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Bypass surgery for coronary artery disease: a vanishing treatment?

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Since the introduction of percutaneous coronary interventions (PCIs) for coronary artery disease, interventional cardiologists have assured me that the time for the surgical approach of the disease is almost over, and they have kept on telling me this through the last 25 years. But if we look at the data of the trends in volumes of PCIs (Figure 1) and cardiac surgery (Figure 2) over the last 25 years in the Netherlands, only a small decrease in surgery volume is shown over the last 10 years, despite a three-fold increase in PCIs.

A similar trend is observed in Canada [1]. Part of the decline in surgery volume is compensated by an increase in valve surgery both in valve replacement and repair. In view of the fact that more and more percutaneous procedures are performed on coronary arteries, and on increasingly complex lesions [2], what are/remain the indications for surgery instead of PCI at this moment?

In the ACC/AHA 2004 guideline update for coronary artery bypass graft surgery [3] an extensive overview is given of the outcomes, patient subsets, management strategies, technology, competence, and economics. Most importantly the indications are discussed. First of all, the most important indication for surgery is the relief of symptoms. The randomized trials of CABG versus PCI have shown that the freedom of symptoms and antianginal medication is superior in the CABG cohorts compared to the PCI cohorts (also in stent trials). Also subsequent procedures are less after surgery than after PCI. On the other hand, hospital stay is longer, and initial costs and complication/mortality rates are higher. Therefore the benefits of CABG have to be balanced against the risks.

The second indication is improvement of survival. In the randomized trials no difference in mortality or (re)infarction was shown between bypass surgery and PCI. On the other hand, in a very large registry [4] in the US it was shown that patients with 3 vessel disease and severe proximal LAD disease had improved survival with surgery compared to PCI. Conversely, single vessel disease patients without proximal LAD involvement were better off with PCI. Another important subset of patients are those with diabetes mellitus.

Figure 1. Trends in volumes of percutaneous coronary interventions over the last 25 years in the Netherlands.
and multivessel disease. The majority of trials and registries favor the use of surgery to improve outcome in patients with diabetes, although no large scale randomized trial data are available.

Thus, what are the primary indications at this moment for bypass surgery instead of PCI for patients with coronary artery disease?

1) Patients with significant left main stenosis.
2) Patients needing concomitant other cardiac surgery (valves etc)
3) Unsuitable coronary anatomy for PCI
4) Severe complications after PCI
5) Patients with diabetes mellitus and multivessel disease
6) Severe triple vessel disease.

However, the indications of surgery versus PCI for coronary artery disease will continuously be under debate as newer technologies both in PCI (drug-eluting stents) and in bypass surgery (minimally invasive surgery) will undoubtedly alter complication rates and prognosis. Moreover, the widespread use of statins, angiotensin-converting enzyme (ACE) inhibitors and anti-platelet therapy will also change the course of the atherosclerotic disease. From a patient perspective, it is likely that many patients will undergo both procedures during their lives.

Because of this important form of therapy in patients with cardiac disease, and because it has clear metabolic associations, we have decided to devote an issue of Heart and Metabolism to cardiac surgery. Out of a large number of topics we have focused on the perioperative setting. Enjoy reading.

REFERENCES

Mechanism of cardiac damage associated with cardiac surgery

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Abstract

During cardiac surgery, myocardial damage is induced by factors such as ischemic injury, reperfusion injury, and the inflammatory response associated with cardiopulmonary bypass. Protective measures designed to attenuate ischemic injury involve rapid elective ischemic arrest with a “cardioplegic” solution containing moderately increased concentrations of potassium to depolarize the myocardial membrane potential. However, this can lead to ionic imbalance and maintained utilization of energy, resulting in damaging reductions in the tissue content of high-energy phosphate. Alternative techniques of arrest, using agents that induce a “polarized” arrest or that influence intracellular calcium mechanisms, have the potential to improve myocardial protection and reduce damage during ischemic arrest.

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Keywords: Myocardium, injury, ischemia, reperfusion, protection

Introduction

Patients requiring cardiac surgery will have experienced some form of myocardial injury, be it ischemic heart disease requiring revascularization or the influence of diseased heart valves on the myocardium. The surgical process is likely to exacerbate any injury as a result of a number of factors associated with the procedure. The cardiac surgeon requires a relaxed, still, and blood-free operating field for optimal application of the technically demanding and delicate manipulations involved in the surgery; this can be achieved most easily by inducing a period of global ischemia in the heart, and during this time the systemic circulation is supported by a heart–lung machine for cardiopulmonary bypass.

The survival of any ischemic myocardium is absolutely dependent on reperfusion, which should be initiated at the earliest opportunity to avoid ischemic injury; however, when a period of extended elective ischemia is imposed (such as during cardiac surgery), protective measures designed to delay the rate of development of ischemic injury are necessary. Thus damage to the heart during cardiac surgery can occur from ischemic injury, from reperfusion injury, and from the activation of the inflammatory response involved in blood (which becomes significantly diluted) circulating through nonbiological tubing of the cardiopulmonary bypass system, which can lead to exacerbation of the ischemia and reperfusion injury by infiltration of the heart and lungs by activated leukocytes and platelets [1], and by activation of the complement system and the coagulation and fibrinolytic systems [2].

Despite the many advances that have been made in cardiac surgery since the first cardiac surgical operations in the mid-1950s, the operative mortality is 1–3%; up to 10% of patients will experience new myocardial dysfunction, and around 24% of high-risk patients will die within 3 years [3]. Thus it is important to understand the nature of the damage to the myocardium that can occur during cardiac surgery and to
continue to explore new ways of attenuating that damage during the surgical process. One of the most important factors involved in cardiac surgery is the induction of elective global ischemia and the consequent arrest of the heart that occurs; the way in which arrest is induced can have a significant impact on the outcome of the surgery.

The induction of ischemia is convenient for the surgeon, but it has potentially serious consequences for the heart (particularly when considering the underlying heart disease). The damage could rapidly progress from a reversible injury (after only a relatively short period of ischemia) to an irreversible injury. Considerable research has been conducted to render surgically induced ischemia less damaging, and to develop protective measures designed to reduce (or, ideally, prevent) this irreversible damage. Over the past 30 years of cardiac surgery, this has routinely involved the use of a “cardioplegic” solution [4] to induce rapid elective myocardial arrest of the heart (in contrast to the arrest after metabolic collapse that is associated with ischemia), thereby significantly reducing myocardial oxygen consumption [5] by approximately 6-fold (at various temperatures) and consequently slowing the utilization of myocardial high-energy phosphates. Such elective cardiac arrest induced during surgery can be achieved in a number of ways, by targeting various points in the excitation–contraction coupling pathway, using various arresting agents (Figure 1).

**Mechanisms of arrest**

**Depolarized arrest**

The method most commonly used to induce cardiac arrest during cardiac surgery involves a cardioplegic solution containing a concentration of potassium that is moderately increased (usually 15–40 mmol/L), compared with that of the extracellular milieu to induce a depolarization of the membrane. Increasing the extracellular potassium concentration of the solution causes the resting membrane potential ($E_m$) to depolarize; at each new potassium concentration, a new resting $E_m$ equilibrium is established. Depolarization to approximately $−65$ mV (corresponding to the inactivation threshold of the fast sodium channel) at a potassium concentration of approximately 10 mmol/L prevents the rapid sodium influx of the action potential and maintains diastole of the myocardium [6]. As the potassium concentration increases, $E_m$ becomes more depolarized, but at approximately $−40$ mV (corresponding to a potassium concentration of about 30 mmol/L) the calcium channel will be activated, promoting calcium overload, which can lead to myocardial damage [6]. Thus there is a relatively narrow window of potassium concentration for “safe” myocardial arrest with increased potassium; most hyperkalemic solutions use a potassium concentration around 16–20 mmol/L (such as the St Thomas’ Hospital solution) and arrest at a membrane potential around $−50$ mV (Figure 2).
However, at the levels of depolarization induced by these potassium concentrations, other noninactivating currents remain active. Voltage-dependent activation and inactivation "gates" of the sodium channel operate at different rates and cause a background influx of sodium via the sodium "window" current [7,8]. This will increase the intracellular calcium concentrations as a consequence of mechanisms such as the sodium–calcium exchanger [9], inducing contracture even in the arrested state and contributing to calcium overload and reperfusion injury [8]. Critical energy supplies are depleted by energy-dependent transmembrane pumps that attempt to correct the abnormal ionic gradients that result [10]; decreased myocardial ATP concentrations are associated with hyperkalemic arrest compared with those observed with alternative means of arrest [11]. Thus, although hyperkalemia remains the most common means of cardiac arrest, it is not necessarily the optimum means of preventing myocardial damage during surgery.

Alternative techniques may avoid the problems (ionic imbalance, maintained metabolism, potassium-induced endothelial injury [12], arrhythmias) that are associated with depolarized arrest, and provide superior protection. Recent studies have concentrated on the induction of polarized arrest or arrest by influencing calcium mechanisms.

### Polarized arrest

Polarized arrest involves maintaining the membrane potential of the arrested heart at or near the resting value. This should provide a number of advantages: maintained ionic balance (particularly of sodium and calcium) and reduced energy requirements. Polarized arrest can be achieved by either sodium channel blockade or potassium channel activation (Figure 1).

Blocking the sodium channel directly prevents the rapid, sodium-induced depolarization of the action potential, and many agents (such as procaine and lidocaine) have previously been used as cardioplegic agents or as additives. Tetrodotoxin, a toxic but potent sodium channel blocker, is an effective and protective cardioplegic agent [10,13]. Recent studies using this agent have demonstrated the benefit of polarized arrest over depolarized arrest for myocardial protection, with $E_m$ during ischemia being maintained around $-70 \text{ mV}$ (Figure 2) and a reduced ionic imbalance, particularly when it is used in conjunction with agents inhibiting sodium influx (a sodium–hydrogen exchange inhibitor and a sodium–potassium–chloride cotransport inhibitor) [14,15].

