



**Health Policy & Clinical Effectiveness
Evidence-Based Care Guideline**

**Inotropic Support with Phosphodiesterase
Inhibitors After Arterial Switch Operation**

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New search August, 2006 (see Development Process section)

Target Population

Inclusions: These guidelines are intended primarily for use in neonates (age ≤ 30 days) who have undergone an arterial switch operation (with or without ventricular septal defect closure).

Exclusions: The guidelines do not address all considerations needed to manage those with the following:

- Significant hypotension.
- Significant post-operative left ventricular outflow tract obstruction.

Target Users

Include but are not limited to (in alphabetical order):

- Clinicians caring for neonates with transposition of the great arteries
- Patient Care staff, including:
 - nurse practitioners
 - nurses
 - pharmacists
- Residents

Introduction

References in parentheses () Evidence strengths in brackets [] (See last page for definitions)

During the arterial switch operation, the left ventricle is acutely converted from the pulmonary to the systemic ventricle. This imposes a significant increase in afterload on the left ventricle and may predispose the patient to acute left ventricular dysfunction in the immediate post-operative period. (Heimisch 1994 [C], Bryant 1998 [C]). Even in patients who appear to be doing well clinically, there is often a decrease in cardiac index over the first 8-24 hours following surgery. (Wernovsky 1995 [A]).

Inamrinone and milrinone are phosphodiesterase inhibitors. They prevent the breakdown of cyclic AMP

and thereby increase activity of a number of cellular systems that are crucial for calcium handling and cardiomyocyte contractile activity. Clinically, phosphodiesterase inhibitors improve myocardial contractility, diastolic relaxation, and cause a decrease in afterload through vasodilation. These agents therefore improve cardiac index and lower left ventricular filling pressure after cardiopulmonary bypass, even in comparison to other inotropes or vasodilators. (Hamada 1999 [B], Laitinen 1999 [B], Berner 1990 [C], Lynn 1993 [C], Chang 1995 [C], Bailey 1997 [C], Kikura 1998 [C]).

Phosphodiesterase inhibition is also of benefit in treating low cardiac output due to pulmonary hypertension, a complication known to occur after arterial switch operation. (Chu 2000 [C], Freeman 1995 [O]).

Because of these beneficial effects on afterload, myocardial function and pulmonary vascular resistance, phosphodiesterase inhibition is a potentially useful treatment for neonates in low cardiac output after an arterial switch operation. Furthermore, it may be useful for prevention of a low cardiac output state in the patient who appears to be doing well, but this has not been extensively studied. These recommendations are based on the most current scientific information and have taken into consideration potential benefits, risks and side effects of treatment.

In developing this guideline, we recognize the paucity of large-scale studies with direct bearing on this particular focus population. The specific recommendations in this guideline are drawn from directly applicable studies where possible, but are largely extrapolated from smaller studies, and from studies more indirectly related to the present issues.

Guideline Recommendations

Clinical Assessments

1. It is recommended that cardiac index be supported to maintain normal to minimally elevated left atrial pressure (5-15 mmHg) with evidence of adequate tissue and organ perfusion as defined by physical exam, urine output $>1\text{cc/Kg/min}$ and no ongoing metabolic acidosis or lactic acidemia.

Note 1: Ongoing metabolic acidosis caused by the continued production of lactic acid has been associated with a poor outcome following cardiac surgery in infants and children. (*Charpie 2000 [C], Munoz 2000 [C]*).

Note 2: Continuous monitoring of arterial blood pressure via an arterial line is recommended. (*Local Expert Consensus [E]*).

Note 3: Continuous monitoring of left atrial pressure with a transthoracic catheter is recommended (*Local Expert Consensus [E]*).

Treatment Recommendations

2. It is recommended that milrinone be considered for any patient following arterial switch operation to prevent the occurrence of low cardiac output over the first 24 hours following arterial switch operation.

Note: There is no direct evidence to suggest that routine use of milrinone following arterial switch operation improves outcome, but this recommendation is based on evidence that cardiac output decreases in the 6-18 hours following cardiopulmonary bypass (*Wernovsky 1995 [A]*) and that phosphodiesterase inhibitors are effective in improving cardiac output after cardiopulmonary bypass (*Hamada 1999 [B], Laitinen 1999 [B], Hoffman 2003 [B], Berner 1990 [C], Lynn 1993 [C], Bailey 1997 [C], Kikura 1998 [C]*).

3. It is recommended that milrinone be started for any patient with a left atrial pressure >15mmHg or with signs or symptoms of low cardiac output. The recommended loading dose of milrinone is 50 mcg/Kg over 30-60 minutes, followed by an infusion at 0.375-0.75 mcg/Kg/min.

