balloon pump or Hemopump[®] was used in 1.9% of the cases (table 3). Of the patients with initial weaning difficulties 6.3% required mechanical circulatory support with intraaortic balloon pump or hemopump.

Outcome related to mixed venous oxygen saturation

Mixed venous oxygen saturation was obtained on arrival to ICU in 101 patients. The majority (n=94) had $SvO_2 \geq 55\%$ and in these patients postoperative morbidity and mortality was negligible compared with those having $SvO_2 < 55\%$ (table 4).

In patients (n=68) who arrived to ICU with $SvO_2 \geq 55\%$ and without history of weaning problems no one developed renal failure, 30-day mortality was zero and five-year survival was 95.6%.

COMMENT

The metabolic strategy was associated with lower 30-day mortality (1.0%) than previously reported in patients with severe LV-dysfunction undergoing CABG (table 5). It was also substantially lower than the expected risk adjusted mortality of 8.3% according to logistic EuroSCORE. Long-term survival was an even more encouraging with a crude 5-year survival of 89.4%.

It is generally accepted that case selection is vital for outcome in patients with poor LV-function undergoing CABG and reviewing the literature one should first appreciate the inherent publication bias present both from authors and journals. Poor or even average results are less likely to be published. Typically the published papers differ from the STS data base from the corresponding time reporting a substantially higher mortality of 7.6% in patients with $EF \leq 0.35$ (48). Furthermore, the majority of studies are highly selected case series excluding patients that required valve procedures, redo-procedures, patients with cardiogenic shock and occasionally only including those that had viable myocardium detected preoperatively or even excluding those that required IABP, had recent preoperative events or died early after surgery. Follow-up is not always complete and the proportion of patients with poor LV-function in relation to total cohort is strikingly high in several series (table 5). The results of the metabolic strategy compare favorably with the literature particularly considering these circumstances. It is also generally accepted that most centers report better than expected mortalities according to EuroSCORE, however, rarely a fraction below 0.2.

The major limitation of this study is that it, like most studies on this high risk group, is retrospective and observational. However, it is one of few studies to address this category of

patients from a perspective of perioperative management and it rises important questions that deserve to be addressed in future studies.

Minimizing myocardial metabolic demands – avoiding inotropes

Postoperative heart failure after CABG is frequently precipitated by myocardial ischemia and infarction(2, 3). As inotropic agents cause an excessive increase in myocardial oxygen expenditure in relation to the hemodynamic effect achieved it is not surprising that they aggravate ischemia and increase the size of evolving myocardial infarction(4, 49). A high incidence of myocardial ischemia and myocardial infarction has been reported in humans when inotropes are used to terminate cardiopulmonary bypass(50, 51). Furthermore, it has recently been shown that also the rate of apoptosis is markedly increased by adrenergic stimulation, which could affect long-term outcome adversely(5, 52).

Alternative measures that can enhance myocardial recovery and function without putting further strain on the heart are particularly desirable in patients with limited myocardial reserve. Our experience demonstrates that traditional pharmacological inotropic support for weaning from cardiopulmonary bypass can be replaced by alternative measures even in patients with severely compromised left ventricular function without jeopardizing renal function. As the confidence in the metabolic strategy grew the use of inotropes for weaning from CPB during the latter half of the studied period was reduced to 2.6%. The average doses of inotropes when used were low (table 3), usually in the dose interval known to enhance renal perfusion.

The use of inotropes is surprisingly poorly documented in available studies on this high-risk group (table 5). Notably publications that report particular strategies to reduce myocardial

work load or other measures associated with low inotrope use report excellent short-term outcome(33, 37, 53, 54) and more favorable long-term outcome(53). By employing non-cardioplegic methods Antunes et al reported use of inotropes in 5.5% of patients without severe LV-dysfunction undergoing CABG. In patients with severe LV-dysfunction 11% required them more than 24 hours and this was associated with an impressive 86% five-year survival, albeit, 5% were lost to follow-up(53).

The only study that clearly documented 100% prophylactic use of phosphodiesterase inhibitors in this subset of patients was associated with good operative mortality of 1.7% in patients with LVEF \leq 0.35 but a less encouraging 55.7% five-year survival(34). The reason for poor long-term outcome was not clear and is probably complex and multi-factorial. It is, however, evident from the debate on aprotinin that it may be difficult to detect a negative effect of a drug on survival on an individual physician basis and even on an institutional basis(55). Therefore, the words of Yusuf et al that it is essential to exclude a negative effect on long-term survival of beta-stimulators and phosphodiesteraseinhibitors before they are incorporated into routine clinical practice deserve to be echoed(56).