Potassium channel openers (such as aprikali, pinacidal, and nicorandil) activate the ATP-dependent potassium channel (KATP channel). Because the relative membrane conductance of the myocardium to potassium is much greater than that to sodium, the myocardial resting $E_m$ (approximately $-85 \text{ mV}$) is close to the equilibration potential of potassium ($E_k$ of approximately $-94 \text{ mV}$). Opening KATP channels increases the difference between these conductances, shifting $E_m$ towards $E_k$ and thereby inducing a hyperpolarization relative to the previous $E_m$ [16], but this only applies if the extracellular potassium concentration remains low. When used at high concentrations, KATP channel openers are believed to exert a cardioprotective effect by inducing membrane hyperpolarization that results in diastolic arrest, and they have been shown to improve protection compared with that achieved with hyperkalemic solutions [17,18]. However, more recent studies have shown that pinacidal (even at concentrations as high as 1 mmol/L) is unable to induce arrest per se, requiring the addition of a sodium channel blocker for complete arrest occurring at $E_m$ values around $-70 \text{ mV}$ [19,20].

Adenosine has also been shown to act as a hyperpolarizing agent [21], and has been used to induce cardioplegic arrest, with mixed results [22–24]. More recently, a combination of lidocaine, a sodium channel blocker, and adenosine has demonstrated effective myocardial protection compared with a hyperkalemic cardioplegic solution [25]; similarly, other studies have demonstrated effective combinations of arresting agents [26].

### Influencing calcium mechanisms

Solutions with a zero, or very low, extracellular calcium concentration rapidly arrest the heart in diastole...
by inhibiting excitation–contraction coupling [27]. This is the basis of some “intracellular type” cardioplegic solution (particularly the original Bretschneider solution [28] and the subsequent Histidine-Tryptophan-Ketoglutarate [HTK] [Custodiol] solution [29]), although combination with a sodium channel blocker (procaine) and a low sodium concentration would also tend to induce a polarized arrest. The HTK solution has shown particular application for long-term preservation of hearts, in addition to other organs (kidney, liver, pancreas), before transplantation.

An alternative approach is to influence the affinity of calcium for intracellular components, and there is current interest in agents that lead to reversible desensitization of the contractile apparatus for calcium. The most widely used is 2,3-butanedione monoxime (BDM), which uncouples myofilament excitation–contraction coupling by inhibiting the formation of crossbridges [30]. BDM has recently been used as a cardioplegic agent [31], demonstrating effective protective properties when compared with conventional depolarizing cardioplegia. Another agent with potential to improve myocardial protection by reducing the damaging effects of depolarized arrest is esmolol, an ultra-short-acting β-blocker with a half-life of only 9 min. The efficacy of using esmolol during cardiac surgery as an alternative to depolarizing cardioplegia has been demonstrated [32], and recent experimental studies [33,34] have shown that the use of multidose infusions of an esmolol cardioplegia solution (at a concentration of 1 mmol/L) provides significantly improved protection during normothermic global ischemia compared with that obtained with a depolarizing cardioplegic solution. Preliminary studies indicate the possibility that esmolol is acting via a calcium desensitization mechanism, but this remains under investigation.

Conclusion

Damage to the myocardium during cardiac surgery is associated with a number of factors, the most important being the induction of elective global ischemic arrest. It is necessary to protect the myocardium against the damaging effects of ischemia; since the mid-1970s, the most widely used protective technique has been to infuse a solution containing a moderately increased concentration of potassium, which leads to a rapid and “safe” diastolic arrest by depolarization of the membrane potential. This is simple to apply and to remove; however, it does not necessarily provide the optimal protection against cardiac damage, particularly in the context of the increasing number of high-risk patients who are older and have more diffuse and severe ischemic heart disease and who undergo cardiac surgery nowadays. Other techniques of arrest, such as inducing a polarized ischemic arrest or arresting the heart by influencing calcium mechanisms may be more suited to preventing the damaging effects of elective ischemia in present-day cardiac surgical patients. In addition, improvements in preventing ischemic damage to the heart will reduce the associated reperfusion injury, and may also mean that any inflammatory response is similarly reduced. However, more characterization and research are required before these alternative techniques can be considered for routine use during cardiac surgery.

REFERENCES


Managing contractile dysfunction after cardiac surgery

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Abstract

Hemodynamic problems in patients’ post cardiac surgery are, in general, complex. Although recovery may be very quick, initial and instant treatment is of high importance to prevent further problems. An intensive care environment with sufficient medical and nurse staffing is best suited to fulfill these requirements. After cardiopulmonary bypass surgery, myocardial stunning is one of the problems encountered, but other contributing factors should be sought, and treatment should be based on the diagnosis. Myocardial stunning can safely be treated pharmacologically with inotropes, and the choice and combination of the inotropic drugs to be used depends on whether additional effects are desired from treatment with vasoactive drugs, if necessary complemented by a mechanical assist device.


Keywords: Cardiac surgery, stunning, vasoactive drugs, intensive care, treatment

Introduction

Patients after cardiac surgery are in general treated in the intensive care unit (ICU). Although recovery from the operation may be rapid, the initial treatment is of utmost importance to prevent additional complications. In the immediate postoperative phase, several potential risks and dangers have to be faced. For prompt and appropriate diagnosis and response, an ICU organization that has sufficient medical and nurse staffing is, in our view, the best environment in which to deal with these problems [1].

Complications after cardiac surgery

Potential complications depend on the consequences of conditions present both before and during the operative procedure. Re-operation, emergency procedures, preoperative use of intra-aortic balloon pump pulsation, congestive heart failure, combined coronary artery bypass graft and valve surgery, older age and pre-existing comorbidity such as renal function loss, chronic obstructive pulmonary disease, diabetes mellitus, and cerebrovascular disease are predictors of postoperative morbidity [2]. In addition, the duration of cardiopulmonary bypass, amount of blood loss, and hemodynamic instability during operation together will determine the clinical status of the patient who arrives in the ICU after cardiac surgery. Several more or less severe derangements are present in the initial phase in the ICU: hypothermia, inadequate intravascular volume, systemic inflammatory response syndrome with capillary leakage, continuing mediastinal blood loss (although this can be minimal), and incomplete emergence from anesthesia. Apart from all this, myocardial dysfunction is present.

Myocardial dysfunction can be related to the preoperative situation, such as diastolic dysfunction with low left ventricular compliance as a result of myocardial hypertrophy, as in the case of chronic hypertension or aortic valve stenosis. Repair of mitral valve incompetence may also unmask left ventricular systolic failure [3]. Furthermore, right ventricular dysfunction may occur, especially in patients with
previous (unknown) pulmonary hypertension. However, apart from all these “common causes”, myocardial dysfunction will occur in all patients, in relation to global myocardial ischemia and restoration of (coronary) blood flow after cardiopulmonary bypass. The postischemic but viable myocardium requires a period of hours to days before function is fully restored. Heyndrickx et al [4] were the first to report that reversibly injured myocardium failed to contract. This prolonged, postischemic dysfunction of viable tissue salvaged by reperfusion is called “stunning”. The duration of stunning is dependent on the duration and extent of ischemia, in addition to the adequacy of the return of arterial flow [5].

Clinical management

The heart is designed to deliver oxygen to peripheral tissues. This delivery must also be adequate directly after cardiac surgery. As outlined above, several factors may jeopardize the delivery of sufficient oxygen by the heart, therefore the clinician should make a diagnosis and determine which factor – or, most often, which several factors – may cause problems in a specific patient. Furthermore, failure of the operation, such as occlusion of bypass grafts or insufficiently corrected valvular lesions, should be considered. A group of clinical parameters are the indicators of insufficient oxygen delivery [6]. These include blood pressure, heart rate, cardiac output/stroke volume, oxygen delivery, central venous or mixed venous saturation, filling pressures, diuresis if not affected by diuretics, serum lactate concentration, and blood gas analysis. In our view, there is no single indicator that possesses sufficient specificity or sensitivity to be reliable in clinical practice.

It is important to realize that, in general, more than one problem is present to a varying degree in the early postoperative course of the cardiac surgical patient. Apart from vasoconstriction caused by hypothermia or related to inadequate filling of the vascular bed, vasodilatation may occur as a result of a systemic inflammatory response, associated with cardiovascular dysfunction. The vasodilatation is accompanied by capillary leakage, which underscores the need for superior surveillance of fluid load and adequate fluid resuscitation in the early phase. Adequate fluid resuscitation establishing “optimal preload” of the ventricles, as we described previously [6], will ensure maximum cardiac performance for the lowest expenditure of energy.

Treatment of stunning

In patients after cardiopulmonary bypass, stunning of the myocardium is, generally speaking, always present. An important feature of the biology of the stunned myocardium is that the tissue responds well to inotropic stimulation. Previous concern that inotropic stimulation of the myocardium worsens long-term recovery of the heart has been shown to be ill-founded: recovery to normal of the stunned myocardium has been found to occur at the same rate as that in myocardium that had not received inotropic stimulation [9,10].

Dobutamine, dopamine, epinephrine, norepinephrine, and phosphodiesterase inhibitors such as enoximone or milrinone can all be used as inotropic drugs to treat myocardial stunning. There are no randomized controlled studies of sufficient power that have compared the efficacy or safety of the different inotropic drugs, therefore making a correct hemodynamic diagnosis and knowledge of the pharmacological properties of these vasoactive drugs are the basis for appropriate prescription. Their properties are listed in Table I.