Note 1: Direct comparison has failed to show any significant hemodynamic differences between inamrinone and milrinone. There are anecdotal reports of less thrombocytopenia with milrinone, so milrinone may be particularly useful for patients in whom phosphodiesterase inhibition is desired, but who are thrombocytopenic or following surgery (*Rathmell 1998 [B], Hamada 1999 [B]*).

Note 2: If hypotension develops, blood pressure support with other inotropic/vasopressor agents may be necessary (*Lynn 1993 [C]*).

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Development Process

The process by which this guideline was developed is documented in the Guideline Development Process Manual. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using the grading scale that follows, and examined current local clinical practices.

To select evidence for critical appraisal by the group for the update of this guideline, the Medline, EmBase and the Cochrane databases were searched. Evidence from 2000 and before was verified for inclusion in the guidelines. Evidence from 2001 through 2005 was reviewed for relevance to the clinical topics/questions to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to inotropic support with phosphodiesterase inhibitors following arterial switch operations and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. April, 2000 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

M	Meta-analysis or Systematic Review	O	Other evidence
A	Randomized controlled trial: large sample	E	Expert opinion or consensus
B	Randomized controlled trial: small sample	F	Basic Laboratory Research
C	Prospective trial or large case series	L	Legal requirement
D	Retrospective analysis	Q	Decision analysis
S	Review article	X	No evidence

A search using the above criteria was conducted for dates of January, 2006 through July, 2006. No relevant articles were found that would require changes to the January, 2006 version of the recommendations.

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline. Experience with the implementation of earlier publications of this guideline has provided information which has been incorporated into this revision. Once the guideline has been in place for four years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed. Hemodynamic stability and length of stay in the CICU are outcome measures that are monitored and reviewed quarterly.

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices. The guidelines have been reviewed and approved by clinical experts not involved in the development process, senior management, Risk Management & Corporate Compliance, other appropriate hospital committees, and other individuals as appropriate to their intended purposes. The guideline is based, in part, on three independent reviews performed by members of Evidence-Based Care Group of Health Policy & Clinical Effectiveness at Cincinnati Children's Hospital and Medical Center (CCHMC) using AGREE criteria (Appraisal of Guidelines for Research and Evaluation). The guideline was developed without external funding.

NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about these guidelines and their supporting evidences contact the Heart Center, Division of Cardiothoracic Surgery at 513-636-4770 or thc@cchmc.org.

REFERENCES

Note: When using the electronic version of this document, “[_____](#)” refers to journal articles that have a hyperlink to the abstract.

Bailey, J. M., B. E. Miller, et al.: A comparison of the hemodynamic effects of amrinone and sodium nitroprusside in infants after cardiac surgery. *Anesth Analg*, 84(2): 294-8., 1997, [C] _____

The phosphodiesterase inhibitor amrinone (AMR) increases cardiac output in children after cardiac surgery. In vitro, amrinone has both positive inotropic and vasodilatory effects. However the relative contribution of these effects to the increases in cardiac output observed clinically is unclear, and it has not been demonstrated that amrinone offers a hemodynamic advantage above that of pure vasodilators in infants. We compared the hemodynamic effects of AMR and sodium nitroprusside (SNP) in 10 infants after cardiac surgery. Cardiac index (CI) was measured by thermodilution after SNP administration, titrated to decrease mean blood pressure (MBP) by 20%, and then after a 1.5-mg/kg bolus dose of AMR. Each patient served as his or her own control. Preload, as measured by left atrial pressure and transesophageal echocardiography (in eight patients), was kept constant throughout the protocol. Both SNP and AMR caused significant decreases in MBP and systemic vascular resistance index (SVRI). However, only AMR resulted in a significant increase in CI. The ratio of fractional increase in CI to fractional absolute decrease in MBP was significantly greater for AMR than SNP, indicating greater efficacy for AMR in the treatment of low cardiac output syndrome and suggesting that, in infants after cardiac surgery, AMR has clinically relevant positive inotropic effects.

Berner, M., C. Jaccard, et al.: Hemodynamic effects of amrinone in children after cardiac surgery. *Intensive Care Med*, 16(2): 85-8, 1990, [C] _____

