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Helsinki, Finland

Evaluation of cardiovascular management in children undergoing open-heart surgery,

with special reference to oxygen consumption and vasoactive support

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Academic Dissertation

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, referred to by the Roman numerals in the text.

I Laitinen PO, Räsänen J. Measured versus predicted oxygen consumption in children with congenital heart disease. Heart 80:601-605, 1998

II Laitinen P, Ahonen J, Olkkola K.T, Peltola K, Rautiainen P, Räsänen J. Pharmacokinetics of amrinone in neonates and infants. J Cardiothorac Vasc Anesth 14:378-382, 2000

III Laitinen P, Happonen J-M, Sairanen H, Peltola K, Rautiainen P. Amrinone versus dopamine and nitroglycerin in neonates after arterial switch operation for transposition of the great arteries. J Cardiothorac Vasc Anesth 13:186-190, 1999

IV Laitinen P, Happonen J-M, Sairanen H, Peltola K, Rautiainen P, Korpela R, Leijala M. Amrinone versus dopamine- nitroglycerin after reconstructive surgery for complete atrioventricular septal defect. J Cardiothorac Vasc Anesth 11:870-874, 1997

In addition, some previously unpublished data will be presented. The publishers of these communications have kindly granted their permission to reproduce the articles in this thesis.

ABBREVIATIONS

AUC area under drug plasma concentration - time curve

AUMC area under the first moment of drug plasma concentration-time curve

AVSD atrioventricular septal defect

BSA body surface area

cAMP cyclic adenosine monophosphate

CaO_2 arterial blood oxygen content

$CavO_2$ arteriovenous blood oxygen content difference

cGMP cyclic guanosine monophosphate

CHD congenital heart disease

CI confidence interval

$ClaO_2$ left atrial blood oxygen content

CL clearance

CPB cardiopulmonary bypass

CO_2 carbon dioxide

$CpaO_2$ pulmonary arterial blood oxygen content

CV coefficient of variation

CvO_2 central venous blood oxygen content

CVP mean central venous pressure

FIO_2 fraction of oxygen in inspired gas

G protein guanine nucleotide-binding protein

ICU intensive care unit

LAP mean left atrial pressure

MAP mean arterial pressure

NN neural network

NO nitric oxide

NO_2 nitric dioxide

NS not significant

O_2 oxygen

O_2ER oxygen extraction ratio

$PaCO_2$ arterial carbon dioxide tension

PaO_2 arterial blood oxygen tension

PAP mean pulmonary artery pressure

PDE phosphodiesterase

PGE_1 prostaglandin E_1

PGI_2 prostacyclin

pHa arterial blood pH

PVR pulmonary vascular resistance

$\dot{Q}p$ pulmonary blood flow

$\dot{Q}p$: $\dot{Q}s$ pulmonary-to-systemic flow ratio

$\dot{Q}s$ systemic blood flow

SD standard deviation

SaO_2 aterial oxyhemoglobin saturation

$ScvO_2$ central venous oxyhemoglobin saturation

$SlaO_2$ left atrial oxyhemoglobin saturation

$SpaO_2$ pulmonary artery oxyhemoglobin saturation

SVR systemic vascular resistance

$T_{½}$ elimination half-life

TGA transposition of great arteries

THAM tris-hydroxymethylaminomethane

$\dot{V}CO_2$ carbon dioxide production

Vd volume of distribution

$\dot{V}O_2$ oxygen consumption

V_{ss} volume of distribution at steady state

INTRODUCTION

Congenital heart disease (CHD) encompasses a wide variety of cardiac and vascular lesions, each requiring different treatment according to their pathophysiological characteristics. This spectrum of malformations can be divided into a limited number of basic pathophysiological categories according to the existence of abnormal shunt pathways and obstructions to blood flow (Young 1980). Many congenital heart defects can be evaluated with echocardiography, and management decisions can be based on noninvasive measurements of blood flow patterns and cardiac function (Sanders et al 1983). However, in some patients, proper management still requires morphologic and hemodynamic evaluation with cardiac catheterization and angiography (Cournand et a1 1953). Patients with increased pulmonary blood flow ($\dot{Q}p$) often need surgery at an early age, before obstructive pulmonary vascular disease develops (Newfeld et al 1977). Elevated pulmonary vascular resistance (PVR) may increase the risk of surgery in patients with CHD (Bando et al 1996). Therefore, precise information of the patient's hemodynamic status is essential for optimal peri- and postoperative cardiovascular care.

The determination of systemic blood flow ($\dot{Q}s$) and $\dot{Q}p$ using the Fick principle depends on quantitation of the arteriovenous oxygen content difference ($CavO_2$) across the vascular bed, and oxygen consumption ($\dot{V}O_2$) values. Using indirect calorimetry, $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) values can be determined, when the inspired and expired oxygen (O_2) and carbon dioxide (CO_2) concentrations and the volume of expired gas are known. The $\dot{V}O_2$ measurement may be difficult especially in young children with CHD, so the $\dot{V}O_2$ values are often estimated from nomograms constructed according to the patient's characteristics (Wessel et al 1969, LaFarge et al 1970, Lindahl 1989). However, the use of linear methods in estimation of the $\dot{V}O_2$ has been shown to result in wide confidence intervals (CI) of the calculated values (Lundell et al 1996, Sherman et al 1997). Furthermore, the linear regression equations predicting $\dot{V}O_2$ are usually based on data obtained from stable subjects undergoing cardiac catheterization, and may not apply to a different patient population in other circumstances, e.g. postoperatively in children recovering from open-heart surgery. There are no studies of nonlinear modelling in $\dot{V}O_2$ prediction.

Acute ventricular failure and pulmonary hypertensive episodes are significant risk factors for morbidity and mortality after reconstructive surgery for CHD (Wernovsky et al 1995a, Bando et al 1995). During open-heart surgery, the pulmonary and coronary circulations are bypassed with extracorporeal circulation, exposing the patient to deleterious inflammatory response and reperfusion injury (Boyle et al 1997). Despite early surgery, PVR may be elevated after cardiopulmonary bypass (CPB), with consequent increase in right ventricular afterload and impairment in the performance of both ventricles (Wessel et al 1993, Celermajer et al 1993). Furthermore, in many patients, ventriculotomy or coronary artery reimplantation further increase the risk of myocardial injury (Castaneda et al 1989).

Several vasoactive regimens have been suggested for postoperative cardiovascular support in patients with CHD, but little data exist to support a choice between any specific agents in children of different ages and cardiac pathophysiologies. Catecholamines have been widely used to support cardiac output after surgery for CHD. They increase cyclic adenosine monophosphate (cAMP) resulting in improved myocardial contraction. However, patients with CHD have reduced myocardial β-adrenoceptor density, which may affect the efficacy of catecholamines (Kozlik-Feldmann et al 1993). Furthermore, increased peripheral vascular resistance to blood flow and excessive chronotropy associated with catecholamine administration may limit their usefulness in some postoperative patients with CHD (Notterman 1991). Systemic vasodilators are also frequently used to reduce ventricular pre-and afterload in these patients (Burrows et al 1986, Hopkins et al 1991). However, hypotension, and increased intrapulmonary shunting are often associated with vasodilator administration (Mookherjee et al 1978). The lack of selectivity on pulmonary vasculature may also limit their efficacy in patients prone to pulmonary hypertension. Phosphodiesterase (PDE) inhibitors improve myocardial performance by increasing cAMP independently of β-adrenergic receptors; hence their efficacy should not be compromised by adrenergic receptor down-regulation (Skoyles et al 1992). The decrease in systemic vascular resistance (SVR) and PVR produced by PDE inhibitors often necessitates preload augmentation to avoid systemic hypotension, especially as these agents are relatively long acting. Furthermore, studies of neonatal piglet myocardium in fact suggest a negative inotropic effect (Ross-Ascuitto et al 1987). Development of thrombocytopenia has also been associated with PDE inhibitor administration (Ross et al 1993). Therefore, controlled clinical comparisons of different vasoactive regimen are required to choose the most efficient and safe postoperative cardiovascular support in neonates and infants with CHD, even though the relative potency of different agents is difficult to establish in these patients.

Developmental changes in children of different ages affect their response to cardiovascular drugs. Maturation of the enzymatic processes of the liver and functions of the kidneys alter metabolism and elimination of these agents. Changes in body composition and protein binding affect the volume of distribution (Vd) and clearance (CL) of the drugs (Kearns et al 1989). While pharmacokinetics of catecholamines in pediatric patients are widely investigated, studies of PDE inhibitor pharmacokinetics in children are more limited (Steinberg et al 1994).

In this study the cardiovascular management in children undergoing reconstructive surgery for CHD was evaluated to develop better means of providing hemodynamic support in the immediate postoperative period in these patients. The utility of linear regression equations and an artificial intelligence neural network (NN) in $\dot{V}O_2$ prediction was elucidated by comparing measured and predicted $\dot{V}O_2$ in a group of children with CHD undergoing preoperative cardiac catheterization. The pharmacokinetics of amrinone were examined to ensure adequate amrinone dosing, and to clarify the distribution and elimination of amrinone and its metabolites in neonates and infants. Finally, the efficacy of amrinone and a combination of dopamine and nitroglycerine for cardiovascular support was assessed in neonates and infants after reconstructive surgery for CHD, and the safety of these vasoactive regimens was evaluated in these patients.

REVIEW OF THE LITERATURE

1. Aspects of postoperative care in children with congenital heart disease

1.1. Pathophysiology of congenital heart disease

The function of the immature cardiopulmonary system is limited during the transformation from fetal circulation into the adult type of circulation even in the absence of CHD. The hemodynamic changes during the first days of life are characterized by functional closure the shunt pathways of ductus arteriosus and foramen ovale, and decrease in the elevated PVR secondary to increased arterial blood O_2 tension (PaO_2), decrease of circulating prostaglandins, expansion of the lungs, and increased pressure in the left side of the heart (Moss et al 1964, Emmanouilides et al 1964, Arcilla et al 1966, Clyman et al 1977). However, the instability of the newborn circulatory system associated with high PVR and right-to-left shunting may continue several days or longer due to abnormal stresses as prematurity, hypoxia, CHD and infections (Hickey, Wessel & Reich 1993).

During early infancy, the myocardium is less compliant than in older children secondary to low elasticity of the immature contractile myofiber mass (Friedman 1972). Volume overload and increased ventricular outflow resistance may lead to ventricular failure, as the noncompliant ventricles are restricted in their ability to alter stroke volume (Thornburg et al 1983). The failure of either ventricle results in increased filling pressure, septal shift and decrease in the stroke volume of the opposite ventricle due to intimate ventricular interaction during the first months of life (Romero et al 1972). The myocardium of a young infant is also more dependent of extracellular calcium than that of older children because the sarcoplasmic reticulum stores and releases calcium inefficiently (Boucek et al 1984). The incomplete sympathetic innervation of the newborn heart is associated with inability to maintain cardiac responses after repeated sympathetic stimulation (Friedman 1972, Erath et al 1982). Parasympathetic innervation of the heart is probably complete at birth (Sinha et al 1973).

The presence of CHD further compromises the performance of the developing cardiovascular system. Even though there are many different kinds of congenital malformations, they can be divided into only a few basic pathophysiological categories depending on the existence of abnormal shunt pathways or obstruction to blood flow. Pulmonary blood flow may be increased secondary to abnormal circulatory pathways between left and right sides of the heart, as in atrial and ventricular

septal defect, atrioventricular septal defect (AVSD), and patent ductus arteriosus. These defects are associated with volume overload of the heart, and volume or pressure overload of the pulmonary circulation (Young 1980). In these patients, an extension in distal muscularization of pulmonary arteries predisposes the patients to increased PVR as response to stress (Hoffman et al 1981). In the obstructive lesions, e.g. coarctation of the aorta, and aortic and pulmonary stenosis, the ventricular workload is increased to overcome the reduced circulation distal to the obstruction. The complex defects may involve both partial or total outflow obstruction as well as shunting. In the complex lesions, like tetralogy of Fallot, pulmonary atresia, and tricuspid atresia, $\dot{Q}p$ may be decreased, resulting in hypoxia. Furthermore, in lesions with common ventricle, transposition of great arteries (TGA), and truncus arteriosus, the shunt may be functional, either increasing or decreasing the $\dot{Q}p$ depending upon the PVR (Young 1980). Understanding the pathophysiological effects of the patient's cardiac malformation is the key to developing a successful management plan to correct the lesion or alleviate its effects on the patient's health.

1.2. Effects of pre-repair hemodynamics on postoperative circulatory function

Cardiac failure secondary to excessive volume or pressure, or intrinsic alterations in myocardial performance, and cyanosis are the major consequences of CHD (Young 1980). In children with complete AVSD, congestive heart failure develops early in infancy with increasing left-to-right shunting as PVR falls. Atrioventricular valve regurgitation may further increase the ventricular volume overload (Bando et al 1995). Increased $\dot{Q}p$ may also decrease lung compliance, increase airway resistance, and obstruct small airways (Stanger et al 1969, Schindler et al 1995, Lanteri et al 1995). In these patients PVR rises rapidly, and is usually significantly elevated by the age of one year (Newfeld et al 1977). This lesion is often associated with Down's syndrome. These patients are prone to upper airway obstruction, sleep apnea, hypoventilation, and pulmonary infections, which also predispose them to pulmonary vascular disease (Spicer 1984, Nespoli et al 1993). Even when reconstructive surgery is performed in early infancy, pulmonary hypertensive events may complicate the recovery of these patients (Hopkins et al 1991, Bando et al 1995).

Transposition of the great arteries in a neonate is compatible with life only if the parallel systemic and pulmonary circulations are connected with a shunt pathway. In patients with TGA and intact ventricular septum, the left ventricle loses its capacity to grow and overcome high afterload as the PVR decreases within the first weeks of life. The left ventricular pressure is better maintained when

TGA is associated with ventricular septal defect. In these patients, however, the PVR may gradually increase, predisposing the child to pulmonary vascular obstructive disease and failure to thrive. Therefore, the arterial switch operation is preferable early in the neonatal period to avoid postoperative left ventricular failure from increased workload, and chronic pulmonary hypertension from excessive blood flow and pressure (Bano-Rodrigo et al 1980, Lecompte et al 1981, Di Donato et al 1989). However, these patients are prone to low cardiac output and increased vascular resistances during the early postoperative period (Wernovsky et al 1995a, Bryant et al 1998).

Patients with univentricular heart often have hypoxia dependent on the magnitude of $\dot{Q}p$. In these patients, the relief of volume overload on the single ventricle after the first-stage palliative procedure is accomplished with creation of a direct connection between the systemic venous circulation and the pulmonary arteries. As the pulmonary and systemic circulations are in series postoperatively, the resistance to $\dot{Q}p$ must be low for efficient systemic ventricular function (Mayer et al 1992, Kaulitz et al 1996). Coagulopathies due to polycytemia and increased blood viscosity, increased blood volume and systemic to pulmonary collateral vessels may also compromise the postoperative course (Henriksson et al 1979, Hetzer et al 1980).

Children with left-to-right shunting and cyanotic heart defects have increased sympathetic activity. Secondary to this elevated tone, these patients present down-regulation and uncoupling of the myocardial and lymphocyte β-adrenoceptors (Ross et al 1987, Kozlik-Friedman et al 1993, Dzimiri et al 1995, Wu et al 1996). In the failing heart, the β_1-adrenoceptors are mainly affected, while the stimulation of mildly uncoupled β_2-adrenoceptors may improve the cardiac function (Bristow et al 1990). The right atrial β-adrenoceptor density has been shown to be lower in patients with severe acyanotic and cyanotic CHD when compared to mild acyanotic CHD. Especially low β-adrenoceptor densities have been found in neonates with aortic stenosis and TGA. In these patients, additional significant β_2-adrenoceptor down-regulation may be present. Even though partial decoupling of the β_2-signal transduction in infants and children with severe CHD has been suggested, in patients with aortic stenosis and TGA the adenylate cyclase activity beyond the β-adrenoceptor level has also been shown to be affected, probably due to an increase in the inhibitory G-protein levels (Kozlik-Friedman et al 1993). Therefore, the efficacy of β_1- as well as β_2-adrenoceptor agonists may be limited in these patients, and drugs augmenting β-adrenergic stimuli

beyond the receptor level, as PDE inhibitors, could be of further advantage in postoperative cardiovascular support (Feldman et al 1990, Brodde 1991).

1.2.1. Hemodynamic evaluation

The correct timing of reconstructive surgery is essential in patients with increased $\dot{Q}p$ or obstruction to pulmonary venous flow. Pulmonary vasoconstriction and fixed pulmonary vascular disease may develop unless the surgical correction is performed early enough (Bush et al 1988). Management decisions in CHD can often be based on noninvasive measurements of blood flow and cardiac function (Sanders et al 1983). However, it is often necessary to perform cardiac catheterization to evaluate the morphologic and hemodynamic status of the patient.

The determination of $\dot{Q}s$ and $\dot{Q}p$ using the Fick principle depends on quantitation of $CavO_2$ across the vascular bed, and $\dot{V}O_2$ values. The SVR and PVR are calculated using pressure differences across the systemic and pulmonary beds and corresponding blood flow values, even though the recruitability of the pulmonary vasculature complicates the use of traditional PVR determinations (Fagard et al 1990, Gorback 1990). Using indirect calorimetry, $\dot{V}O_2$ and $\dot{V}CO_2$ values can be determined, when the inspired and expired O_2 and CO_2 concentrations and the volume of expired gas are known. However, anaerobic metabolism, as well as differences in the produced and exhaled CO_2 may affect the indirect calorimetry measurements (Ferrannini 1988). Methods using a pneumotachograph, or a Douglas bag for gas volume determination, an infrared CO_2 analyzer, a mass spectrometer, as well as a paramagnetic O_2 analyzer have been used in $\dot{V}O_2$ determination (Wessel et al 1969, Lindahl 1989, Lundell et al 1996). These methods have been demonstrated to have small interobservational variation (Lindahl 1989, Lundell et al 1996). However, these equipment require frequent calibration to give reliable results. In addition, the measurements may be sometimes cumbersome if mechanical ventilation and high a fraction of O_2 in inspired gas (FIO_2) are needed (Nunn et al 1989). Commercial metabolic monitors with direct measurement of the difference between inspired and expired O_2 concentrations, gas dilution principle for flow measurements, and possibility to study both mechanically ventilated and spontaneously breathing patients are available (Meriläinen 1987,Takala et al 1989, Weyland et al 1993). Cuffed tracheal tubes to prevent gas loss from the breathing circuit are often necessary for reliable results in

mechanically ventilated patients (Chwals et al 1992). The $\dot{V}O_2$ measurement may be difficult especially in young children, so the $\dot{V}O_2$ values are often estimated from nomograms constructed according to the patient's characteristics (Wessel et al 1969, LaFarge et al 1970, Lindahl 1989). However, the use of linear methods in estimation of the $\dot{V}O_2$ has been shown to result in wide CI of the calculated values (Lundell et al 1996, Sherman et al 1997). Furthermore, the linear regression equations predicting $\dot{V}O_2$ are usually based on data obtained from stable subjects, and are not easily applied to different patient populations in other clinical situations, e.g. after open-heart surgery to assess changes in relationship of $\dot{V}O_2$ and O_2 delivery in response to vasoactive medications. There are no studies in which artificial intelligence NN has been used to improve the predictive accuracy of the regression equations. It is a pattern recognition technique that does not assume or require a mathematical relationship between the independent and dependent variables. It consists of a set of processing units, which simulate neurons and are interconnected to allow signals to travel through the network. The computational power of NN derives from the density and complexity of the interconnections, and its ability to learn from experience during the development process (Cross et al 1995).