Some studies in patients with vasodilatory shock suggest that epinephrine is associated with impairment of the splanchnic circulation and, thereby, increases in serum lactate concentration [11]. We therefore prefer dobutamine, if necessary in combination with low-dose norepinephrine, as the first-choice drug for inotropic support to counteract β2-receptor-mediated vasodilatation. Dopamine, a naturally occurring catecholamine, can also be given as an inotropic agent, although we consider the diuretic properties of dopamine (through stimulation of renal tubular sodium-potassium-chloride cotransport [12]) problematic.

Table 1. Effects of naturally occurring and synthetic catecholamines on adrenergic receptors and dopamine (DA) receptors.

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>DA1</th>
<th>DA2</th>
<th>α1</th>
<th>α2</th>
<th>β1</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>0</td>
<td>0</td>
<td>0-1*</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2</td>
<td>1</td>
<td>1-2*</td>
<td>0-1</td>
<td>1-2</td>
<td>0-1*</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1-2</td>
<td>1-2</td>
<td>1</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1-2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

0 = no effect; 2 = strong stimulation.

*Dose-dependent effect, seen mainly with higher doses.
Table II. Suggested hemodynamic treatment (combined with “optimal” preload) in patients exhibiting signs of insufficient oxygen delivery as indicated by, for example, low mixed venous saturation, lactic acidosis, or poor organ perfusion.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood pressure</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>CO &gt; 4.5 L/min</td>
<td>Norepinephrine + low-dose dobutamine (or dopamine)</td>
</tr>
<tr>
<td>CO 3–4.5 L/min</td>
<td>Dobutamine + titrated norepinephrine</td>
</tr>
<tr>
<td>CO &lt; 3 L/min</td>
<td>SNP + dobutamine if no improvement in parameters</td>
</tr>
<tr>
<td>Normal or high blood pressure</td>
<td>Dobutamine + titrated SNP</td>
</tr>
<tr>
<td>CO &gt; 4.5 L/min</td>
<td>Dobutamine + titrated SNP + enoximone/milrinone</td>
</tr>
<tr>
<td>CO 3–4.5 L/min</td>
<td>Consider enoximose or milrinone instead of dobutamine</td>
</tr>
<tr>
<td>CO &lt; 3 L/min</td>
<td></td>
</tr>
<tr>
<td>High-dose β-blocker therapy before operation</td>
<td></td>
</tr>
</tbody>
</table>

Values have been averaged for a 70–75-kg man. CO, cardiac output; SNP, sodium nitroprusside.

dopaminergic receptors) not always desirable; the use of diuretic agents will offset the information that can be gathered by measuring urinary output as a measure of the adequacy of peripheral perfusion [12].

Patients undergoing cardiac surgery frequently will have been treated with β-blockers before operation. It is therefore not to be expected that β-receptor mimetics will be sufficiently efficacious in that particular situation. Phosphodiesterase enzyme inhibitors increase intracellular calcium by inhibiting the breakdown of cyclic adenosine monophosphate, thereby bypassing the β-receptor. Phosphodiesterase inhibitors such as enoximone and milrinone can be described as ‘inodilators’, because they exhibit both inotropic and vasodilatory effects. The hemodynamic effect is comparable to that of dobutamine. Therefore, in the case of previous use of (high-dose) β-blockers, enoximone (or milrinone) should be given – and, if it’s necessary to maintain sufficient perfusion pressure, in combination with norepinephrine – instead of the commonly used inotropics. Enoximone can also be given in case of pulmonary hypertension and imminent right ventricular failure. In the case of (too) low perfusion pressure and (relatively) high cardiac output with systemic vasodilatation, norepinephrine can be given as drug of first choice, for its inotropic and mainly vasodilatory effects. Although the use of norepinephrine is feared by some cardiac surgeons for its presumed coronary vasoconstriction, older studies have already demonstrated that this agent induces coronary vasodilatation, reduces myocardial infarct size, enhances endocardial blood supply, and helps maintain a perfusion pressure sufficient to ensure coronary perfusion [13–16].

Apart from inotropic drugs, vasodilators should be used in cases of high afterload and high systemic vascular resistance. For reducing left ventricular afterload, sodium nitroprusside is the most appropriate drug to use in the ICU setting. The choice of a concomitant inotropic drug in such a situation is, of course, a drug with the least vasodilatory effects or even vasodilating effects, such as dobutamine or enoximone (Table II).

If pharmacological treatment of expected transient stunning is insufficient or is anticipated to be insufficient, the use of mechanical support such as intra-aortic balloon pulsation is indicated.

Conclusion

Hemodynamic problems in patients’ post cardiac surgery are, in general, complex. After cardiopulmonary bypass surgery, myocardial stunning is one of the problems encountered, but other contributing factors should also be sought, and treatment should be based on the diagnosis. Myocardial stunning can safely be treated pharmacologically with inotropes, and the choice and combination of the inotropic drugs to be used depends on whether additional effects are desired from treatment with vasoactive drugs, if necessary complemented by a mechanical assist device.

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Main clinical article
Managing contractile dysfunction after surgery

Value of perioperative transesophageal echocardiography

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Abstract

At present, transesophageal echocardiography (TEE) is a powerful diagnostic modality in the perioperative setting. The assessment of regional and global myocardial function is the most important clinical application. Furthermore, TEE in combination with stress (atrial pacing, pharmacologic stress, volume loading) provides important additional information about myocardial ischemia, myocardial viability, and dynamic mitral regurgitation. Assessment of native valve function and repair, especially of the mitral valve, has been common clinical practice, improving the outcome of valvular repair in many surgical centers. Recent progress in transducer technology and computerized image processing also brings three-dimensional and contrast-enhanced TEE closer to the operating room. Finally, miniaturization of probes and automated contour detection techniques make TEE a sensitive and continuous monitor of global and segmental left ventricular function. This review will focus on novel emerging and innovative technologies in TEE for perioperative evaluation.

Keywords: Transesophageal echocardiography, stress echocardiography, 3-dimensional echocardiography, contrast echocardiography, automated border detection, perioperative care

Introduction

Transesophageal echocardiography (TEE) has evolved rapidly since its initial use in the 1970s [1,2] until, today, it is increasingly gaining popularity for the anatomical and hemodynamic evaluation of patients in the perioperative setting. Common indications for the technique are summarized in Table I. Stress TEE using atrial pacing, pharmacologic stress, or volume loading is potentially available for the patient treated with a respirator, for detection of myocardial ischemia and for evaluation of dynamic mitral regurgitation. Recent advances in ultrasound instrumentation and computer technology have led to dynamic 3-dimensional echocardiography, thus introducing a new era in cardiovascular imaging. Furthermore, evolution in the field of contrast echocardiography, using contrast agents capable of pulmonary passage, can further enhance diagnostic imaging and might bring myocardial contrast echocardiography to the operating room. Developments in quantification techniques, together with miniaturization of the probes, will allow continuous monitoring of the patient in the perioperative setting. Selection of the particular TEE examination should therefore be tailored to clinical circumstances.

Perioperative monitoring of myocardial ischemia

Perioperative applications of TEE enable continuous monitoring of surgical procedures without disturbing the sterile field of work, thus allowing for the non-invasive evaluation of regional and global left ventricular function (Figure 1). In addition, the technique can accurately identify new regional wall motion abnormalities as markers of myocardial hypoperfusion before and immediately after bypass.
During surgery, several nonischemic mechanisms may modify the left ventricular contractile function, either directly or through changes in position of the heart within the thorax. The most important cause of nonischemic alteration of segmental wall motion abnormalities is represented by opening of the thoracic cavity or pericardium, or both, which can modify the movement of the interventricular septum from a reduced systolic motion towards a paradoxical movement. The interpretation of the septum motion can also be confounded by discoordinated patterns of contraction caused by bundle branch block or ventricular pacing. However, when the septum is viable, it thickens appreciably during systole.

Segmental hypokinesis represents the majority of transient segmental wall motion abnormalities, but it has been shown that hypokinetic segments have the greatest mismatch between perfusion and contraction. Therefore, not all segmental wall motion abnormalities are indicative of myocardial ischemia. However, a sudden decrease in segmental contraction by a reduction in myocardial thickening is almost certainly the result of myocardial ischemia. Tissue Doppler imaging is a promising technique for quantifying myocardial ischemia and viability. It estimates circumferential or longitudinal velocities of the moving myocardium by detecting the phase shifts of ultrasound signals reflected by myocardial tissue. Alterations in systolic and diastolic velocities and isovolumetric relaxation time during acute myocardial ischemia can thus be assessed [3].

Assessment of native valve function and repair

Transesophageal echocardiography provides information of greatest value in mitral reconstructive surgery. The pathomorphology of the diseased valve and subvalvular apparatus can be clearly defined by TEE, which may have an important impact on the feasibility of surgery and the surgical strategy during operation. This is of importance in surgical correction of mitral

### Table 1. Common indications for transesophageal echocardiography in the perioperative setting

- Monitoring of left ventricular systolic and diastolic function
- Monitoring of ischemia and viability
- Valvular disease and repair, eg in mitral regurgitation
- Prosthetic valve dysfunction
- Endocarditis and its complications
- Unexplained hypotension and intravascular volume status
- Monitoring of right ventricular function
- Intracardiac masses
- Suspicion of pericardial tamponade, constriction, or mediastinal bleeding
- Hypoxemia, to exclude right-to-left shunting across a patent foramen ovale or atrial septum defect
- Aortic dissection
- Complications after myocardial infarction
- Cardiac complications in chest trauma

Figure 1. Short-axis (SAX) transgastric view at 0° of the mid-segments of the left ventricle, providing insight into the efficiency of coronary perfusion in all three coronary distribution areas, thus giving immediate information on global and regional systolic left ventricular function. Epicardial contours are drawn on the left; endocardial contours on the right.
regurgitation, because valve repair has been shown to be more beneficial than valve replacement, and to improve long-term survival.