The hemodynamic effects of amrinone were assessed in seven children following cardiac surgery. Amrinone was administered as a bolus of 1 mg kg⁻¹ body wt., followed by continuous infusion at 10 micrograms kg⁻¹ min⁻¹ for 1 h and two stepwise increases to 20 and 40 micrograms kg⁻¹ min⁻¹ for 30 min each. Hemodynamic data were obtained and plasma concentrations of amrinone measured 1 h after the bolus dose and immediately before each increment of the infusion rate. Amrinone levels ranged from 0.7 to 2.3 mg l⁻¹. Administration of amrinone lowered systemic vascular resistance from 20.0 +/- 4.3 to 16.5 +/- 4.6 mmHg l⁻¹ min⁻¹ m⁻² (p less than 0.05) and reduced mean arterial pressure from 71.7 +/- 9.5 to 62.6 +/- 13.5 mmHg (p less than 0.05) at the highest infusion rate, confirming the known vasodilative effect of the drug. However, these effects did not result in a statistically significant increase in stroke volume (35.0 +/- 7.5 to 35.5 +/- 7.0 ml m⁻², NS) or cardiac index (3.10 +/- 0.50 to 3.20 +/- 0.40 l min⁻¹ m⁻²). One additional patient, in whom a higher loading dose was tried in order to achieve a higher plasma concentration, developed systemic hypotension. A correlation was established between the plasma concentrations of amrinone and the percentage decrease in systemic resistance (r = 0.70, p less than 0.05). These results suggest that in children after open heart surgery, amrinone acts primarily as a systemic vasodilator, with questionable inotropic effect. Accordingly, its use should be restricted to children with severe cardiac failure and documented highly elevated afterload.

Bryant, R. M., R. L. Shirley, et al.: Left ventricular performance following the arterial switch operation: use of noninvasive wall stress analysis in the postoperative period. *Crit Care Med*, 26(5): 926-32., 1998, [C] _____

OBJECTIVE: To determine postoperative left ventricular mechanics following the arterial switch operation (ASO). **DESIGN:** Prospective, cohort study. **SETTING:** Pediatric cardiac recovery room. **PATIENTS:** Nine neonates with transposition of the great arteries undergoing the ASO within the first week of life. **INTERVENTIONS:** Noninvasive ejection phase indices: shortening fraction (% SF), corrected mean velocity of circumferential shortening (VCFc), and wall stress analysis were used to calculate indices of specific left ventricular systolic mechanics. The % SF and VCFc were respectively adjusted for left ventricular afterload (end-systolic wall stress) to derive an index for left ventricular performance (stress-shortening relation) and contractility (stress-velocity relation). Left ventricular preload was assessed as the variance between the performance and contractility indices. All indexed data are reported as mean Zscore (i.e., number of standard deviations from the mean of a normal age- and body surface area- adjusted population). A mean Zscore of < -2 or > 2 was regarded as a significant variance from normal. Transmitral Doppler flow patterns were recorded at each postoperative interval and analyzed for isovolumic relaxation time (IVRT) as an index of left ventricular compliance. **MEASUREMENTS AND MAIN RESULTS:** All nine patients did well clinically and completed the study. Noninvasive parameters were measured at mean intervals of 3 (early), 23 (intermediate), and 48 hrs (late postoperative) relative to the time of arrival in the cardiac recovery room. Postoperative left ventricular performance was decreased throughout the early (-4.0 +/- 1.5 SD), intermediate (-4.1 +/- 2.8), and late (-3.5 +/- 1.3) phases of recovery. In contrast, the overall left ventricular contractility remained normal throughout the three postoperative intervals (0.2 +/- 1.8, -1.2 +/- 1.9, and -1.0 +/- 1.6, respectively), although three of the nine patients had a diminished stress-velocity index during the study period. Left ventricular afterload was within normal range in the early (0.1 +/- 1.7) and intermediate (1.5 +/- 1.9) phases of recovery, but increased in the late postoperative period (2.5 +/- 2.9). Left ventricular preload was decreased significantly throughout the early (-4.2 +/- 1.3), intermediate (-2.8 +/- 2.0), and late (-2.5 +/- 1.0) postoperative phases. All nine patients demonstrated decreased preload during the recovery period. IVRT was decreased in the post-ASO patients at each phase of recovery compared with normal data (p < .001). **CONCLUSIONS:** Left ventricular performance is impaired in infants during the period immediately following the ASO. A persistent preload deficit closely matches the pattern of impaired ventricular performance. Decreased IVRT points to impaired ventricular compliance as the etiology of the altered preload. In contrast, left ventricular contractility remains normal in the majority of post-ASO patients. Decreased contractility may account for impaired ventricular performance in selected cases.

Chang, A. C., A. M. Atz, et al.: Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. *Crit Care Med*, 23(11): 1907-14., 1995, [C] _____

