Amrinone, in combination with norepinephrine, is an effective first-line drug for difficult separation from cardiopulmonary bypass

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A crucial element for weaning patients from cardiopulmonary bypass (CPB) rests on the selection of an appropriate therapeutic regimen. Amrinone, a phosphodiesterase III inhibitor, combines inotropic support with pulmonary and systemic vasodilatation, without increasing heart rate (HR) or myocardial oxygen consumption. These characteristics should be useful in the failing heart during weaning from CPB. Nineteen patients were included in this prospective, open-labelled, phase IV study when systolic blood pressure (SBP) <80 mmHg, and diastolic pulmonary artery pressure (DPAP) >15 mmHg or central venous pressure (CVP) > 15 mmHg, during progressive separation from CPB. At that moment, CPB flow was increased to alleviate heart failure and amrinone administered as a bolus (0.75 mg · kg^{-1}) followed by an infusion (10 μg · kg^{-1} · min^{-1}). Weaning from CPB was then resumed and haemodynamic variables (SBP, DPAP, CVP and HR) were compared with those measured at CPB flow when failure had first occurred. Failure to wean from CPB occurred at 57 ± 28% of full pump flow. After the amrinone bolus, DPAP and CVP decreased by 20% and 21% respectively. Subsequently, 16 patients required the infusion of norepinephrine (4–8 μg · min^{-1}) to maintain a SBP >80 mmHg. Heart rate remained unchanged after the bolus of amrinone, after separation from CPB, and no arrhythmias were noted. Successful weaning from CPB was possible 12 ± 8 min after the amrinone bolus. Weaning resulted in a cardiac index similar to that measured pre-bypass. Amrinone is rapidly effective during weaning from CPB and, in combination with norepinephrine, provides the necessary inotropic support during this unstable period.

Lorsque le sevrage de la circulation extracorporelle (CEC) s'avère difficile, le choix d'un régime thérapeutique approprié est d'une importance capitale. L'amrinone, un inhibiteur de la phosphodiestérase de type III, augmente l'inotropie et dilate les circulations pulmonaire et systémique, sans augmenter la fréquence cardiaque ou la consommation d'oxygène du myocarde. Ces caractéristiques pharmacologiques devraient être bénéfiques durant le sevrage de la CEC. Furent inclus dans cette étude prospective de phase IV dix-neuf patients dont la pression artérielle systémique (PAS) était <80 mmHg alors que la pression diastolique de l'artère pulmonaire (PDAP) >15 mmHg ou la pression veineuse centrale >15 mmHg durant le sevrage lent et progressif de la CEC. Lors de l'échec du sevrage, le débit de la CEC était augmenté de façon à soulager la défaillance cardiaque et un bolus d'amrinone était administré (0.75 mg · kg^{-1}), suivi d'une perfusion (10 μg · kg^{-1} · min^{-1}). Le sevrage était alors repris et les paramètres hémodynamiques comparés au débit de CEC où l'échec était survenu initialement. L'échec du sevrage survint à 57 ± 28% du plein débit de CEC. Après le bolus d'amrinone, la PDAP et la PVC diminuèrent de 20% et de 21% respectivement. Par la suite, une perfusion de norépinéphrine (4–8 μg · min^{-1}) fut requise chez 16 patients afin de maintenir la PAS > 80 mmHg. Le rythme cardiaque demeura stable après l'administration du bolus d'amrinone et

Key words
SURGERY: cardiac;
PHARMACOLOGY: amrinone;
SYMPATHETIC NERVOUS SYSTEM: pharmacology, norepinephrine.

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Supported by a grant from Sanofi-Winthrop, Inc., and presented at the Annual Meeting of the Canadian Anaesthetists' Society, Toronto, Canada, 1992.

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Accepted for publication March 4, 1993

après le sevrage de la CEC, et aucune arythmie ne fut notée. Les patients furent complètement sevrés de la CEC 12 ± 8 min après le bolus d'amrinone et leur index cardiaque après la CEC était superposable à celui mesuré avant la CEC. Ainsi, l'amrinone agit rapidement et efficacement durant le sevrage de la CEC et, en association avec la norépinéphrine, procure au myocarde le support inotrope nécessaire durant cette période de grande instabilité hémodynamique.