Metabolic support

The rationale for intravenous glutamate infusion and high-dose glucose-insulin-potassium (GIK) has been described previously (40). Intravenous glutamate infusion was used both to prevent postoperative heart failure and for treatment of postoperative heart failure. Because of the potent vasodilatory effects and the need for careful monitoring of blood glucose and electrolytes high-dose GIK was reserved for treatment of postoperative heart failure (46).

The present data do not permit any inference regarding functional or metabolic recovery. However, we and other have previously shown that both glucose-insulin-potassium (GIK) and glutamate can enhance the metabolic and functional recovery of the postischemic heart(40, 49, 57-63). In contrast to inotropes the improvement in hemodynamic state is achieved without undue increase in myocardial oxygen demand. Also, insulin is a powerful anti-apoptotic agent in contrast to adrenergic drug(64).

Both glutamate and high-dose GIK treatment was associated with substantially lower mortality than predicted by EuroSCORE. Although EuroSCORE underestimates mortality in general this may not be the fact in high risk patients as was illustrated by a recent conference report on levosimendan given prophylactically in high-risk patients and for treatment of postoperative heart failure(65).

Unloading of the heart - Extended CPB

Premature use of inotropic drugs for weaning from cardiopulmonary bypass has been shown to impede metabolic and functional recovery of the heart in animals(66).

Some degree of extended CPB was employed in virtually all patients and CPB was substantially extended in patients with weaning difficulty with an average reperfusion time of approximately 80 minutes to permit myocardial recovery during metabolic support. The potential adverse effects of CPB are well known and short perfusion times and even avoidance of CPB are advocated by many surgeons. However, our results suggest that under certain circumstances the benefits of unloading the heart may outweigh the drawbacks of CPB. These results are in agreement with Royster et al who found that long pump times were associated with lower need for inotropes after coronary surgery on patients with LVEF \leq 0.45(6).

We acknowledge that liberal use of IABP may be a useful strategy to preserve myocardium in critically ill patients. Dietl et al reported a substantially lower operative mortality compared to historic controls when liberal use of preoperative IABP was adopted in patients with severe LV-dysfunction(28). Although we preferred an IABP in favor of increasing the dose of inotropic drugs such as dobutamine above 5μ /kg/min the need for IABP was low with the metabolic strategy.

Pharmacological after-load reduction played an essential role in the metabolic strategy which is illustrated by the frequent use of nitroprusside and furthermore, high-dose GIK provides a powerful and protracted vasodilation. Inodilators were used sparsely because of a reluctance to combine these drugs with high-dose GIK.

Monitoring

It is essential that hemodynamic variables monitored correlate with clinical outcome. The treatment targets for cardiac output have not been scientifically validated but it appears that many centers aim for a cardiac index exceeding 2.3 or 2.5 L/min(50). In our opinion this will lead to overuse of inotropes as we have previously found that anesthetized low risk patients undergoing CABG with uneventful postoperative course had an average cardiac index of 2.1 L/min with SvO₂ exceeding 70% and excellent recovery of myocardial metabolism(67). In contrast, we have reported that if patients treated according to the metabolic strategy arrived in ICU without inotropes and SvO₂ exceeding 55% the risk of subsequent circulatory problems requiring ICU stay > 2 days because of cardiorespiratory morbidity was 1.1% (45). The results of the present study demonstrate that these findings are valid also for patients with preoperatively compromised LV-function. However, we emphasize that SvO₂ is evaluated in

conjunction with other hemodynamic data and hemodynamic targets tailored after the individual patients (table 1).

Later in the postoperative course it is conceivable that adrenergic stimulation is less detrimental as the myocardium has been provided time to recover from the ischemic insult sustained during surgery. Hence, inotropes were used in low doses in the ICU to promote urinary output in just over one third of the patients overall and two thirds of those that presented with weaning problems.

It can be argued that a strategy that accepts low cardiac outputs could jeopardize perfusion of vital organs. Renal function is a sensitive marker of the adequacy of hemodynamic treatment. This report and previous experience shows that patients with compromised ventricular function and even overt postoperative heart failure can be treated with a low incidence of renal complications(40). In this study an increase of s-creatinine by 50% or more compared to preoperative values was found in 2.9 % of the cases, which is substantially lower than the 16% overall incidence (same definition) after CABG surgery reported from a comparable Scandinavian Center(42). In the latter study multivariable analysis identified the use of adrenergic drugs as an important determinant for development of postoperative renal failure(42).

