

# The need for inotropic drugs in anesthesiology and intensive care

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The management of the failing heart represents an increasingly frequent challenge to both anesthesiologists and intensive care physicians, due to the increased prevalence of ventricular dysfunction in the population and to the ever-expanding indications for the surgical treatment of cardiac disease. Inotropic drugs are nowadays invaluable therapeutic tools in the treatment of perioperative heart failure and of the different forms of heart failure found in intensive care unit clinical practice. Postoperative myocardial dysfunction is a major concern in the setting of cardiac surgery since it is extremely frequent and is related to a greater morbidity and mortality. The different forms of heart failure, the rationale and the indications for the use of inotropic drugs in anesthesiology and intensive care are discussed in this review.

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Perioperative heart failure is nowadays a major clinical problem, and perioperative cardiac morbidity is the leading cause of death following surgery and anesthesia<sup>1</sup>. As a result of the demographic changes in western populations, steadily moving towards an increase in average age, the number of patients with extensive cardiovascular disease presenting for both cardiac and non-cardiac surgery has dramatically grown. Moreover, an increasing number of sicker and older patients with ventricular dysfunction is now undergoing cardiac surgery because of the ever-expanding indications for surgical intervention, supported by continuous technologic improvements: patients with a more impaired ventricular performance, less correctable fundamental disease and highly unstable preoperative states are being increasingly submitted to surgery, and cardiac surgery in octogenarians is no longer an exception<sup>2,3</sup>. Finally, specific requirements and procedures of cardiac surgery, aimed at achieving a bloodless surgical field and a quiescent heart, constitute an inevitable additional insult to the heart.

Demographic and epidemiological changes in the population have analogous implications in the context of intensive care medicine. The increasing prevalence of congestive heart failure in the population<sup>4</sup> determines a more frequent finding of this severe comorbidity even in patients requiring crit-

ical care for other indications. A particular pattern of myocardial dysfunction may also be observed in septic shock patients<sup>5</sup>. Obviously, the same considerations about the intraoperative management of heart failure regard the postoperative care of the cardiac surgical patient. For all of these reasons, the management of the failing heart (either acute or chronic with a superimposed acute event) represents an increasingly frequent challenge to the intensive care physician and even more to the anesthesiologist. Pharmacological research has over many years yielded important therapeutic tools to be employed in these settings.

## Inotropic drugs in non-cardiac surgery

In the setting of non-cardiac surgery, there obviously is less need for intravenous inotropes. Modern anesthesia (both intravenous and inhalatory) creates a particular status (protection from pain reflexes, blunting of the sympathetic response, vasodilation) which is beneficial to the failing heart. Nevertheless, the use of inotropes may be required in case of<sup>6</sup>:

- atrioventricular or sino-atrial blocks (especially in the elderly or in patients with pre-existing conduction system disease); the use of chronotropic drugs (isoproterenol) when pacing is not available or feasible;

- urgency/emergency surgery, or elective major surgery (hepatic, vascular), in patients with hemodynamic derangement determining an insult to a heart with an unknown reduced coronary reserve, or with preexisting valvular disease;
- elective or urgent major vascular surgery (thoracic or abdominal aortic surgery) in patients with known chronic heart failure, in whom aortic clamping procedures may give rise to an excessive afterload for the failing heart;
- myocardial dysfunction in septic shock patients admitted to surgery;
- perioperative pulmonary thromboembolic complications.

Patients with a reduced/depressed systolic heart function will otherwise (in the majority of non-cardiac surgical settings) benefit from vasodilation and protection from sympathetic responses determined by anesthetic drugs. The anesthetic management will obviously focus on the proper monitoring of the cardiac function and on the optimization of preload, afterload and eventually on heart rate and rhythm, but rarely resort to inotropic drugs. Postoperative management may also require monitoring in an intensive care setting. There might be, in some cases of excessive vasodilation, the need for vasoconstrictors rather than inotropes, in order to maintain an adequate coronary perfusion pressure.