When myocardial dysfunction results in the low output syndrome (LOS) after cardiac surgery, a crucial element for weaning patients from cardiopulmonary bypass (CPB) rests on an appropriate therapeutic regimen. A recent review of our practice at the Montreal Heart Institute showed that cardiac surgery is becoming more complex, and is being performed on older, sicker patients. Reoperations and emergency surgeries are more frequent than ten years ago.[1] The incidence of compromised ventricular function has increased both in patients coming for valvular surgery and for coronary artery surgery.[1] At this point of time, 54.4% of our patients require some form of inotropic support to separate from, or after, CPB (1,528/2,811 patients in our current database). Thus, the need for inotropic support during emergence from CPB may be expected to remain or even increase in the future, despite controversy as to the optimal agent(s) that should be used.[2-5]

Traditionally, catecholamines have been the mainstay of ventricular support in the period surrounding cardiac surgery. Sympathomimetics successfully increase cardiac output (CO), but at the expense of tachycardia and the production of dysrhythmias.[6,7] These undesirable side effects produce an imbalance in the myocardial oxygen supply/demand ratio.[8] Consequently, an increase in HR may be associated with ischaemia, and may also increase the risk for postoperative myocardial infarction, as demonstrated in patients undergoing coronary artery bypass grafting.[9]

Amrinone, a bipyridine derivative, is a selective phosphodiesterase (PDE III) inhibitor, approved for intravenous use in 1984 in the United States of America. Amrinone increases intracellular cyclic AMP (cAMP) by inhibiting its hydrolysis by PDE III. This increase of cAMP promotes the phosphorylation of proteins which, in turn, influence calcium in the cell by three mechanisms: (1) sarcolemmal calcium influx through slow calcium channels is increased, (2) a faster release of stored calcium from the sarcoplasmic reticulum is allowed, and (3) the rate of myocardial relaxation is improved by enhanced removal of calcium from the myofilaments.[10] Thus, amrinone not only improves contraction during systole, but also enhances relaxation during diastole, the so-called lusitropic effect of amrinone. In addition to this inotropic and lusitropic cardiac action, inhibition of PDE III leads to dilatation of the peripheral and pulmonary vasculatures.

In cardiac surgical patients, amrinone has been used successfully to support cardiac function and reduce pulmonary vascular resistance in patients waiting for cardiac transplantation.[11] Before surgery, amrinone is also effective for the treatment of right heart failure and pulmonary hypertension associated with mitral stenosis.[12] Numerous reports and studies attest to the efficacy of amrinone to treat the LOS after open heart surgery.[13-19] During surgery, Royster *et al.* administered amrinone to seven patients, with severe left ventricular contractile dysfunction at cardiac catheterization, to facilitate separation from CPB. Amrinone was found to be a successful first-line inotropic agent in this situation.[20] Not unexpectedly, the combination of inotropic support and pulmonary and systemic vasodilatation, without an increase in HR or myocardial oxygen consumption,[21] proved to be useful characteristics of amrinone during weaning from CPB. However, post-surgical cardiac function was not assessed in these patients, and amrinone was administered in anticipation of the need for inotropic support,[20] rather than for the treatment of established LOS.

Therefore, we undertook the present study to describe the efficacy of amrinone as the first-line inotrope to facilitate separation from CPB in patients developing LOS during attempted weaning from extracorporeal circulation.

Methods

The study was approved by the Institutional Review Board and by the Ethics Committee of the Montreal Heart Institute. Patients gave informed consent to participate in this open-labelled, stage IV drug evaluation and were included if they required inotropic support (based on pre-defined criteria) during weaning from CPB. Patients were not enrolled in the study if they met the following criteria: (1) patients with severe uncorrected outflow obstruction due to aortic or pulmonic valve disease, (2) preoperative clinically significant renal or hepatic dysfunction, thrombocytopenia or coagulopathy, (3) known hypersensitivity to amrinone, (4) serious dysrhythmia, uncontrollable ventricular tachycardia, and (5) pregnant or nursing women.

On the morning of surgery, patients received their usual cardiac medication, pre-medication with morphine 0.1–0.15 mg · kg^{-1} and scopolamine 0.4 mg *im*, and supplemental oxygen by nasal cannula. Upon arrival in the operating room, intravenous, radial, and pulmonary artery catheters were inserted under local anaesthesia, after application of a 2-lead ECG (D_2 and V_5), a non-invasive

blood pressure monitor, and a pulse oximeter. During anaesthesia and surgery, CO_2 and anaesthetic agents were continuously monitored in the gases expired by the patient. Nasopharyngeal and urinary bladder temperatures were measured routinely.