Decisions based on TEE findings made at the time of operation may affect both early and late survival, and the need for reoperation or replacement of the valve during operation. In this respect, 3-dimensional TEE may become more and more important. 3-Dimensional echocardiography displays a bird’s-eye view of the mitral valve, either looking down from the left atrium or looking up from the left ventricle. Thus 3-dimensional reconstruction allows spatial perception of all integrated components of the mitral valvular complex, such as the atroventricular orifice and leaflets (Figure 2). In patients with mitral valve regurgitation, 3-dimensional echocardiography allows detailed visualization of mobility, the coaptation zone, the extent of prolapse, perforation, erosion, retraction, and restriction of valve leaflets [4–6].

Evaluation of endocarditis

Transesophageal echocardiography is abnormal in endocarditis, with the demonstration of either a vegetation-like mass (Figure 3) or a lesion that frequently or almost always results from the endocarditis process such as an abscess (echolucent space), leaflet perforation (Figure 4), fistula, prosthetic valve dehiscence, and paravalvular regurgitation. TEE is the most sensitive technique for the diagnosis of endocarditis, with a sensitivity of approximately 90%. Further diagnostic improvements might be obtained using 3-dimensional echocardiography, revealing complications of endocarditis by views in any plane, including the surgeon’s view. The immense diagnostic potential of TEE, especially in the setting of infective endocarditis, has led to a revision of the diagnostic criteria to include echocardiographic findings as a major diagnostic criterion.

Investigation of cardiac masses

Transesophageal echocardiography has been shown to be superior to transthoracic echocardiography for visualization of left atrial thrombi, aortic atheroma and other cardiac thrombi, tumors (Figure 5), or vegetations, as possible sources of cardiac embolism. In this respect, the value of 3-dimensional echocardiography has yet to be determined, but is promising [7].

Aortic atheromas are also an important cause of stroke during open heart surgery. The increasing number of elderly patients with severe atheromatous disease of the aorta has focused clinical interest on management of severe atheroma of the ascending aorta and the associated risk of intraoperative embolization. Intraoperative TEE provides unique information on the localization and composition of aortic atheroma that may alter the conduct of the operation, especially with regard to the site of cross clamping of the aorta. If atheromas are detected in the arch or in the ascending aorta, the intraoperative stroke rate is significantly increased compared with that in patients without atheroma.
Stress transesophageal echocardiography

In patients in the perioperative setting, stress TEE using atrial pacing, dobutamine, or volume loading offers a valuable extension of its diagnostic ultrasound capabilities. In this regard, we evaluated the capability of simultaneous TEE and atrial pacing [8]. The technique had a high accuracy and diagnostic yield in assessing myocardial ischemia, multivessel disease, and ischemic mitral regurgitation [9]. Alternatively, dobutamine and dipyridamole may be used in TEE [8–11], see also Table II. Potential indications for stress TEE are evaluation of myocardial ischemia in patients with a nondiagnostic transthoracic window, ambiguous results from different tests, accurate measurement of myocardial...
viability, ‘unexplained’ heart failure, evaluation of dynamic mitral regurgitation, measurement of coronary flow reserve, and distribution of myocardial perfusion using intravenous contrast agents.

In addition, TEE is a method of distinguishing viable from nonviable myocardium. Contractile reserve is consistent with myocardial viability and characterized by baseline wall motion abnormalities that improve with low-dose dobutamine. Perioperative stress echocardiography holds promise as a technique that may differentiate ischemic from nonischemic dysfunction, and enhances therapeutic rationalization when low-output syndromes are treated.

Contrast-enhanced transesophageal echocardiography

The appearance of a myocardial ‘blush’ after contrast injections into the coronary arteries triggered the development of myocardial contrast echocardiography as a means of noninvasive assessment of myocardial perfusion [12]. Importantly, simultaneous assessment of regional anatomy and perfusion and of function, together with the ability to perform serial measurements with a high degree of spatial and temporal resolution became possible (Figure 6). With the advent of new and more stable (second-generation) transpulmonary contrast agents, in addition to important improvements in imaging techniques (such as second-harmonic imaging), visually detectable myocardial contrast can be produced via the intravenous route. Second-harmonic TEE probes are now available and are important for the assessment of myocardial contrast. Alternatively, intra-aortic (or intracoronary) contrast injections using a pigtail catheter in the operating room or critical care unit and second-harmonic TEE might potentially be useful to diagnose perfusion of specific myocardial areas in the setting of patients treated acutely with a respirator [13]. Absence of perfusion, defined as reduced opacification of myocardial segment(s) after a contrast injection, predicts morbidity (heart failure) and absence of viability in that area. In a perioperative setting, myocardial contrast echocardiography has been found to be helpful in determining the adequacy

Table II. Sensitivity and specificity of stress transesophageal echocardiography for detection of coronary artery disease (ischemia) or myocardial viability.

<table>
<thead>
<tr>
<th></th>
<th>No. studies</th>
<th>n</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacing</td>
<td>3</td>
<td>126</td>
<td>91 (83–91)</td>
<td>96 (91–100)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2</td>
<td>121</td>
<td>89 (82–89)</td>
<td>100 (93–100)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>1</td>
<td>32</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>Myocardial viability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>1</td>
<td>42</td>
<td>92</td>
<td>88</td>
</tr>
</tbody>
</table>

Values are number or % (range).
of cardioplegia solution; it also identified a group of patients with significantly worse postoperative outcome in terms of need for inotropic support [14].

**Monitoring global left ventricular function**

Newly commercially available automatic border detection systems can be used in combination with TEE monitoring. Acoustic Quantification (Philips, Andover, Massachusetts, USA) uses the difference in backscatter between blood and myocardium, thus facilitating quantitative description of the endocardial boundaries [15]. During continuous monitoring, within a selected region of interest, several cross-sectional areas (using video frames: 30 frames per second) from a short-axis cross-sectional view of the left ventricle are provided, in addition to plots of derived variables such as the fractional area change and rate of change of area versus time (Figure 1). Limitations of this automatic border detection system are the facts that papillary muscles are presented outside the cross-sectional areas and that no epicardial border detection can be performed, and the technique is thus not helpful in estimating left ventricular wall thickness. However, a load-independent measure of contractility in real-time from TEE monitoring and peripheral pressure can be obtained [15]. Because Acoustic Quantification is a pixel-classification technique rather than a true contour detection, only overall blood area can be calculated, not regional wall motion. Using minimum-cost contour tracking with cardiac management systems (ECHO-CMS) (MEDIS Medical Imaging Systems, Leiden, The Netherlands), continuous, connective, smooth contours allow calculations of regional wall motion, volume estimations, and user corrections. However, at present, this Quantification technique needs an off-line analysis workstation and user interaction [16].

Both Acoustic Quantification and ECHO-CMS are operator dependent and require much practice. The use of intravenous contrast might provide more consistent and reproducible results in the future, enabling appropriate treatment to be initiated without delay.

**Conclusion**

Development that are in progress will further influence the perioperative application of TEE. Stress TEE is a realistic option today, 3-dimensional TEE is already commercially available, and second-harmonic TEE has been introduced recently. Despite new developments in computed tomography and magnetic resonance imaging technologies, giving excellent spatial and temporal resolution, the relative low cost, speed, portability, and on-line results of TEE are much in favor of this technique in the management of patients in the perioperative setting. At present, TEE has a major impact on diagnosis in acute and subacute disease states in patients who are hemodynamically compromised. Further developments in automated...
border detection systems will allow continuous monitoring of the critical care patient, to guide the clinician to appropriate and more timely medical and surgical therapy.

REFERENCES

Metabolic interventions during cardiac surgery: focus on glucose–insulin–potassium

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Abstract

Metabolic modulation of postischemic myocardium by means of glucose, insulin and potassium (GIK) infusion has been used in the setting of acute myocardial infarction and cardiac surgery for the past 45 years. However, due to the wide range in reported infusion methods and outcome data and the lack of understanding of the mode of action of GIK, this technique is still controversial. In addition the risk of severe hypoglycemia is substantial. In the present mini-review a historical overview, the present situation, and future perspectives of the use of GIK are discussed.

Keywords: GIK, AMI, CABG, hyperglycemia, morbidity, mortality

Introduction

Since the days of the first cardiac surgical operations in the previous century, myocardial preservation has been an essential component of the successful outcome of these procedures. Although many different techniques to achieve myocardial preservation and modulation have been described over the past 50 years, this review will focus on the use of glucose–insulin–potassium (GIK) in patients with (post) ischemic myocardium.