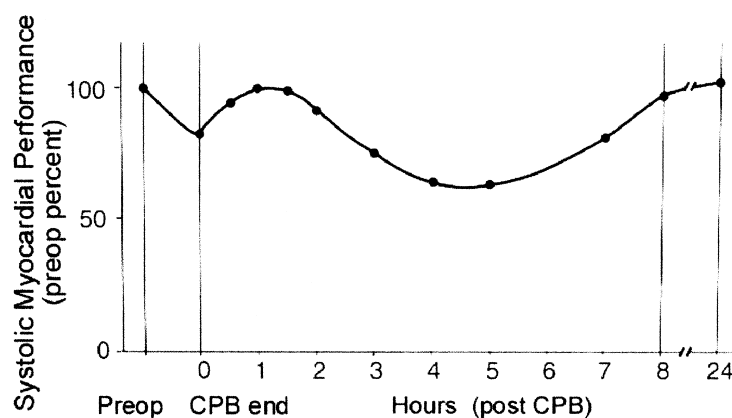
### Inotropic drugs in cardiac surgery

**Postoperative myocardial dysfunction.** A significantly impaired ventricular performance is a common occurrence after cardiac surgery, both in patients with a normal or abnormal preoperative ventricular function<sup>7-10</sup>. Along with a decreased cardiac index, even the right and left ventricular ejection fractions may be decreased to 35 to 75% of their pre-cardiopulmonary bypass (CPB) levels. In fact, current techniques used to achieve an optimal surgical environment include the use of CPB, the infusion of cardioplegia solutions with intervening peri-

ods of ischemia and reperfusion of the previously ischemic heart after aortic cross-clamp removal. Since many years, several factors have been found to contribute to myocardial dysfunction secondary to cardiac surgical procedures: the ischemic insult of aortic cross-clamping<sup>11</sup>, inadequate myocardial protection<sup>12</sup>, hypothermia with cardioplegia and topical iced solutions<sup>12</sup>, surgical trauma, inadequate surgical repair, activation of the complement cascade by CPB<sup>13</sup>, reperfusion injury<sup>14</sup>, premature or excessive titration of inotropic agents<sup>15</sup>. The very techniques used to avoid perioperative injury may thus themselves contribute to this complication.

The postoperative ventricular dysfunction following cardiac surgery is quite similar to, and may be termed as a form of, myocardial stunning: a myocardial dysfunction following a brief ischemic event, unassociated with morphologic injury (necrosis), and thus reversible after a period of convalescence<sup>16,17</sup>. The heart undergoing this type of surgery is in fact subjected to ischemic and reperfusion injury at multiple points during the operation<sup>18</sup>, resulting in various degrees of cytosolic calcium accumulation, free oxygen radical generation, and myocyte and myocardial edema. Although originally observed in the regionally ischemic myocardium after temporary coronary occlusion<sup>19</sup>, post-surgical stunning includes both regional and global dysfunction, since regional wall motion abnormalities have an impact on the global performance, and aortic cross-clamping and cardioplegic arrest actually determine a controlled global ischemia. In contrast to regional stunning, which is mainly unilateral, post-surgical stunning may involve both the right and left ventricles<sup>7,20,21</sup>.

Weaning from CPB represents a critical phase in which the eventual ventricular dysfunction may fully appear, and inotropic drug support may be required. Many studies have in the past identified and monitored systolic myocardial dysfunction during the first hours to days following cardiac surgery. A biphasic pattern of depression occurs (Fig. 1): the recovery from the initial compromise after having weaned from CPB is followed



**Figure 1.** Recovery pattern of cardiac function: postoperative changes in the systolic myocardial performance after heart surgery in patients undergoing cardiopulmonary bypass (CPB), shown as the percentage of the preoperative myocardial performance. Adapted from Royster<sup>22</sup>.

by a second period of low myocardial performance which reaches its nadir 3 to 6 hours after weaning from CPB. The time to full recovery is usually 8 to 24 hours, but the return to baseline function is often delayed in patients with a worse preoperative ventricular function<sup>20-22</sup>. This knowledge is really important in deciding whether or not to begin inotropic therapy (for example in a patient with an adequate, but borderline, ventricular performance immediately after weaning from CPB), and in the timing of weaning from inotropic support (once required, it should be maintained for at least 10 to 12 hours, or much longer in patients with a poor preoperative function).

Postoperative ventricular dysfunction does not only influence the systolic performance. After CPB, the compliance and relaxation properties of the left ventricle may be decreased, and the diastolic pressure-volume relationship shifted upward, with an inadequate ventricular filling or, at least, adequate filling at the expense of elevated filling pressures<sup>23,24</sup>, predisposing to a decreased coronary blood flow and compromised subendocardial perfusion. More commonly, diastolic dysfunction results as a consequence of the inability of the left ventricle to empty, but some patients may present with this problem as the predominant factor contributing to the low cardiac output after CPB<sup>25</sup>. This is particularly true in patients with marked left ventricular hypertrophy (hypertrophic obstructive cardiomyopathy, aortic stenosis, hypertensive cardiomyopathy) in whom the effects of CPB and aortic cross-clamping may dangerously exacerbate a preexisting diastolic dysfunction.