Anaesthesia was induced with a combination of midazolam (0.15 $mg \cdot kg^{-1}$) and an opioid (fentanyl 50 $\mu g \cdot kg^{-1}$ or sufentanil 5–8 $\mu g \cdot kg^{-1}$), and supplemented with a volatile agent as necessary. Pancuronium in combination with vecuronium was used to provide muscular relaxation. A complete haemodynamic profile was obtained after induction of anaesthesia, prior to sternotomy. Management of CPB was as follows. A bubble oxygenator (Bentley 10 plus, Bentley Laboratories Inc., CA) was primed with 1,500–2,000 ml crystalloid solution containing 5,000 units heparin and flows of 2.4 $L \cdot min^{-1} \cdot m^{-2}$ (normothermia) to 1.8 $L \cdot min^{-1} \cdot m^{-2}$ (hypothermia) were obtained with a Sarns (Sarns Inc., Ann Arbor, Michigan) roller pump. In most patients, mild systemic hypothermia to 32°C (urinary bladder temperature) was maintained during aortic cross-clamping and the myocardium was preserved by infusion of cold crystalloid or blood cardioplegic solution into the aortic root. Two surgeons preferred to maintain normothermia throughout CPB in their patients.

Patients were rewarmed to a urinary bladder temperature of 35°C and ventilation with oxygen 100% was resumed. Slow and progressive weaning from CPB was then attempted, after return of a stable cardiac rhythm (spontaneous or pacemaker-induced). Patients were included in the study if systolic blood pressure (SBP) was less than 80 mmHg, and diastolic pulmonary artery pressure (DPAP) or/and central venous pressure (CVP) was/were greater than 15 mmHg during progressive separation from CPB without inotropic or mechanical support of cardiac function. When failure to wean was established according to these criteria, CPB flow was increased to alleviate heart failure and amrinone 0.75 $mg \cdot kg^{-1}$, diluted in 50 ml of saline, administered in two to three minutes, followed by an infusion of 10$\mu g \cdot kg^{-1} \cdot min^{-1}$. Weaning from CPB was then resumed down to CPB flow where failure had first occurred (CPB_{fail}) and post-amrinone haemodynamic variables were measured. Post-amrinone haemodynamic data (HR, SBP, DPAP and CVP) were compared with the haemodynamic variables measured at CPB_{fail}. After acquisition of the post-amrinone haemodynamic data, norepinephrine (NE) was infused to maintain SBP above 80 mmHg when necessary.

Patient demographics, ASA physical status, preoperative left ventrical ejection fraction, surgical intervention, duration of surgery, total duration of CPB, time between CPB_{fail} and successful separation from CPB, occurrence of dysrhythmias, and the use of other inotropes were recorded. A second complete haemodynamic profile was obtained immediately after weaning from CPB.

Results are presented as mean ± SD. Post-induction and post-separation haemodynamic profiles, and pre- and post-amrinone haemodynamic data at CPB_{fail}, were compared with Student's t test for paired data. A $P < 0.05$ was considered significant.

TABLE I Patient demographics and surgical procedures performed

Sex	10M / 9F
Age	56 ± 10 years
Height	164 ± 7 cm
Weight	72 ± 16 kg
ASA physical status III/IV	11 / 8
Left ventricular ejection fraction ($n = 11$)	52 ± 12%
Preoperative medications	
- Nitrates ($n = 10$)	
- β-blockers ($n = 7$)	
- Calcium antagonists ($n = 10$)	
- Digitalis ($n = 6$)	
Valve/revascularization	7 / 12
Internal mammary artery/vein graft ($n = 12$)	14 / 19

TABLE II Comparisons of haemodynamic profiles during and after separation from CPB

	Post-induction	*CPB_{fail}*	*Post-amrinone*	*Post-CPB*
SBP (mmHg)	106 ± 20	72 ± 5	77 ± 11	97 ± 16
DPAP (mmHg)	18 ± 5	20 ± 5	16 ± 4*	21 ± 5
CVP (mmHg)	12 ± 4	14 ± 4	11 ± 4*	14 ± 4†
HR (beats · min^{-1})	64 ± 15	80 ± 13	81 ± 13	83 ± 11†
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.4 ± 0.5	n/a	n/a	2.6 ± 0.6
SVR (dynes · sec · cm^{-5})	1160 ± 284	n/a	n/a	1060 ± 390
PVR (dynes · sec · cm^{-5})	180 ± 110	n/a	n/a	169 ± 110

All data mean ± SD.
*$P < 0.05$ compared with CPB_{fail}.
†$P < 0.05$ compared with post-induction.
n/a: not available.