It has been known for decades that administration of insulin in patients who have experienced ischemic events may have positive effects on morbidity and mortality. In 1962, Sodi-Pallares et al [1] showed, in experimental animals and in patients with acute myocardial infarction, that infusion of GIK reduced electrocardiographic signs of ischemia, reduced ventricular ectopy, limited infarct size, and improved survival. After this classic publication, enthusiasm for the use of GIK was somewhat dampened by a report from the Medical Research Council of the UK stating that GIK treatment failed to show any positive effect on survival in patients with acute myocardial infarction. However, publications describing the beneficial effect of “the metabolic cocktail” in patients with acute myocardial infarction continued to appear regularly. In 1995, Malmberg et al [2] demonstrated that insulin–glucose infusion improved long-term prognosis in diabetic patients with acute myocardial infarction. In 1997, Fath-Ordoubadi and Beatt [3] described a meta-analysis of nine randomized placebo-controlled studies all using GIK in patients with acute myocardial infarction. In 1997, Fath-Ordoubadi and Beatt [3] described a meta-analysis of nine randomized placebo-controlled studies all using GIK in patients with acute myocardial infarction. In 1998, the Estudios Cardiologicos LatinoAmerica (ECLA) study group [4] showed significant GIK-induced reduction in mortality in patients with acute myocardial infarction who also underwent a reperfusion strategy. In 2003, van der Horst et al [5] showed that the use of GIK therapy as an adjunct to coronary angioplasty in patients with acute myocardial infarction led to reduced mortality in patients with Killip class 1 only. Surprisingly, two recent large
New therapeutic approaches

Harry B. van Wezel

In the early days of cardiac surgery, GIK was used to induce cardioprotection and for weaning off bypass. However, the technique was more or less abandoned with the introduction of St Thomas’ cardioplegia and hypothermic cardiopulmonary bypass techniques in the mid-1970s and the subsequent availability of inotropic agents such as dopamine and dobutamine, and anesthetic agents with minimal cardiodepressant and vasodilatory effects such as the synthetic opioids.

In the 1980s, GIK therapy was “rediscovered” in the setting of cardiac surgery, for several reasons, including: an increase in the number of patients with unstable coronary syndromes (ie, severe myocardial ischemia before operation) requiring emergency coronary artery bypass grafting (CABG), the introduction of warm cardioplegia and cardiopulmonary bypass techniques (possibly allowing improved metabolic stimulation of normal myocardial enzyme function), and, more generally, because it appeared that the limits of adequate cardioprotection had been reached, especially in the growing cohort of elderly cardiac surgical patients with a history of severe, long-established coronary artery disease, chronic heart failure, and reduced contractile reserve before operation. This type of patient, in particular, frequently requires prolonged episodes of extracorporeal circulation for complicated coronary revascularization. In such patients, hemodynamic abnormalities and acute heart failure frequently develop after extracorporeal circulation.

Serious cardiovascular complications usually begin in the period after extracorporeal circulation. At that time, acute ventricular failure may develop—a condition probably caused by posts ischemic dysfunction or myocardial stunning. This phenomenon may thus be superimposed on pre-existing impaired ventricular function before operation.

The standard treatment consists of large doses of inotropic agents, glyceryl trinitrate, peripheral vaso-pressors, or combinations thereof, and intra-aortic balloon pumping. The use of β-adrenoceptor-stimulating therapy at high infusion rates, in particular, is associated with a number of undesirable side effects, including tachycardia and increased oxygen requirement of the (postischemic and dysfunctional) myocardium, and is often effective for only a limited period of time. The last of these may be the result of acute β-receptor downregulation, an increase in plasma lipids in the presence of high endogenous and exogenous catecholamine concentrations, insulin resistance, and a reduction in myocardial glucose uptake and utilization.

Merhige et al [10] performed a study to test the hypothesis that adrenergic stimulation suppresses myocardial uptake of glucose. They measured myocardial activity of \(^{18}\text{F}\)2-fluoro-2-deoxyglucose (FDG) in glucose-loaded dogs, randomly studied during dopamine infusion, during insulin infusion, and during their combined infusion. They concluded that myocardial uptake of FDG was significantly decreased when animals were treated with dopamine, compared with treatment of the same animals with insulin \((P < 0.03)\) or a combination of insulin and dopamine. The results demonstrated that dopamine inhibits the myocardial uptake of FDG by increasing the concentration of circulating free fatty acids, and that this inhibition can be reversed by insulin on the basis of substrate availability and competition [10]. These findings may have clinical importance in patients requiring long-term treatment with exogenous catecholamines.

During the past 10 years, the considerations described above led to renewed interest in the role of GIK therapy in patients undergoing CABG, especially after extracorporeal circulation and in the intensive care period. In 1995, Svedjeholm et al [11] used GIK successfully in an open, uncontrolled study in patients with heart failure. They reported almost full recovery of hemodynamic performance in the majority of patients at 6 h after bypass. In 1997, Lazar et al [12] undertook a randomized placebo-controlled study in patients with unstable angina during urgent CABG, and described reduced inotropic requirement, improved cardiac index, and requirements for a shorter duration of intensive care and shorter total hospital stay, associated with GIK therapy. Also in 1997, Taegtmeyer et al [13] reported a retrospective analysis of cardiac surgical patients with impaired left ventricular function randomly treated with GIK or placebo. They concluded that an “aggressive” therapy of posts ischemic dysfunctional myocardium appeared to be beneficial when pharmacological and mechanical measures had failed to improve cardiac function.

In 2001, van den Berghe and coworkers [14] demonstrated that intensive insulin therapy reduced...
morbidity and mortality in critically ill patients. They showed that, in particular, a subgroup of cardiac surgical patients receiving intensive insulin therapy (blood glucose concentrations between 4.4 and 6.1 mmol/L), starting at the time of their arrival in the intensive care unit and continuing until they were discharged to the ward, benefited significantly. This pivotal study showed for the first time that mortality can be significantly improved in cardiac surgical patients using “metabolic modulation”.

In 2000 and in 2004, Lazar et al [15,16] showed that the use of GIK led to reduced perioperative morbidity in diabetic individuals undergoing CABG. This was an important finding, because the findings of a study involving more than 140 000 patients undergoing CABG have confirmed that diabetes mellitus is a significant risk factor for short-term morbidity and mortality in this group [17].

Summarizing the findings of these studies using GIK techniques in cardiac surgical patients, there appears to be a beneficial effect of this approach on postoperative morbidity and mortality. This should be sufficient reason to develop further effective and safe techniques for the intravenous delivery of GIK and to unravel its mode of action.

**Mechanisms involved in the beneficial effect of glucose–insulin–potassium**

In spite of the widespread use of different GIK strategies in cardiac surgery and acute myocardial infarction, the exact mode of action underlying this approach remains to be elucidated. GIK research initially focused on and demonstrated the ability of insulin to influence substrate flux through myocardial metabolic pathways and transmembrane signaling. Furthermore, GIK infusions were found to attenuate postischemic disturbances in lipid and glucose homeostasis, in the setting of CABG and in acute myocardial infarction [1–11]. Recent evidence from animal studies suggested that GIK has the potential to reduce the inflammatory response [18]. In patients with acute myocardial infarction, Chaudhuri et al [19] were the first to demonstrate the anti-inflammatory effects of insulin, as reflected by a reduction in the absolute increase in postischemic concentrations of C-reactive protein and serum amyloid A. In 2005, Visser et al [20] showed for the first time in patients undergoing CABG that GIK, applied as a hyperinsulinemic normoglycemic clamp, has anti-inflammatory effects, as reflected by a significant reduction in postoperative C-reactive protein and serum amyloid A concentrations and a reduction in postoperative leukocytosis. This innovative approach to maintaining tight glycemic control may be useful, because acute (stress) hyperglycemia frequently develops in patients undergoing CABG, and it has been demonstrated in both rats and humans that proinflammatory cytokine concentrations are increased by acute hyperglycemia [21,22]. In addition, it has been demonstrated that stress hyperglycemia per se is associated with adverse outcome of CABG and acute myocardial infarction [23,24].

Future studies in (high-risk) cardiac surgical patients are required to assess the effect of different GIK infusion techniques on perioperative inflammatory control and its hypothetical association with reduced perioperative morbidity and mortality. This is especially important as, with increasing numbers of elderly and diabetic patients, the cohort of high-risk patients will grow during the next decades. Other fields of interest that may be beneficially affected by perioperative infusion of GIK include: the coagulation cascade, complement activation, neurohumoral stress responses, parameters reflecting insulin resistance (ketone bodies and lactate), the lipid profile, and leukocyte function.

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Protective effects of trimetazidine before and after coronary artery bypass surgery

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Abstract

Trimetazidine, a 3-ketoacyl coenzyme A thiolase inhibitor, is a well known metabolically active antianginal and anti-ischemic drug with cardioprotective effects in patients with diabetes, depressed left ventricular function, or both. In this review, emphasis is given to the beneficial effects of preoperative treatment with trimetazidine in patients undergoing coronary artery bypass surgery under cardiopulmonary bypass. In view of these cardioprotective effects, treatment with trimetazidine should be extended to the long-term postoperative period, especially in patients with incomplete revascularization or recurrent angina.

Keywords: Coronary artery bypass surgery, trimetazidine, myocardial ischemia, cardioprotection

Trimetazidine is a safe and well tolerated antianginal and anti-ischemic drug that has been widely used in Europe over the past 20 years [1–7]. It has a metabolic mechanism of action, which ensures optimization of myocardial energy metabolism through partial inhibition of fatty acid oxidation in cardiac myocytes, resulting in a shift of energy production from fatty acid β-oxidation to glucose oxidation [8,9]. At the biochemical level, trimetazidine acts by inhibiting 3-ketoacyl coenzyme A thiolase, the last enzyme in the mitochondrial chain of fatty acid oxidation [10]. To date, no deleterious pathophysiological or pharmacological interactions of trimetazidine with other drugs used in ischemic heart disease have been reported.

A series of recent studies yielded consistent evidence suggesting a cardioprotective action of trimetazidine in patients with ischemic cardiomyopathy [11,12] and in patients with diabetic coronary artery disease with depressed left ventricular function [13,14]. This cardioprotective effect consists of a significant progressive [12] and long-term [12–14] enhancement of left ventricular function and myocardial viability [11].