If adrenergic drugs are used in high doses, vasoconstrictive properties will be more pronounced and renal perfusion may be jeopardized. In contrast, there is evidence, albeit limited, that GIK and amino acid infusion may enhance renal perfusion(68). Also, potential delay of recovery at cellular level or aggravation of evolving myocardial infarction by inotropic stimulation could lead to more severe and prolonged states of low output syndrome.

The metabolic strategy comprises a multimodal approach and although it is difficult to discern the relative importance of each issue from the present study all major aspects have been addressed separately by our group and others. To fully elucidate the clinical role of metabolic support adequately powered randomized trials are necessary and desirable. On the other hand, from other areas of surgical research it has been argued that it may be difficult to improve clinical outcome with single measures and that a multimodal approach might be necessary to achieve such aims(69).

To conclude our initial five-year experience with the metabolic strategy in patients with preoperatively compromised left ventricular function was associated with encouraging results. The metabolic strategy allowed restrictive use of inotropes and was associated with short-term and long-term survival that compares favorably with the literature and that was substantially better than risk-adjusted expected mortality in this high-risk cohort. Renal function was well preserved suggesting that mixed venous oxygen saturation and urinary output served as adequate markers of hemodynamic state. Randomized trials with glutamate and high-dose GIK are warranted to elucidate their role in the treatment of high risk patients undergoing surgery for ischemic heart disease.

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Table 1. Minimum accepted SvO₂ in relation to systolic arterial pressure (SAP) and other hemodynamic variables. The right column indicates acceptable and desired SAP during various circumstances. PHF = postoperative heart failure. Desired *atrial filling pressures guided by pre- and postoperative evaluation with echocardiography. Both hypovolemia and over filling avoided and the Starling curve, thus, not employed to maximize cardiac output.

SvO₂	SAP mmHg	Atrial pressures*	Urinary output	Comment
> 50%	>130	Hypovolemia and over filling avoided	>1 ml / kg BW	High SAP accepted and desired in patients with critical arterial stenoses
> 55%	111-130	Hypovolemia and over filling avoided	>1 ml / kg BW	Normally desired postoperative SAP
> 60%	91-110	Hypovolemia and over filling avoided	>1 ml / kg BW	Acceptable postoperative SAP Desired in patients with PHF
> 65%	71-90	Hypovolemia and over filling avoided	>1 ml / kg BW	Low SAP accepted first minutes after weaning from CPB
> 70%	60-70	Hypovolemia and over filling avoided	>1 ml / kg BW	Low SAP accepted first minutes after weaning from CPB

Table 2. Preoperative and intraoperative data given as percentages and numbers of total within brackets or mean \pm standard deviation. AMI = acute myocardial infarction. LVEF = left ventricular ejection fraction. COPD = chronic obstructive pulmonary disease. NYHA = New York Heart Association. Urgent procedure = urgent surgery required but scheduled within a few days. Emergency procedure = surgery within 24 hours. CI = confidence interval. LITA = left internal thoracic artery.

Preoperative data	
Age (years)	65 \pm 9
Female gender	19.2% (20/104)
Weight (kg)	80 \pm 13
Length (cm)	172 \pm 7
Diabetes	20.2% (21/104)
Hypertension	31.7% (33/104)
Peripheral artery disease	17.5% (18/103)
COPD	7.9% (8/101)
s-Creatinine (μ mol/L)	106 \pm 21
Atrial fibrillation	6.7% (7/104)
Left Main Stenosis \geq 50%	22.1% (23/104)
Unstable angina	29.8% (31/104)
Intravenous nitrates	20.2% (21/104)
AMI within 4 weeks	28.8% (30/104)
Cardiogenic shock	1.9% (2/104)
NYHA class III or IV	89.4% (93/104)
LVEF	0.30 \pm 0.05
Logistic EuroSCORE	8.3 (95% CI 5.8-10.8)
Intraoperative data	
Urgent procedure	27.9% (29/104)
Emergency procedure	4.8% (5/104)
Re-do procedure	1.9% (2/104)
CABG+valve procedure	6.7% (7/104)
Number of bypassed vessels	3.5 \pm 1.3
Use of LITA	94.2% (98/104)
Cross clamp time (minutes)	41 \pm 22
CPB time (minutes)	95 \pm 46

Table 3. Hemodynamic treatment and postoperative data given as percentages and numbers of total within brackets or mean \pm standard deviation. Mechanical circulatory support = use of intra-aortic balloon pump or Hemopump[®]. GIK = glucose - insulin - potassium. CPB = cardiopulmonary bypass. ICU = intensive care unit. SvO₂ = mixed venous oxygen saturation. LVEF = left ventricular ejection fraction.