In addition to myocardial stunning and the disease process for which the surgery is being conducted, other factors may contribute to the postoperative ventricular dysfunction with further acute ischemic injury: unfortunate events before the institution of CPB (severe hypotension secondary to pump failure, tachycardia, ventricular fibrillation, other arrhythmias, failed angioplasty with dissection or pre-occlusion), inadequate cardioplegia delivery (inappropriate technique, native vessel stenosis), ventricular distension, incomplete revascularization, and surgical complications (inadvertent coronary lesions, graft lumen obstructions).

**Predictors of the need of inotropic support.** Several studies have found a correlation between pre- and intraoperative factors and inotropic drug requirements, both in coronary artery bypass and other cardiac surgery<sup>7,20,22,26-29</sup>. A poor left ventricular function continues to be the most important predictor of a postoperative low output syndrome and of the necessity of inotropic drugs. Other widely recognized predictors are older age, a prolonged aortic cross-clamping and the indices of preoperative ventricular dysfunction (Table I)<sup>6,19,21,26-28,30</sup>. However, some patients not meeting any predictive criteria fail to satisfactorily wean from CPB in spite of the various predictors currently used.

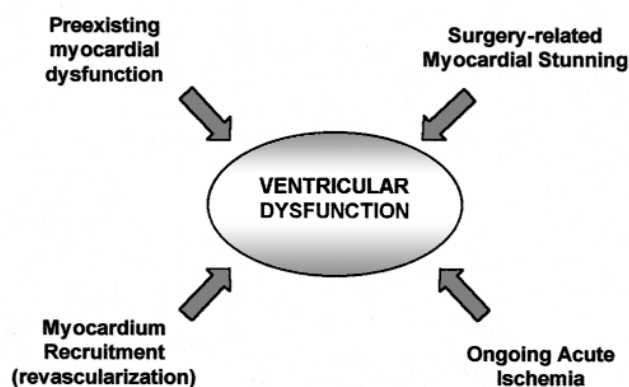
**Table I.** Predictive factors of inotropic support, as highlighted by several studies<sup>6,19,21,26-28,30</sup>.

Low ejection fraction (< 45%)
History of congestive heart failure
Cardiomegaly
High LVEDP following ventriculogram
MI within 30 days of operation*
Older age (> 70 years)
Longer duration of aortic cross-clamping
Prolonged cardiopulmonary bypass*
Urgent operation
Re-operation*
Female gender*
Diabetes mellitus*

LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction. \* statistical significance for coronary artery bypass surgery only.

Four main factors must anyway be taken into account when considering the use of an inotropic drug, as they closely interact in determining the magnitude of postoperative heart failure and the difficulty in weaning from CPB (Fig. 2): 1) the extent of preexisting ventricular dysfunction; 2) the phenomenon of cardiac surgery-related myocardial stunning; 3) possible ongoing acute ischemia (which must be treated, prior to or while supporting the heart with inotropes); 4) the improved ventricular function resulting from the restoration of blood flow to the chronically ischemic or hibernating myocardium following coronary artery bypass grafting (when performed).

**When to use an inotrope.** Even though in some institutions inotropes are routinely administered after weaning from CPB, a better rationale may be based on the following criteria: a) the expected need for inotropes, bearing in mind the above-mentioned preoperative and intraoperative criteria and the expected pathophysiology of the specific underlying pathology (for example, after valve replacement of an isolated severely stenotic aortic valve, inotropic support will rarely be required); b)



**Figure 2.** Factors determining the extent of postoperative ventricular dysfunction and potential troubles in weaning from cardiopulmonary bypass.

clinical evidence of depressed myocardial function, as guided by hemodynamic monitoring (measurement of heart rate, blood pressure, cardiac output, visual inspection of the heart, transesophageal echocardiographic inspection); c) empirical drug choice and titration, with careful hemodynamic monitoring. Prolonged, inappropriate or excessive treatment with inotropic medication may in fact augment the perioperative ischemic injury<sup>15,30</sup> and adversely affect myocardial function and weaning from CPB; this is especially true when tachycardia, arrhythmias and oxygen consumption are enhanced.

The initiation of inotropic drugs before weaning from CPB is controversial and has not been thoroughly evaluated in large controlled clinical studies, but the consequences of a failed wean may be severe (ventricular distention, additional pump time, systemic hypotension/hypoperfusion, subsequent need for multiple inotropes or mechanical assistance, neurological sequelae, additional costs). Many authors therefore advocate early inotropic intervention, on the basis of the expected need, to provide the heart with the increase in contractility necessary to support the circulation and expedite weaning, with beneficial effects<sup>31-33</sup>.