OBJECTIVE: To evaluate the hemodynamic effects of intravenous milrinone in neonates with low cardiac output after

cardiac surgery. **DESIGN:** Prospective cohort study. **SETTING:** Pediatric cardiac intensive care unit. **PATIENTS:** Ten neonates with low cardiac output (cardiac index of ≤ 3.0 L/min/m²) after corrective cardiac surgery were enrolled in the study. The neonates' ages ranged from 3 to 27 days (median 5) and their weights ranged from 2.0 to 4.8 kg (median 3.7). The diagnoses were: transposition of the great arteries (n = 6, including two with ventricular septal defect), tetralogy of Fallot (n = 2), truncus arteriosus (n = 1), and total anomalous pulmonary venous connection (n = 1). **INTERVENTIONS:** Milrinone was intravenously administered in three stages: a) baseline stage, in which patients had a stable hemodynamic status, ventilation and gas exchange, hemostasis, and body temperature; b) loading stage, in which a 50 microgram/kg intravenous loading dose of milrinone was administered over 15 mins; and c) infusion stage, in which milrinone was continuously infused at 0.50 microgram/kg/min for 30 mins. **MEASUREMENTS AND MAIN RESULTS:** The mean heart rate increased after the loading stage (149 +/- 13 to 163 +/- 12 beats/min, $p < .01$) but slowed during the infusion stage (154 +/- 11 beats/min, $p < .01$ vs. loading stage). Both right and left atrial pressures were lowered in all ten neonates. Compared with baseline, mean arterial pressure decreased after the loading stage (66 +/- 12 to 57 +/- 10 mm Hg, $p < .01$) but did not decrease further at the infusion stage (59 +/- 12 mm Hg); changes in mean pulmonary arterial pressure were comparable. Cardiac index increased from a baseline mean of 2.1 +/- 0.5 to 3.0 +/- 0.8 L/min/m² ($p < .01$) with the loading stage, and was maintained at 3.1 +/- 0.6 L/min/m² during the infusion stage. Systemic vascular resistance index decreased below baseline values with loading, from 2136 +/- 432 to 1336 +/- 400 dyne.sec/cm⁵.m² ($p < .01$), and pulmonary vascular resistance index also decreased with loading dose of milrinone, from 488 +/- 160 to 360 +/- 120 dyne.sec/cm⁵.m² ($p < .01$). There was no change in the rate pressure index, an indirect measurement of myocardial oxygen consumption, throughout the study. **CONCLUSIONS:** Administration of milrinone in neonates with low cardiac output after cardiac surgery lowers filling pressures, systemic and pulmonary arterial pressures, and systemic and pulmonary vascular resistances, while improving cardiac index. Milrinone increases heart rate without altering myocardial oxygen consumption. While milrinone appears to be effective and safe during short-term use, the relative distribution of inotropic and vasodilatory properties of milrinone remains to be elucidated.

Charpie, J. R., M. K. Dekeon, et al.: Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg*, 120(1): 73-80., 2000, [C] _____ ↗.

OBJECTIVES: Neonates with congenital heart disease may appear hemodynamically stable after operation and then suddenly experience catastrophic decompensation. An improved means of predicting which infants will suddenly die in the early postoperative period may lead to lifesaving interventions. Studies indicate that blood lactate level is proportional to tissue oxygen debt, but information linking lactate levels with outcome in infants after operation is limited. We sought to determine whether a change in lactate level over time was predictive of a poor outcome defined as death within the first 72 hours or the need for extracorporeal membrane oxygenation. **METHODS:** To test this hypothesis, we studied prospectively 46 infants who were less than 1 month old and were undergoing complex cardiac surgical palliation or repair. Postoperative arterial oxygen saturation, bicarbonate, and lactate levels were recorded on admission to the intensive care unit and every 3 to 12 hours for the first 3 days. **RESULTS:** Thirty-seven patients had a good outcome, and 9 patients

had a poor outcome. Mean initial lactate level was significantly greater in patients with a poor outcome (9.4 +/- 3.8 mmol/L) than in patients with a good outcome (5.6 +/- 2.1 mmol/L; $P = .03$). However, an elevated initial lactate level of more than 6 mmol/L had a low positive predictive value (38%) for poor outcome. In contrast, a change in lactate level of 0.75 mmol/L per hour or more was associated with a poor outcome ($P < .0001$) and predicted a poor outcome with an 89% sensitivity value, a 100% specificity value, and a 100% positive predictive value. **CONCLUSIONS:** Serial blood lactate level measurements may be an accurate predictor of death or the requirement for extracorporeal membrane oxygenator support for patients who undergo complex neonatal cardiac surgery.

Chu, C. C., S. M. Lin, et al.: Effect of milrinone on postbypass pulmonary hypertension in children after tetralogy of Fallot repair. *Chung Hua I Hsueh Tsa Chih (Taipei)*, 63(4): 294-300., 2000, [C] _____ ↗.