Because the increased resistance to $\dot{Q}p$ in patients with CHD has been found to increase the risks of reconstructive surgery (Bush et al 1988, Bando et al 1996), the preoperative evaluation of the patient should be based on precise information of pulmonary vascular tone and its reversibility. Several vasodilating agents, such as 100 % O_2, tolazoline, prostacyclin (PGI_2) and inhaled nitric oxide (NO), have been used to test the reactivity of pulmonary vascular bed preoperatively to determine the stage beyond which reconstructive surgery is no longer indicated (Bush et al 1988, Roberts et al 1993, Winberg et al 1994, Berner et al 1996, Turanlahti et al 1998). The assessment of the actual vasodilator capacity is important because the increased muscularity of the pulmonary vasculature may be a reversible lesion (Hoffman et al 1981). In this setting, the accurate determination of patient's hemodynamic status is necessary.

1.3.Reconstructive cardiac surgery and early postoperative circulatory function

The primary determinants of the results of successful constructive cardiac surgery are the adequacy of surgical repair and myocardial protection (Najafi et al 1969, Kirklin et al 1981). Even though the cardiac surgical procedure itself often improves cardiac output, the intraoperative myocardial damage may decrease it during the early postoperative period. Cardiac failure due to procedural reasons can occur after any cardiac repair, but it is more common after intracardiac operations requiring ventriculotomy. It may be the result of incomplete or inadequate operation, mechanical problems, such as undrained pericardial bleeding and pleural effusions causing cardiac tamponade, myocardial edema and chamber dilatation in a closed chest, and tension pneumothorax (Kirklin & Barrat-Boyes 1993). The complexity of surgery predisposes the patients also to postoperative bleeding, which may compromise the postoperative cardiovascular stability (Williams et al 1999a). It is often difficult to distinguish between changes in pulmonary performance produced by sternotomy, external cooling of the heart, general anesthesia, mechanical ventilation, and CPB, as they are all associated with pulmonary atelectasis (Wilcox et al 1988, Jain et al 1991, Weissman 1999, Cox et al 2000). However, the deterioration of functional residual capacity, lung compliance, venoarterial admixture, and the elevated alveolar-arterial O_2 gradient secondary to these changes may further impair the postoperative cardiac performance (Weissman 1999).

In patients with AVSD, restoration of a competent left-sided atrioventricular valve, and elimination of residual intracardiac communications are critical to the outcome (Bando et al 1995). These patients are also prone to transient postoperative nodal rhythms secondary to damage to the conductive tissue (Chen et al 1968). In patients with TGA, the origins and distribution of the coronary arteries are variable. Adequate coronary blood flow after transfer of the coronary arteries to the neoaorta without narrowing or distortion is required for a successful arterial switch operation. Unusual coronary anatomy predisposes these patients for complicated postoperative course (Wernovsky et al 1995b). Supraventricular and ventricular tachycardias, as well as complete heart block may also exist postoperatively and worsen the cardiac performance (Di Donato et al 1989). Patients with Fontan operations for single ventricle have high venous pressure in the right atrium, as well as in the hepatic and mesenteric vascular beds. This predisposes the patients to pleural effusions and high intra-abdominal venous pressure, which may complicate early postoperative recovery (Fontan et al 1990, Kaulitz et al 1996). Supraventricular tachycardia, and strokes also have been reported after a Fontan procedure (Driscoll et al 1992). In general, early closure of left-to-right shunts results in normal ventricular function (Cordell et al 1976, Baylen et al 1977). In patients

with preoperatively increased $\dot{Q}p$ the surgical correction of abnormal pulmonary hemodynamics favorably affects immediate postoperative respiratory mechanics (Lanteri et al 1995). However, a long-standing left-to-right shunt with volume overload and preoperatively increased PVR may result in persisting cardiac failure requiring vasoactive medications long after reconstructive surgery (Jamarkani et al 1972, Burrows et al 1988).

1.4. Effects of cardiopulmonary bypass on postoperative circulatory function

The inflammatory response associated with major surgery is particularly pronounced after cardiac surgery and CPB. The myocardium, pulmonary system, splanchnic bed and kidneys are the most important targets that contribute to the postoperative course after cardiac surgery. The blood-surface-interaction during the CPB has been suggested to be the main trigger for cell injury. The activation of coagulation, the kallikrein system, fibrinolysis, and the complement system, as well as the cytokines activate the expression of leukocyte adhesion molecules on the surface of endothelial cells. Once adherent to the endothelium, neutrophils release oxygen-derived free radicals and cytotoxic proteases, which contribute to the capillary leak resulting in the postoperative extracellular volume overload and electrolyte imbalance (Royston 1997, Hill et al 1997a). Endotoxemia is also a potent stimulant to further complement activation, and endothelial cell activation resulting in the up-regulation of leukocyte adhesion molecules. This may derive from a translocation of bacteria from the gut during splanchnic ischemia (Boyle et al 1997). However, tissue ischemia, hypothermia, relative hypotension during nonpulsative flow, hemodilution, and administration of blood products and pharmacological agents, such as heparin and protamine, may affect the inflammatory response (Royston 1997). Despite interindividual variation in the response to the inflammation during CPB, neonates and infants, and patients who require long CPB times, are especially at risk to systemic effects of endothelial injury (Kirklin et al 1983).

Myocardial injury associated with cardiac surgery is effected by both ischemia and reperfusion injury. During ischemia, there is a downregulation in cellular ATP secondary to lack of O_2, and hydrogen ion and lactate accumulation (McCord 1985). Microemboli, ventricular fibrillation and increased histamine production by basophiles may lead to ischemia during the bypass and predispose the patient to postoperative arrhythmias and low cardiac output (Buckberg et al 1975, Seghaye et al 1996). Reperfusion injury is characterized by intracellular calcium accumulation, and subsequent formation of oxygen-derived free radicals after a period of temporary ischemia (McCord

1985). The myocardium is affected by the reperfusion injury during the induction phase of cardioplegia, intermittent infusions of cardioplegic solution during the CPB, and after the removal of the aortic cross-clamp (Vinten-Johansen & Hammond 1993). The free radicals alter the sarcolemmal sodium homeostasis resulting in swelling of the myocytes with reduced postischemic blood flow and ventricular compliance (Kloner et al 1983). Low postbypass cardiac indexes, decreased perfusion necessitating inotropic support after CPB, and inhibition of the myocardial contractile response to β-adrenergic stimulation have been shown to correlate with increased levels of cytokines and activated complement components (Kirklin et al 1983, Gulick et al 1989, Seghaye et al 1993, Hennein et al 1994). The neutrophil adhesion to myocytes by adhesion molecules is associated with myocardial reperfusion injury after CPB as well (Byrne et al 1992, Wilson et al 1993). However, the immature complement receptors and neutrophil migration have been suggested to protect neonates with CHD undergoing cardiac operations from postoperative complications, even though complement activation is comparable to that in older children (Seghaye et al 1994). Large amounts of endogenous NO, possibly secondary to increased levels of inducible NO due to exposure to cytokines and endotoxins, have also been implicated in myocardial reperfusion injury (Hill et al 1997b).

Ischemic injury to the pulmonary endothelial cells while they are excluded from the circulation during CPB, or the exposure of the lungs to the entire cardiac output, as well as the activated inflammatory process and decreased white cell deformability may lead to postperfusion syndrome in the lung (Wilson et al 1971, Miller et al 1997, Gilliland et al 1999). Moreover, surfactant inhibition, that predisposes the lungs to alveolar and small airway collapse, is suggested to be associated with CPB (McGowan et al 1993, Paul et al 1999). In response to ischemia-reperfusion injury, hypoxia and exposure to cytokines the endothelial cells lose their ability to promote vasodilatation by constitutively expressing relaxant factors as NO, prostacyclin, and adenosine, whereas vasoconstriction is further aggravated by release of endothelin, thromboxane A, and angiotensin II. This imbalance may contribute to the lung injury in children with pulmonary hypertension, whose endothelium-dependent pulmonary artery relaxation is already impaired preoperatively, and may deteriorate further with CPB and increased plasma endothelin levels (Wessel et al 1993, Celermajer et al 1993, Komai et al 1993, Verrier et al 1996, Morita et al 1996).

In children with normal or decreased preoperative $\dot{Q}p$ a significant increase in the static elastance has been demonstrated after CPB, indicating that extracorporeal circulation may have deleterious impact on lung function. This may be due to atelectasis, increased extravascular lung water, and

release of vasoconstrictive agents (Lanteri et al 1995, Hiramatsu et al 1997). However, non-endothelium-derived agents such as catecholamines may also influence the pulmonary vascular tone in this setting.

Mucosal hypoperfusion, and microvessel occlusion secondary to platelet, leukocyte, and erythrocyte aggregation may affect bowel wall permeability to endotoxin, and contribute to the activation of the inflammatory response, sepsis, and multiorgan system failure (Andersen et al 1993, Biffl et al 1996). The reperfused gut may also induce mast cell activation and priming of circulating neutrophils, resulting in pulmonary injury secondary to sequestration of the neutrophils (Koike et al 1994, Boros et al 1995). The preoperatively impaired gut mucosal perfusion associated with lesions with decreased $\dot{Q}s$ may further deteriorate after CPB despite adequate surgical correction (Booker et al 1996). Liver is involved in glucose production and lactate clearance, synthesis of plasma proteins, immune function, drug metabolism, and clearance of intravascular debris. Alterations in these functions affect postoperative recovery of the cardiac surgical patient (Shangraw 1993). Long duration of CPB and repair of complex cardiac defects may lead to hepatocellular dysfunction, postoperative pancreatitis, and increased lactate levels (Collins et al 1983, Toffaletti et al 1986, Fernandez-del-Castillo et al 1991). Even though no specific lactate concentration has been demonstrated to predict outcome in pediatric cardiac patients, increased levels are associated with complicated postoperative course (Hatherill et al 1997, Munoz et al 2000). Fluid accumulation secondary to changes in body temperature, hemodilution, plasma oncotic pressure, interstitial fluid pressure and capillary permeability, is related to the duration of CPB, and young age (Cleland et al 1966, Utley 1993, Simpson et al 1993). Postoperative renal dysfunction is also associated with increased plasma levels of complement components, cytokines, and increased release of neutrophil granular proteases (Kirklin et al 1983, Seghaye et a 1993). Fluid retention may contribute to the postoperative need for diuretics, osmotic and oncotic agents, and vasoactive drugs (Utley 1993).

Young children demonstrate marked stress response secondary to surgery and CPB (Anand et al 1990). This response is characterized by suppression of insulin secretion, and increase in catecholamines, glucagon, cortisol, growth hormone, ACTH, and vasopressin levels (Weissman 1990, Anand et al 1990). The increased catecholamine levels may affect systemic and pulmonary vasculature postoperatively. Cortisol excess impairs the ability of insulin to stimulate glucose utilization and to reduce hepatic gluconeogenesis. Furthermore, impaired glucose uptake has been observed during the early postoperative period. The increased secretion of catecholamines and

growth hormone is associated with elevated free fatty acid levels secondary to stimulated lipolysis, resulting in impaired myocardial contractility and increased irritability (Hirvonen et al 1978, Vik-Mo et al 1981, Weissman 1990). The vasopressin-induced vasoconstriction may adversely affect the renal, coronary, and splanchnic circulations (Philbin et al 1979). Thyroid hormone levels have been shown to decrease during CPB in children with CHD, and this decrease is associated with prolonged and complicated postoperative course (Saatvedt et al 1998).

The use of hypothermia during CPB increases myocardial tolerance to the ischemia associated with aortic cross-clamp and cardioplegia. Reduction of myocardial O_2 demand by using total CPB, diastolic arrest, venting of the heart, and controlled reperfusion decreases the mismatch between myocardial O_2 supply and demand (Senning 1952, Buckberg et al 1977,Vinten-Johansen & Hammond 1993, Gates, Cushen & Laks 1993). The use of hypothermia delays the neutrophil-endothelial cell adhesion but does not prevent it (De Leist et al 1995). Normothermic perfusion does not produce more profound inflammatory response when compared with hypothermic and moderately hypothermic CPB (Birdi et al 1999). Hemofiltration and the use of leukocyte-depleted blood may decrease plasma levels of complement components and cytokines, and prevent reperfusion injury in pediatric patients (Breda et al 1989, Journois et al 1994a, Hayashi et al 2000). However, postischemic contractile function may be stunned for a period of time until energy production and excitation-contraction coupling recover (Braunwald et al 1982). Increased vascular permeability, arterial hypoxemia and ventilation-perfusion abnormalities may further increase the PVR, and compromise cardiac performance (Kirklin et al 1983, Burrows et al 1986, Westaby 1987, Hopkins et al 1991). Persistent postoperative arrhythmias, while a subtle manifestation of ischemic injury, may directly contribute to low cardiac output after surgery (Smith et al 1983). Moreover, the β-adrenoceptor desensitization and uncoupling associated with CHD may be further aggravated during CPB, affecting the efficacy of postoperative cardiovascular support (Schranz et al 1993).

Pharmacokinetics of drugs are also influenced by CPB. Hemodilution, hypothermia, hypotension, changes in regional blood flow, acid-base status, exclusion of the lungs from the circulation, as well as possible sequestration of the drug in bypass equipment may affect the drug pharmacokinetics and pharmacodynamics (Rosow 1993). The degree of plasma protein binding, and Vd of the drug may have effect on the drug concentration during the bypass. Decreased hepatic and renal blood flows may impair the metabolism and excretion of the drugs, and changes in acid-base status may affect their distribution. After re-establishment of the pulmonary circulation the pharmacological effects

of drugs with uptake in lungs may be increased (Mets 2000). These changes may contribute to the postoperative hemodynamics in patients undergoing cardiac surgery.

1.5. Anesthetic management and postoperative circulatory function

The goals of the anesthetic management of a child with CHD are to assure a comfortable intra- and postoperative course, provide cardiovascular stability, and attenuate the stress response to noxious stimuli. Hormonal and metabolic stress responses to cardiac surgery and CPB have been shown to correlate with postoperative morbidity and mortality in neonates despite hemodynamic stability (Anand et al 1990, Anand et al 1992). As the patients with complex CHD have limited myocardial reserve postoperatively, stressful interventions may further compromise cardiopulmonary function. Pain, wakefulness and agitation may lead to pulmonary hypertensive crises and sudden death after reconstructive surgery in patients with pulmonary hypertension (Hopkins et al 1991). The extension of anesthetic period postoperatively and ventilatory control to avoid hypoventilation and acidosis have been associated with reduced postoperative morbidity in high-risk patients (Wernovsky et al 1995a, Wernovsky et al 1995b, Bando et al 1996).

The choice of anesthetic agents depends on the preoperative cardiovascular status of the patient. Young children with complex CHD associated with decreased myocardial reserve, intracardiac shunting, or compromised forward flow require different anesthetic management than older, asymptomatic children with noncomplicated defects in whom fast postoperative recovery is expected. Inhalation anesthetics that may be safely used in some uncompromised patients with CHD are often not well tolerated in critically ill infants due to their depressant effects on myocardium (Kawana et al 1995). Intravenous ketamine provides hemodynamic stability in children with CHD, even though increase in PVR has been suggested in adult cardiac patients with unprotected airways (Spotoft et al 1979, Hickey et al 1985b). It improves gas exchange and chest compliance in patients with small airway obstruction that may be associated with increased $\dot{Q}p$ (Schindler et al 1995, Lanteri et al 1995,Yossef-Ahmed et al 1996). However, in some patients, e.g. those with severe left heart valvular obstruction, the cardiovascular stimulation produced by ketamine may be not desirable. Furthermore, the use of ketamine in patients with depleted endogenous catecholamine stores due to critical illness may result in impaired cardiac performance (Christ et al 1997). Propofol has been demonstrated to reduce systemic arterial pressure and SVR in patients with CHD, with no effects on cardiac rhythm (Lebovic et al 1992, Friesen et al 1996).

However, in children undergoing CPB propofol administration has been associated with favorable hemodynamic and reduced stress response (Laycock et al 1992). Its use with opiates in uncomplicated postoperative pediatric cardiac patients has been devoid of significant adverse effects (Martin et al 1997). In patients with left-to-right shunts, propofol is well tolerated, whereas in patients with right-to-left shunts it may reverse shunt flow. The systemic afterload reduction produced by propofol may be harmful in patients with severe left heart outflow obstruction, as well as in patients whose $\dot{Q}p$ depends on the balance between SVR and PVR (Williams et al 1999b). Midazolam causes only minor hemodynamic changes when combined with opiates in adult cardiac patients (Kleinschmidt et al 1997). However, midazolam boluses combined with opiate infusions decrease cardiac output, mixed venous blood O_2 content, and $\dot{V}O_2$ in hemodynamically stable children after open-heart surgery, suggesting that midazolam infusion may be preferable especially in children with complex surgical correction (Shekerdemian et al 1997).

Neuromuscular blockade is often induced with long-acting nondepolarizing agents in young children with complex CHD. Pancuronium bromide is well tolerated in these patients, and the increased sympathetic activity associated with its administration may be advantageous if cardiac output is low (Maunuksela et al 1981, Cabal et al 1985). However, residual neuromuscular blockade secondary to usage of long-acting agents may impair the respiratory function postoperatively (Buzello et al 1978, Van Oldenbeek et al 1999). Shorter-acting muscle relaxants have been used without significant cardiac side effects in children without cardiac defects (Brandom 2000). There are few studies on the effects of these agents in critically ill children with CHD. Hypotension secondary to histamine release by neuromuscular blocking drugs may be of disadvantage especially in patients who do not tolerate decrease in SVR. The lack of vagolytic action of these agents may also be not desirable when used with high-dose opiates (Salmenperä et al 1983).

High-dose opiates provide hemodynamic stability and suppression of metabolic and hormonal stress response in critically ill children (Hickey et al 1985a, Anand et al 1992, Duncan et al 2000). However, when combined with benzodiazepines, fentanyl and sufentanil have been demonstrated to provide more complete suppression of cardiovascular and hormonal responses to intense stimulation in children with CHD (Morgan et al 1987, Barankay et al 1992). Alfentanil has been used in patients in whom early extubation has been desirable. However, when administrated with inhaled anesthetics, alfentanil boluses may produce bradycardia in infants with CHD (den Hollander et al 1988).

2. Postoperative vasoactive support in children recovering from open-heart operations

In the postoperative management of a child with complex CHD, manipulation of all determinants of cardiac output, namely heart rate, preload, afterload and contractility, is often required (Thys & Dauchot 1993). Temporary pacemakers are frequently used to provide adequate heart rate and atrioventricular synchrony. Low diastolic compliance in young children allows limited margin for volume loading to increase stroke volume (Thornburg et al 1983). Therefore, administration of vasoactive agents according to the underlying pathophysiology of the cardiac defect is often necessary.