**Choice of the inotrope.** The ideal positive inotropic agent should enhance contractility (both right and left ventricular) without any significant increase in heart rate, preload, afterload, and myocardial oxygen consumption. It should also enhance the diastolic function, maintain the diastolic coronary perfusion pressure and thus an adequate myocardial blood flow<sup>34</sup>. It finally should have rapid titration times and onset of action and a short half-life. But no ideal inotrope exists, and neither does an inotrope without some limitation in its use. The currently available inotropic drugs include beta-adrenergic agonists (dopamine, dobutamine, epinephrine, isoproterenol, norepinephrine, dopexamine), phosphodiesterase (PDE) inhibitors (amrinone, milrinone, enoximone), and the recently introduced calcium sensitizers (levosimendan). As known, the first two groups of drugs both act by increasing the intracellular cyclic adenosine monophosphate (cAMP) and calcium concentrations, while the third does not. Other pharmacological agents (vesnarinone, saterinone, pimobendan, forskolin) have in the past been tried without success. A detailed description of the pharmacology of inotropes goes beyond the aim of this review, but some of the properties of these drugs and some theoretical concepts of inotropic administration in the context of perioperative heart failure will be here discussed.

*Catecholamines* are the mainstay of current inotropic treatment and they exert a positive inotropic effect mainly by stimulation of the cardiac beta-receptors; they can be divided into more potent (epinephrine, isoproterenol, noradrenaline) and milder (dopamine, dopexamine, dobutamine). Dopamine and dopexamine do not act as direct beta-agonists, as they achieve part of their effect by releasing the myocardial norepinephrine stores or by preventing the re-uptake of norepinephrine.

The dose-dependent effects of *dopamine* (acting on the dopaminergic receptors) are not specific and are influenced by receptor regulation, intra- and interindividual variability and drug interactions; its alpha-mediated vasoconstrictor action (mainly at high doses) renders it more suitable when a combination of inotropic support and vasoconstriction is required. Initially the inotrope of choice after cardiac surgery, dopamine has now been shown to cause more tachycardia than epinephrine at comparable doses<sup>35</sup> and to determine higher filling pressures than dobutamine for similar hemodynamic indices<sup>36</sup>. In addition to its dopaminergic action, *dopexamine* (synthetic analogue of dopamine) has a higher affinity for beta<sub>2</sub> than beta<sub>1</sub> receptors and may determine an increase in splanchnic blood flow and urinary output. In the management of patients after CPB, it was found to induce tachycardia<sup>37</sup> with an increase in cardiac index equivalent to that of dobutamine<sup>38</sup> and with vasodilation<sup>39</sup>. As a result of its dopaminergic properties, dopexamine may be valuable in the patients with septic shock after CPB<sup>40</sup>. *Dobutamine*, with a predominant beta<sub>1</sub> activity and a balanced peripheral beta<sub>2</sub> and alpha<sub>1</sub> activation, increases the cardiac output and reduces the diastolic filling pressures, with a mild dilating effect on the systemic vascular resistance. In paced cardiac surgery patients, dobutamine increases myocardial oxygen supply and coronary blood flow, unlike dopamine, which tends to worsen the oxygen supply-demand balance<sup>41</sup>: dobutamine seems to be therefore a more suitable inotrope in coronary artery disease. But, being the increases in heart rate a major determinant of myocardial oxygen consumption, these favorable effects could be lost when dobutamine induces tachycardia. After coronary artery surgery, dobutamine produces a less favorable heart rate response compared to equipotent doses of epinephrine<sup>42</sup>. Dobutamine also shows a greater inotropic effect on the right ventricular myocardium than dopamine<sup>43</sup>. The development of tolerance (within 48-72 hours) in prolonged administration is one of the limits of its use<sup>44</sup>.

With regard to *epinephrine*, traditional concerns have stressed an association with tachycardia, vasoconstriction and myocardial ischemia<sup>45</sup>, but this appears not to be true at low doses, due to a prevalent stimulation of beta-adrenoreceptors (after cardiac surgery, epinephrine 0.01 to 0.03 µg/kg/min induces less tachycardia compared with dobutamine 2.5-5 µg/kg/min, for a similar hemodynamic improvement)<sup>42</sup>. Epinephrine is a potent inotrope for both the right and left ventricles. *Norepinephrine*, mainly through an alpha-adrenergic action but not devoid of beta-stimulating activity, may benefit patients in whom it is necessary to maintain an adequate perfusion pressure, such as in right ventricular dysfunction or excessive vasodilator states. *Isoproterenol* has potent chronotropic and arterial vasodilator (both systemic and pulmonary) effects, due to its beta<sub>1</sub> and beta<sub>2</sub> activity. Limited in use in most patients with coronary artery disease<sup>46</sup>, it is the inotrope of choice in

acute bradyarrhythmias, atrioventricular blocks and orthotopic heart transplantation.