BACKGROUND: Postbypass pulmonary hypertension in surgical correction of tetralogy of Fallot (TOF) is a risk for right ventricular failure. Effective management remains a major challenge. Milrinone is a new drug with a unique mechanism of "inodilation", which offers both inotropic and vasodilatory effects. We attempted to determine if application of milrinone could improve cardiopulmonary dysfunction in children after TOF repair. **METHODS:** We studied 10 children with postbypass pulmonary hypertension after TOF repair within six months. Heart rate, systolic pulmonary arterial pressure (PAP), systolic arterial blood pressure (SBP), pulmonary capillary wedge pressure and PAP/SBP ratio were recorded. Standard cardiopulmonary bypass (CPB) was performed. After CPB, if PAP/SBP was more than 0.5, pulmonary hypertension was suspected and milrinone was administered with a loading dose of 20 micrograms/kg followed by continuous infusion of 0.2 microgram/kg/minute. Hemodynamics were compared before and after administration of milrinone to evaluate its effect. **RESULTS:** significant reduction in PAP/SBP ratio within 15 minutes was found after administration of milrinone. The effect persisted for 24 hours during continuous infusion of milrinone. No remarkable adverse effect was noted in the study. **CONCLUSIONS:** We conclude that milrinone is effective in the management of pulmonary hypertension following CPB in children who underwent TOF repair.

Freeman, J., S. Y. DeLeon, et al.: Acute pulmonary hypertension complicating the arterial switch procedure. *Pediatr Cardiol*, 16(6): 297-300., 1995, [O] _____ ↗.

Two neonates undergoing arterial switch procedure developed life-threatening pulmonary hypertension intraoperatively. In one patient, bradycardia, hypotension, and electrocardiographic (ECG) evidence of myocardial ischemia suddenly occurred 20 minutes after uneventful weaning from cardiopulmonary bypass. Lifting a palpably hypertensive main pulmonary artery (MPA) resulted in reproducible hemodynamic improvement. Because the patient was already on full ventilatory support and a nitroglycerin infusion, the MPA was suspended onto the anterior chest wall. In the other patient, after removal of intraoperative drapes, severe generalized swelling and cyanosis were noted. The central venous pressure had risen to 25 mmHg, and the PO₂ had dropped to 52 mmHg on 100% FIO₂. The

systolic arterial pressure and ECG remained normal. Immediate reexploration revealed a palpably hypertensive MPA. The coronary arteries implanted more laterally on the neo-aorta were uncompromised. Amrinone loading and infusion produced immediate improvement. We believe that surgeons should be aware that pulmonary hypertension can cause coronary artery compression and right heart failure in neonates undergoing the arterial switch procedure. Lateral placement of the coronary artery and aggressive use of pulmonary vasodilators can minimize the problem.

Hamada, Y., K. Kawachi, et al.: Effects of single administration of a phosphodiesterase III inhibitor during cardiopulmonary bypass: comparison of milrinone and amrinone. *Jpn Circ J*, 63(8): 605-9., 1999, [B] _____ ↗.

The effects of phosphodiesterase III (PDE III) inhibitors administered after aortic declamping during cardiopulmonary bypass (CPB) for open heart surgery were investigated. Ten patients (group M) were administered milrinone (50 microg/kg) after aortic declamping during CPB, 10 patients were administered amrinone (1 mg/kg) at the same time during their surgery (group A), and 10 patients served as controls with no drug administered (group C). Soon after bolus infusion of the PDE III inhibitor, perfusion pressure dropped significantly in groups M and A. However, after release of CPB and at the end of surgery, there was no difference in aortic pressure between the 3 groups. There were also no differences between the groups in heart rate, pulmonary artery pressure, and pulmonary capillary wedge pressure. After weaning from CPB, the cardiac index was high and systemic vascular resistance index was low in groups M and A. There were no significant differences in the need for additional catecholamines and time for rewarming between groups. No adverse reactions were observed. A single administration of a PDE III inhibitor during CPB was useful for post-CPB management of patients undergoing open heart surgery. Amrinone reduced perfusion pressures more than milrinone, but cardiac indices and aortic pressures after weaning from CPB showed no differences between group M and group A patients.

Heimisch, W., H. Meisner, et al.: Bi-ventricular function assessed intraoperatively before and after anatomical correction of transposition of the great arteries. *Eur J Cardiothorac Surg*, 8(10): 525-31, 1994, [C] _____ ↗.

After anatomical correction of transposition of the great arteries (TGA), the left ventricle (LV) is forced to develop systemic pressures without having had time for adaptation. Thus, one might expect dilatation of the LV at least in the very early intraoperative period following the operation. In nine patients with TGA aged 8-24 days (median 9.5 days) which were selected for arterial switch operation (ASO), Dacron-patch mounted thin piezoceramic transducers were attached intraoperatively by fibrin glue to opposite epicardial surfaces of the right (RV) and/or LV for continuous assessment of external minor diameters (RVD, LVD; sonomicrometry) before and after correction. Right and left ventricular pressures (RVP, LVP) were measured simultaneously and pressure-diameter loops were generated. Right and left ventricular power indices (RVPI, LVPI: = HRxVPxVsD) was calculated from heart rate, ventricular pressures, and systolic shortening of the respective ventricular diameter (RVsD, LVsD). Data obtained during circulatory steady-state immediately before extra-corporeal circulation (ECC) and up to 45 min after ECC were compared. By avoiding volume overload (CVP < or = 10 mmHg) at weaning off ECC and by lowering the systemic vascular resistance and, thus, LV afterload (approximately 8 micrograms.kg-1