There has been increasing interest in the use of trimetazidine in diabetic patients, even those without overt ischemic heart disease, in view of its novel mechanism of action and its relevance in targeting the changes in myocardial energy metabolism that are observed in diabetes. The cardiac myocyte of the diabetic patient shows a shift in energy metabolism from glucose oxidation to fatty acid oxidation [15], which to a certain extent resembles the situation observed during the reperfusion phase after an episode of myocardial ischemia [16]. The energy metabolism profile in the diabetic heart reflects a state of permanent reperfusion after mild ischemia. This may help to explain the higher coronary morbidity and mortality in diabetic patients with coronary disease, as well as the higher prevalence of heart failure in diabetic individuals. By restoring the abnormal myocardial energy metabolism, trimetazidine may play a very important role in the long-term treatment of diabetic patients, even in the absence of clinically overt ischemic heart disease.

Coronary artery bypass surgery has a very important role in the long-term therapeutic strategy for ischemic...
Heart disease. Its purpose is to improve quality of life and reduce long-term coronary risk. Diabetic patients in whom coronary artery bypass surgery is indicated frequently have increased perioperative risks, even though their systolic left ventricular function may be preserved. In coronary patients with left ventricular dysfunction undergoing coronary artery surgery, preoperative enhancement of systolic function, minimization of perioperative ischemic risk and postoperative cardiac dysfunction, and accelerated functional recovery of hibernating myocardium are important issues. Trimetazidine has an important contribution to make in this setting.

The findings of several small-scale, double-blind, placebo-controlled studies, carried out in patients undergoing coronary artery bypass surgery under cardiopulmonary bypass, suggest a cardioprotective effect of trimetazidine. Fabiani et al [17] showed that preoperative use of trimetazidine (together with addition of the drug to the cardioplegic solutions) resulted in a reduction in surgical ischemia-reperfusion lesions. Tünerir et al [18] (Figure 1) found that preoperative use of trimetazidine was followed by a significantly smaller release of troponin T after surgery, with a reduction in surgical ischemia-reperfusion lesions. Another small-scale overt, placebo-controlled, parallel-group study [19] performed in patients with diabetes or left ventricular dysfunction, or both, who underwent coronary surgery under cardiopulmonary bypass, showed that patients treated with trimetazidine before operation displayed a clear trend toward reduction in perioperative ischemic events and requirement for inotropic drug treatment, and a significant reduction in early postoperative complications (triple composite endpoint: prevalence 11% compared with 56% in the control group; \( P < 0.005 \)).

Achieving complete revascularization during coronary artery bypass surgery is rarely possible. In most patients, several lesions remain out of reach of the surgical procedure. Consequently, and despite the fact that many patients become clinically asymptomatic, the territories of the arteries that were not operated upon should be protected by pharmacological therapy. Postoperative treatment should therefore include anti-ischemic drugs in combination with lifestyle interventions to address the risk of coronary events and slow down the progression of atherosclerotic disease. Here again, trimetazidine has a pivotal role, even in asymptomatic patients (in whom warning signs that would normally prompt the use of sublingual glyceryl trinitrate are lacking during ischemic episodes), and particularly so in diabetic individuals and patients with persistent depression of left ventricular function.

Recurrence of angina after surgical revascularization is now an emerging problem, mainly in diabetic patients. The causes of this phenomenon are several: progression of the atheromatous disease in the native arterial beds [20]; atheroma-like degeneration in the bypass conduits [20]; nonoptimal secondary preventive therapy after surgery; persistent lack of compliance with the medical treatment. In this setting, the technical difficulties and the greater risks attached to reintervention (percutaneous interventions or repeat surgery), especially in diabetic or elderly patients [20,21], confer a central role on medical treatment. Identification of “forgotten” risk factors, optimization of antihypertensive therapy, and prevention of new coronary events, by means of antianginal and antiischemic drug therapy, are crucial. Use of trimetazidine and other measures addressing small-vessel and microcirculatory dysfunction may result in important clinical improvement as far as angina is concerned. A review of the first TRIMetazidine in POLand (TRIM-POL) I trial data and a subanalysis of the TRIMPOL II trial in patients who underwent revascularization [21] (Figure 2) confirmed the positive clinical impact of trimetazidine in these patients. For the reasons

**Figure 1.** In patients undergoing coronary artery bypass grafting, the troponin T concentration (concn) was significantly \( (P < 0.001) \) lower in the group pretreated with trimetazidine (Vastarel; \( \rightarrow \)) than in the placebo group (\( \rightarrow \)). (Modified from Tünerir et al. [18], with permission.)

**Figure 2.** Effective relief of symptoms with trimetazidine (Vastarel) in patients with recurrent angina at baseline (W0) and after 12 weeks (W12). *\( P < 0.01 \). (Modified from Szwed [21], with permission.)
mentioned above, the addition of trimetazidine to the medical treatment regimen will be of greatest benefit to diabetic patients and patients with depressed left ventricular function.

Conclusion

There is increasing evidence that the action of trimetazidine on myocardial energy metabolism is responsible both for the antianginal effect of the drug and for the cardioprotection that is evident in patients with coronary disease who have diabetes or depressed left ventricular function, or both. Trimetazidine elicits progressive and sustained improvement in ventricular function. During coronary artery bypass surgery under cardiopulmonary bypass, trimetazidine contributes to reducing surgical ischemia-reperfusion damage, with a consequent reduction in perioperative ischemic events and need for inotropic drug treatment. In patients undergoing coronary artery bypass surgery, because of the antianginal, anti-ischemic, and cardioprotective effects of trimetazidine, its use may be extended to the long-term postoperative period, mainly in individuals with incomplete revascularization and patients with recurrent angina. In diabetic patients, even those without overt ischemic heart disease, trimetazidine may have a pivotal cardioprotective role.

REFERENCES

Hibernating myocardium and coronary artery bypass surgery

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Abstract

Left ventricular dysfunction occurs commonly as a result of coronary artery disease and may be associated with hibernating myocardium, a state of resting myocardial dysfunction resulting from reduced coronary blood flow that can be partially or completely reversed after myocardial revascularization. Assessment of myocardial viability can be achieved by several different methods, none of which is currently regarded as the gold standard. A readily available noninvasive method is dobutamine stress echocardiography. Surgical revascularization in patients with left ventricular dysfunction and suspected hibernating myocardium is associated with significant improvement in symptoms and outcome compared with medical treatment. However, selection of patients is of paramount importance.

Keywords: Coronary artery disease, hibernating myocardium, myocardial stunning, surgical revascularization

Case report

An 83-year-old man was referred to the chest pain clinic with a 1-year history of progressive exertional angina that had recently become more frequent (Canadian Cardiac Society [CCS] grade III) and breathlessness on exertion (New York Heart Association [NYHA] grade III). The patient had a past history of hypercholesterolemia, hypothyroidism, and had been an ex-smoker for 15 years. He performed an exercise stress test (Bruce protocol) as part of the initial assessment and completed 2 min 37s. The test was stopped because of chest pain associated with significant ST-segment depression (3.5 mm) in precordial leads V4 and V5 (Figure 1). He was started on a medication regimen comprising bisoprolol and a glyceryl trinitrate spray in addition to aspirin and atorvastatin, and was referred for a coronary angiogram.

Coronary arteriography revealed an occluded right coronary artery that filled retrogradely, a normal left main stem, severe diffuse disease in the left anterior descending artery, and a proximally occluded circumflex artery (Figure 2). Left ventricular injection suggested moderate ventricular function. A subsequent transthoracic echocardiogram revealed hypokinesia of the lateral, mid, and inferior apical left ventricular walls, with an estimated ejection fraction of 50–55%. The patient’s case was discussed in a joint Cardiology–Cardiac surgery meeting and he was felt to be a candidate for surgery if evidence of viable myocardium could be demonstrated. A dobutamine stress echocardiogram was requested.

On stress echocardiography, all myocardial segments demonstrated increased contractility in response to low-dose dobutamine, suggestive of viability (Figure 3), with 2–3 mm anterolateral ST-segment depression in leads V3–V6 on the electrocardiogram.

The patient underwent on-pump double coronary artery bypass surgery with a left internal mammary artery anastomosed to the distal left anterior descending artery and a saphenous vein graft to the first Obtuse Marginal (OM1) branch of the circumflex artery. His postoperative recovery was relatively uneventful, but he developed a superficial sternal...
infection, which responded to flucloxacillin. At 6-week follow-up, he was symptomatically much better, with an improved exercise tolerance (CCS grade I, NYHA grade II).

Discussion

Coronary artery disease, presenting as myocardial ischemia or infarction, is a leading cause of left ventricular dysfunction, with significant associated morbidity and mortality. Through better understanding of the pathophysiological mechanisms of left ventricular dysfunction and developments in cardiac imaging, it has become apparent that dysfunctional myocardium may remain potentially viable, affording an opportunity to restore blood flow by means of revascularization [1].

“Hibernating myocardium” (Table I) is a term used to describe a chronic condition of resting left ventricular dysfunction, caused by reduced coronary blood flow, that can be partially or completely reversed after

Figure 1. Exercise stress test showing significant ST-segment depression in the anterior territory. Baseline trace on the left, maximum (MAX.) ST-segment changes on the right. METs, metabolic equivalent of task units.

Figure 2. Angiogram showing a diffusely diseased left anterior descending artery and a proximal 90% circumflex stenosis. Retrograde filling of the right coronary artery from the left system suggests that this vessel is occluded.
myocardial revascularization, by reducing myocardial oxygen demand, or both [2,3].

A phenomenon of reversible global left ventricular dysfunction after a brief period of coronary arterial occlusion and reperfusion has also been identified, and is referred to as “myocardial stunning”, a state of postischemic myocardial dysfunction [4]. This state may contribute to reversible cardiac failure after acute infarction (with or without thrombolysis), immediately after coronary artery bypass grafting (CABG) or subsequent to cardiac arrest [2]. It has also been postulated that repetitive, intermittent ischemic episodes leading to a chronic myocardial stunned state could underlie the baseline contractile dysfunction of hibernating myocardial segments [5,6].