Comparative studies have not shown clinically significant differences among the various *PDE III inhibitors*: they all share a significant inotropic effect (not altered by previous beta-blocker therapy or beta-receptor downregulation), a pulmonary and systemic vasodilator action, fewer chronotropic effects than dobutamine<sup>47</sup>, with an apparent favorable effect on myocardial oxygen consumption<sup>48</sup>. The use of PDE inhibitors has been reported to be beneficial in the treatment of right heart failure<sup>49</sup>, and in determining vasodilation of arterial coronary bypass grafts and native vessels<sup>50,51</sup>. Even though by increasing the intracellular cAMP concentration all inotropic agents also improve diastolic function, PDE inhibitors seem to exert a greater lusitropic effect compared to epinephrine<sup>52</sup>, perhaps because they also cause a significant afterload reduction. Compared to dobutamine, PDE inhibitors also seem to have a lesser proarrhythmic effect<sup>53</sup>. Potential drawbacks include a possible excessive vasodilator effect (associated with bolus administration) and the long duration of action.

*Levosimendan*, a novel calcium-sensitizing agent with inodilator properties, works with a dual mechanism of action: it increases contractility without increasing oxygen consumption through calcium sensitization, and it produces venous, arterial, and coronary vasodilation through smooth muscle  $K_{ATP}$  channels<sup>54</sup>. It may also exert a beneficial effect on diastolic function through the calcium dependency of its troponin C sensitization<sup>55,56</sup>, and through its anti-stunning effect<sup>54</sup>. Though limited, the presently available perioperative experience with levosimendan after coronary bypass surgery is encouraging, showing a hemodynamic benefit comparable to that of dobutamine or PDE inhibitors, without a significant increase in oxygen consumption<sup>57,58</sup>.

**Indications in specific settings.** As described above, the problem of postoperative myocardial dysfunction is quite a complex matter, and a clear understanding of its principles and features in different clinical settings is important when deciding which inotropic drug(s) is/are to be used. Different types of clinical scenarios of heart failure can be encountered during weaning from CPB (Table II).

During coronary artery bypass graft surgery, inotropes may be needed in case of preexisting ventricular dysfunction or in case of unsuccessful revascularization if the intra-aortic balloon pump alone is not enough (along with the pharmacological treatment of ischemia). In most cases, myocardial recruitment by revascularization will otherwise determine no or only mild inotrope requirement in this setting<sup>59</sup>. In the emergency revascularization of acute myocardial infarction, dobutamine and PDE inhibitors may be the most beneficial inotropes, as they may better influence the oxygen delivery/consumption balance<sup>41,53</sup>.

**Table II.** Common clinical settings of heart failure encountered in cardiac surgery, mainly during weaning from cardiopulmonary bypass.

Previous reduced EF after CABG, or unsuccessful revascularization
Inotropic support during off-pump CABG
Left heart failure in surgical treatment of dilated cardiomyopathy (mitral valve surgery, high-risk conventional revascularization, dynamic cardiomyoplasty, Batista procedure)
Left ventricular dysfunction after ventricular aneurysm resection
Ventricular dysfunction after valvular surgery
Ventricular dysfunction after ascending aorta or aortic arch surgery
Right or biventricular failure after heart transplantation
Right heart failure after LVAD implantation
Right heart failure in lung transplantation
Right heart failure in pulmonary thromboendarterectomy
Heart failure in emergency cardiac surgery (acute valvular disease, ascending aorta dissection, acute MI, cardiac tamponade)
Ventricular dysfunction in congenital heart disease correction

CABG = coronary artery bypass graft; EF = ejection fraction; LVAD = left ventricular assist device; MI = myocardial infarction.

Cardiac output during off-pump coronary artery bypass graft surgery is reduced due to both right and left ventricular dysfunction<sup>60</sup>, mainly when the heart is displaced out of the pericardium for grafting the circumflex artery. When the Trendelenburg position, fluid infusion and a vasoconstrictor do not suffice to restore acceptable hemodynamics, the use of inotropes with no or only a mild vasodilator action (dopamine, dobutamine) is required<sup>61</sup>.