2.1. Catecholamines

Dopamine is a naturally occurring immediate precursor of norepinephrine, with a variety of dose-dependent effects on α-, β-, and dopaminergic receptors. At low doses it stimulates renal dopaminergic D_1-and D_2-receptors, resulting in vasodilatation in the coronary, renal, mesenteric, and cerebral circulations. This effect is mediated by increased production of cAMP by postsynaptic D_1-receptors, and inhibition of norepinephrine release by presynaptic D_2-receptors. At moderate doses, dopamine exerts a dose-dependent β_1-adrenergic agonist effects with resultant increase in heart rate, stroke volume, and cardiac output, but with little effect on peripheral arterial resistance. At high doses α_1-adrenergic effects increase systemic arterial and venous pressures, left ventricular filling pressures, and decrease mesenteric and renal blood flow. Increased myocardial $\dot{V}O_2$, arrhythmias, suppression in insulin secretion and accelerated glucose production may be associated with dopamine administration especially at high doses (Notterman 1991, Seri 1995).

The dose of dopamine necessary for adequate inotropic support varies with age. Neonates and infants require higher doses of dopamine to achieve significant increase in cardiac output than older children or adult patients after cardiac surgery. Fortunately, the same age-dependency holds true for adverse side effects as well (Perez et al 1986, Outwater et al 1990, Bhatt-Mehta et al 1991). This variation may be secondary to differences in the sympathetic innervation of the heart and peripheral tissues, cardiac catecholamine stores, compliance of the myocardium, and dopamine pharmacokinetics (Friedman 1972, Erath et al 1982, Steinberg et al 1994). Dopamine has been suggested to act as a pulmonary vasoconstrictor in children with pulmonary vascular obstructive

disease undergoing cardiac catheterization, as well as in infants after CPB (Driscoll et al 1979, Booker et al 1995). However, in contrast to these results, not even high doses of dopamine affected pulmonary vascular tone adversely in some children with CHD (Outwater et al 1990). This could possibly be explained by differences in the pre-existing pulmonary hypertension despite similar surgical procedures. In infants and children with CHD, dopamine increases renal blood flow and glomerular filtration rate independently from increase of cardiac output (Girardin et al 1989, Outwater et al 1990). In addition to the specific effects of dopamine on renal function, its administration has been suggested to increase liver blood flow postoperatively in children with CHD (Mitchell et al 1995). Dopamine is frequently used in patients with TGA and AVSD for postoperative inotropic support (Wernovsky et al 1995a, Bando et al 1995, Bando et al 1996). Dopamine pharmacokinetics in children are outlined in Table 1.

Dobutamine, a synthetic catecholamine, is β_1-selective, and has a low affinity for β_2- and α-receptors (Zaritsky et al 1984). Dobutamine has no dopaminergic effects and does not stimulate the release of endogenous catecholamines (Tuttle et al 1975). In critically ill children, an improvement in the systolic cardiac function and increase in heart rate has been shown even when small doses are used. However, plasma dobutamine concentration necessary to initiate hemodynamic responses varies widely (Berg et al 1993). When compared with dopamine in young children undergoing cardiac surgery, similar hemodynamic actions of the two drugs have been demonstrated in a blinded, double crossover study. However, dopamine increased PAP and PVR significantly in high doses probably secondary to the α-adrenergic receptor effect (Booker et al 1995). Dopamine is not superior to dobutamine for protection of renal function in children after CPB (Wenstone et al 1991). The pharmacokinetic data of dobutamine in children are presented in Table 1.

Epinephrine, a naturally occurring catecholamine, has α-, β_1- and β_2-adrenergic effects. At low doses, myocardial contractility increases and SVR decreases secondary to effects on β-receptors. However, as the dose increases, the α - adrenergic effects become predominant, leading to increased peripheral resistance to blood flow. At high doses, myocardial irritability and arrhythmias may occur. Increased heart rate and contractility may affect myocardial $\dot{V}O_2$ adversely (Notterman 1991). Furthermore, epinephrine administration may impair splanchnic perfusion in situations when the regional O_2 balance is compromised (Meier-Hellmann et al 1997). Epinephrine has a significant calorigenic response; it stimulates lipolysis, and accelerates glycogenolysis, and gluconeogenesis, leading to production of lactate. Epinephrine administration also is associated with a decrease in

serum potassium levels (Sjöström et al 1983, Macdonald et al 1985). Epinephrine infusions are often used in children with pulmonary hypertension undergoing reconstructive surgery for further inotropic support (Bando et al 1996). Pharmacokinetic data of epinephrine in children are presented in Table 1.

Norepinephrine, like epinephrine, is a naturally occurring catecholamine with predominantly α-adrenergic action, though some β_1-adrenergic effects have been demonstrated. Administration of norepinephrine results in arteriolar constriction in many vascular beds. Additionally, like epinephrine, norepinephrine increases preload secondary to venous constriction. Increase in SVR and blood pressure often leads to vagal reflex slowing of heart rate. Cardiac output either remains unchanged or decreases slightly (Zaritsky et al 1984). Increase in PVR and splanchnic and renal vasoconstriction also have been shown to result from norepinephrine administration. The metabolic effects of norepinephrine are similar to epinephrine (Notterman 1991). Pharmacokinetic data of norepinephrine in children is limited (Table 1).

Isoprenaline is a synthetic derivative of norepinephrine with nonspecific β-adrenergic agonist activity. The principal therapeutic effects associated with isoprenaline are chronotropic and inotropic, peripheral vasodilatation augmenting the chronotropic action, pulmonary vasodilatation, and bronchial smooth muscle relaxation. Isoprenaline is used for the treatment of bradycardia, reactive pulmonary hypertension and status asthmaticus (Steinberg et al 1994). However, decreased diastolic blood pressure and shortened diastole during tachycardia may impair myocardial O_2 delivery (Matson et al 1978), an effect especially undesirable in children with abnormal coronary vasculature. Ventricular and atrial tachyarrhythmias, and increase in intrapulmonary shunting also may occur (Notterman 1991). Pharmacokinetics of isoprenaline in children are presented in Table 1.

Dopexamine, a synthetic catecholamine, is regarded mainly as an agonist at the D_1-, D_2- , and β_2-receptors, while β_1-adrenoceptor effects are considered weak (Brodde 1988). Its sympathomimetic action is indirect, secondary to inhibition of uptake$_1$(neuronal tissue uptake of norepinephrine) and potentiation of endogenous noradrenaline effects (Mitchell et al 1987, Napoleone et al 1992). Dopaminergic and indirect sympathomimetic actions appear to predominate at low doses (Geisser et al 1997). An increase in arterial pressure, arterial pH and urine output have been associated with dopexamine administration in critically ill neonates (Kawczynski et al 1996). In older children after surgery for CHD, dopexamine increased cardiac index and heart rate significantly, while no

significant effect on stroke volume index and PVR could be shown. Decrease in SVR was observed only at high doses of dopexamine, suggesting predominantly β_1-adrenoceptor activation (Habre et al 1996). These results differ from studies in adult cardiac patients in whom the decrease in SVR has been proposed as the main action of dopexamine (Stephan et al 1990, Sherry et al 1997). This discrepancy may be due to variation in the extent of the β-adrenoceptor downregulation in the different patient groups under study. The effects of dopexamine on renal function are controversial. Even though improved creatinine CL following dopexamine administration has been shown in adults after cardiac surgery, no renal vascular vasodilation could be demonstrated in pediatric patients (Habre et al 1996, Berendes et al 1997). Furthermore, postoperative increase in renal vascular resistance occurs to a similar extent in both dopexamine and placebo groups in adults (Sherry et al 1997). Dopexamine administration reduces the gastrointestinal tract permeability following CPB, and attenuates the endotoxin-mediated increase in cytokine levels (Sinclair et al 1997, Berendes et al 1997). When administered to infants undergoing CPB, it increases gastric mucosal perfusion after rewarming from profound hypothermia (Booker et al 2000). In noncardiac surgical adult patients under mechanical ventilation dopexamine administration has not resulted in impairment of pulmonary gas exchange (Hachenberg et al 1998). However, no reports on pulmonary effects of dopexamine in children undergoing cardiac surgery are available. Pharmacokinetic data on dopexamine in children have not been published so far (Table 1).

2.2. Vasodilators

Vasoconstriction secondary to increased sympathetic activity associated with heart failure increases the cardiac afterload (Ross et al 1987, Thys & Dauchot 1993). Reduction of ventricular workload postoperatively is important especially in neonates and infants, as their limited cardiac performance is further compromised by surgery and CPB. Several different intravenous vasodilators have been used to manipulate afterload in children after cardiac surgery. Administration of sodium nitroprusside and nitroglycerine provide vasodilation by releasing intracellular NO that activates soluble guanylate cyclase and increases the production of cyclic guanosine monophosphate (cGMP) (Gruetter et al 1981, Moncada et al 1991). Basal release of endogenous NO in both systemic and pulmonary circulations appears to lead to constant inhibition of smooth muscle contraction (Rees et al 1989). In patients with left ventricle dysfunction, sodium nitroprusside has been shown to dilate mainly arterial resistance vessels, even though venous capacitance vessels are also affected.

Table 1. *Pharmacokinetic parameters of different catecholamines in children.*

Catecholamine	CL (ml/kg/min)	Vd (l/kg)	$T_{½}$ (minutes)	Metabolism route
Dopamine	115 in neonates and infants (Bhatt-Mehta et al 1991) 83 ± 28 in children < 2 years (Notterman et al 1990) 46 ± 17 in children > 2 years (Notterman et al 1990)	1.8 in neonates and infants (Bhatt-Mehta et al 1991)	7 in neonates and infants (Bhatt-Mehta et al 1991)	Liver, kidneys, pulmonary endothelium (Seri 1995) Methylation, deamination or conjugation to sulphate (Steinberg et al 1994)
Dobutamine	82 ± 3 (Berg et al 1993)	0.07-5.64 (Schwartz et al 1991)	α-phase: 1.7 ± 0.2 β-phase: 26 ± 12 (Schwartz et al 1991)	Liver, kidneys Methylation, glucuronidation $Uptake_2$ (Steinberg et al 1994)
Isoprenaline	43 ± 5 (Reyes et al 1993)	0.22 ± 0.06 (Reyes et al 1993)	4.2 ± 1.5 (Reyes et al 1993)	Liver, kidneys Methylation $Uptake_2$ (Steinberg et al 1994)
Epinephrine	29 ± 16 (Fisher et al 1993)	Not reported	β-phase: 2 (Steinberg et al 1994)	Liver, kidneys Methylation, deamination $Uptake_2$ (Steinberg et al 1994)
Norepinephrine	Not reported	Not reported	2-2.5 (Steinberg et al 1994)	Liver, kidneys Methylation, deamination $Uptake_1$ and uptake $_2$ (Steinberg et al 1994)
Dopexamine	Not reported	Not reported	Not reported	Not reported

Values are given as mean ± standard deviation, mean, or range.

Abbreviations: CL, clearance; Vd, volume of distribution; $T_{½}$, elimination half-life.

Nitroglycerin has a predominant effect on venous capacitance vessels, but some arterial vasodilative effects can be seen as well (Kirsten et al 1998). These drugs improve cardiac performance in children with CHD, especially when combined with inotropic agents (Benzing et al 1979, Bando et al 1996). In patients with CHD, sodium nitroprusside has been demonstrated to reduce complement activation during CPB (Seghaye et al 1996). Methemoglobinemia and production of cyanide may lead to tissue anoxia when sodium nitroprusside is administrated in high doses (Ivankovich et al 1983). The elimination half-life ($T_{½}$) of sodium nitroprusside is 3-4 minutes in adults (Weir et al 1989). Nitroglycerine concentration declines rapidly after cessation of administration because of vascular metabolism. The CL of nitroglycerine, also affected by cardiac output, is 0.3-1.0 l/kg/min, the plasma half-life is 2.8 ± 0.9 minutes, and the Vd is 3 l/kg in adults (McNiff et al 1981, Fung 1987). The pharmacokinetics of nitrosovasodilators have not been well characterized in children with CHD (Table 2). However, it has been suggested that there are no significant aberrations from adult pharmacokinetics during pediatric use (Kirsten et al 1998).

Intravenous prostaglandin E_1 (PGE_1), and PGI_2 have been used to improve postoperative cardiac performance in patients with right heart failure (D´Ambra et al 1985). However, the vasodilating effect of intravenous prostaglandins on systemic vasculature may limit their use in critically ill children during the postoperative period (Turanlahti et al 1998). Long-term administration is well tolerated in children with pulmonary hypertension who fail conventional therapy (Rosenzweig et al 1999). In adults, the CL of $PGE_1$and PGI_2 is 20 ml/kg/min, and the Vd is 0.8 l/kg (Kirsten et al 1998). The terminal half-life of PGE_1 has a α -phase of 0.2 ± 0.1 minutes and a β -phase 8.2 ± 6.3 minutes (Cawello et al 1994). The disposition of PGI_2 after discontinuation of infusion is biphasic with half-lives of 3 and 30 minutes in adults (Kirsten et al 1998). The pharmacokinetics of the PGE_1 and PGI_2 have not been established in critically ill children with CHD (Table 2).

Hypotension, increase in intrapulmonary shunting from attenuated hypoxic pulmonary vasoconstriction, and reduced PaO_2 may follow nitrate administration (Mookherjee et al 1978, Radermacher et al 1989). Different intravenous vasodilators have been used in the management of children with pulmonary hypertension associated with CHD, even though the lack of selectivity on pulmonary circulation may limit their use in these patients (Houde et al 1993).

Inhaled exogenous NO provides selective vasodilation of pulmonary arteries, improvement in arterial oxygenation, and right ventricular performance postoperatively in children with pulmonary

hypertension and after Fontan-type repair of CHD (Miller et al 1994a, Journois et al 1994b, Goldman et al 1995, Schulze-Neick et al 1997). However, in controlled randomized trials inhaled NO has offered little advantage over conventional therapy in patients with increased pulmonary artery pressure postoperatively (Russell et al 1998, Day et al 2000). These findings may be affected by the patient entry criteria, the underlying cardiac pathophysiology, conventional therapy used, as well as the NO doses used in these studies. Preoperatively, NO has been used to test the reversibility of pulmonary hypertension (Roberts et al 1993, Winberg et al 1994, Berner et al 1996, Turanlahti et al 1998). Since NO is rapidly inactivated by binding to hemoglobin, its vasodilatory effect seems to be restricted to the pulmonary vasculature without significant systemic action (Frostell et al 1993). However, NO bound to hemoglobin may have a prolonged effect on systemic circulation secondary to formation of S-nitrosothiols (Jia et al 1996). Pulmonary edema may occur during NO therapy in patients with severe left ventricular failure, probably secondary to increase in pulmonary venous return (Bocchi et al 1994). The antithrombotic effect of NO has been suggested in adults with adult respiratory distress syndrome, but the significance of this finding has not been confirmed in children with CHD (Samama et al 1995). Determination of the lowest effective dose of NO is important, because a combination of NO and high FIO_2 leads rapidly to production of toxic nitric dioxide (NO_2), and the inactivation of NO may lead to methemoglobinemia especially in neonates with immature methemoglobin reductase activity (Foubert et al 1992, Miller et al 1994b, Mansouri et al 1993). The use of very low-dose inhaled NO has been shown to be effective in some patients with postoperative pulmonary hypertension (Miller et al 1994a, Beghetti et al 1995).

The alternative use of inhaled PGI_2 has been proposed for postoperative pulmonary hypertension, but the local adverse effects of this agent, as well as its effects on platelet function, during prolonged administration in critically ill children are unknown (Zwissler et al 1995, Pappert et al 1995, Haraldsson et al 1996, Forrest et al 1999).

Table 2. *Pharmacokinetics of intravenous vasodilators in children.*

Vasodilator	CL (ml/kg/min)	Vd (l/kg)	$T_{½}$ (minutes)	Metabolism route
Nitroprusside	Not reported	Not reported	Not reported	Kidneys Degradation to cyanide and detoxification to thiocyanate (Kirsten et al 1998)
Nitroglycerine	Not reported	Not reported	Not reported	Liver Arteriovenous extraction, vascular metabolism (Fung 1987, McNiff et al 1981)
Prostacyclin	Not reported	Not reported	Not reported	Liver and kidneys (Kirsten et al 1998)
Prostaglandin E_1	Not reported	Not reported	Not reported	Lungs and liver (Kirsten et al 1998)

Abbreviations: CL, clearance; Vd, volume of distribution; $T_{½}$, elimination half-life.

2.3. Phosphodiesterase inhibitors

Phosphodiesterase inhibitors are non-glycoside, non-sympathomimetic drugs, with a competitive inhibitory action on the PDE isoenzyme III. They increase intracellular cAMP levels in myocytes and vascular smooth muscle cells by inhibiting the hydrolysis of cAMP, which leads to increased inotropy, peripheral vasodilatation, and enhanced myocardial relaxation (Honerjäger 1991, Skoyles et al 1992). Unlike catecholamines, PDE inhibitors have been shown to improve myocardial performance without raising myocardial $\dot{V}O_2$ or increasing afterload (Benotti et al 1980, Sakaki et al 1998). They do not appear to be accompanied by the β-receptor desensitization and downregulation, but may shift the β_1- to β_2- adrenoceptor ratio toward β_2- adrenoceptors (Feldman et al 1990). Evidence is also available that the PDE activity is not altered in human heart failure (De Mello 1996). The ability of β-adrenergic agonists to stimulate adenylate cyclase is decreased in neonates, probably due to uncoupling of β-adrenoceptors and adenylate cyclase activity at early age (Baum et al 1997). However, age does not affect the PDE inhibitor effect (Foged et al 1990).

Amrinone and milrinone are bipyridine derivatives, whereas enoximone and piroximone are imidazole derivatives providing selective PDE III inhibition (Skoyles et al 1992).

In neonatal piglet hearts, negative inotropic effects from amrinone administration have been observed (Ross-Ascuitto et al 1989). In pediatric patients after cardiac surgery, amrinone increases cardiac output and decreases SVR (Lynn et al 1993, Sorensen et al 1996). Amrinone has been suggested to act mainly as a systemic vasodilator without significant inotropic effect (Berner et al 1990). However, when compared with sodium nitroprusside, amrinone provides a significantly larger increase in cardiac output per unit decrease in blood pressure (Bailey et al 1997). This discrepancy may be explained by differences in the dosing regimen, volume loading to provide stable preload, and the baseline condition of the patients in these studies. Administration of amrinone has resulted in reduction of high PVR in children undergoing cardiac catheterization as well as after cardiac surgery (Wessel et al 1989, Robinson et al 1993). Additive effects have been demonstrated when catecholamines are administered concomitantly with amrinone in adults after CPB (Royster et al 1993). The dosing recommendations established to achieve therapeutic serum concentrations in adults have resulted in wide range of serum amrinone levels in children, all with acceptable cardiac performance (Edelson et al 1981, Allen-Webb et al 1994). The relationship between amrinone concentration and hemodynamic response is unknown in children undergoing cardiac surgery for CHD. Refractory hypotension has been reported to follow amrinone overdosing (Lebovitz et al 1995). Peritoneal dialysis is ineffective in treatment of toxic amrinone overdose (Lawless et al 1993). The pharmacokinetics of amrinone in children have been previously studied in heterogeneous patient populations (Lawless et al 1989, Allen-Web et al 1994). In adults amrinone CL is affected by acetylator phenotype; in slow acetylators it is approximately 50 % of that in fast acetylators (Hamilton et al 1987). Increased incidence of slow acetylation has been observed in young children (Szorady et al 1987, Pariente-Khayat et al 1991). However, in children from 1 to 160 months of age no age-related differences in amrinone elimination have been observed (Allen-Web et al 1994). There is little information on amrinone pharmacokinetics in neonates during the first four weeks of life (Lawless et al 1989, Allen-Web et al 1994, Williams et al 1995). The pharmacokinetic data of amrinone in children are presented in Table 3.