Results

According to our criteria, 19 eligible patients required inotropic support during separation from CPB and were included in the study. Patient demographics, preoperative left ventricular ejection fraction, and surgical interventions performed are presented in Table I. The post-induction haemodynamic profile was normal (Table II). Duration of CPB was 116 ± 22 min, while surgery lasted 253 ± 52 min. The aorta was cross-clamped during 69 ± 19 min, and separation from CPB was first attempted 29 ± 19 min after the aorta was unclamped.

Failure to wean occurred at 57 ± 28% of full CPB flow. Post-amrinone, DPAP and CVP decreased by 20% and 21% respectively (Table II). Blood pressure and HR remained unchanged after administration of amrinone (Table II), and no dysrhythmias were noted. Weaning was accomplished in 12 ± 8 min in all patients. A NE infusion (4–8 $\mu g \cdot min^{-1}$) was required in 16 patients to maintain SBP over 80 mmHg. The haemodynamic profile after separation from CPB showed an increased CVP and HR when compared to post-induction values. Post-CPB HR was not different from HR during weaning from CPB. Post-CPB, SBP, DPAP, cardiac index (CI), systemic and pulmonary vascular resistances (SVR and PVR) were not different from post-induction values.

Two patients required intravenous nitroglycerin for the treatment of ischaemia, and dobutamine was infused in one patient because of a CI of 1.8 $L \cdot min^{-1} \cdot m^{-2}$ after separation from CPB despite administration of amrinone and NE. Preoperative intra-aortic balloon counterpulsation (IABC) was continued postoperatively in one patient. Two patients required IABC eventually in the ICU, but not for separation from CPB. One of these two patients sustained a postoperative myocardial infarction. There were no deaths.

Discussion

To our knowledge, apart from a subset of seven patients in the study by Dupuis *et al.*,[22] this is the only report on the use of amrinone as the first-line inotrope to treat incipient heart failure during attempted separation from CPB after cardiac surgery. Amrinone was administered therapeutically, rather than on the presumption that separation from CPB would be difficult. Failure to wean, i.e., incipient heart failure or LOS, was based on objective haemodynamic criteria. Criteria are always somewhat arbitrary, but the ones chosen for the present study are compatible with those published in standard textbooks.[23,24] While a PDAP or a CVP of more than 15 mmHg may not, *per se*, be diagnostic of left- or right-sided ventricular failure, the association of a relatively high filling pressure with a low systolic blood pressure (less than 80 mmHg) is usually a reliable indicator of forthcoming difficulties with separation from CPB in our experience. In other words, patients who cannot generate a SBP of more than 80 mmHg, with a filling pressure of 15 mmHg or more, will often require inotropic support.

Weaning from CPB is always an intense period for the anaesthetist and the surgeon. During this time it is difficult to implement protocols that do not closely parallel accepted practice. The main advantage of a protocol such as the one described is that it was readily acceptable to all members of the team, while relying on objective criteria for decision-making. Our protocol reflects the usual conduct of CPB at our institution. The development of such standardized protocols for the study of inotropes during separation from CPB is important, since CO cannot be measured until the process is completed. While it can be argued that the observed improvement in inotropy may be due to the prolongation of CPB *per se*, the rapidity with which separation was accomplished following the administration of amrinone suggests that the drug itself was effective, rather than the extension of the reperfusion period. However, the effect of time will always be a limitation of this type of study. Also, this was an open-labelled study and a double-blind, randomized controlled experiment will be necessary to confirm our results.

Uncertainty exists as to the appropriate dose of amrinone required in cardiac surgical patients. In patients with congestive heart failure, Edelson *et al.* demonstrated a linear relationship between the plasma concentration of amrinone and increases in CO, with a plasma concentration of 1.7 $\mu g \cdot ml^{-1}$ resulting in an average increase in CO of 30%.[25] Bailey *et al.* have demonstrated that plasma concentrations above this threshold level of therapeutic effect can be maintained only with the administration of a bolus dose of amrinone of 1.5–2 $mg \cdot kg^{-1}$, followed by an infusion of 10 $\mu g \cdot kg^{-1}$.[26] Three reasons may explain the effectiveness of smaller doses in clinical practice. First, contrary to patients with congestive heart failure, inotropic support is often required for only a short time, while the myocardium recovers from the period of ischaemia secondary to aortic cross-clamping. Second, all patients may not require a 30% increase of CO to achieve successful separation from CPB. Third, 16 of 19 patients required NE to increase SBP. In addition to its α effects, NE also has potent β effects and the apparent effectiveness of the 0.75 $mg \cdot kg^{-1}$ loading dose of amrinone may have been exaggerated by the β-receptor stimulation of NE. Nevertheless, in practice, the doses of amrinone used in this study (those recommended by the manufacturer) are usually sufficient to produce the required therapeutic effect.[19] The use of these lower doses may blunt the decrease in SVR often noted with the administration of higher doses. Should a further increase in CO be required upon discontinuation of CPB, an additional bolus of amrinone 0.75 $mg \cdot kg^{-1}$ may be administered to increase plasma concentration.