In patients with preexisting chronic heart failure (especially those presenting for the surgical treatment of a dilated cardiomyopathy: mitral valve surgery, revascularization, remodeling surgery), the myocardium presents unique features attributable to chronic catecholamine hyperstimulation:  $\beta_1$  receptor downregulation with a reduction in receptor density (proportional to the severity of systolic dysfunction), a shift in proportion of  $\beta_1$  vs  $\beta_2$  receptors (from the normal 80:20 to 60:40)<sup>62,63</sup>, and low intracellular levels of cAMP<sup>64</sup>. Furthermore, acute changes in beta-adrenergic receptor function can also occur during cardiac surgery<sup>65,66</sup>. Catecholamine stimulation alone is thus submaximal, reaching a *plateau* effect on adenylyl cyclase<sup>62</sup>, and even the response to PDE inhibitors alone could be blunted (by a reduced intracellular cAMP pool): combination therapy (i.e. a PDE inhibitor administered along with a beta-adrenergic inotrope, dobutamine or epinephrine) may therefore be the treatment of choice in these patients, exploiting a synergistic action and minimizing the side effects of the single drugs (PDE inhibitors may cause excessive vasodilation, counteracted by catecholamine alpha-stimulation, and vice versa). As a chronically dysfunctional myocardium is also characterized by the depletion of the myocardial stores of nor-epinephrine<sup>67</sup>, indirect beta-adrenergic agents (dopamine, dopexamine) would be inadequate.

The same principles apply in case of extreme ventricular dysfunction: severe myocardial stunning (due to

surgical complications determining long aortic cross-clamping times or, in emergency surgery, to pre-CPB ischemia inducing extensive reperfusion injury) may require important inotropic support with combination therapy.

When choosing an inotropic agent, the problem of diastolic dysfunction must be taken into account. When marked ventricular hypertrophy is present (severe aortic stenosis, hypertrophic obstructive cardiomyopathy) and is complicated by the onset of edema subsequent to inadequate myocardial protection, the use of beta-adrenergic agents may worsen the diastolic function with a decrease in cardiac output. No inotropes at all (or inotropes with a better effect on ventricular relaxation, such as PDE inhibitors, if systolic dysfunction coexists) should be used. The maintenance of adequate preload and perfusion pressures is also essential<sup>68</sup>. For similar reasons, after the resection of a ventricular aneurysm (which may greatly reduce the compliance of the left ventricular chamber), a better therapeutic choice to enhance the diastolic function would be to administer PDE inhibitors. During partial left ventriculectomy surgery (Batista procedure) both problems of severe systolic and diastolic dysfunction coexist, frequently requiring a combination of inotropes, vasoconstrictors, and mechanical support<sup>69</sup>.

With regard to valvular surgery, the ventricular response to successful surgery varies according to the various forms of valve disease<sup>70</sup>. After aortic valve replacement for moderately severe aortic stenosis, the afterload is markedly reduced, but left ventricular hypertrophy and diastolic dysfunction persist: inotropic support is rarely needed, unless inadequate myocardial protection or prolonged aortic cross-clamping complicate the procedure. All other left-sided valvular diseases may bare a certain degree of systolic dysfunction induced by the long-standing abnormal loading conditions of the ventricle. After successful aortic valve replacement for chronic aortic insufficiency, ventricular dilation and dysfunction persist, requiring adequate preload and inotropes. With mitral stenosis, preoperative atrial fibrillation and pulmonary hypertension may limit the potential for the recovery of full function, whereas with chronic mitral regurgitation, surgical correction acutely increases the afterload in a dilated heart: in both cases, treatment with inotropes is warranted. Acute aortic and mitral regurgitation both pose a great risk of severe ventricular dysfunction after surgical correction and require aggressive inotropic support even preoperatively. Finally, tricuspid regurgitation is almost always associated with right ventricular dysfunction (both for pulmonary hypertension and primary ventricular failure), and hence inotropes are beneficial even in this context.

Although the carefully selected and well preserved transplanted heart has a normal contractile function, it lacks the normal autonomic control of chronotropy and inotropy because of the interruption of the autonomic

innervation. Routine inotropic support after orthotopic cardiac transplantation thus includes isoproterenol (to increase the automaticity, inotropism and pulmonary vasodilation) and dopamine (to add further support whilst maintaining the systemic perfusion pressures)<sup>71</sup>. The most frequent problems derive from: the sudden exposure of the unconditioned donor right ventricle to an excessive afterload stress imposed by the elevated pulmonary vascular resistance, with right heart failure<sup>72</sup>; the prolonged graft ischemia or inadequate myocardial protection (excessive pre-harvesting catecholamine exposure), with possible biventricular failure. Both these situations require aggressive inotropic support and the management of right ventricular failure<sup>71</sup>.