Milrinone lowers filling pressures, SVR, and PVR, while improving cardiac index in neonates after cardiac surgery as well as in pediatric patients with septic shock (Chang et al 1995, Lindsay et al 1998). Milrinone, similarly to amrinone, increases the inotropic state of the myocardium, when compared to nitroprusside for a matched reduction in mean aortic pressure or SVR in patients with

heart failure (Jaski et al 1985). Milrinone administration has resulted in reduced endotoxin and interleukin levels in adults undergoing CPB when compared with placebo, but it does not confer protection against splanchnic ischemia over dopamine (Mollhoff et al 1999, McNicol et al 1999). Moreover, the higher amount of colloids given before CPB in the milrinone-treated group when compared to placebo group may have contributed to the observed effects. The pharmacokinetics of milrinone in children are presented in Table 3.

The administration of enoximone improved cardiac performance in neonates and infants with postoperative low-output states refractory to high-dose catecholamine therapy. A transient fall in systemic arterial pressure, responding to volume loading, was observed during enoximone therapy; no bleeding disturbances or arrhythmias were noted (Schranz et al 1989, Hausdorf 1993). However, enoximone did not provide advantage in inotropic and vasodilating effects over a combination of dobutamine and phenoxybenzamine in children with tetralogy of Fallot and AVSD. This result may have been confounded by the low loading dose of enoximone administered during the CPB (Innes et al 1994). Improvement in O_2 delivery associated with enoximone did not prevent gastric mucosal acidosis even though endotoxin levels were significantly diminished in adults after CPB (Loick et al 1997). No studies on enoximone pharmacokinetics are available in children. Piroximone has been successfully used to increase cardiac index and decrease SVR in adult cardiac surgical patients (Hausen et al 1992), but no studies on its administration on pediatric patients have been published so far. The $T_{½}$ of enoximone is 4.3 hours, and that of piroximone is 1.3 ± 0.2 hours in adults (Skoyles et al 1992, Fauvel at al 1995).

Thrombocytopenia has been associated with amrinone administration secondary to nonimmune-mediated peripheral platelet destruction, decreased platelet survival time and increased numbers of megathrombocytes. Exposure to N-acetylamrinone, the primary metabolite of amrinone, has been suggested to be toxic to platelets especially in patients with rapid acetylator phenotype (Ross et al 1993). However, no hemorrhagic complications have been reported with short-term administration of PDE inhibitors in pediatric patients (Berner et al 1990, Lynn et al 1993). In adult cardiac patients, milrinone, enoximone, and piroximone administration do not cause significant changes in platelet number or function during the first 24 postoperative hours beyond the usual effects of cardiac surgery and CPB (Boldt et al 1992, Kikura et al 1995). However, in infants and children receiving milrinone after cardiac surgery, thrombocytopenia occurred in 58 % of the patients, and the risk

increased with duration of the infusion (Ramamoorthy et al 1998). This difference may be explained by the shorter observation time in adult patients.

Table 3. *Pharmacokinetic data of PDE III inhibitors in children.*

PDE III inhibitor	CL (ml/kg/min)	Vd (l/kg)	$T_{½}$ (hours)	Metabolism route
Amrinone	2.9 ± 1.7 in neonates and infants (Lawless et al 1989) 2.2 ± 0.9 in children (Sorensen et al 1996) 2.5 ± 1.5 in children (Allen- Webb 1994)	1.7 in children < 1 year (Lawless et al 1989) 1.0 ± 0.4 in children (Allen-Webb et al 1994)	12.7-15.6 in neonates 3.8-6.4 in infants (Lawless et al 1989) 5.5 ± 2.3 in children (Allen-Webb et al 1994)	Liver, kidneys Acetylation, glucuronidation, glutathione addition (Steinberg et al 1994)
Milrinone	3.8 in infants 5.9 in children (Ramamoorthy et al 1998)	0.9 in infants 0.7 in children (Ramamoorthy et al 1998) 1.5 ± 1.0 (Lindsay et al 1998)	0.6-10.9, mean 1.5 (Lindsay et al 1998)	Mainly by kidneys (Skoyles et al 1992)
Enoximone	Not reported	Not reported	Not reported	Mainly by liver Sulphoxidation (Skoyles et al 1992)
Piroximone	Not reported	Not reported	Not reported	Kidneys (Fauvel et al 1995)

Values are given as mean ± standard deviation, mean, or range.

Abbreviations: CL, clearance; Vd, volume of distribution; $T_{½}$, elimination half-life.

3. Summary of the literature review

In summary, lesions with increased $\dot{Q}p$, such as AVSD, are associated with volume overload of the heart, and volume or pressure overload of the pulmonary circulation that predispose the patients to extension of distal muscularization in pulmonary arteries and increased PVR (Newfeld et al 1977, Young 1980). Even when reconstructive surgery is performed in early infancy, pulmonary hypertensive events may complicate the recovery of these patients (Hopkins et al 1991, Bando et al 1995). In neonates with TGA, the left ventricle loses its capacity to grow and overcome high afterload as the PVR decreases within the first weeks of life. In these patients, however, the gradually increasing PVR predisposes the child to pulmonary vascular obstructive disease and

increased risks of surgery. Therefore, the correct timing of reconstructive surgery is essential for the successful correction of these defects (Bano-Rodrigo et al 1980, Bush et al 1988, Bando et al 1996).

Precise determination of cardiac output is required when the hemodynamic status of the patient and the actual vasodilator capacity of the pulmonary vascular bed are assessed preoperatively. The determination of $\dot{Q}s$ and $\dot{Q}p$ using the Fick principle depends on quantitation of $CavO_2$ across the vascular bed, and $\dot{V}O_2$. The use of indirect calorimetry to determine $\dot{V}O_2$ and $\dot{V}CO_2$, resulting from measurements of the inspired and expired O_2 and CO_2 concentrations and the volume of expired gas, may be sometimes cumbersome during mechanical ventilation and when high FIO_2 are needed (Nunn et al 1989, Takala et al 1989, Weyland et al 1993). The $\dot{V}O_2$ measurement may be especially difficult in children with CHD, so the $\dot{V}O_2$ values are often estimated from nomograms constructed according to the patient's characteristics (Wessel et al 1969, LaFarge et al 1970, Lindahl 1989). The use of linear methods in estimation of the $\dot{V}O_2$ has been shown to result in wide CI of the calculated values (Lundell et al 1996, Sherman et al 1997). Furthermore, the linear regression equations predicting $\dot{V}O_2$ are usually based on data obtained from stable subjects undergoing cardiac catheterization, and are not easily applied to different patient populations in other clinical situations. There are no studies in which nonlinear artificial intelligence NN has been used to improve the predictive accuracy of the regression equations (Cross et al 1995).

The patients with AVSD and TGA are prone to low cardiac output and increased vascular resistances during the early postoperative period secondary to the combined effects of underlying cardiac pathophysiology, anesthetic management, surgery itself, and use of CPB (Kirklin et al 1981, Anand et al 1992, Wernovsky et al 1995a, Bando et al 1996, Royston 1997). Children with CHD have increased sympathetic activity. Secondary to this elevated tone, these patients present down-regulation and uncoupling of the myocardial and lymphocyte β-adrenoceptors (Ross et al 1987, Kozlik-Friedman et al 1993, Dzimiri et al 1995, Wu et al 1996). Especially low β-adrenoceptor densities have been found in neonates with aortic stenosis and TGA. In these patients, additional significant β_2-adrenoceptor down-regulation may be present (Kozlik-Friedman et al 1993). Therefore, the efficacy of β_1- as well as β_2-adrenoceptor agonists may be limited in these patients (Feldman et al 1990, Brodde 1991).

Even though the cardiac surgical procedure itself often improves cardiac output, the intraoperative myocardial damage may decrease it during the early postoperative period. It may be the result of incomplete operation, and several mechanical problems (Kirklin & Barrat-Boyes 1993). In patients with AVSD, restoration of a competent left-sided atrioventricular valve, and elimination of residual intracardiac communications are critical to the outcome (Bando et al 1995). In patients with TGA, adequate coronary blood flow after transfer of the coronary arteries to the neoaorta without narrowing or distortion is required for a successful arterial switch operation. Unusual coronary anatomy predisposes these patients for complicated postoperative course (Wernovsky et al 1995b).

Pronounced inflammatory response is associated with cardiac surgery and CPB. The myocardium, pulmonary system, splanchnic bed and kidneys are important targets that contribute to the postoperative course after cardiac surgery. Tissue ischemia, hypothermia, relative hypotension during nonpulsative flow, hemodilution, and administration of blood products and pharmacological agents may affect the inflammatory response (Royston 1997). Despite interindividual variation in the response to the inflammation during CPB, neonates and infants, and patients who require long CPB times, are especially at risk to systemic effects of endothelial injury (Kirklin et al 1983). The use of hypothermia during CPB increases myocardial tolerance to the ischemia associated with aortic cross-clamp and cardioplegia. Reduction of myocardial O_2 demand by using total CPB, diastolic arrest, venting of the heart, and controlled reperfusion decreases the mismatch between myocardial O_2 supply and demand (Senning 1952, Buckberg et al 1977,Vinten-Johansen & Hammond 1993, Gates, Cushen & Laks 1993). However, the use of hypothermia does not prevent the neutrophil-endothelial cell adhesion even though it is delayed (De Leist et al 1995). Hemofiltration and the use of leukocyte-depleted blood may decrease plasma levels of complement components and cytokines, and prevent reperfusion injury in pediatric patients (Breda et al 1989, Journois et al 1994a, Hayashi et al 2000).

Hormonal and metabolic stress responses to cardiac surgery and CPB correlate with postoperative morbidity and mortality in neonates despite hemodynamic stability (Anand et al 1990, Anand et al 1992). The extension of anesthetic period postoperatively and ventilatory control to avoid hypoventilation and acidosis have been associated with reduced postoperative morbidity in high-risk patients (Hopkins et al 1991, Wernovsky et al 1995a, Wernovsky et al 1995b, Bando et al 1996). High-dose opiates provide hemodynamic stability and suppression of metabolic and hormonal stress response in critically ill children (Hickey et al 1985a, Anand et al 1992, Duncan et

al 2000). When combined with benzodiazepines, opiates provide more complete suppression of cardiovascular and hormonal responses to intense stimulation in children with CHD (Morgan et al 1987, Barankay et al 1992). Midazolam infusion is preferable in children with complex surgical correction receiving also opiates (Shekerdemian et al 1997). Pancuronium bromide is well tolerated in these patients, and the increased sympathetic activity associated with its administration may be advantageous if cardiac output is low (Maunuksela et al 1981, Cabal et al 1985).

Secondary to the above mentioned pre- and perioperative effects administration of vasoactive support is often necessary postoperatively. Dopamine, epinephrine and nitroglycerine are frequently used in inotropic support in these patients (Wernovsky et al 1995a, Bando et al 1996). Neonates and infants need higher doses of dopamine to achieve significant increase in cardiac output than older children or adult patients after cardiac surgery (Perez et al 1986, Outwater et al 1990, Bhatt-Mehta et al 1991). Dopamine has been suggested to act as a pulmonary vasoconstrictor in children with pulmonary vascular obstructive disease undergoing cardiac catheterization, as well as in infants after CPB (Driscoll et al 1979, Booker et al 1995). However, not even high doses of dopamine affected pulmonary vascular tone adversely in some children with CHD (Outwater et al 1990). At low epinephrine doses, myocardial contractility increases and SVR decreases secondary to effects on β-receptors. However, as the dose increases, the α -adrenergic effects become predominant, leading to increased peripheral resistance to blood flow. At high doses, myocardial irritability and arrhythmias may occur. Increased heart rate and contractility may affect myocardial $\dot{V}O_2$ adversely (Notterman 1991). Epinephrine administration may also impair splanchnic perfusion in situations when the regional O_2 balance is compromised (Meier-Hellmann et al 1997).

Reduction of the increased ventricular workload postoperatively is important especially in neonates and infants, as their limited cardiac performance is further compromised by surgery and CPB (Ross et al 1987, Thys & Dauchot 1993). Administration of nitroglycerine provides vasodilation predominantly in venous capacitance vessels, but some arterial vasodilative effects can be seen as well (Kirsten et al 1998). Nitroglycerine improves cardiac performance in children with CHD, especially when combined with inotropic agents (Bando et al 1996). However, hypotension, increase in intrapulmonary shunting from attenuated hypoxic pulmonary vasoconstriction, and reduced PaO_2 may follow nitrate administration (Mookherjee et al 1978, Radermacher et al 1989). Lack of selectivity on pulmonary circulation may sometimes limit the use of intravenous vasodilators in patients with reactive pulmonary vasculature (Houde et al 1993).

Unlike catecholamines, PDE inhibitors have been shown to improve myocardial performance without raising myocardial $\dot{V}O_2$ or increasing afterload (Benotti et al 1980, Sakaki et al 1998). They do not appear to be accompanied by the β-receptor desensitization and downregulation, but may shift the β_1- to β_2- adrenoceptor ratio toward β_2- adrenoceptors (Feldman et al 1990). In patients with CHD, especially in neonates with TGA, drugs augmenting β-adrenergic stimuli beyond the receptor level, such as PDE inhibitors, can be useful in postoperative cardiovascular support (Feldman et al 1990, Brodde 1991, Kozlik-Friedman et al 1993). In children after cardiac surgery, amrinone increases cardiac output and decreases SVR (Lynn et al 1993, Sorensen et al 1996). It has been suggested to act mainly as a systemic vasodilator without significant inotropic effect (Berner et al 1990). However, amrinone provides a significantly larger increase in cardiac output per unit decrease in blood pressure when it is compared with sodium nitroprusside (Bailey et al 1997). Administration of amrinone has resulted in reduction of high PVR in children undergoing cardiac catheterization and after cardiac surgery (Wessel et al 1989, Robinson et al 1993). Additive effects have been demonstrated when catecholamines are administered concomitantly with amrinone in adults after CPB (Royster et al 1993). The decrease in peripheral vascular resistances produced by amrinone often necessitates preload augmentation to avoid systemic hypotension, especially as amrinone is relatively long acting (Lawless et al 1989, Lebovitz et al 1995). Development of thrombocytopenia has been associated with PDE inhibitor administration (Ross et al 1993). However, no hemorrhagic complications have been reported with short-term administration of amrinone in pediatric patients so far (Berner et al 1990, Lynn et al 1993).

The pharmacokinetics of amrinone in children have been previously studied in heterogeneous patient populations (Lawless et al 1989, Allen-Web et al 1994). In children from 1 to 160 months of age no age-related differences in amrinone elimination have been observed (Allen-Web et al 1994). There is little information on amrinone pharmacokinetics in neonates during the first four weeks of life (Lawless et al 1989, Allen-Web et al 1994, Williams et al 1995).

AIMS OF THE PRESENT STUDY

The purpose of this work was to evaluate cardiovascular management in children undergoing open-heart surgery. The specific aims were in detail as follows:

1. To evaluate the utility of the linear regression equations and the artificial intelligence NN in $\dot{V}O_2$ prediction by comparing measured and predicted $\dot{V}O_2$ at preoperative cardiac catheterization in a group of children with CHD (I).

2. To examine pharmacokinetics of amrinone in neonates and infants after open-heart surgery for CHD (II).

3. To assess the efficacy and safety of amrinone and a combination of dopamine and nitroglycerine in neonates after arterial switch operation for TGA, and in infants after reconstructive surgery for complete AVSD, during the first 18 postoperative hours in the intensive care unit (ICU) (III, IV).

MATERIALS AND METHODS

This study was conducted at the Hospital for Children and Adolescents, University of Helsinki, Finland, with the approval of the institutional Ethics Committee. Parental written informed consent was obtained from the patients in the prospective studies.

1. Patients and study designs

A total of 221 patients with CHD were enrolled in studies I-IV. In study I, 125 children with various CHD undergoing preoperative cardiac catheterization were studied. In study II, 29 neonates and infants receiving amrinone medication after reconstructive surgery for TGA or AVSD were included. Thirty-five neonates with TGA, scheduled for arterial switch operation, participated in study III. In study IV, 32 infants scheduled for elective repair of AVSD were enrolled. The patients in study II were a subgroup of patients in papers III and IV. Three patients in study I were also enrolled in study IV. Study I excluded patients with weight greater than 25 kg or FIO_2 above 0.60. In studies III and IV, patients with residual left-to-right shunts, or with hemodynamic difficulties requiring out-of-protocol treatment were excluded. The measurements during FIO_2 of 0.85 or higher or during NO therapy were also excluded in studies III and IV. The study designs are presented in Table 4.

2. Anesthetic management (I, II, III, IV)

The anesthesia was standardized in each study. In study I, oral flunitrazepam (0.1 mg/kg, maximum dose 2 mg) was given as premedication. EMLA cream (Astra, Södertälje, Sweden) was applied on the groins and hands of the patients before arrival to the catheterization laboratory. Glycopyrrolate, 5 µg/kg, was administered to all patients. Anesthesia was induced with intravenous ketamine (1-5 mg/kg) and maintained with ketamine infusion (1-3 mg/kg/h). Supplemental boluses of fentanyl were given as needed. The trachea was intubated with a cuffed tube, if mechanical ventilation (Servo 900, Siemens, Solna, Sweden) was required. In these patients, neuromuscular blockade was provided with pancuronium bromide or atracurium besylate. The groins of spontaneously breathing patients were infiltrated with a local anesthetic.

Table 4. *Study designs.*

Study	Study set-up	Intervention	Main goal
I	Retrospective	$\dot{V}O_2$ measured with indirect calorimetry was compared with predicted $\dot{V}O_2$ calculated according regression equations by Lindahl (1989), Wessel et al (1969) and Lundell et al (1996), and estimates produced with artificial NN	To test the utility of the regression equations and NN based estimates in $\dot{V}O_2$ determination, and their effect on PVR calculation
II	Prospective	Amrinone bolus, followed by maintenance infusion was given postoperatively in 15 neonates and 14 infants	To determine the possible differences in amrinone pharmacokinetics between the groups
III	Prospective, randomized, double blind	Amrinone bolus, followed by maintenance infusion (in 16 neonates) and a combination of dopamine and nitroglycerine (in 19 neonates) were compared postoperatively	To assess the possible differences in hemodynamic profile, ICU and hospitalization times, adverse effects, and outcome between the groups
IV	Prospective, randomized, double blind	Amrinone bolus, followed by maintenance infusion (in 17 infants) and a combination of dopamine and nitroglycerine (in 15 infants) were compared postoperatively	To assess the possible differences in hemodynamic profile, ICU and hospitalization times, adverse effects, and outcome between the groups

Abbreviations: $\dot{V}O_2$, oxygen consumption; PVR, pulmonary vascular resistance; NN, neural network; ICU, intensive care unit.