Several tests can assist in the evaluation of myocardial viability and contractile reserve and the identification of patients in whom there is the potential for recovery of left ventricular dysfunction with revascularization. These tests include myocardial perfusion imaging by thallium scanning or positron emission tomography (PET) – an increase in inotropy using

**Table 1. Characteristics of myocardial hibernation and methods of detection.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Method of detection</th>
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<tbody>
<tr>
<td>Persistent wall abnormality</td>
<td>Detected on echocardiography or ventriculography</td>
</tr>
<tr>
<td>Low myocardial blood flow</td>
<td>Reflected by defect in perfusion by thallium scanning or PET</td>
</tr>
<tr>
<td>Evidence of viability of at least some of the affected myocardial segments</td>
<td>Demonstrated by PET or simulation of contraction by inotropic agents (stress echo)</td>
</tr>
<tr>
<td>Functional improvement following return of normal coronary blood flow</td>
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PET, positron emission tomography.
pharmacological or nonpharmacologic stimulation during left ventriculography, echocardiography, or PET. Computed tomography and magnetic resonance imaging can also detect hibernating myocardium.

Detecting viable myocardium, whether hibernating or stunned, is of paramount clinical importance. The best method to assess viability, and the gold standard to which the techniques should be held, remain unclear. In the patient described here, dobutamine stress echocardiography was utilized. This method of noninvasive assessment of detecting hibernating myocardium has emerged as an important, readily available technique familiar to most cardiac surgeons [7]. Stress echocardiography examines the “inotropic reserve” of dysfunctional but viable myocardium through stimulation by inotropic agents—most commonly dobutamine, but also dopamine [8]. Viable myocardium shows improved global (ejection fraction) or regional contractile function (inotropic reserve), as assessed by simultaneous transthoracic echocardiography, in response to these agents [9].

It has been demonstrated in patients with myocardial viability on dobutamine stress echocardiography that a better outcome occurred with surgical revascularization than with medical treatment [10]. Similarly, the results of stress echocardiography can predict long-term outcome on the basis of the degree of myocardial viability (as measured by the number of segments, out of 12) before and after CABG [11]. However, despite a high predictive value, this method does appear to underestimate the extent of viable myocardium compared with results from thallium perfusion scanning [12]. The potential for recovery is assumed to be great enough to recommend revascularization when the total of hibernating and ischemic, but still functioning, myocardium is more than 60% of the left ventricle. In contrast, when more than 40% of the left ventricle is considered to be scarred or is metabolically inactive, surgical mortality is much greater, and the likelihood of the recovery of left ventricular dysfunction from CABG is much less. Accordingly, this generally means that the anterior wall territory as supplied by the left anterior descending artery must be viable [5,13,14].

In addition to myocardial viability, the degree of left ventricular enlargement is another important factor for the surgeon to take into account before considering the patient for revascularization. Several studies have demonstrated a relationship between left ventricular end-systolic volume as assessed by echocardiography and improvement in left ventricular dysfunction after CABG. When the left ventricular end-diastolic dimension is greater than 7 cm, operative mortality is likely to be high [15,16].

**Conclusion**

Most [17–20], but by no means all [21,22], studies have shown that revascularization of hibernating myocardium—identified by various techniques, including dobutamine stress echocardiography—can improve left ventricular dysfunction, clinical...
symptoms, and outcome, compared with what is achieved with medical therapy.

The indications, choice, and sequence of investigations in patients with left ventricular dysfunction and suspected hibernating myocardium remain a topic of debate, but several algorithms have been proposed (Figure 4). Essentially, all algorithms should include clinical assessment of heart failure, imaging to evaluate the presence of myocardial viability, and, if the patient is a candidate for invention, a coronary angiogram to assess their suitability for revascularization.

REFERENCES


Cardiac surgeons in the UK have been collecting outcome data at a national level since 1977. Data are now collected in considerable detail, and enable preoperative prediction of risks with increasing precision. The United Kingdom Cardiac Surgical Register has now metamorphosed into the National Adult Cardiac Surgical Database, which is becoming a powerful national tool for predicting perioperative risk and recording the success rates for cardiac operations.

The headline news is that a patient’s risk of death at the time of cardiac surgery has reduced dramatically over the past 25 years. Crude mortality rates compiled by the United Kingdom Cardiac Surgical Register show that the in-hospital risk of mortality for primary isolated coronary bypass grafting decreased from more than 6% in 1977 to 2% in 2003 [1]. These are pooled figures for all patients, including emergencies and salvage procedures, and illustrate a remarkable success rate for treating a disease that itself carries a high risk of premature death. Figures for primary isolated heart valve operations, and combined operations for valve and coronary disease show a similar trend (Table I).

Not surprisingly, this improvement has come in parallel with a huge expansion in the number of operations performed in the UK and Ireland, from approximately 7000 in 1977 to nearly 37 000 in 2003. This increase in numbers, together with the commitment of cardiac surgeons to meticulous and extensive collection of data, has enabled the development of sophisticated systems for predicting the risk of surgical mortality. The main systems in use are the Parsonnet score, the Euroscore, and Bayesian modeling. The Parsonnet and Euroscore systems are additive models that lend themselves readily to outpatient or bedside use. Various risk factors for mortality, including demographic variables, severity of illness and comorbidity, and the complexity of the proposed procedure, incur numerical scores that are added together. In the Parsonnet system, the total score determines one of five risk bands for the patient, ranging from very low, through moderate, to very high risk. The Euroscore system has been devised so that the additive score equates numerically to the actual predicted risk expressed as a percentage. For this reason, and because it is the most simple to use, Euroscore is the system preferred by most UK cardiac surgeons (Table II).

The fundamental flaw with both additive models is their reliance on historic outcomes, which leads to a tendency to overestimate the magnitude of the risk of mortality if outcomes continue to improve with time. An alternative strategy is to use Bayesian modeling, which is complex and requires computer assistance. The advantages are that it should be possible to make predictions for the individual patient on the basis of known outcomes for the hospital, or even for the surgical team. This requires real-time access to large data sets, which are currently being collected as part of the National Adult Cardiac Surgical Database project. Partly because of its complexity, Bayesian modeling is also the most accurate method for the prediction of risk and is sensitive to gradual changes in outcomes. Disadvantages include the needs both to
ensure completeness of data entry and to establish a reliable information technology infrastructure, including dedicated staff to administer it. As ever, the limiting factor is cost, but the potential value of this system in terms of quality assurance and detecting poor performance is likely to make it available within a few years.

Death is the easiest surgical complication to measure: the data are unequivocal and binary. Nationally, all deaths are registered locally and eventually reach the Office for National Statistics, which is linked to the National Adult Cardiac Surgical Database. In due course, this will provide longer-term survival data for patients after cardiac surgery and will permit survival analysis and predictions for individual patients according to all the variables used in the Euroscore system, and others such as geographical factors. Some long-term survival data of this kind are already available from the United Kingdom Heart Valve Registry, which has data on valve implantations since 1986.

Inevitably, cardiac surgery entails risks of other adverse outcomes, and many patients are more concerned about the possibility of stroke, prolonged ventilator dependency, or an operation failing to relieve their symptoms. Anxieties are also often expressed about longer-term outcomes, including the need for repeat surgery. Informed consent to surgery also needs to consider minor complications that may be disconcerting but are expected to resolve without longer-term sequelae. These include atrial fibrillation, renal dysfunction, wound infections, sternal malunion, paresthesiae, and others. Quantifying these other risks is much more difficult, because the evidence base is incomplete. In part, this is because of the complexity of collecting the data, particularly as wide variation can exist in the severity and duration of nonfatal complications, which consequently are difficult to quantify and analyze statistically.

Nevertheless, numerous studies have addressed the prediction of risk of stroke. We know that the risk factors for postoperative stroke include increasing age, a history of stroke or transient ischemic attack, known cerebrovascular disease, and open-heart surgery such as valve repair or replacement, as opposed to coronary bypass, which takes place largely on the surface of the heart. The majority of perioperative strokes are presumed to be embolic, either from atheroma dislodged from the diseased intima of the ascending aorta during surgical manipulation or clamping, or from thrombus. Many of these strokes can resolve quite rapidly, sometimes within days. In general, the rates of postoperative stroke have declined in recent years, despite continued increase in the average age of patients presenting for surgery. The reasons for this are not clear, and are probably multifactorial, including the widespread preoperative prescription of statins.

Table I. UK and Ireland mortality rates for cardiac surgical operations (first-time procedures) in 1977 and 2003.

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>1977</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td></td>
<td>6.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Valve</td>
<td></td>
<td>9.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Valve + CABG</td>
<td></td>
<td>16.9</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Table II. The Euroscore additive risk model for cardiac surgery. Preoperative scores for a specific patient are added to obtain a percentage mortality risk for the procedure.

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Age (per 5 years over 60 years)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>1</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Chronic lung disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Extracardiac arteriopathy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Neurological dysfunction</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine concentration (&gt; 200 mmol/L)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Critical preoperative state</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac status</td>
<td>Active endocarditis</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unstable angina</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderate LV function (EF 30–50%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Poor LV function (EF &lt; 30%)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction within 90 days</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension (&gt; 60 mm Hg)</td>
<td>2</td>
</tr>
<tr>
<td>Operation status</td>
<td>Previous cardiac surgery</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Emergency</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Other than isolated CABG</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Surgery on thoracic aorta</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Surgery for postinfarct septal rupture</td>
<td>4</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass grafting; EF, ejection fraction; LV, left ventricle.
Communicating surgical risks to patients is a delicate art. The right balance of keeping expectations realistic without frightening the patient can be difficult to find, and is always open to legal challenge. To add to the difficulties, patients’ perceptions of the concept and magnitude of risk show wide variation, as does their appetite for information. Current guidance advises full discussion and quantification of the risks of death, stroke, and any other major complication that may affect the decision to consent to surgery, together with mention of minor complications that occur relatively frequently and of which the patient should be forewarned.