Hemodynamic treatment	
Intravenous glutamate	39.4% (40/104)
GIK	27.9% (29/104)
Inotropes for weaning from CPB	6.7% (7/104)
Mechanical circulatory support	1.9% (2/104)
Nitroprusside	53.8% (54/104)
Angiotensin / norepinephrine	21.2% (22/104)
Diuretic dose of inotropes in ICU	37.5% (39/104)
Milrinone	2.9% (3/104)
Postoperative data	
SvO ₂ on arrival to ICU (%)	65.8 \pm 7.4
Perioperative myocardial infarction	10.6% (11/104)
Atrial fibrillation	35.3% (36/102)
s-Creatinine (μ mol/L)	112 \pm 30
Increase of s-Creatinine \geq 50% preop	2.9% (3/103)
Acute renal failure – STS definition	1.0% (1/103)
Dialysis	1.0% (1/104)
Neurological complication	2.9% (3/104)
Sternal wound infection	3.8% (4/104)
Ventilator treatment > 24hours	8.8% (10/103)
ICU stay (days)	1.9 \pm 2.3
Hospital stay (days)	10.1 \pm 3.3
30-day mortality	
overall (LVEF <0.40)	1.0% (1/104)
LVEF \leq 0.35 (n=91)	1.1% (1/91)
LVEF \leq 0.30 (n=65)	1.5% (1/65)
5-year survival	
overall (LVEF <0.40)	89.4% (93/104)
LVEF \leq 0.35 (n=91)	89.0% (81/91)
LVEF \leq 0.30 (n=65)	84.6% (55/65)

Table 4. Outcome related to SvO₂ on arrival to ICU. Results are given as percentages and numbers of total within brackets or mean ± standard deviation.

Outcome related to SvO₂ on arrival to ICU	SvO₂ ≥55% (n=94)	SvO₂ < 55% (n=7)	p-value
SvO ₂ on arrival to ICU (%)	67.0 ± 6.1	49.7 ± 3.3	<0.0001
Perioperative myocardial infarction	6.4% (6/94)	42.9% (3/7)	0.015
Increase of s-Creatinine ≥ 50% preop	1.1% (1/93)	28.6% (2/7)	0.012
Acute renal failure – STS definition	0% (0/93)	14.3% (1/7)	0.07
Dialysis	0% (0/94)	14.3% (1/7)	0.07
Neurological complication	2.1% (2/94)	14.3% (1/7)	0.20
Sternal wound infection	2.1% (2/94)	28.6% (1/7)	0.02
Ventilator treatment > 24hours	7.4% (7/94)	42.9% (3/7)	0.02
30-day mortality	0% (0/94)	14.3% (1/7)	0.07
5-year survival	93.6% (88/94)	71.4% (5/7)	0.09

Table 5. Overview of studies on patients with severe LV-dysfunction undergoing CABG. LVEF = Left ventricular ejection fraction. Patients / Selection criteria present number of studied patients, selection and exclusion criteria, incomplete follow-up if given and the proportion of the studied cohort in relation to the surgeons or institutions corresponding CABG cohort. AMI = acute myocardial infarct. Hemodynamic management provides data if given about pharmacological and mechanical circulatory support. Also alternative specific measures to enhance recovery or protect the heart besides conventional cardioplegia are commented. IABP = intra-aortic balloon pump. LOS= low cardiac output syndrome. CI = cardiac index. LVAD = Left ventricular assist device. GIK = glucose-insulin-potassium. CPB= cardiopulmonary bypass. Operative mortality presents 30-day mortality or in-hospital mortality*. Five-year survival is with few exceptions given as cumulative five-year survival according to Kaplan-Meier. Crude five-year survival is denoted by **.