In studies II, III, and IV, oral ketamine (10 mg/kg) was given as premedication 15 minutes before intravenous induction of anesthesia. Anesthesia was induced with alfentanil 30 µg/kg and midazolam 300 µg/kg, and maintained with alfentanil 1-2 µg/kg/min, midazolam 1-2 µg/kg/min, and isoflurane. The trachea was intubated with a cuffed tube, facilitated with pancuronium bromide. Percutaneous peripheral arterial cannulation and central venous cannulation with a triple-lumen catheter were performed after the induction of anesthesia. Vancomycin 40 mg/kg divided into four daily doses, or cefuroxime 90 mg/kg divided into three daily doses were used routinely to prevent endocarditis. At the end of CPB, anticoagulation was reversed with protamine, 2 mg/kg, given slowly into a peripheral vein. After arrival in the ICU, the patients were sedated with continuous infusion of fentanyl, 3 µg/kg/h, while neuromuscular blockade was continued with

pancuronium bromide infusion, 20-30 µg/kg/h. Supplemental fentanyl (1-2 µg/kg) and pancuronium (0.1 mg/kg) were given as needed. The patients were mechanically ventilated (Newport Breeze, Newport Medical Instruments, Inc. Newport Beach, CA) to an arterial carbon dioxide tension ($PaCO_2$) of 3.0 to 3.3 kPa and a pHa of 7.5 to 7.6 during the study period. Alkalemia was maintained with tris-hydroxymethylaminomethane (THAM) as needed. Prior to suctioning of the airway, the patients received alfentanil 20-30 µg/kg and were manually hyperventilated with 100 % O_2. In infants, the neuromuscular blockade was reversed and the patient was allowed to wake up on the first postoperative day, if recovery had been uneventful. In neonates, the anesthetic period was extended to the second postoperative day.

3. Surgical technique (II, III, IV)

Mainly two experienced surgeons in studies II, III and IV performed the operations. Cardiopulmonary bypass was established with venous caval cannulas and ascending aortic cannula. Aortic cross-clamping was used in all patients. In studies III and IV, the surgical technique did not vary between patients. In study III, the Lecompte maneuver was used in all patients, and the neopulmonary artery was reconstructed with a pericardial pantaloon patch. Ventricular septal defect, when present, was closed with a polytetrafluoroethylene patch. In study IV, after the duct closure and right atriotomy, the interventricular and interatrial communications were closed with polytetrafluoroethylene patches as needed. Two competent, nonstenotic atrioventricular valves were created by suturing the clefts in the valves. In studies III and IV, left atrial and pulmonary artery catheters were inserted at surgery under direct vision. Temporary epicardial pacemaker leads and peritoneal dialysis catheters were also placed in all patients. Patients in study II were a subgroup of patients in studies III and IV.

4. Management of cardiopulmonary bypass (II, III, IV)

In studies II and III, and IV, CPB was conducted using a Masterflo 34, Lilliput 300, or Lilliput 400 membrane oxygenator (Dideco, Mirandola, Italy) with priming volumes of 500 ml, 300 ml, and 400 ml, respectively. The circuit was primed with 4 % albumin and fresh whole blood, to achieve a hematocrit of 25 %. Mannitol (150-200 mg/kg), calcium chloride (30 mg for each 100 ml of fresh whole blood) and heparin were added to the prime. Deep hypothermia, 15°C in neonates and 18°C in infants, with intermittent cold blood cardioplegia (100 ml Plegisol, Abbot Lab., North Chicago,

Illinois, USA, for each 100 ml of fresh whole blood, supplemented with aspartate, glutamate and THAM) were used in all patients. Total circulatory arrest was used in neonates with coexisting aortic coarctation. All patients received a warm (37°C) blood reperfusion cardioplegia just before removal of the aortic cross-clamp. Hemofiltration to a hematocrit of 32 % to 42 %, and induction of metabolic alkalemia (pHa of 7.5 to 7.6) with THAM were performed before discontinuation of CPB.

5. Administration of the vasoactive regimen (II, III, IV)

Just before removal of the cross-clamp in studies II and III, while a warm blood reperfusion solution was infused via the aortic root, the patients randomized to the amrinone group were given a loading dose of amrinone, 2 mg/kg (Lawless et al 1989, Williams et al 1995), from a covered syringe into the venous reservoir of the bypass circuit. The patients randomized to the dopamine-nitroglycerine group received the same volume of 4 % albumin, also from a covered syringe in a double-blind manner. The loading dose was followed by a maintenance infusion of either amrinone or a combination of dopamine and nitroglycerine from a covered syringe into the covered medial lumen of the central venous catheter when the nasopharyngeal temperature of the patient was increased to 32-34 °C during the rewarming period. Amrinone, 3 mg/ml, in 0.45 % saline, was infused 0.15 ml/kg/h to give a dose of 7.5 µg/kg/min (Lawless et al 1989, Allen-Webb et al 1994). Dopamine, 200 mg, nitroglycerin, 40 mg, and 3 ml of a yellow vitamin solution (Soluvit, Pharmacia, Sweden), were mixed with 0.45 % saline to a total of 100 ml. This mixture, indistinguishable by color from the amrinone solution, was also infused 0.15 ml/kg/h to give dopamine 5 µg/kg/min and nitroglycerine 1 µg/kg/min (Wernovsky et al 1995b, Bando et al 1996). No other infusions were given through the medial lumen of the central venous catheter.

Inhaled NO was administered for pulmonary vasodilation if systolic pulmonary artery pressure increased to more than 80 % of systolic blood pressure. An open-label epinephrine infusion into the proximal lumen of the central venous catheter was started according to the clinical judgment of the attending anesthesiologist, based on deterioration of the cardiac performance, or poor contractility seen with the echocardiography. Weaning from the vasoactive medications was performed in the ICU also on the basis of clinical improvement in the patient's cardiac condition, supported by results of echocardiography. The infusion rate of the vasoactive medications was reduced 0.1 ml/hour in every two to four hours if no deterioration in the patient's clinical condition was

observed. Patients in study II were a subgroup of neonates and infants randomized in the amrinone group.

6. Measurements

The age, gender, weight, height and body surface area (BSA) of the patients, comorbidities, type of cardiac malformation and preoperative treatment for heart failure were recorded. The decision of operability and outcome were recorded in patients in study I. The CPB time, aortic cross-clamp time, and circulatory arrest time, postoperative blood drainage volumes, need for peritoneal dialysis, duration of mechanical ventilation, ICU care, total hospitalization time, and outcome, were registered in patients in studies III and IV. The duration of vasoactive support was recorded in patients in studies II, III and IV. The sampling regimens are presented in Table 5.

6.1. Determination of hemodynamic parameters (I, III, IV)

In studies I, III and IV an open-circuit, indirect calorimetry device (Deltatrac, Datex-Engström, Helsinki, Finland, or Deltatrac II, Datex-Engström, Helsinki, Finland) was used to measure $\dot{V}O_2$. The calorimeter was calibrated according to the instructions supplied by the manufacturer before each measurement in study I and daily in studies III and IV. The measurements were performed once every minute after a 10-minute stabilization period, for at least 10 minutes. While the child was breathing room air spontaneously (I), a transparent canopy covered the child's head and upper chest. The expiratory gases were captured from inside the canopy by a continuous flow of gas into the calorimeter. Escape of expiratory gas was prevented with a soft plastic skirt attached to the rim of the canopy. If supplemental O_2 was used (Deltatrac II, Datex-Engström, Helsinki, Finland), the expiratory gases were fed through a mixing chamber (I). During mechanical ventilation, the calorimeter was connected to the outlet port of the ventilator and expired gas was collected through a mixing chamber into the metabolic monitor (I, III, IV).

Table 5. *Sampling regimens.*

Study	Time and site of sampling	Data obtained
I	When stable conditions were achieved after induction of anesthesia: During the catheterization; From superior and inferior caval vein, pulmonary artery, right atrium and ventricle, left atrium and ventricle, and aorta (if feasible)	$\dot{V}O_2$ measured with indirect calorimetry, FIO_2, heart rate Blood pressures and oxygen contents
II	After the induction of anesthesia; at 5, 10, 20, and 30 minutes after the loading dose (from the venous line of CPB); every 6 hours during the maintenance infusion; and at 2, 12, 24, and 48 hours after the end of the infusion (from peripheral artery) In patients on peritoneal dialysis, the concentrations in the dialysate were determined from samples taken at the time of each blood sample. Daily from the day of surgery up to fourth postoperative day; From peripheral artery	Plasma and dialysate concentrations of amrinone, N-acetylamrinone, and N-glycolylamrinone Serum creatinine and serum transaminase values
III	Two-hourly from 4 to 18 hours after separation from CPB; From superior caval vein, pulmonary artery, left atrium and peripheral artery Daily from the day of surgery up to fourth postoperative day; From peripheral artery, and from chest radiographs	Heart rate, rhythm, rectal temperature, $\dot{V}O_2$ measured with indirect calorimetry, FIO_2, epinephrine dose Blood pressures and oxygen contents Platelet count, serum creatinine and serum transaminase values, positioning of the tracheal tube and monitoring lines
IV	Two-hourly from 4 to 18 hours after separation from CPB; From superior caval vein, pulmonary artery, left atrium and peripheral artery Daily from the day of surgery up to fourth postoperative day; From peripheral artery, and from chest radiographs	Heart rate, rhythm, rectal temperature, $\dot{V}O_2$ measured with indirect calorimetry, FIO_2, epinephrine dose Blood pressures and oxygen contents Platelet count, serum creatinine and serum transaminase values, positioning of the tracheal tube and monitoring lines

Abbreviations: $\dot{V}O_2$, oxygen consumption; FIO_2, fraction of oxygen in inspired gas; CPB, cardiopulmonary bypass.

In study I, the predicted $\dot{V}O_2$ values were calculated from the following regression equations. According to Lindahl (1989), in children weighing < 10 kg, $\dot{V}O_2$ (ml/min) = 6.8 × weight (kg) + 8.0, and in those > 10 kg, $\dot{V}O_2$ (ml/min) = 4.0 × weight (kg) + 35.8. In the equation published by Wessel et al (1969), $\dot{V}O_2$ (ml/min) = 144.8 × BSA (m^2) + 5.6. According to Lundell et al (1996), in children under 3 years of age, $\dot{V}O_2$ (ml/min) = 0.40 × weight (kg) + 1.91 × height (cm) + 0.17 × heart rate (beat/min) - 91.0. In males older than 3 years, $\dot{V}O_2$ (ml/min) = 157.9 × BSA (m^2) + 0.79 × heart rate (beat/min) - 61.8. In females older than 3 years, $\dot{V}O_2$ (ml/min) = 159.0 × BSA (m^2) + 0.77 × heart rate (beat/min) - 61.6.

For NN training and testing in study I, the data set consisting of 125 patient records was normalized so that all variables had values ranging from 0 to 1. Two separate data sets were then formed using random selection; 101 records were selected to train the NN, while the remaining 24 records were used for testing the accuracy of the trained network. A NN was first trained and tested with input consisting of age, gender, height, weight and heart rate, the variables used by Lundell et al (1996) to estimate $\dot{V}O_2$ with linear regression. To provide the NN with additional information to improve its estimate of $\dot{V}O_2$ nine further variables were added in a second analysis to describe the patient, the cardiac lesion and the measurement of $\dot{V}O_2$: BSA, $\dot{V}O_2$ calculated according to Lindahl´s equation (1989), mean pulmonary arterial pressure (PAP), mean arterial pressure (MAP), systolic pulmonary-to-systemic pressure ratio, cyanotic versus acyanotic nature of the cardiac malformation, hemoglobin concentration, presence of heart failure, and whether the $\dot{V}O_2$ measurement was performed with a canopy or a ventilator. The output requested from the NN was a number representing the normalized estimate of $\dot{V}O_2$. The absolute estimates of $\dot{V}O_2$ were calculated by reversing the normalization process. A backpropagation NN simulated with a software package was used (NNmodel, Neural Fusion, Middletown, NY, USA). The NN configuration was determined by repeated efforts to train networks of various configurations with the training data set. The final network consisted of an input layer of five or 14 neurons, depending of the number of input variables, an intermediate layer of four neurons, and one output neuron. Prior to training, the NN was initialized by setting its internal weights to random numbers. The training data set was

then fed into the NN, allowing it to 'learn' by adjusting its internal weights after each record was processed, according to the difference between the estimated and true $\dot{V}O_2$. Observation during training indicated that 2000 passes of the training data set was sufficient for learning. After learning was complete, the testing data set was analyzed with the network, and the resulting NN estimates of $\dot{V}O_2$ were compared to the corresponding measured values.

Pulmonary and systemic blood flow indexes and corresponding resistances were calculated using the Fick principle in studies I, III and IV as follows: Oxygen contents were calculated as 1.36 x hemoglobin (g/l) x oxyhemoglobin saturation (SO_2) (%) + dissolved O_2. $\dot{Q}$s index (l/min/m^2) = $\dot{V}O_2$ (ml/min/m^2)/arterial blood oxygen content (CaO_2) - central venous blood oxygen content (CvO_2), and $\dot{Q}$p index (l/min/m^2) = $\dot{V}O_2$ (ml/min/m^2)/left atrial blood oxygen content ($ClaO_2$) - pulmonary arterial blood oxygen content ($CpaO_2$). The ratio between pulmonary and systemic blood flows was determined as $\dot{Q}$p: $\dot{Q}$s. PVR index (Wood units x m^2) = PAP - mean left atrial pressure (LAP)/$\dot{Q}$p index using both measured (I, III, IV) and predicted (I) $\dot{V}O_2$ values. SVR index (Wood units x m^2) = MAP - mean central venous pressure (CVP)/$\dot{Q}$s index. Oxygen extraction ratio (O_2ER) was defined as CaO_2 - $CpaO_2$ /CaO_2 (III, IV).

6.2. Determination of pharmacokinetic parameters (II)

Plasma was separated from the blood samples and stored at -20°C until analysis. Concentrations of amrinone, N-acetylamrinone, and N-glycolylamrinone were measured with high-performance liquid chromatography and ultraviolet detection with wavelength of 340 nm (Lawless et al 1990). WIN 41,417 (Sanofi) was used as the internal standard. The detection limit was 0.09 µg/ml for amrinone and N-acetylamrinone, and 0.1 µg/ml for N-glycolylamrinone. The intra-assay coefficient of variation (CV) for amrinone was 3.6 % at 0.17 µg/ml and 5.7 % at 1.86 µg/ml (n =10), that for N-acetylamrinone 5.5 % at 0.17 µg/ml and 6.1 % at 0.47 µg/ml (n =10), and that for N-glycolylamrinone 5.8 % at 0.17 µg/ml and 5.5 % at 1.86 µg/ml (n =10). The inter-assay CV for amrinone was 15.1 % at 0.30 µg/ml, 7.1 % at 2.00 µg/ml, and 3.7 % at 4.99 µg/ml (n =25), that for N-acetylamrinone 9.7 % at 0.29 µg/ml, 6.2 % at 0.49 µg/ml, and 5.3 % at 0.99 µg/ml (n =25), and

that for N-glycolylamrinone 8.9 % at 0.29 µg/ml, 7.2 % at 0.50 µg/ml, and 6.5 % at 1.00 µg/ml (n =25).

To characterize the pharmacokinetics of amrinone, its plasma CL, volume of distribution at steady-state (V_{ss}), and $T_{½}$ were calculated. The CL was determined by dividing the total dose of amrinone by the area under the drug plasma concentration-time curve [$AUC_{(0-\infty)}$]. The $AUC_{(0-\infty)}$ was calculated using the logarithmic trapezoidal rule. The elimination rate constant (k_{el}) was determined by regression analysis of the log-linear part of the curve. $T_{½}$ was calculated from $T_{½} = \ln 2/k_{el}$. Because of the small number of samples during the elimination phase, k_{el} and $T_{½}$ could not be determined in 2 neonates and in 3 infants. In these patients, the mean k_{el} value of their age group was used for the calculation of those pharmacokinetic variables dependent on the k_{el} value. Values for V_{ss} were calculated using the noncompartmental equation: V_{ss} = dose x ($AUMC/AUC^2$) – (T x dose/2 x AUC), where AUMC is the area under the first moment of the plasma concentration-time curve, and T the duration of infusion (Perrier et al 1982). The relationship of the CL, V_{ss}, and $T_{½}$ to the BSA was determined. The ratio of the plasma concentration of N-acetylamrinone to that of amrinone was determined and the area under this ratio-time curve from 0 to 60 hours [$AUC_{(0-60)}$] and the total area (AUC_{tot}) in each patient were calculated. The relationship between the CL of amrinone and the mean values of serum transaminases, and creatinine was determined. The concentration of amrinone in the dialysate was analyzed similarly as the plasma amrinone concentration.

7. Statistical analysis

Prior to study I, a power calculation for a 20 % difference in PVR index between the methods, with the probability of type α error of 5 % and a probability of type β error of 20 %, yielded a sample size of 100 patients. In this calculation, standard deviation (SD) of the changes expected was assumed to be 3.5 Wood units x m^2. The agreement between the measured and predicted $\dot{V}O_2$ values was assessed by plotting the relative error of predicted $\dot{V}O_2$ against the average of measured and predicted values using the Bland and Altman method (Bland et al 1986). Analysis of variance was used to evaluate the influence of nominal variables, and stepwise linear regression was used to evaluate the influence of continuous variables on the precision of the predicted $\dot{V}O_2$ in study I. The

group means between canopy and ventilator measurements were compared with Student's unpaired t-test. The error of calculated $\dot{V}O_2$ was compared to the error of the two NN estimates with Student's t-test for means of two samples. Results are presented as mean ± SD and range.

In study II, the pharmacokinetic parameters between the groups were compared using Student's unpaired t-test. The results are presented as mean ± SD. The relationship of the CL, V_{ss}, and $T_{½}$ to the BSA, and between the CL of amrinone and the mean values of serum transaminases, and creatinine was determined by using Pearson's correlation coefficient.

Prior to studies III and IV a power calculation for a 20 % difference in cardiac index and PVR index with a probability of type α error of 5 % and a probability of type β error of 20 % yielded a sample size of 12 patients for each study group.

The group means were compared with Student's unpaired two-tailed t-test, and analysis of variance for repeated measures was used to compare hemodynamics between study groups in studies III and IV. Post hoc pairwise tests were performed for variables with significant differences in the analysis of variance in study III. The results of studies III and IV are presented as mean ± SD, and 95 % CI for mean values.

In every study, the differences were considered statistically significant when the probability of the type α error was less than 5 %.