min-1 dobutamine), the LV developed systemic pressure (70 +/- 7 vs. 41 +/- 4 mmHg) at unchanged diastolic LV end-diastolic pressure (LVedP) (10 +/- 3 mmHg). Left ventricular power index increased by 45 +/- 25%, although the extent of systolic shortening of LVD was reduced by 20 +/- 10%. Simultaneously, the RV was effectively unloaded (RVedP: 8 +/- 3 vs 11 +/- 6 mmHg; RVP: 39 +/- 7 vs 53 +/- 9 mmHg; RVPi: -42 +/- 27%).(ABSTRACT TRUNCATED AT 250 WORDS)

Hoffman, T. M., G. Wernovsky, et al.: Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation*, 107(7): 996-1002, 2003, [B] _____ ↗.

BACKGROUND: Low cardiac output syndrome (LCOS), affecting up to 25% of neonates and young children after cardiac surgery, contributes to postoperative morbidity and mortality. This study evaluated the efficacy and safety of prophylactic milrinone in pediatric patients at high risk for developing LCOS. **METHODS AND RESULTS:** The study was a double-blind, placebo-controlled trial with 3 parallel groups (low dose, 25- microg/kg bolus over 60 minutes followed by a 0.25- microg/kg per min infusion for 35 hours; high dose, 75- microg/kg bolus followed by a 0.75- microg/kg per min infusion for 35 hours; or placebo). The composite end point of death or the development of LCOS was evaluated at 36 hours and up to 30 days after randomization. Among 238 treated patients, 25.9%, 17.5%, and 11.7% in the placebo, low-dose milrinone, and high-dose milrinone groups, respectively, developed LCOS in the first 36 hours after surgery. High-dose milrinone significantly reduced the risk the development of LCOS compared with placebo, with a relative risk reduction of 55% (P=0.023) in 238 treated patients and 64% (P=0.007) in 227 patients without major protocol violations. There were 2 deaths, both after infusion of study drug. The use of high-dose milrinone reduced the risk of the LCOS through the final visit by 48% (P=0.049). **CONCLUSIONS:** The use of high-dose milrinone after pediatric congenital heart surgery reduces the risk of LCOS.

Kikura, M., J. H. Levy, et al.: A bolus dose of 1.5 mg/kg amrinone effectively improves low cardiac output state following separation from cardiopulmonary bypass in cardiac surgical patients. *Acta Anaesthesiol Scand*, 42(7): 825-33., 1998, [C] _____ ↗.

BACKGROUND: The aim of this study was to evaluate the efficacy of 1.5 mg/kg bolus of amrinone on low cardiac output (CO) state following emergence from cardiopulmonary bypass (CPB) in cardiac surgical patients. **METHODS:** Immediately after emergency from CPB, 14 patients with a cardiac index (CI) less than 2.2 l.min-1.m-2 despite administration of inotropes and nitroglycerin, received 1.5 mg/kg amrinone over 3 min without changing catecholamine infusion rates (amrinone group). Hemodynamics and left ventricular short axis views with transesophageal echocardiography were recorded at baseline, 3, 4, and 10 min following amrinone administration. Left ventricular filling volumes were maintained constant by volume reinfusion from the CPB reservoir. We matched the data of the amrinone group with the other 14 patients who did not receive amrinone (non-amrinone group) to evaluate the

efficacy of amrinone in low CO state. RESULTS: At baseline, CI (1.8 +/- 0.1 l.min-1.m-2) in the amrinone group was significantly lower than CI (3.0 +/- 0.2) in the non-amrinone group. Following amrinone administration, CI and velocity of circumferential fibershortening corrected for heart rate (Vcfc) significantly increased, and systemic vascular resistance index and pulmonary vascular resistance index significantly decreased from the baseline within 10 min without changes in heart rate, mean arterial blood pressure, or pulmonary artery occlusion pressure, and became equivalent with those of the non- amrinone group. CONCLUSIONS: A 1.5 mg/kg amrinone loading dose to patients in a low CO state, despite catecholamine therapy immediately after emergence from CPB, effectively improves ventricular function when loading conditions are maintained constant.

Laitinen, P., J. M. Happonen, et al.: Amrinone versus dopamine and nitroglycerin in neonates after arterial switch operation for transposition of the great arteries. *J Cardiothorac Vasc Anesth*, 13(2): 186-90., 1999, [B] _____ ↗.