For most patients, the risks of cardiac surgery are low, and significantly lower than the risk of not operating.

REFERENCE

### Sexual Dysfunction and Cardiac Risk (the Second Princeton Consensus Conference)


Recent studies have highlighted the relation between erectile dysfunction (ED) and cardiovascular disease. In particular, the role of endothelial dysfunction and nitric oxide in ED and atherosclerotic disease has been elucidated. Given the large number of men receiving treatment for ED, concerns regarding the risk for sexual activity triggering acute cardiovascular events and potential risks of adverse or unanticipated drug interactions need to be addressed. A risk stratification algorithm was developed by the First Princeton Consensus Panel to evaluate the degree of cardiovascular risk associated with sexual activity for men with varying degrees of cardiovascular disease. Patients were assigned to three categories: low, intermediate (including those requiring further evaluation), and high risk. This consensus study from the Second Princeton Consensus Conference corroborates and clarifies the algorithm and emphasizes the importance of risk factor evaluation and management for all patients with ED. The panel reviewed recent safety and drug interaction data for three phosphodiesterase (PDE)-5 inhibitors (sildenafil, tadalafil, vardenafil), with emphasis on the safety of these agents in men with ED and concomitant cardiovascular disease. Increasing evidence supports the role of lifestyle intervention in ED, specifically weight loss and increased physical activity, particularly in patients with ED and concomitant cardiovascular disease. Special management recommendations for patients taking PDE-5 inhibitors who present at the emergency department and other emergency medical situations are described. Finally, further research on the role of PDE-5 inhibition in treating patients with other medical or cardiovascular disorders is recommended.

**Commentary**

The First Princeton Consensus Conference in 1999 established important guidelines for evaluating cardiac patients and counseling them on the safety of sexual intercourse and the treatment of erectile dysfunction. The Second Conference updated these guidelines and reviewed in detail the treatments available for erectile dysfunction. In this paper, the phosphodiesterase type-5 inhibitors are discussed from the point of view of being both a treatment for erectile dysfunction and an exciting form of cardiovascular therapy. Management recommendations include risk assessment and specific disease advice; the cardiac safety of treatments of erectile dysfunction is also considered, supported by two practical algorithms. There is a statement on hypogonadism and testosterone treatment, and emphasis on the importance of primary care management, prevention and lifestyle modification – “towards a patient-centred approach”. With vascular disease recognized as the most important cause of erectile dysfunction, and erectile dysfunction being in turn recognized as a marker of cardiovascular risk in men with erectile dysfunction but no cardiac history, these guidelines are essential reading for all involved in treating cardiac patients and those with erectile dysfunction.

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### Downregulation of peroxisome proliferator-activated receptor-alpha gene expression in a mouse model of ischemic cardiomyopathy is dependent on reactive oxygen species and prevents lipotoxicity


The peroxisome proliferators-activated receptor-α (PPARα), a transcription factor that modulates fatty acid metabolism, regulates substrate preference in the heart. In acute ischemia there is a switch in substrate preference from fatty acids to glucose, but the expression of metabolic genes in repetitive ischemia is not well described. In a mouse model of ischemic cardio-
myopathy induced by repetitive ischemia/reperfusion, we postulated that downregulation of PPARα is regulated by reactive oxygen species and is necessary for maintaining contractile function in the heart. Repetitive closed-chest ischemia/reperfusion (15 min) was performed daily in C57/BL6 mice, mice overexpressing extracellular superoxide dismutase, and mice treated with the PPARα agonist, WY-14,643. Echocardiography, histology, and expression of candidate genes were measured at 3, 5, 7, and 28 days of repetitive ischemia/reperfusion and 15 and 30 days after discontinuation of the ischemia/reperfusion. Repetitive ischemia/reperfusion was associated with a downregulation of PPARα-regulated genes and levels of both myosin heavy chain isoform transcripts, which was reversible on discontinuation of ischemia/reperfusion. Overexpression of extracellular superoxide dismutase prevented the downregulation of PPARα-regulated genes and myosin isogenes by repetitive ischemia/reperfusion. Furthermore, reactivation of PPARα in mice exposed to repetitive ischemia/reperfusion worsened contractile function, induced microinfarctions, and increased the intramyocardial deposition of triglyceride – features suggestive of cardiac lipotoxicity.

We conclude that the expression of metabolic and myosin isoform genes in repetitive ischemia/reperfusion is mediated by reactive oxygen species. Furthermore, we suggest that downregulation of PPARα in repetitive ischemia/reperfusion is an adaptive mechanism that is able to prevent lipotoxicity in the ischemic myocardium.

Commentary

The heart normally metabolizes a balance of fatty acids and carbohydrates to support the high energy demands of the heart. In severe hypertrophy and heart failure, this balance of fuel use is shifted, such that fatty acid metabolism is decreased and the heart shifts to using a greater amount of glucose as a source of energy. This shift in energy metabolism is accompanied by alterations in the expression of metabolic genes, such that genes that modulate fatty acid metabolism are downregulated whereas genes controlling glucose metabolism are upregulated. An important nuclear transcriptional factor controlling this process is PPARα. A decrease in PPARα decreases the expression of a number of genes of fatty acid metabolism in cardiac hypertrophy and heart failure. The hibernating myocardium – a condition characterized by a reversible cardiac dysfunction – also shows a decrease in the expression of genes controlling fatty acid metabolism. What was not clear is whether this downregulation of genes controlling fatty acid metabolism contributes to contractile dysfunction in hibernating myocardium, cardiac hypertrophy, or heart failure. This study by Dewald et al provides compelling data to show that downregulation of fatty acid metabolic genes in a mouse experimental model of repetitive ischemia and reperfusion is an adaptive mechanism that is able to protect the heart. They also show that reactivation of the expression of genes of fatty acid metabolism (by treatment of mice with a PPARα agonist) worsens contractile function, induces microinfarctions, and increases intramyocardial accumulation of lipid. These data suggest that downregulation of fatty acid metabolism in hibernating myocardium is an adaptive mechanism, and that the modulation of metabolism to inhibit fatty acid oxidation may provide a pharmacological target for cardioprotection in repetitive ischemia and reperfusion.

Gary Lopaschuk

Reperfusion-induced translocation of δPKC to cardiac mitochondria prevents pyruvate dehydrogenase reactivation


Despite the disparity in evidence regarding pyruvate dehydrogenase (PDH) activity, cardiac efficiency and recovery of contractile function in postischemic hearts can be improved by pharmacological stimulation of PDH or infusion of pyruvate. Therefore, identification of factors that regulate PDH activity during ischemia/reperfusion may enhance the potential for therapeutic intervention. PDH is responsible for the conversion of pyruvate derived from glycolysis to acetyl coenzyme A for Krebs cycle activity and represents a highly regulated and critical site for the control of glycolytic flux and the production of ATP. Enzyme activity is regulated, in part, by phosphorylation- and dephosphorylation-dependent inhibition and activation, respectively. The aim of this study was to investigate signaling mechanisms that control inhibition and reactivation of PDH during reperfusion. We tested the hypothesis that the redox-sensitive δ-isofrom of protein kinase C (δPKC) is involved in regulation of PDH during reperfusion. Rat hearts were perfused in the Langendorff mode, and a specific peptide inhibitor of δPKC was used to test the contribution of δPKC to ischemia- and reperfusion-induced alterations in PDH activity. In addition, hearts were infused with H2O2 to gain insight into potential mechanisms responsible for concerted regulation of δPKC and PDH during ischemia/reperfusion. Finally, in-vitro experiments were performed to address potential mechanisms by which δPKC influences the phosphorylation state of PDH.
Commentary

PDH was shown to decline in activity during cardiac ischemia. Although a fractional regain in PDH activity occurred on reperfusion, the activity of the enzyme remained depressed relative to control values. δPKC translocated to the mitochondria during reperfusion, and prevention of δPKC translocation resulted in complete recovery in PDH activity. Thus δPKC prevents reactivation or promotes continued inhibition of PDH (or both) in response to cardiac reperfusion. Reperfusion of ischemic myocardium is associated with enhanced generation of free radicals, and pro-oxidants have been shown to regulate protein function either directly or indirectly through the modulation of other regulatory molecules, one example of which is the novel δ isoform of PKC. Infusion of the δPKC activator H$_2$O$_2$ during normoxic perfusion, to mimic one aspect of cardiac reperfusion, resulted in a loss of PDH activity that was largely attributable to translocation of δPKC to the mitochondria. Evidence indicates that reperfusion-induced translocation of δPKC is associated with phosphorylation of one subunit (the E1α subunit) of PDH, and this phosphorylation inhibits its activity. In this study, H$_2$O$_2$-dependent loss of PDH activity was partially prevented by the inhibition of δPKC translocation. In contrast, prevention of translocation of δPKC to the mitochondria during reperfusion resulted in full reactivation of PDH. This difference may be explained by previous findings that translocation of δPKC to the mitochondria results in release of cytochrome c that could, in turn, amplify mitochondrial production of free radicals. Thus prevention of translocation of δPKC to the mitochondria during reperfusion would be expected to prevent δPKC- and redox-dependent inhibition of PDH.

Danielle Feuvray