RESULTS

The characteristics of patients that completed the studies are shown in Table 6. In study III, two of the 35 randomized neonates were excluded because of residual left-to-right shunts, one of them requiring reoperation on the second postoperative day. However, the treatment regimen in these two patients was not changed. Two other neonates were excluded because of postoperative hemodynamic difficulties requiring out-of- protocol treatment. Of the included patients, left atrial data could not be obtained in one neonate in both groups because of catheter displacement. Two patients in the dopamine-nitroglycerine group and one patient in the amrinone group required NO inhalation during the study period - their data during the NO therapy were excluded from analysis. All other data from these five patients were included. Four neonates in the amrinone group and two neonates in the dopamine-nitroglycerine group had abnormal coronary anatomy. Two neonates in the dopamine-nitroglycerine group had coexisting coarctation of the aorta. Five neonates in the amrinone group and four neonates in the dopamine-nitroglycerine group had coexisting ventricular septal defect.

In study IV, four of the randomized 32 infants were excluded, two because of severe pulmonary hypertension requiring extensive out-of- protocol management, one because of partial, rather than complete, AVSD, and one because of severe postoperative mitral insufficiency. Of the included patients, left atrial data could not be obtained from one infant in both groups because of catheter displacement. One patient in the amrinone group required continuous NO inhalation for eleven hours during the study period; her data during the NO therapy were excluded from the analysis. All other data from these three patients were included. One infant with Klinefelters`syndrome was included in dopamine-nitroglycerine group.

Table 6. *Patient characteristics.*

Study	Number of patients	Diagnosis	Down's syndrome	Female/male	Age (years)	Weight (kg)	BSA (m2)
I	125	Various CHD	34/125	73/52	1.88 ± 2.09	9.0 ± 4.2	0.42 ± 0.15
II	29	AVSD, TGA	14/29	12/17	0.18 ± 0.19	4.2 ± 0.8	0.24 ± 0.03
III	31	TGA	0/31	11/20	0.02 ± 0.02	3.7 ± 0.5	0.22 ± 0.02
IV	28	AVSD	25/28	20/8	0.33 ± 0.11	4.6 ± 0.7	0.26 ± 0.03

Data is presented as mean ± standard deviation.

Abbreviations: CHD, congenital heart disease; AVSD, atrioventricular septal defect; TGA, transposition of great arteries; BSA, body surface area.

1. Measured versus predicted oxygen consumption during preoperative cardiac catheterization in children with congenital heart disease (I)

Of the 125 measurements, 84 were performed in spontaneously breathing patients using the canopy. The regression lines for measured $\dot{V}O_2$ and $\dot{V}O_2$ predicted according to Lindahl (1989), plotted against weight are shown Figure 1. The relative bias and precision of the $\dot{V}O_2$ values predicted according to regression equation by Lindahl are presented in Figure 2a and the corresponding values using the regression equation by Wessel et al (1969) in Figure 2b. The relative biases of the predicted $\dot{V}O_2$ and the precisions produced by the different methods are shown in Table 7.

Since calculations based on the equation published by Wessel et al (1969) and Lundell et al (1996) resulted in poorer precision than those based on the equation published by Lindahl (1989), the subsequent comparisons were made using Lindahl´s equation (1989). The relationship between PVR index calculated using measured $\dot{V}O_2$ and predicted $\dot{V}O_2$ is shown in Figure 3. Even though in three patients with left-to-right shunts, two of them with Down's syndrome, and one patient with left heart downstream obstruction, the use of predicted $\dot{V}O_2$ in calculation of PVR index would have resulted in overestimation of PVR index, all these patients underwent surgical correction successfully. In four patients with Down's syndrome and left-to-right shunts, the use of predicted $\dot{V}O_2$ would have underestimated the calculated PVR index. One of these patients died of postoperative pulmonary hypertension; the others survived.

Age, weight, gender, BSA, MAP, PAP, heart rate, hemoglobin or $\dot{Q}p$: $\dot{Q}s$ ratio had no statistically significant influence on the error of predicted $\dot{V}O_2$ when analyzed with analysis of variance and linear regression. Heart failure or type of cardiac malformation did not affect the error either.

There was a statistically significant difference in the bias of the predicted $\dot{V}O_2$ between measurements made with a canopy compared to those made in mechanically ventilated patients. The bias averaged 7 %, (range -50 % to 43 %) in spontaneously breathing patients, and -5 %, (range -66 % to 30 %) in mechanically ventilated patients, ($p < 0.03$).

The addition of other input variables than those found in published equations to the NN did not produce a marked improvement in the estimation of $\dot{V}O_2$. Even though the NN estimated $\dot{V}O_2$ with higher precision, there was no statistically significant difference in the error of $\dot{V}O_2$ calculated according to the equation published by Lindahl (1989), and the error of the NN estimates of $\dot{V}O_2$.

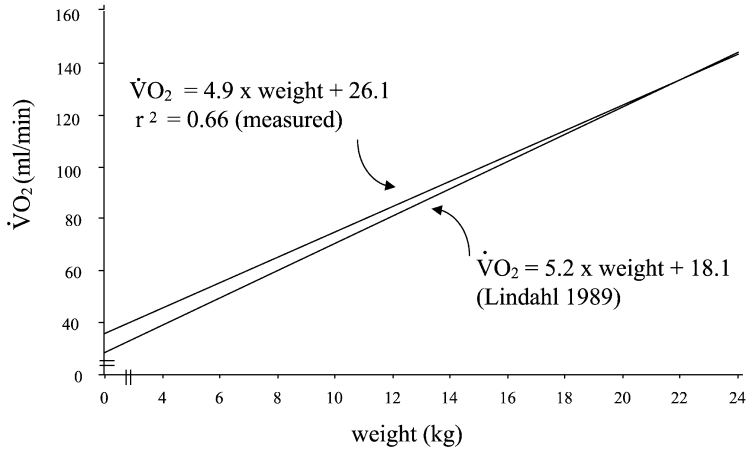

Figure 1. *The regression lines for measured $\dot{V}O_2$ values (ml/min), and predicted $\dot{V}O_2$ values (ml/min) according to Lindahl (1989), plotted against weight (kg). Abbreviations: $\dot{V}O_2$, oxygen consumption.*

Table 7. *The relative biases of the predicted $\dot{V}O_2$ and the precisions produced by the different methods.*

Method of producing predicted $\dot{V}O_2$ values	Bias of the predicted $\dot{V}O_2$ (range) (%)	Precision (%)
Equation by Lindahl (1989)	3 (-66 to 43)	± 42
Equation by Wessel et al (1969)	0 (- 69 to 39)	± 44
Equation by Lundell et al (1996)	- 16 (- 94 to 100)	± 51
Neural network	6 (-19 to 30)	± 29

Abbreviations: $\dot{V}O_2$, oxygen consumption.

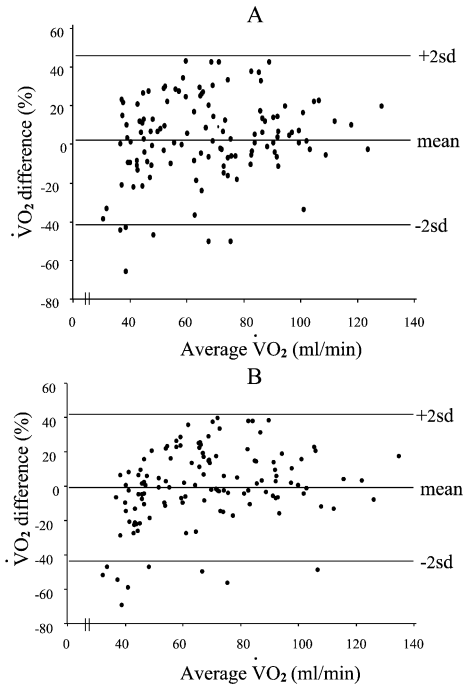

Figure 2a. *The relative bias and precision of the predicted $\dot{V}O_2$ values (ml/min) according to regression equation by Lindahl (1989). Abbreviations: $\dot{V}O_2$, oxygen consumption.*

Figure 2b. *The relative bias and precision of the predicted $\dot{V}O_2$ values (ml/min) according to regression equation by Wessel et al (1969). Abbreviations: $\dot{V}O_2$, oxygen consumption.*

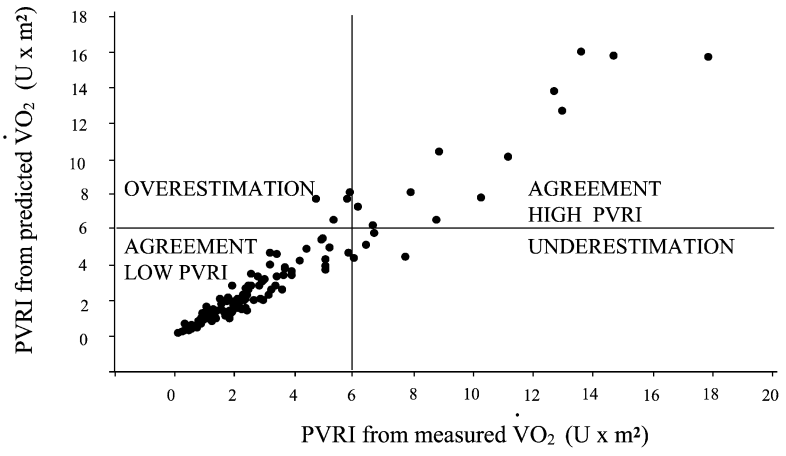

Figure 3. *The relationship between measured and predicted PVRI (Wood units x m^2) according to Lindahl regression equation (1989). Abbreviations: PVRI, pulmonary vascular resistance index.*

2. Pharmacokinetics of amrinone in neonates and infants after open-heart surgery for congenital heart disease (II)

The plasma concentrations of amrinone in neonates and infants are presented in Figure 4. The amrinone plasma concentrations were between 1.5 to 6 µg/ml in all patients, even though they were approximately 30 % lower in infants than in neonates. The delay (mean ± SD, range) between the bolus dose of amrinone and start of the maintenance infusion was 26 ± 14 minutes (from 6 to 57 minutes) in neonates and 11 ± 7 minutes (from 5 to 29 minutes) in infants. The difference of the delay was secondary to differences in the surgical technique and management of CPB in the two patient groups. The duration of the amrinone infusion in the neonates was 114 ± 45 hours (from 66 to 216 hours) and that in the infants 120 ± 78 hours (from 42 to 342 hours).

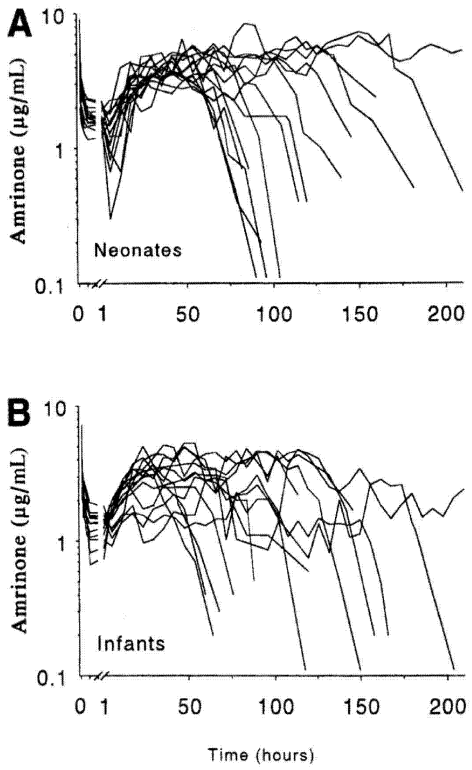

Figure 4. *Plasma concentrations (µg/ml) of amrinone in 15 neonates (A) and in 14 infants (B) after a bolus dose of 2 mg/kg followed by a continuous infusion of 7.5 µg/kg/min of amrinone. Note the axis break at 1 hour to clarify the decrease of the plasma concentrations after the bolus dose of amrinone. In 1 neonate and in 1 infant, the duration of the infusion was longer than 200 hours.*

Amrinone CL was statistically significantly lower, 2.4 ± 0.9 ml/kg/min, in neonates, compared with 3.2 ± 1.2 ml/kg/min in infants ($p < 0.05$). The V_{ss} was significantly smaller, 0.8 ± 0.6 l/kg, in neonates, when compared with 1.6 ± 1.1 l/kg in infants ($p < 0.05$). The $T_{½}$ was also significantly longer in neonates than in infants (10.7 ± 6.7 hours and 6.1 ± 1.4 hours, respectively, $p < 0.03$). A linear correlation was detected between the CL of amrinone and the BSA ($r = 0.67$; $p < 0.05$) but not between the V_{ss} and the BSA or the $T_{½}$ and the BSA. There was no linear correlation between amrinone CL and serum creatinine, or transaminases. The ratio between plasma concentration of N-acetylamrinone and amrinone did not differ between neonates and infants. No patient had a detectable plasma concentration of N-glycolylamrinone.

Peritoneal dialysis was required due to impaired urinary output in two neonates and two infants. The concentrations of amrinone in plasma and in the dialysate in these patients are shown in Figure 5.

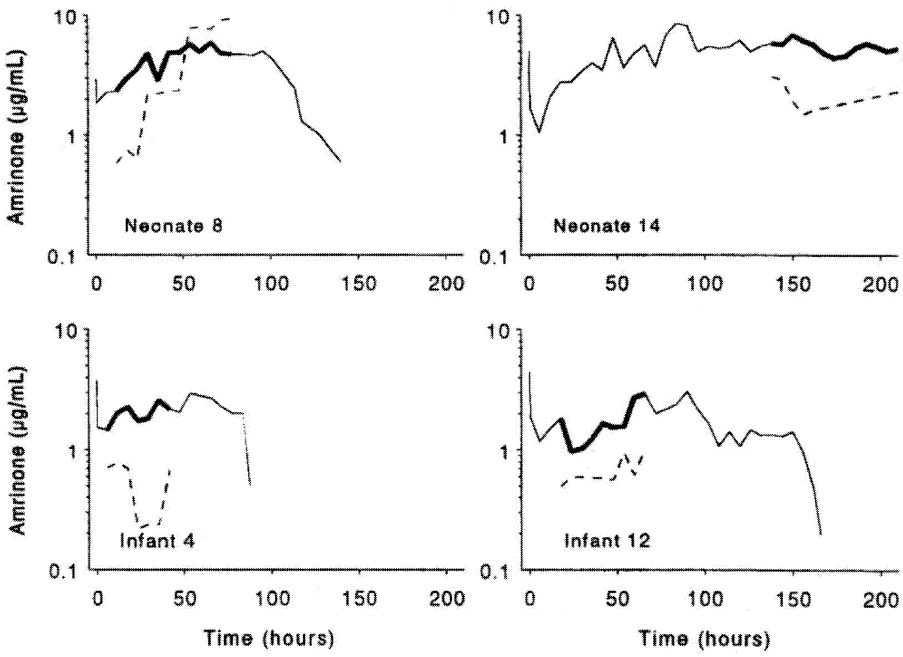

Figure 5. *Concentrations of amrinone in plasma (solid line) and in dialysate (dotted line) in 2 neonates and in 2 infants requiring peritoneal dialysis. The bold line represents the plasma concentrations during peritoneal dialysis.*

3. Amrinone versus dopamine-nitroglycerine after reconstructive surgery for congenital heart disease in neonates and infants (III, IV)

There were no differences in the CPB time, aortic cross-clamp time, and circulatory arrest time between the study groups. The cardiopulmonary variables of the groups during the study period are presented in Table 8.

3.1. Systemic and pulmonary blood flow

The $\dot{Q}s$ and $\dot{Q}p$ indexes of the neonates recorded during the study period are presented Figure 6. The $\dot{Q}s$ index was significantly higher in the amrinone group, $p < 0.04$. The $\dot{Q}p$ index was higher in the amrinone group, but not statistically significantly ($p = 0.06$). The post-hoc pairwise test revealed significant difference in the $\dot{Q}s$ index at 4, 6 and 8 hours after separation from CPB between the groups. The $\dot{Q}s$ and $\dot{Q}p$ indexes of the infants recorded during the study period are presented in Figure 7. The $\dot{Q}s$ and $\dot{Q}p$ indexes were significantly higher in the amrinone group, $p < 0.03$ and $p < 0.01$, respectively.

3.2. Systemic and pulmonary vascular resistance

The SVR and PVR indexes of the neonates are shown in Figure 8. The SVR index was significantly lower in the amrinone group, $p < 0.02$. The PVR index was lower in the amrinone group, but not statistically significantly ($p = 0.05$). There was a significant difference in the SVR index at 4, 6, 8 and 16 hours after discontinuation of CPB in the post-hoc pairwise test. The SVR and PVR indexes of the infants are shown in Figure 9. The SVR index was significantly lower in the amrinone group, $p < 0.04$. The PVR index was lower in the amrinone group, but not statistically significantly.

3.3. Oxygen extraction ratio

The O_2ER in the dopamine-nitroglycerine group was higher in neonates (0.34 ± 0.08), and infants (0.41 ± 0.07), compared to the neonates (0.28 ± 0.06; $p < 0.02$) and infants (0.34 ± 0.08; $p < 0.02$) in the amrinone group.

Table 8. *Cardiopulmonary variables of the study groups.*

	Amrinone (neonates)	Dopamine-NTG (neonates)	Amrinone (infants)	Dopamine-NTG (infants)
pHa	7.51 ± 0.07	7.51 ± 0.06	7.46 ± 0.06	7.46 ± 0.07
$PaCO_2$(kPa)	3.48 ± 0.62	3.33 ± 0.52	3.63 ± 0.71	3.78 ± 0.76
PaO_2/FiO_2	23.4 ± 11.2	29.6 ± 10.6	39.3 ± 11.5	33.3 ± 11.5
Heart rate (beat/min)	165 ± 16	164 ± 19	145 ± 16	146 ± 18
Hemoglobin (g/l)	155 ± 15	153 ±17	139 ± 16	135 ±14
Rectal temperature (°C)	37.0 ± 0.7	37.0 ± 0.8	37.6 ± 0.5	37.6 ± 0.6
Oxygen consumption ($ml/min/m^2$)	109 ± 16	104 ± 16	177 ± 22	162 ± 21
Mean blood pressure (mmHg)	48 ± 6	52 ± 9	56 ± 9	57 ± 8
Mean pulmonary artery pressure (mmHg)	16 ± 3	17 ± 4	21 ± 5	20 ± 4
Mean central venous pressure (mmHg)	6 ± 2	6 ± 2	7 ± 2	7 ± 2
Mean left atrial pressure (mmHg)	6 ± 2	6 ± 2	6 ± 3	6 ± 2
SaO_2 (%)	95 ± 3	96 ± 3	98 ± 2	97 ± 2
$SpaO_2$ (%)	68 ± 7	64 ± 9	65 ± 8	58 ± 7*
$ScvO_2$ (%)	62 ± 9	59 ± 12	58 ± 10	52 ± 10
$SlaO_2$ (%)	95 ± 3	97 ± 2°	98 ± 2	97 ± 2
$\dot{Q}p:\dot{Q}s$	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
Epinephrine (patients)	12	15	8	5
Epinephrine (ug/kg/min)	0.06 ± 0.04	0.06 ± 0.07	0.11 ± 0.07	0.04 ± 0.02

Values are given as mean ± standard deviation.