OBJECTIVE: To compare the efficacy and safety of amrinone and a combination of dopamine and nitroglycerin in neonates after reconstructive surgery for transposition of the great arteries. DESIGN: A prospective, randomized, double-blind study. SETTING: Pediatric intensive care unit in a university hospital. PARTICIPANTS: Thirty-five neonates with transposition of the great arteries.

INTERVENTIONS: A loading dose of amrinone, 2 mg/kg, followed by a maintenance infusion of 7.5 microg/kg/min, were administered to 16 neonates before separation from cardiopulmonary bypass. The remaining 19 patients were administered a combination of dopamine, 5 microg/kg/min, and nitroglycerin, 1 microg/kg/min. An open-label epinephrine infusion was administered in both groups as required. MEASUREMENTS AND MAIN RESULTS: The circulatory state of the patients was evaluated from 4 to 18 hours after cardiopulmonary bypass. The systemic blood flow index, calculated using the Fick principle, was higher in the amrinone group (1.7+/-0.5 L/min/m² [mean +/- SD]) compared with the dopamine-nitroglycerin group (1.4+/-0.4 L/min/m²; p < 0.04). The systemic vascular resistance in the amrinone group was lower (26+/-8 Wood units x m²) than in the dopamine- nitroglycerin group (35+/-12 Wood units x m²; p < 0.02). The oxygen extraction ratio was higher in the dopamine-nitroglycerin group (0.34+/- 0.08) compared with the amrinone group (0.28+/-0.06; p < 0.02). Lower platelet counts were observed in the amrinone group, but no difference in hemorrhagic complications was seen between the groups. CONCLUSION: With the dosage regimen used, supplemented with epinephrine, amrinone provides a higher cardiac output and more favorable oxygen dynamics than a combination of dopamine and nitroglycerin.

Lynn, A. M., G. K. Sorensen, et al.: Hemodynamic effects of amrinone and colloid administration in children following cardiac surgery. *J Cardiothorac Vasc Anesth*, 7(5): 560-5., 1993, [C] _____ ↗.

Amrinone was used as the sole vasoactive medication in 9 of 14 children (aged 5 months to 8.25 years) given the drug following open repair of congenital cardiac lesions. Four children received a concomitant dopamine infusion and one infant had the infusion stopped after 5 hours for low mean arterial pressure (49 mmHg). In the 10 children receiving only amrinone, cardiac index increased 21% (range, 0 to 94%) after a total loading dose of 4.5 mg/kg given over 1 hour. Four of 14 patients (29%) required dopamine infusions to maintain mean arterial pressure over 55 mmHg and in these children

cardiac index increased from baseline and was maintained during the amrinone infusion. Preload was held constant by administration of whole blood or plasmanate during amrinone loading; a decrease in systemic vascular resistance index was seen resulting in a stable arterial blood pressure. Minimal chronotropic effect was seen and no arrhythmias occurred. The sole child with postoperative pulmonary hypertension had a beneficial decrease in pulmonary artery pressure, increase in cardiac index, and stable systemic blood pressure during amrinone use. Cardiac index changes during amrinone loading in these children were variable and less clearly related to serum levels than reported in adults. Pharmacokinetic analysis in 12 children showed a clearance of 3.4 mL/min/kg, a volume of distribution of 1.65 L/kg, and an elimination half-life of 5.75 hours. Decreases in platelet counts were seen in 6 children and platelet transfusion was needed in 1; thus, serial platelet counts should be monitored.(ABSTRACT TRUNCATED AT 250 WORDS)


Munoz, R., P. C. Laussen, et al.: Changes in whole blood lactate levels during cardiopulmonary bypass for surgery for congenital cardiac disease: an early indicator of morbidity and mortality. *J Thorac Cardiovasc Surg*, 119(1): 155-62., 2000, [C] _____ ↗.

OBJECTIVE: Our objective was to evaluate the change in lactate level during cardiopulmonary bypass and the possible predictive value in identifying patients at high risk of morbidity and mortality after surgery for congenital cardiac disease. METHODS: We prospectively studied lactate levels in 174 nonconsecutive patients undergoing cardiopulmonary bypass during operations for congenital cardiac disease. Arterial blood samples were taken before cardiopulmonary bypass, during cardiopulmonary bypass (cooling and rewarming), after cardiopulmonary bypass, and during admission to the cardiac intensive care unit. Complicated outcomes were defined as open sternum as a response to cardiopulmonary instability, renal failure, cardiac arrest and resuscitation, extracorporeal membrane oxygenation, and death. RESULTS: The largest increment in lactate level occurred during cardiopulmonary bypass. Lactate levels decreased between the postbypass period and on admission to the intensive care unit. Patients who had circulatory arrest exhibited higher lactate levels at all time points. Nonsurvivors had higher lactate levels at all time points. A change in lactate level of more than 3 mmol/L during cardiopulmonary bypass had the optimal sensitivity (82%) and specificity (80%) for mortality, although the positive predictive value was low. CONCLUSIONS: Hyperlactatemia occurs during cardiopulmonary bypass in patients undergoing operations for congenital cardiac disease and may be an early indicator for postoperative morbidity and mortality.