Right ventricular dysfunction may occur in different perioperative settings (heart transplantation<sup>72</sup>, lung transplantation<sup>73</sup>, pulmonary thromboendarterectomy<sup>74</sup>, left ventricular assist device implantation<sup>75</sup>, inadequate myocardial protection), and the pharmacological approach to this condition deserves particular mention. A high right ventricular filling pressure (traditional volume loading in right ventricular infarction treatment) restores normal hemodynamics only if the pulmonary vascular resistance, right ventricular contractility, and interventricular septum geometry are normal<sup>34</sup>. Successful management must thus include: a reduction in right ventricular afterload (pulmonary vasodilators, better if selective, with a non-systemic action)<sup>76</sup>; the augmentation of the contractile strength (inotropes effective on the right ventricular myocardium: dobutamine, isoproterenol, epinephrine, PDE inhibitors) with the aim of reducing the right ventricular size and improve left ventricular filling; the maintenance of the aortic blood pressure, especially if high fixed pulmonary resistance is present (vasoconstrictors may augment the right ventricular performance when the coronary perfusion pressure is reduced by the increased right ventricular end-diastolic pressure)<sup>77,78</sup>.

After heart transplantation, right heart failure may develop immediately or during the early postoperative period<sup>71</sup>, especially in patients with significant preoperative pulmonary hypertension. In lung transplantation, several critical stages place the usually hypertrophied right ventricle at a high risk of failure<sup>79</sup>: the induction of anesthesia (hypotension), the initiation of positive-pressure ventilation (increase in right ventricular afterload, hyperinflation with circulatory collapse), the institution of one lung ventilation (severe hypoxia), the clamping of the pulmonary artery (sudden increase in afterload), the unclamping of the pulmonary artery (profound hypotension). Norepinephrine, in addition to low-dose epinephrine (or dobutamine) and cautious fluid loading, is often invaluable in this difficult setting<sup>73</sup>. After thromboendarterectomy, inotropes may be necessary in case of significant preoperative right ventricular dysfunction or if surgery is not successful in re-establishing the patency of the pulmonary vessels, taking care to avoid a supranormal cardiac output (responsible for

overflow to the reperfused areas and causing reperfusion pulmonary edema)<sup>74</sup>. Norepinephrine may also be helpful. Finally, after left ventricular assist device implantation varying degrees of right ventricular failure usually occur and these patients are invariably in a state of vasodilator shock; both inotropes (dobutamine and amrinone) and vasoconstrictors (norepinephrine) are beneficial. Severe refractory vasodilation may require the addition of epinephrine<sup>75</sup>.

### Inotropic drugs in the intensive care setting

Besides the need for inotropic drugs in the postoperative care of the cardiac surgical patient, which follows the above-mentioned principles, other intensive care unit (other than coronary) clinical scenarios may require the use of intravenous inotropes (Table III). A brief review of these clinical settings is discussed below.

Patients with chronic heart failure may be admitted to the intensive care unit when the acute exacerbation is so severe as to warrant mechanical ventilation. In this group of patients, if refractory to standard first-line therapy with diuretics and vasodilators, short-term inotropic treatment (dobutamine, PDE inhibitors) is commonly performed with benefit<sup>80,81</sup>.

If adequately resuscitated using fluids, patients with septic shock develop a hyperdynamic circulatory state (low systemic resistance, high cardiac output). Nevertheless, sepsis-related myocardial dysfunction is one manifestation of this complex cardiovascular derangement, and the metabolic demand can exceed myocardial performance: even though in case of sepsis, cardiogenic shock with a low cardiac output is rare, normotensive sepsis and septic shock are associated with a reduced post-resuscitation left ventricular ejection fraction<sup>82-84</sup>, acute ventricular dilation<sup>82,84</sup> and a depressed response to volume resuscitation (flattening of the Frank-Starling relationship)<sup>85,86</sup>, which typically peak within the first few days and resolve by 7 to 10 days in survivors<sup>82</sup>. Besides a decreased contractility, myocardial compliance abnormalities may also have a sub-