Abbreviations: NTG, nitroglycerine; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; FIO_2, fraction of oxygen in inspired gas; SaO_2, arterial oxyhemoglobin saturation; $SpaO_2$, pulmonary artery oxyhemoglobin saturation; $ScvO_2$, central venous oxyhemoglobin saturation; $SlaO_2$, left atrial oxyhemoglobin saturation; $\dot{Q}p:\dot{Q}s$, pulmonary-to-systemic flow ratio.

*P< 0.006 in infants, °P< 0.009 in neonates

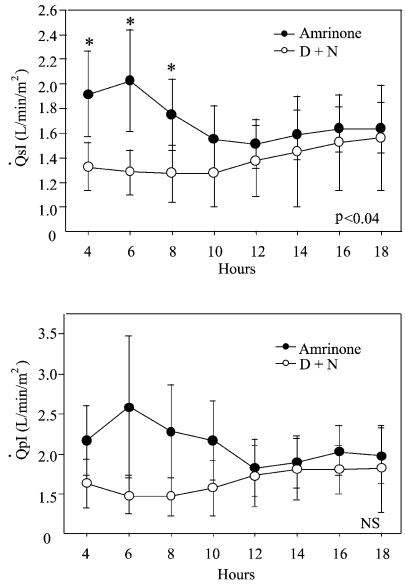

Figure 6. *Systemic ($\dot{Q}$sI) and pulmonary ($\dot{Q}$pI) flow indexes from 4 to18 hours after separation from cardiopulmonary bypass in neonates. Values are given as mean ± 95 % confidence interval. Abbreviations: D+N, combination of dopamine and nitroglycerine; NS, not significant.*

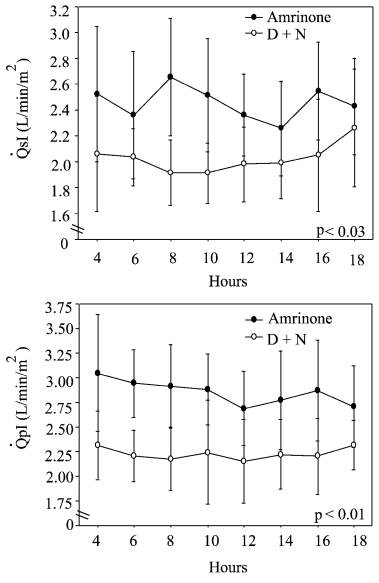

Figure 7. *Systemic ($\dot{Q}$sI) and pulmonary ($\dot{Q}$pI) flow indexes from 4 to18 hours after separation from cardiopulmonary bypass in infants. Values are given as mean ± 95 % confidence interval. Abbreviations: D+N, combination of dopamine and nitroglycerine*

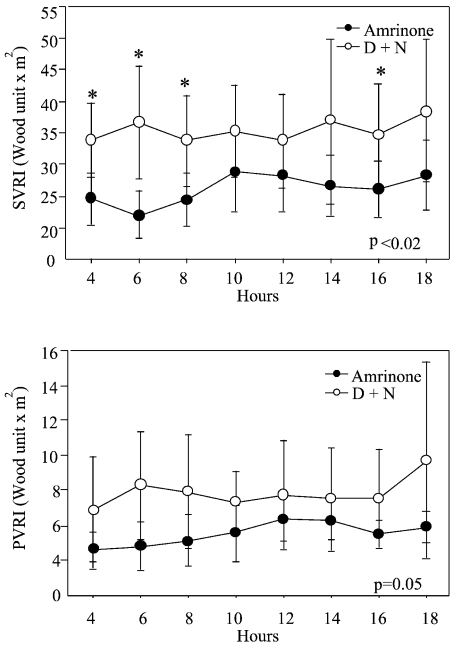

Figure 8. *Systemic (SVRI) and pulmonary (PVRI) vascular resistance indexes from 4 to 18 hours after separation from cardiopulmonary bypass in neonates. Values are given as mean ± 95 % confidence interval. Abbreviations: D+N, combination of dopamine and nitroglycerine.*

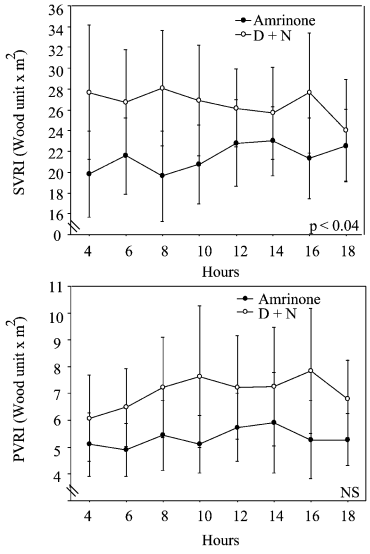

Figure 9. *Systemic (SVRI) and pulmonary (PVRI) vascular resistance indexes from 4 to 18 hours after separation from cardiopulmonary bypass in infants. Values are given as mean ± 95 % confidence interval. Abbreviations: D+N, combination of dopamine and nitroglycerine; NS, not significant.*

3.4. Adverse effects

The average preoperative platelet count was in the normal range in both neonatal groups and infant groups. Eight neonates in the amrinone group and six neonates in the dopamine-nitroglycerine group received platelet transfusions during the operation in accordance with the institutional guidelines for hemostasis in neonates. The platelet counts from the day of operation to the fourth postoperative day are shown in Figure 10a. There was a significant difference in the platelet counts of the third and fourth postoperative day in the post-hoc pairwise analysis. Two neonates in the dopamine-nitroglycerine group were transfused with platelets during the second and the third postoperative days. In the amrinone group, a platelet transfusion was given to one neonate on the sixth postoperative day. No significant difference was observed in blood drainage volumes up to the third postoperative day.

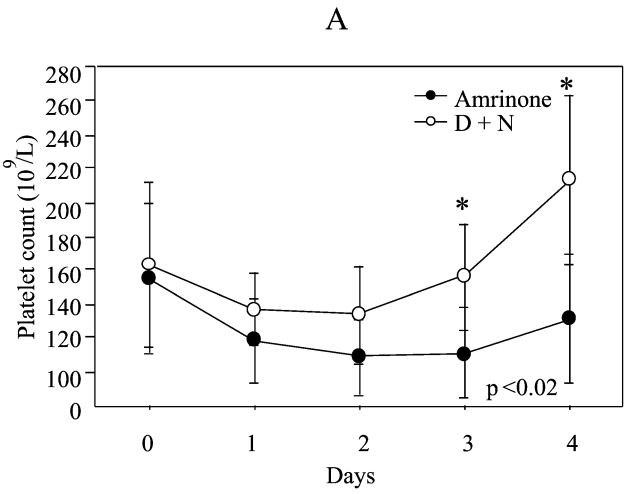

Figure 10a. *Platelet counts from the day of surgery to the fourth postoperative day in neonates. Values are given as mean ± 95 % confidence interval. Abbreviations: D+N, combination of dopamine and nitroglycerine.*

One infant in the amrinone group received platelet transfusion during the surgery because of difficulties in achieving surgical hemostasis despite normal platelet count. Two infants in the amrinone group received platelet transfusions during the second and the third postoperative days due to platelet counts of 20 x 10^9/l in both cases. In the dopamine-nitroglycerine group, a platelet transfusion was given to one infant on the first postoperative day (platelet count 51 x 10^9/l). The

platelet counts from the day of operation to the fourth postoperative day are presented in Figure 10b. No significant difference was observed in blood drainage volumes in infants up to the first postoperative day.

The average pre- and postoperative serum creatinine values were in the normal range with no difference observed between the study groups in neonates and infants. There was no significant difference in the serum transaminase values between the groups.

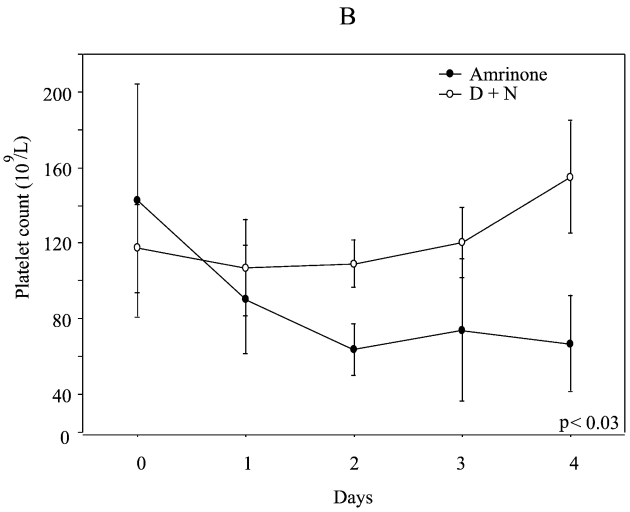

Figure 10b. *Platelet counts from the day of surgery to the fourth postoperative day in infants. Values are given as mean ± 95 % confidence interval. Abbreviations: D+N, combination of dopamine and nitroglycerine.*

3.5. Perioperative morbidity and mortality

Two patients in both neonatal groups required delayed sternal closure because of myocardial edema. In two additional neonates in the dopamine-nitroglycerine group, the sternum was reopened on the fourth postoperative day because of cardiac tamponade after removal of the pulmonary and left atrial catheters. Peritoneal dialysis was required in three neonates in the amrinone group and four neonates in the dopamine-nitroglycerine group because of reduced diuresis during the study period.

Separation from CPB was complicated by right ventricular dysfunction and hypotension that was probably aggravated by coronary artery air in three infants in the amrinone group. No intracoronary

air problems were observed in the dopamine-nitroglycerine group. The epinephrine dose received by those three patients was higher (0.15-0.23 µg/kg/min) than that of other study patients, (0.06 ± 0.03 µg/kg/min in the amrinone group, 0.04 ± 0.02 µg/kg/min in the dopamine-nitroglycerine group; NS). However, the hemodynamic trends observed in the entire study group were not changed during the reanalysis of the data with these three patients excluded. Hemorrhagic problems after the operation were not seen in any infant. Five patients in both infant groups required peritoneal dialysis because of oliguria during the study. There was no difference in ascites production between the groups.

There were no statistically significant differences observed in the need for mechanical ventilation between the groups of neonates (71 ± 37 hours, from 27 to 149 hours, in the amrinone group and 92 ± 68 hours, from 23 to 249 hours in the dopamine-nitroglycerine group), and infants (81 ± 56 hours, from 23 to 187 hours, in the amrinone group and 89 ± 70 hours, from 25 to 189 hours in the dopamine-nitroglycerine group). In neonates, the length of stay in the ICU was 5 ± 2 days (from 3 to 11 days) in the amrinone group and 6 ± 4 days (from 3 to 16 days) in the dopamine-nitroglycerine group. The duration of intensive care period in infants was 5 ± 3 days (from 2 to 14 days) in the amrinone group and 7 ± 3 days (from 3 to 11 days) in the dopamine-nitroglycerine group (NS). The total duration of hospitalization was 12 ± 3 days, from 8 to 18 days, in the neonates of the amrinone group and 12 ± 5 days, from 6 to 26 days, in the neonates of the dopamine-nitroglycerine group. The hospitalization time in infants was 14 ± 6 in both groups, ranging from 6 to 26 days in the amrinone group and from 7 to 28 days in the dopamine-nitroglycerine group.

One neonate in the amrinone group died on the eight postoperative day because of septicemia caused by strangulation of the ileum. There was no mortality among the infants in the study.

DISCUSSION

This series of four studies was designed to evaluate cardiovascular management in children undergoing open-heart surgery. The utility of linear regression equations and artificial NN in $\dot{V}O_2$ prediction was elucidated at preoperative cardiac catheterization in patients with CHD. The efficacy and safety of amrinone and a combination of dopamine and nitroglycerine in neonates and infants were assessed after reconstructive surgery for CHD. Amrinone pharmacokinetics were also examined to ensure adequate amrinone dosing, and to clarify the distribution and elimination of amrinone and its metabolites in these patients.

The first study demonstrated that nonlinear method based on artificial intelligence NN did not statistically significantly increase the accuracy of predicted $\dot{V}O_2$ when variables used in linear regression equations were employed. In study II, both the CL and the V_{ss} were lower and the $T_{½}$ longer in neonates than in infants. No significant difference in the rate of acetylation between these age groups was observed. Studies III and IV are the first ones to evaluate the hemodynamic effects amrinone and dopamine-nitroglycerine in a prospective, double-blind manner. The results show that both amrinone and a combination of dopamine and nitroglycerine provide acceptable circulatory support in neonates after reconstructive surgery for TGA (III), and in infants after reconstructive surgery for complete AVSD (IV). However, the hemodynamic profile was more favorable in patients receiving amrinone: the $\dot{Q}$s index was significantly higher, and the peripheral vascular resistances, as well as the O_2ER values were significantly lower in the amrinone group compared to the dopamine-nitroglycerine group.

1. Determination of oxygen consumption in children with congenital heart disease

Indirect calorimetry is a method in which the type and rate of substrate utilization and energy metabolism are estimated from measurement of gas exchange. When carbohydrate, fat, and protein are oxidized, O_2 is consumed, and heat and CO_2 produced. However, anaerobic metabolism, as well as differences in the produced and exhaled CO_2 may affect the indirect calorimetry measurements (Ferrannini 1988). Routine measurement equipment for $\dot{V}O_2$ in children has been available only recently. Methods using a pneumotachograph, a Douglas bag, an infrared CO_2

analyzer, a mass spectrometer, as well as a paramagnetic O_2 analyzer have been used in $\dot{V}O_2$ determination (Wessel et al 1969, Lindahl 1989, Lundell et al 1996). These methods have small interobservational variation (Lindahl 1989, Lundell et al 1996). However, these equipment require frequent calibration to give reliable results. Furthermore, the measurements during mechanical ventilation and when high FIO_2 are needed may be cumbersome. With metabolic monitor Deltatrac, (Datex-Engström, Helsinki, Finland), the measurements can be made both in spontaneously breathing and mechanically ventilated patients, even when a high fraction of inspired oxygen is used (Meriläinen 1987). With this device, the mean $\dot{V}O_2$ difference has been shown to average -3.2 % and the precision ± 23 % when compared to mass spectrometry and wet gas spirometry in ventilated pediatric patients with $\dot{V}O_2$ ranging from 20 to 50 ml/min. The variability of $\dot{V}O_2$ measurement was further reduced to ± 12.7 % if measurements with inspiratory and expiratory O_2 fraction difference and mixed expiratory CO_2 fraction below 0.03, and FIO_2 higher than 0.6 were excluded. The device has not been validated for flows under 20 ml/min (Weyland et al 1994). However, when studying mechanically ventilated patients, cuffed tracheal tubes to prevent gas loss from the breathing circuit are often necessary for reliable results (Chwals et al 1992). Heart failure associated with left-to-right shunts has been shown to increase $\dot{V}O_2$, probably due to increased sympathetic activity (Kennaird 1976). In addition, physical activity state, level of sedation and changes in body temperature during the measurement affect $\dot{V}O_2$ (Baum et al 1967, Wessel et al 1969, Fixler et al 1974, Shapiro et al 1966).

The $\dot{V}O_2$ has been found to be proportional to body weight in healthy, spontaneously breathing anesthetized children and in children with CHD during mechanical ventilation. No differences were observed in $\dot{V}O_2$ in children with and without CHD (Lindahl 1989). Despite differences in methods and study populations, the regression lines of study I and Lindahl's study (1989) describing measured $\dot{V}O_2$ as a function of body weight were remarkably similar (Figure 1). However, neither of the regression equations were accurate in predicting $\dot{V}O_2$ - despite the small relative bias of the predicted $\dot{V}O_2$ the degree of agreement was not high between the measured and predicted $\dot{V}O_2$ values (Figure 2a). In 6 % of children in study I the use of predicted $\dot{V}O_2$ values according to

equation published by Lindahl (1989) would have result in misestimation of calculated PVR index when plotted against PVR index from measured $\dot{V}O_2$ (Figure 3). Even though the number of these children is small, and the management decisions of CHD hardly depend on any cut-off value of PVR index, the use of predicted values may lead to inaccurate evaluation of the hemodynamic status in an individual patient. Oxygen uptake and BSA were found to have a linear relationship in sedated, spontaneously breathing patients with CHD (Wessel et al 1969). In sedated children with CHD under three years of age, who were breathing room air spontaneously, the body dimensions and heart rate influenced $\dot{V}O_2$. In older children, gender, BSA, and heart rate affected $\dot{V}O_2$ significantly (Lundell et al 1996). Agreement between the measured and predicted $\dot{V}O_2$ according to these equations was not higher when compared with the equation created by Lindahl (1989). The use of an artificial intelligence NN, a pattern recognition technique that does not assume or require a mathematical relationship between the independent and dependent variables, produced less variability in its estimate of $\dot{V}O_2$ than the models that assume linear effects of these variables on $\dot{V}O_2$, even when the same variables were used. However, the addition of other variables describing the patient as input variables to NN did not make its prediction any more accurate from that based on age, gender, height, weight and heart rate. Furthermore, the difference in the error of $\dot{V}O_2$ calculated according to the equation published by Lindahl (1989), and the error of the NN estimates of $\dot{V}O_2$ was not statistically significant. Some variability in the error of measured and predicted $\dot{V}O_2$ may inevitably arise from the $\dot{V}O_2$ measurements performed with metabolic monitor Deltatrac, especially when 67 % of the measurements in the study I were performed in spontaneously breathing patients using the canopy mode. The large relative error of predicted $\dot{V}O_2$ represents the large interindividual variation in circulatory compromise and metabolic rate in the patients of the study I. Biological variation of the patients may have effected variation in $\dot{V}O_2$, even though no statistically significant influence of the tested variables on the error of predicted $\dot{V}O_2$ was found. Variation in body temperature also may have introduced variation in $\dot{V}O_2$ in this study (Shapiro et al 1966). The fact that the increased number of input variables describing the patient to NN did not make its prediction of $\dot{V}O_2$ any more accurate than that based on variables found relevant in linear

regression equations, suggests that these methods of $\dot{V}O_2$ prediction may be of limited value in the even more complex setting of recovery from pediatric open-heart surgery.

In both studies III and IV, administration of amrinone was associated with a slightly although not statistically significantly higher $\dot{V}O_2$ than the combination of dopamine and nitroglycerine. However, no significant thermogenic effect of amrinone has been shown in previous studies (Robinson et al 1993, Ruttimann et al 1994). Furthermore, there was no statistically significant difference in the epinephrine dose required in amrinone and dopamine-nitroglycerine groups. The higher cardiac output in the amrinone groups was associated with improved overall O_2 dynamics in neonates as well as in infants. In neonates of study III, the $\dot{V}O_2$ values were found to be rather low. A gas leak in the breathing circuit can produce an underestimate of $\dot{V}O_2$ (Chwals et al 1992). However, cuffed tracheal tubes were used to prevent gas loss from the circuit in the patients of the present study. Hyperventilation and alkalosis induced in the neonates may have affected the $\dot{V}CO_2$ measurements (Ferrannini 1988). Sedation and full ventilatory support may also have influenced the metabolic rate of our patients, resulting in lower $\dot{V}O_2$ values than reported in spontaneously breathing patients in this age group (Lundell et al 1996). The significant difference in the $\dot{V}O_2$ between spontaneously breathing and mechanically ventilated patients despite stable conditions in study I further supports this contention. Measurement errors may have affected especially some of the $\dot{V}O_2$ values observed in the neonates of study III, as the measured values were near the lower limits of validation (Weyland et al 1994).