Study	LVEF	Patients / Selection criteria	Comment / Hemodynamic management	Operative mortality	5-year survival
Goor 1992(8)	EF<0.45	n=178 Isolated CABG Proportion 21%		5.6%	80%
Topkara 2005(70)	EF 0.31-0.40	n=11365 NY State Isolated CABG Proportion 20.5%	Preoperative IABP 6.5%	2.7%*	No long-term follow up
Hochberg 1983(9)	EF 0.20-0.40	n=425 Isolated first time CABG Proportion not given	Preoperative IABP 10.6%	11%*	60% (3 years)
Christakis 1992(10)	EF 0.20-0.40	n=2539 Isolated CABG Proportion 20.4%	1982-1990 Preoperative IABP 6% LOS 20%	4.8%	No long-term follow up
Yau 1999(11)	EF 0.20-0.40	n=4107 Isolated CABG Proportion 19.9%	1982-1997 LOS 14%	4%	No long-term follow up
O'Keefe 1993(12)	EF≤0.40	n=100 Isolated first time CABG Proportion not given		5%*	76%
Soliman Hamad 2008(13)	EF≤0.40	n=75 Isolated first time CABG Prospective study Elective procedures No AMI<1month Implantation of IABP was exclusion criteria Proportion not given	Implantation of IABP was exclusion criteria	4%	89.3% (8 years)
Svedjeholm 2009	EF<0.40	n=104 CABG with or	Metabolic strategy See table 3.	1.0%	89.4%**

		without valve 2 surgeons Proportion 13.4%	Inotropes for weaning 6.7%		
Alderman 1983(14)	EF≤0.35	n=231 First time CABG LV-aneurysmectomy 30.8% 15 CASS-sites Proportion not given	CASS 1974-1979	6.9%	68%
Chan 1996(32)	EF≤0.35	n=57 Isolated first time CABG Elective procedures Stable CAD No preoperative events < 4weeks No left main stenosis Proportion not given	No details given but these patients appear to be identical to Shah 2003(34)	1.7%	73% Transplant free survival
Moshkovit z 1997(33)	EF≤0.35	n=75 OPCAB 24% emergency procedures Single surgeon 10% lost to follow up Proportion not given	GIK and IABP intraoperatively in selected cases Postoperative inotropic support 20%	2.7%	Four-year survival 73%
Cimochow ski 1997(48)	EF≤0.35	n=111 Isolated CABG Proportion 5.8%	GIK Glutamate/aspartate cardioplegia Triiodothyronine Preoperative IABP 20.7% Intraoperative IABP 9.9% Inotropes if CI < 2.0L Ultrafiltration	1.8%	No long- term follow up
Shah 2003(34)	EF≤0.35	n=57 Isolated first time CABG Prospective study Elective procedures No preoperative events < 4 weeks Proportion 13.7%	Milrinone preemptively to achieve CI > 2.5 L	1.7%	55.7%
Hillis 2006(15)	EF≤0.35	n=349 Isolated first time CABG Proportion not given	Preoperative IABP 14%	5.5%	72% alive after a median of 3.8 years
Svedjehol m 2009	EF≤0.35	n=91 CABG with or without valve 2 surgeons	Metabolic strategy Glutamate 43% GIK 32% Inotropes for weaning 6.6%	1.1%	89.0%**

		Proportion 11.7%	IABP 2.2%		
Trachiotis 1998(35)	EF 0.25- 0.34	n=588 Isolated first time CABG Proportion 5%	1981-1995 IABP 10.6%	3.4%	71%
Topkara 2005(70)	EF 0.21- 0.30	n=5772 NY State Isolated CABG Proportion 10.4%	Preoperative IABP 12% Intra-/postop IABP 5.3%	4.1%*	No long- term follow up
Shapira 1995(71)	EF≤0.30	n=74 Isolated CABG Includes patients that survived the first 2 months Proportion not given		Included patients that survived 2 months	86.5%
Elefteriades 1997(16)	EF≤0.30	n=135 Isolated CABG Critically ill 27% Single surgeon Follow-up 95% Proportion 13.2%	Preoperative IABP 46% Intraoperative IABP 21% Intraoperative inotropic support 25% AICD 26%	5.2%*	71% (4.5 years)
DiCarli 1998(17)	EF≤0.30	n=43 Isolated CABG Redo 26% Proportion not given	IABP 30%	9.8%	78%
Kawachi 1997(18)	EF≤0.30	n=50 Isolated CABG Excluded patients without preoperative LV-angiogram Proportion 5.0%		8.0%*	No long- term follow up
Samady 1999(19)	EF≤0.30	n=135 Isolated CABG Single surgeon Late mortality reported for cardiac deaths and those that survived surgery Proportion 13.2%	IABP 67%	5%	75% of survivors free from cardiac death at 5 years
Luciani 2000(36)	EF≤0.30	n=167 Isolated CABG No AMI<4 weeks Viable myocardium Proportion 2.9%	Preoperative IABP 7.7%	1.7%	75%
Trehan 2003(54)	EF≤0.30	n=176 Isolated first time CABG Viable myocardium 86.5% OPCAB	Prophylactic IABP 14% Inotropes 6.8%	2.3%*	No long- term follow up