As mentioned above, norepinephrine given to 16 of our 19 patients may have contributed to part of the inotropic response upon completion of separation from CPB. However, NE was infused at a rate of 4–8 $\mu g \cdot min^{-1}$ while it has been shown that NE 10 $\mu g \cdot min^{-1}$ results in an unchanged or decreased CO and an increased SVR.[27] Also, it is our clinical experience in patients separated from CPB with amrinone alone, who

subsequently require NE to maintain an adequate perfusion pressure, that the infusion of NE does not increase CO any further, but may even decrease CO slightly. Nonetheless, it has been demonstrated that amrinone potentiates the action of dobutamine[28] and epinephrine[29] to increase CO. Further studies will be necessary to delineate the relative contributions of both drugs to the observed favourable outcome.

With the exception of NE, catecholamines and β-adrenergic agonists accelerate HR, although to a variable degree. On the contrary, HR remained unchanged with the administration of doses of amrinone resulting in increases in CO in a study by Naccarelli *et al.*[30] In patients without cardiac disease, β-agonists rarely cause important arrhythmias or myocardial ischaemia. However, patients with underlying coronary artery disease or preexisting arrhythmias are at much greater risk.[27] With phosphodiesterase inhibitors, serious proarrhythmia is uncommon but can occur. The adverse reactions to intravenous administration of amrinone gathered from 326 patients included arrhythmia in 4% of cases.[31] In the present report, amrinone was not associated with an acceleration of HR or the production of dysrhythmias in the 19 patients studied. Furthermore, given the potentiation of dobutamine and epinephrine by amrinone, the administration of amrinone as a first-line drug prior to separation from CPB should prove useful to decrease the dose and undesirable side effects of these inotropes.

Apart from its favourable effects on HR and myocardial oxygen consumption, two other, more theoretical, reasons militate in favour of the use of amrinone to support the failing heart after coronary artery bypass surgery. First, it has been shown *in vitro* that phosphodiesterase inhibitors dilate human internal mammary artery rings. Thus, the systemic administration of phosphodiesterase inhibitors could vasodilate and prevent, or treat, acute spasm of grafted mammary arteries.* Second, amrinone inhibits intracoronary thrombus formation and protects against myocardial ischaemia in dogs.[32] In fact, there is evidence in humans to suggest that amrinone may decrease the incidence of myocardial infarction after cardiac surgery.[22]

The choice of the vasoactive drug administered to maintain an acceptable perfusion pressure is important also, with respect to the effects of these drugs on flows through the arterial or venous conduits grafted during coronary artery surgery, and to their effect on myocardial performance. Of the three vasoactive agents commonly used to increase blood pressure after CPB, only phenylephrine adversely affects IMA graft flow, while norepinephrine and epinephrine do not modify or increase IMA graft flow respectively.[33] All three agents produce an increase in flow through saphenous vein grafts.[33] As for the effect of vasopressors on myocardial performance, phenylephrine has no direct effect, while norepinephrine and epinephrine are potent inotropes which may further increase myocardial performance, previously enhanced by phosphodiesterase inhibition. But, while low doses of epinephrine produce little tachycardia,[34] augmenting the dose will result in an increase in HR eventually.[27] Hence, norepinephrine is a logical first choice to support perfusion pressure when used in combination with amrinone. Low-dose epinephrine may be a good alternative, especially when some increase in HR can be tolerated or is desired.

In conclusion, amrinone was used as the first-line drug after an unsuccessful attempt at weaning from CPB. Failure to wean was based on objective criteria. Amrinone was administered therapeutically rather than prophylactically or for treatment of a LOS following separation from CPB as had been published previously. Separation was accomplished promptly after the bolus of amrinone with no arrhythmia or tachycardia. However, a clinically important decrease in systemic pressure was observed, but corrected easily with 4–8 $\mu g \cdot min^{-1}$ NE. Amrinone (0.75 $mg \cdot kg^{-1}$ followed by an infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was rapidly effective during weaning from CPB and, in combination with NE, provided the necessary inotropic support during this unstable period.

Acknowledgments

We would like to thank the surgeons of the Montreal Heart Institute for their participation in the study, and Ms Christiane Lussier for her expert secretarial assistance.

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