2. Amrinone pharmacokinetics in neonates and infants

In previous studies, the pharmacokinetics of amrinone in children have been examined in heterogeneous patient populations. Therefore, little is known about amrinone pharmacokinetics in neonates during the first four weeks of life (Lawless et al 1989, Allen-Web et al 1994, Williams et al 1995). In study II, both the CL and the V_{ss} were smaller and the $T_{½}$ longer in neonates than in infants. The results of the present study support the observations in previous studies despite the methodological differences (Lawless et al 1989, Allen-Web et al 1994, Sorensen 1996). However, Lawless et al (1989) did not observe any differences in Vd between neonates and infants. The

authors determined the CL by dividing the infusion rate by the plasma concentration of amrinone at the end of the infusion and calculated the Vd during the elimination phase instead of the V_{ss} used in the present study. Although this study was not planned for elucidation of concentration-response relationship in children, the amrinone plasma concentrations, that were found to be approximately 30 % lower in infants than in neonates, resulted in steady-state plasma concentrations of 1.5 to 6 µg/ml, which have been shown to be effective in adults (Edelson et al 1981).

Amrinone is metabolized by acetylation and glucuronidation in the liver, while 40 % is excreted in the urine (Kullberg et al 1981, Steinberg et al 1994). In adult cardiac surgical patients, plasma protein binding of amrinone is 21 %, and it is not affected by surgery and CPB. Further, the pharmacokinetic profile in these adult patients was not significantly affected by CPB when compared with healthy volunteers (Bailey et al 1991). There is lack of information on the effects of anesthesia, surgery and CPB on the pharmacokinetics of amrinone in children with CHD. In previous studies, the pharmacokinetics have been examined mainly in the ICU in heterogeneous groups of children under different anesthetic management (Lawless et al 1989, Allen-Web et al 1994). The plasma protein binding of amrinone in young children with low plasma protein levels has not been reported. However, in children undergoing cardiac surgery, a reduction in the Vd of amrinone is suggested during hypothermic CPB when compared with values found during the postoperative period. Furthermore, approximately 20 % of the loading dose administered into the CPB circuit becomes unavailable secondary to sequestration in bypass equipment (Williams et al 1995). These factors may affect the total plasma concentration of amrinone during surgery. The renally excreted N-acetylamrinone, the major metabolite, accounts only 2 % of the total dose of amrinone in adults (Kullberg et al 1981). Slow acetylation of caffeine and sulfadimidine has been found in young children (Szorady et al 1987, Pariente-Khayat et al 1991). However, no difference was observed in the ratio of the plasma concentration of N-acetylamrinone to that of amrinone in the present study indicating no significant differences in the rate of acetylation between these age groups. This finding confirms previous results (Allen-Webb et al 1994) and suggests that the maturation of hepatic amrinone N-acetylation capacity is complete already during the first weeks of life. Allen-Webb et al (1994) have shown in one neonate that renal CL accounts for the majority of total amrinone CL. Therefore, the slow elimination of amrinone in neonates may be mainly due to their immature renal function. The fact that amrinone plasma concentration did not increase in patients with renal failure and peritoneal dialysis, indirectly supports the contention that peritoneal dialysis contributed to the elimination of amrinone. However, it is also possible that elimination of

amrinone through alternative metabolic routes increased in these patients. Unfortunately, the design of the present study does not allow any conclusions on this matter.

3. Hemodynamics in neonates and infants during amrinone or dopamine-nitroglycerine administration after reconstructive surgery for congenital heart disease

The cardiac pathophysiology of neonates with TGA and infants with complete AVSD is characterized by two major hemodynamic problems after reconstructive surgery: low cardiac output and reactive pulmonary vasculature. Since patients with TGA and AVSD represent two distinct age groups and maturational states of the cardiovascular system, they were separated in the present study.

Dopamine, epinephrine and nitroglycerine are frequently used in vasoactive support in these patients. Dopamine is typically infused from 5 to 10 µg/kg/min, nitroglycerine from 0.5 to 10 µg/kg/min, and epinephrine form 0.05 to 0.4 µg/kg/min in many institutions (Wernovsky et al 1995a, Wernovsky et al 1995b, Bando et al 1995, Bando et al 1996). Amrinone is often infused from 5 to 10 µg/kg/min (Lawless et al 1989, Wernovsky et al 1995b). The relative potency of the vasoactive agents in the present study is difficult to establish. Neonates and infants require higher doses of dopamine to achieve significant increase in cardiac output than older children or adult patients after cardiac surgery (Perez et al 1986, Outwater et al 1990, Bhatt-Mehta et al 1991). In addition to pulmonary vasodilatation, nitroglycerine may induce also systemic vasodilatation, which may be especially harmful if the right ventricle is failing (Burrows et al 1986). Dosing of amrinone according to guidelines established to achieve therapeutic serum concentrations in adults has produced a wide range of blood levels in children, all associated with clinically acceptable cardiac performance (Edelson et al 1981, Lawless et al 1989, Allen-Webb et al 1994). The responses to catecholamines and PDE inhibitors also may be altered by chronic heart failure and β-adrenoceptor down-regulation and uncoupling. In many children with CHD, most of the β-adrenoceptor down regulation is β_1- subtype selective, but in neonates with TGA additional significant β_2-adrenoceptor down- regulation may be present (Kozlik-Feldmann et al 1993). In the present study, the cardiac output was significantly higher in the amrinone groups. The dose of epinephrine required both in neonates and infants was rather high, but not statistically significantly different between the groups. A higher dose of dopamine may have provided some increase in the cardiac

output in the patients in dopamine-nitroglycerine groups. However, the ability of β-adrenergic agonists to stimulate adenylate cyclase is decreased in young children, while there is no age-dependency in the PDE inhibitor effect (Foged et al 1990, Baum et al 1997). Therefore, it is unlikely that increased dose of dopamine would have resulted in significantly improved overall cardiac performance in the dopamine-nitroglycerine groups, because even the combined effect of dopamine and epinephrine on β-adrenoceptors, supplemented with nitroglycerine, failed to improve it more than the combination of amrinone and epinephrine. Further, the argument that an increase in the vasodilator dose in the dopamine-nitroglycerine groups would have produced higher cardiac output is countered by the finding in a previous study, in which amrinone administration resulted in increased cardiac output per unit decrease in afterload secondary to positive inotropic effect when compared with a pure vasodilator (Bailey et al 1997).

Inotropic agents are often evaluated by measuring hemodynamic response to a stepwise increase in dose (Berner et al 1990, Outwater et al 1990). This approach was not considered possible in studies III and IV, because effective levels of vasoactive agents often are already required for separation from CPB in neonates with TGA and infants with AVSD (Wernovsky et al 1995a, Bando et al 1995). Moreover, baseline values obtained shortly after separation from CPB at the time of cardiovascular instability may have limited validity. A cross-over design would allow the comparison of treatments on the same subjects (Hills et al 1979). However, the effect of time on the postoperative recovery would probably confound the comparison of two vasoactive regimens, as the postoperative course of these patients is often characterized by a transitory decrease in cardiac output during the first postoperative night (Wernovsky et al 1995a). Furthermore, the $T_{½}$ of amrinone significantly exceeds that of dopamine and nitroglycerine, making random-order crossover impossible (Lawless et al 1988, Notterman et al 1990, Bhatt-Mehta et al 1991, Allen-Webb et al 1994).

The use of catecholamines to enhance cardiac output after pediatric cardiac surgery is compromised by a potential increase in PVR (Booker et al 1995). In study III, an open–label epinephrine infusion was administered postoperatively in 12 neonates in the amrinone group, and 15 neonates in the dopamine-nitroglycerine group. Eight infants were given epinephrine in the amrinone group, and five infants in the dopamine-nitroglycerine group in study IV. In both neonates and infants, there was a tendency for lower PVR index in the amrinone group, which did not reach statistical significance. In the infants, the $\dot{Q}p$ was significantly higher in the amrinone group while PAP

showed no difference between the groups, suggesting a fall in the resistance of pulmonary vasculature in infants receiving amrinone. In the neonates, the $\dot{Q}s$ index was statistically significantly higher in the amrinone group, while no significant difference was observed in $\dot{Q}p$: $\dot{Q}s$ between the groups. Therefore, to claim absence of a difference in pulmonary hemodynamics between amrinone and dopamine-nitroglycerine on the basis of this study in neonates would carry a high risk of a type β statistical error. Even though the administration epinephrine infusion through the proximal lumen of the central venous line may affect the pulmonary vasodilating effects of the study regimen, extra left atrial lines were not inserted in these patients to avoid this phenomenon (Fullerton et al 1993), but the drugs were administered following the routine clinical practice of most institutions, including ours.

The SVR index in the amrinone group was significantly lower than in the dopamine-nitroglycerine group while there was no difference in the left and right atrial pressures, suggesting similar volume loading in all study groups of neonates (III) and infants (IV). Despite the lower SVR index in amrinone group, no difference in the MAP was observed between the study groups. The need for volume loading during amrinone administration has been reported previously (Lynn et al 1993, Bailey et al 1997). However, the loading dose of amrinone in the present study was given into the venous reservoir of the bypass circuit just prior to removal of the aortic cross-clamp. This technique of amrinone administration may be beneficial in avoiding the possible reduction of MAP and coronary circulation in these patients, even though some of the loading dose may become bound to the bypass circuit (Williams et al 1995). The average left atrial oxyhemoglobin saturation ($SlaO_2$) was significantly lower in the neonates receiving amrinone, but not in infants under same medication, when compared with dopamine-nitroglycerine groups. The low $SlaO_2$ in neonates may result from more pronounced intrapulmonary shunting associated with CPB, further accelerated by the vasodilatory effects of amrinone (Kirklin et al 1983). However, this phenomenon proved not to be deleterious in the neonates, as the higher cardiac output was associated with more favorable O_2ER in the amrinone group.

The principal side effect of prolonged amrinone therapy is thrombocytopenia secondary to amrinones effect on megakaryocytes or platelets, which decreases platelet survival (Ross et al 1993). Even in the present study, low platelet counts in the amrinone group were observed up to the fourth postoperative day both in neonates and infants. However, the lower platelet counts in the

amrinone group were not associated with increased postoperative blood loss. The two neonates, who had their sternum reopened to control bleeding after removal of pulmonary artery and left atrial lines, were receiving dopamine and nitroglycerine.

SUMMARY AND CONCLUSIONS

Postoperative cardiovascular care of the patients with CHD is often complicated by low cardiac output and reactive pulmonary vasculature. In addition to the underlying cardiac pathophysiology, preoperative hemodynamic status, surgery and conduction of CPB, as well as anesthetic management affect postoperative cardiac performance. Furthermore, the response to vasoactive regimen may vary with the underlying cardiac defect, age, and degree of heart failure. The present study was conducted to evaluate cardiovascular management in children undergoing open-heart surgery. The utility of linear regression equations and nonlinear artificial intelligence NN in $\dot{V}O_2$ prediction was evaluated at preoperative cardiac catheterization by comparing measured and predicted $\dot{V}O_2$ in a group of children with CHD (I). Pharmacokinetics of amrinone in neonates and infants after open-heart surgery for CHD (II) were also examined to ensure adequate amrinone dosing and to clarify the distribution and elimination of amrinone and its metabolites in these patients. Finally, the efficacy and safety of amrinone and a combination of dopamine and nitroglycerine was assessed in neonates after arterial switch operation for TGA, and in infants after reconstructive surgery for complete AVSD, during the first 18 postoperative hours in the ICU (III, IV).

In study I, 125 children with CHD undergoing cardiac catheterizations were studied retrospectively. The $\dot{V}O_2$ was measured using indirect calorimetry. The predicted values were calculated from regression equations by Lindahl (1989), Wessel et al (1969), and Lundell et al (1996). Influence of age, gender, weight, height, cardiac malformation, heart failure, heart rate, hemoglobin, MAP, PAP, and $\dot{Q}p$: $\dot{Q}s$ on the precision of the predicted $\dot{V}O_2$ were evaluated. An artificial NN was employed to produce an estimate of $\dot{V}O_2$ using the variables found in the published regression equations as well as other variables describing the patient. Lindahl´s equations produced the highest precision (± 42 %) of the regression-based estimates. The corresponding average bias of the predicted $\dot{V}O_2$ was 3 % (range from –66 % to 43 %). When equations by Wessel et al (1969) and Lundell et al (1996) were used, the bias and precision were 0 % (range from –69 % to 39 %) and ± 44 %, and –16 % (range from –94 % to 100 %) and ± 51 %, respectively. When the NN was used, the bias was 6 % (range from –19 % to 30 %) and precision ± 29 %. Even though the NN estimated $\dot{V}O_2$ with higher

precision, there was no statistically significant difference in the error of $\dot{V}O_2$ calculated according to the equation published by Lindahl (1989), and the error of the NN estimates of $\dot{V}O_2$.

Fifteen neonates with TGA and 14 infants with AVSD participated in a prospective study (II) after reconstructive surgery. Blood samples to determine plasma concentrations of amrinone, N-acetylamrinone, and N-glycolylamrinone were drawn before amrinone administration, after the loading dose of 2 mg/kg given during the CPB, and every 6 hours during the maintenance infusion of 7.5 µg/kg/min, and until 48 hours after cessation of the infusion. The amrinone plasma concentrations were between 1.5 to 6 µg/ml in all patients, even though they were approximately 30 % lower in infants than in neonates. Amrinone CL was significantly lower, 2.4 ± 0.9 ml/kg/min, in neonates, compared with 3.2 ± 1.2 ml/kg/min in infants ($p < 0.05$). The V_{ss} was significantly smaller, 0.8 ± 0.6 l/kg, in neonates, when compared with 1.6 ± 1.1 l/kg in infants ($p < 0.05$). The $T_{½}$ was also significantly longer in neonates than in infants (10.7 ± 6.7 hours and 6.1 ± 1.4 hours, respectively, $p < 0.03$). The correlation between amrinone CL and BSA was linear. The ratio between plasma concentration of N-acetylamrinone and amrinone did not differ between neonates and infants. No patient had a detectable plasma concentration of N-glycolylamrinone

In studies III and IV, 35 neonates and 32 infants participated in prospective, randomized, double blind studies. Amrinone loading dose, 2 mg/kg, was followed by a maintenance infusion, 7.5 µg/kg/min in 16 neonates and 17 infants before separation from the CPB. The remaining patients received a combination of dopamine, 5 µg/kg/min, and nitroglycerine, 1 µg/kg/min. An open-label epinephrine infusion and inhaled NO were available for further vasoactive support. The circulatory state of the patients was evaluated two-hourly from four to 18 hours after CPB using the Fick principle and measured $\dot{V}O_2$ values. The $\dot{Q}s$ index was significantly higher in the amrinone groups when compared with dopamine-nitroglycerine groups (in neonates 1.7 ± 0.5 l/min/m^2, and 1.4 ± 0.4 l/min/m^2, respectively, $p < 0.04$, and in infants 2.5 ± 0.7 l/min/m^2, and 2.0 ± 0.6 l/min/m^2, respectively, $p < 0.03$). The SVR index was significantly lower in the amrinone groups than in the dopamine-nitroglycerine groups (in neonates 26 ± 8 Wood units x m^2, and 35 ± 12 Wood units x m^2, respectively, $p < 0.02$, and in infants 21 ± 6 Wood units x m^2, and 27 ± 8 Wood units x m^2, respectively, $p < 0.04$). The O_2ER was also significantly lower in the amrinone groups compared with the dopamine-nitroglycerine groups (in neonates 0.28 ± 0.06, and 0.34 ± 0.08, respectively, p <

0.02, and in infants 0.34 ± 0.08, and 0.41 ± 0.07, respectively, $p < 0.02$). The PVR index was lower in the amrinone groups than in the dopamine-nitroglycerine groups, but not statistically significantly (in neonates 5.5 ± 1.9 Wood units x m^2, and 7.9 ± 4.2 Wood units x m^2, respectively, $p = 0.05$, and in infants 5.3 ± 2.0 Wood units x m^2, and 7.1 ± 3.0 Wood units x m^2, respectively). There was no statistically significant difference in the epinephrine dose required in both groups of neonates and infants. Platelet counts were significantly lower in the amrinone groups, but no difference in blood loss or hemorrhagic complications were observed between the study groups. The need for mechanical ventilation in neonates was 71 ± 37 hours, from 27 to 149 hours, in the amrinone group and 92 ± 68 hours, from 23 to 249 hours, in the dopamine-nitroglycerine group, and in infants 81 ± 56 hours, from 23 to 187 hours, in the amrinone group and 89 ± 70 hours, from 25 to 189 hours, in the dopamine-nitroglycerine group. In neonates, the length of stay in the ICU was 5 ± 2 days (from 3 to 11 days) in the amrinone group and 6 ± 4 days (from 3 to 16 days) in the dopamine-nitroglycerine group. The duration of intensive care period in infants was 5 ± 3 days (from 2 to 14 days) in the amrinone group and 7 ± 3 days (from 3 to 11 days) in the dopamine-nitroglycerine group. The total duration of hospitalization was 12 ± 3 days, from 8 to 18 days, in the neonates of the amrinone group and 12 ± 5 days, from 6 to 26 days, in the neonates of the dopamine-nitroglycerine group. The hospitalization time in infants was 14 ± 6 in both groups, ranging from 6 to 26 days in the amrinone group and from 7 to 28 days in the dopamine-nitroglycerine group. One neonate in the amrinone group died on the eight postoperative day because of septicemia caused by strangulation of the ileum. There was no mortality among the infants in the study.

The results presented here allow the following conclusions to be made:

1.The methods based on artificial intelligence NN do not provide statistically significantly higher agreement in preoperative $\dot{V}O_2$ prediction than the nomograms based on linear regression technique in patients with CHD. If predicted values are used, the large interindividual biological variation in these patients should be taken into account. The measurement of $\dot{V}O_2$, even though subject to measurement errors, is preferable in the hemodynamic evaluation of these patients.

2. Amrinone is eliminated at a slower rate in neonates than in infants. The rate of acetylation of amrinone appears to be similar; the differences in the elimination capacity of amrinone are mainly due to the immature renal function in neonates.

3. Use of either amrinone or the combination of dopamine and nitroglycerine, supplemented with epinephrine, results in acceptable cardiovascular support in neonates recovering from arterial switch operations and in infants after reconstructive surgery for AVSD. However, amrinone provides a higher cardiac output, lower peripheral vascular resistance, and more favorable O_2 dynamics in patients prone to low cardiac output and increased PVR. Amrinone administration results in lower platelet counts than administration of dopamine and nitroglycerine with no difference in blood loss or hemorrhagic complications.

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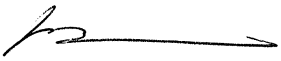

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