stantial role in this form of reversible myocardial depression<sup>84,86</sup>. Right ventricular dysfunction (with a reduction in ejection fraction and dilation) parallels left ventricular failure, independently of the increase in right ventricular afterload<sup>82,87-89</sup>. Moreover, the cardiovascular profiles of non-survivors are characterized by an inability to dilate their ventricles, or by persistence of the ventricular dysfunction and of the hyperdynamic state<sup>89,90</sup>. It is thus now understood that acute reversible ventricular dilation may represent an adaptive response to septic stress<sup>91</sup>. Recent studies have shown that patients with sepsis and septic shock can exhibit resistance to the normal vasopressor and inotropic action of catecholamines<sup>92</sup>, and that a preserved response to dobutamine stimulation can be used to differentiate survivors and non-survivors<sup>93,94</sup>. Part of the complex pathogenesis of this peculiar form of myocardial dysfunction is probably attributable to adrenergic desensitization<sup>92</sup>, in addition to, or as a consequence of, the effects of humoral and intracellular mediators, such as cytokines and nitric oxide<sup>95</sup>.

Being the main aim of the hemodynamic management of septic shock the re-establishment of an adequate systemic perfusion and oxygenation, the mainstay of treatment includes the optimization of the preload and the use of vasopressors and inotropes<sup>96</sup>. Different inotropic drugs are used to treat sepsis-induced cardiac dysfunction, mainly dobutamine. In a recent *in vitro* study, a greater effectiveness of amrinone over epinephrine has been observed<sup>97</sup>, but the clinical use of inodilators in this setting may be limited by their potent systemic vasodilator effect<sup>98</sup>. Calcium sensitization has been proposed as a new approach to increase myocardial contractility, and is still under investigation. Catecholamines with beta-mimetic effects are often also used to increase oxygen delivery: under conditions of an adequate volume replacement, dobutamine increases the cardiac output and oxygen delivery to a greater extent than dopamine<sup>99</sup>. However, conflicting results emerge from different studies trying to demonstrate an improved survival with supranormal goal-directed therapy (targeted at a supranormal cardiac index)<sup>100,101</sup>, and the question as to whether dobutamine or dopamine should be first used in the treatment of septic shock cannot yet be answered<sup>102</sup>.

Even though functional cardiac injuries can be frequently observed as a result of blunt trauma<sup>103</sup>, patients with myocardial contusion/concussion requiring inotropic support are rare<sup>104,105</sup>, unless previous chronic heart failure is present or complications of polytrauma ensue: the population of traumatized patients is often younger than the one with the highest prevalence of cardiac disease, and the non-surgical complications of cardiac trauma are usually mild.

Patients with severe chronic obstructive pulmonary disease, despite the presence of pulmonary hypertension, usually have a normal right ventricular contractility<sup>106</sup>,

**Table III.** Clinical settings of heart failure encountered in (non coronary) intensive care units.

Postoperative care of cardiac surgery patients
Non-surgical causes of heart failure requiring mechanical ventilation: chronic heart failure with superimposing critical illness or precipitating factors, severe myocarditis
Septic shock patients with myocardial dysfunction
Myocardial contusion in thoracic trauma or polytrauma
Right ventricular dysfunction in mechanically ventilated patients with acute respiratory failure (severe chronic obstructive pulmonary disease, acute asthma)
Right ventricular dysfunction in acute respiratory distress syndrome patients
Cardiogenic shock in patients with severe pulmonary thromboembolism

and, even when admitted to the intensive care unit for acute respiratory failure requiring mechanical ventilation, rarely need to be treated with inotropes, unless other complicating factors intervene. In patients with the acute respiratory distress syndrome a chain of events may lead to right ventricular dysfunction: severe hypoxia with reactive pulmonary vasoconstriction can determine pulmonary hypertension; furthermore, mechanical ventilation with high pressure regimens determines both an increase in the right ventricular afterload and a reduction in the right ventricular preload. This creates extremely unfavorable conditions for the right ventricle, posing a great risk of right ventricular ischemia and failure. The failing right ventricle may also interfere with the correct left ventricular functioning due to the interventricular dependency<sup>107</sup>. Part of the complex therapeutic approach to the acute respiratory distress syndrome includes fluid restriction, so as not to worsen the lesional edema. Hence, norepinephrine is commonly used in order to maintain the perfusion pressures; dobutamine may also be used to improve the contractility of the right ventricle and maintain an adequate cardiac output<sup>108</sup>.

Finally, acute massive pulmonary thromboembolism determines a severe form of right ventricular failure which may necessitate aggressive inotropic support (dopamine, dobutamine, epinephrine), if fluid infusion therapy and vasoconstrictors (norepinephrine) alone cannot maintain hemodynamic stability<sup>109</sup>.

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