Rathmell, J. P., R. C. Prielipp, et al.: A multicenter, randomized, blind comparison of amrinone with milrinone after elective cardiac surgery. *Anesth Analg*, 86(4): 683-90., 1998, [B] _____ ↗.

Amrinone and milrinone are phosphodiesterase inhibitors with positive inotropic effects useful for the treatment of ventricular dysfunction after cardiac surgery. Forty-four patients undergoing elective cardiac surgery at four centers received either amrinone (n = 22) or milrinone (n = 22) in a randomized,

blind fashion. Immediately after separation from cardiopulmonary bypass (CPB), two bolus doses of either amrinone 0.75 mg/kg or milrinone 25 microg/kg were administered over 30 s, separated by 5 min. Hemodynamic measurements were recorded before each dose and at the end of the 10-min study. Both amrinone and milrinone increased the cardiac index (48% vs 52%, $P =$ not significant [NS] for amrinone and milrinone, respectively). There was a small increase in mean arterial pressure (MAP) after amrinone administration (from 68 \pm 3 to 72 \pm 3 mm Hg at 10 min, $P < 0.05$) with no significant change in MAP after milrinone administration. Central venous pressure was significantly higher in the amrinone group at baseline and 5 min (12 vs 10 mm Hg and 11 vs 10 mm Hg, respectively; $P < 0.05$). Systemic and pulmonary vascular resistances decreased significantly and to a similar extent after either amrinone or milrinone administration. Phenylephrine was required in 11 of 22 patients receiving amrinone and in 11 of 22 patients receiving milrinone to maintain arterial blood pressure. The proportion of patients requiring an intravascular volume infusion (15 of 22 vs 17 of 22, $P =$ NS) and the total fluid volume infused were similar (402 \pm 57 vs 350 \pm 49 mL, $P =$ NS for amrinone and milrinone, respectively). Amrinone and milrinone seem to have similar hemodynamic effects after CPB, with the exception of blood pressure, although the need for vasopressor support of blood pressure did not differ. Selection between these two drugs may include nonhemodynamic considerations such as cost. Implications: Amrinone and milrinone are drugs that improve cardiac contraction. Their effects have never been directly compared in patients. We found that amrinone and milrinone produced similar hemodynamic effects in adult patients undergoing cardiac surgery. Choice between the two drugs can be based on nonhemodynamic considerations such as cost.

Wernovsky, G., D. Wypij, et al.: Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*, 92(8): 2226-35., 1995, [A] [_____](#) 

BACKGROUND: The neurological morbidity associated with prolonged periods of circulatory arrest has led some cardiac surgical teams to promote continuous low-flow cardiopulmonary bypass as an alternative strategy. The nonneurological postoperative effects of both techniques have been previously studied only in a limited fashion. **METHODS AND RESULTS:** We compared the hemodynamic profile (cardiac index and systemic and pulmonary vascular resistances), intraoperative and postoperative fluid balance, and perioperative course after deep hypothermia and support consisting predominantly of total circulatory arrest or low-flow cardiopulmonary bypass in a randomized, single-center trial. Eligibility criteria included a diagnosis of transposition of the great arteries and a planned arterial switch operation before the age of 3 months. Of the 171 patients, 129 (66 assigned to circulatory arrest and 63 to low-flow bypass) had an intact ventricular septum and 42 (21 assigned to circulatory arrest and 21 to low-flow bypass) had an associated ventricular septal defect. There were 3 (1.8%) hospital deaths. Patients assigned to low-flow bypass had significantly greater weight gain and positive fluid balance compared with patients assigned to circulatory arrest. Despite the increased weight gain in the infants assigned to low-flow bypass, the duration of mechanical ventilation, stay in the intensive care unit, and hospital stay were similar in both groups. Hemodynamic measurements were made in 122 patients. During the first postoperative night, the cardiac index decreased (32.1 \pm 15.4%, mean \pm SD), while pulmonary and systemic vascular resistance increased. The measured cardiac index was < 2.0 L \cdot min $^{-1}$ \cdot m $^{-2}$ in

23.8% of the patients, with the lowest measurement typically occurring 9 to 12 hours after surgery. Perfusion strategy assignment was not associated with postoperative hemodynamics or other nonneurological postoperative events. **CONCLUSIONS:** After heart surgery in neonates and infants, both low-flow bypass and circulatory arrest perfusion strategies have comparable effects on the nonneurological postoperative course and hemodynamic profile.