		Single surgeon Proportion 12.5%			
Tan 2006(37)	EF≤0.30	n=107 Isolated first time CABG Patients unable to curtail smoking excluded Proportion not given	IABP 15% Inotropes for weaning from CPB 21%	1.9%	72.3%
Shapira 2006(38)	EF≤0.30	n=115 Isolated CABG Proportion 4.7%	Preoperative IABP 28%	2.6%*	76%
Filsoufi 2007(39)	EF≤0.30	n=495 Isolated CABG Cardiogenic shock excluded Proportion 18%		3.6%*	75%
Svedjeholm 2009	EF≤0.30	n=65 CABG with or without valve 2 surgeons Proportion 8.4%	Metabolic strategy Glutamate 57% GIK 42% Inotropes for weaning 7.7% IABP 3.1%	1.5%	84.6%**
Ascione 2003(20)	EF<0.30	n=250 Isolated CABG Proportion 4.8%	Inotropes 81% ON PUMP Inotropes 41% OPCAB	4%*	Three- year survival 83%
Antunes 2003(53)	EF<0.30	n=141 Isolated CABG mean age 58 years 94% male 8.5% unstable 7 patients lost to follow-up Proportion 3.4%	Non-cardioplegic methods Restrictive use of inotropes (11.3% had them > 24 hours)	2.8%	86%
Appoo 2004(21)	EF<0.30	n=430 Isolated CABG Alberta Province Proportion 5.5%	Different surgical centers and methods for evaluation of LVEF	4.4%	77.7%
Milano 1993(22)	EF≤0.25	n=118 Isolated CABG 2 patients lost to follow up Proportion not given	1981-1991 Preoperative IABP 23.5%	11%	57.5%
Langenburg 1995(23)	EF≤0.25	n=96 Isolated CABG No emergency cases	IABP 10%	8%	No long- term follow up
Christenson 1995(24)	EF≤0.25	n=91 First time CABG Aneurysmectomy	IABP 14.3% LOS 36.3%	14.3%	No long- term follow up

		16% Proportion 5.4%			
Baumgartner 1998(25)	EF≤0.25	n=61 Isolated CABG No emergency cases Proportion not given	Preoperative IABP 18% IABP total 41%	8%	No long-term follow up
Bouchart 2001(26)	EF≤0.25	n=141 Isolated first time CABG Proportion not given	Preoperative IABP 18% Inotropes for weaning from CPB 55%	7.0%	70%
DeRose 2005(27)	EF≤0.25	n=544 Isolated CABG Proportion not given		5.5%	68%
Dietl 2006(28)	EF≤0.25	n=163 Isolated CABG Cardiogenic shock excluded	Preoperative IABP 23% 1/37 died < 30 days in patients with preoperative IABP	11.7%	No long-term follow up
Trachiotis 1998(35)	EF<0.25	n=156 Isolated first time CABG Proportion 1.3%	1981-1995 IABP 10.7%	3.8%	64%
Lansman 1993(29)	EF≤0.20	n=42 CABG with or without concomitant procedure Proportion 2.0%	Preoperative IABP 7% Intraoperative IABP 17% Postoperative IABP 2%	4.8%	34% (6 years)
Kaul 1996(30)	EF≤0.20	n=210 Isolated CABG Patients with LV-end diastolic dimension >70mm excluded Proportion 5.8%	Preoperative IABP 21% IABP total 40%	7%	73%
Topkara 2005(70)	EF≤0.20	n=2442 NY State Isolated CABG Proportion 4.4%	Preoperative IABP 23.1% Intra-/postop IABP 8.4% LVAD 0.7%	6.5%*	No long-term follow up
Hochberg 1983(9)	EF<0.20	n=41 Isolated first time CABG No proportion given		37%*	15% (3 years)
Christakis 1992(10)	EF<0.20	n=487 Isolated CABG Proportion 3.9%	1982-1990 Preoperative IABP 15%	9.8%	No long-term follow up
Mickleborough 2000(31)	EF<0.20	n=125 Isolated CABG Single surgeon Proportion 5.3%	1982-1997 Temperature mapping to guide cardioplegia	4%*	72%