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Intraoperative hemodynamic instability during and after separation from cardiopulmonary bypass: importance, mechanism and prevention

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Résumé

Chaque année, environ 1 à 1,25 million d'individus subiront une chirurgie cardiaque. [1] Environ 36 000 chirurgies cardiaques sont effectuées au Canada et 8000 procédures au Québec (http://www.ccs.ca). Le vieillissement de la population aura pour conséquence que la chirurgie cardiaque sera offerte à des patients de plus en plus à risque de complications, principalement en raison d'une co-morbidité plus importante, d'un risque de maladie coronarienne plus élevée, [2] d'une réserve physiologique réduite et par conséquent un risque plus élevé de mortalité à la suite d'une chirurgie cardiaque. L'une des complications significatives à la suite d'une chirurgie cardiaque est le sevrage difficile de la circulation extracorporelle. Ce dernier inclut la période au début du sevrage de la circulation extracorporelle et s'étend jusqu'au départ du patient de la salle d'opération. Lorsque le sevrage de la circulation extracorporelle est associé à une défaillance ventriculaire droite, la mortalité sera de 44 % à 86 %. [3-7] Par conséquent le diagnostic, l'identification des facteurs de risque, la compréhension du mécanisme, la prévention et le traitement du sevrage difficile de la circulation extracorporelle seront d'une importance majeure dans la sélection et la prise en charge des patients devant subir une chirurgie cardiaque. Les hypothèses de cette thèse sont les suivantes : 1) le sevrage difficile de la circulation extracorporelle est un facteur indépendant de mortalité et de morbidité, 2) le mécanisme du sevrage difficile de la circulation extracorporelle peut être approché d'une façon systématique, 3) la milrinone administrée par inhalation représente une alternative préventive et thérapeutique chez le patient à risque d'un sevrage difficile de la circulation extracorporelle après la chirurgie cardiaque.

Mots-clés : ventricule droit, circulation extracorporelle, chirurgie cardiaque, instabilité hémodynamique, échocardiographie transoesophagienne, hypertension pulmonaire

Abstract

Every year, 1 million to 1.25 million patients worldwide undergo cardiac surgery. [1] Up to 36,000 cardiac surgeries are performed each year in Canada and close to 8000 in Quebec (http://www.ccs.ca). Because of the aging of the population, cardiac surgery will increasingly be offered to patients at a higher risk of complications. Indeed, elderly patients have increased co-morbidities, and aging is also a significant risk factor in the prevalence of coronary artery disease. [2] The consequence is a reduced physiologic reserve, hence an increased risk of mortality. These issues will have a significant impact on future healthcare costs, because our population undergoing cardiac surgery will be older and more likely to develop postoperative complications. One of the most dreaded complications in cardiac surgery is difficult separation from cardiopulmonary bypass (CPB). The definition of difficult separation from CPB includes the time period from when CPB is initiated and until the patient leaves the operating room. When separation from CPB is associated with right ventricular failure, the mortality rate will range from 44% to 86%. [3-7] Therefore the diagnosis, the preoperative prediction, the mechanism, prevention and treatment of difficult separation from CPB will be crucial in order to improve the selection and care of patients and to prevent complications for this high-risk patient population. The hypotheses of this thesis are the following: 1) difficult separation from CPB is an independent factor of morbidity and mortality, 2) the mechanism of difficult separation from CPB can be understood through a systematic approach, 3) inhaled milrinone is a preventive and therapeutic approach in the patient at risk for difficult weaning from CPB after cardiac surgery.

Keywords : Right ventricle; Cardiopulmonary bypass; Cardiac surgery; Hemodynamic instability; Transesophageal echocardiography; Pulmonary hypertension.

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Abbreviations

2D	two-dimensional
A dur	duration of mitral inflow A-wave
A	peak late or atrial diastolic flow velocity
ABC	Airway-Breathing-Circulation
AC	aortic occlusion
ACC/AHA	American College of Cardiology and American Heart Association
ACE	angiotensin converting enzyme
ACS	abdominal compartment syndrome
Am	atrial mitral annular velocity
AML	anterior mitral leaflet length
AMP	adenosine monophosphate
ANCOVA	analysis of covariance
ANOVA	analysis of variance
Ao	aorta
AoV	aortic valve
AP	arterial pressure
APP	abdominal perfusion pressure
AR	aortic regurgitation
AR	atrial reversal
ASD	atrial septal defect
At	atrial tricuspid annular velocity
AVR	aortic valve replacement
BART	Blood Conservation Using Antifibrinolytics in a Randomized Trial
BMI	body mass index
BP	blood pressure
BSA	body surface area

CABG	coronary artery bypass grafting
CAD	coronary artery disease
CARE	Cardiac Anesthesia Risk Evaluation
CASS	Coronary Artery Surgery Study
CBF	cerebral blood flow
CHF	congestive heart failure
CI	cardiac index
CI	confidence interval
CK	creatinine kinase
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CTICU	cardiothoracic intensive care unit
CVD	cerebrovascular disease
CVP	central venous pressure
D	diastolic
DAP	diastolic arterial pressure
DPAP	diastolic pulmonary arterial pressure
DSB	difficult separation from bypass
DT	deceleration time
E	early
ECMO	extra-corporeal membrane oxygenator
EDA	end-diastolic area
EDV	end-diastolic volume
EF	ejection fraction
EKG	electrocardiogram
Em	early mitral annular velocity
EOA	effective orifice area
ESA	end-systolic area

ESV	end-systolic volume
Et	early tricuspid annular velocity
ET	ejection time
FAC	fractional area change
Fem	Femoral
FRC	functional residual capacity
Gd	gradient
GEE	generalized estimating equation
HR	heart rate
HVF	hepatic venous flow
IABP	intra-aortic balloon pump
IAH	intra-abdominal hypertension
IAP	intra-abdominal pressure
ICU	intensive care unit
iEOA	indexed effective orifice area
IL	interleukin
iMil	Inhaled milrinone
iNO	inhaled nitric oxide
$iPGI_2$	inhaled prostacyclin
IU	international unit;
IV	intravenous
IVC	interior vena cava
IVCT	isovolumic contraction time
IVRT	isovolumic relaxation time
LA	left atrium
LAA	left atrial appendage
LADt	left atrial transverse dimension
LAP	left atrial pressure
LCOS	low cardiac output syndrome

LHV	left hepatic vein
LIJV	left internal jugular vein
LIMA	left internal mammary artery
LOF	low output failure
LUPV	left upper pulmonary vein
LV	left ventricle or left ventricular
LVAD	left ventricular assist device
LVDD	left ventricular diastolic dysfunction
LVEDA	left ventricular end-diastolic area
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
LVESA	left ventricular end-systolic area
LVFAC	left ventricular fractional area change
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
LVWMSI	left ventricular wall motion score index
MAP	mean arterial pressure
MAV	mitral annular velocity
MHI	Montreal Heart Institute
MI	myocardial infarction
MPAP	mean pulmonary artery pressure
MPI	myocardial performance index
MR	mitral regurgitation
MV	mitral valve
MVO_2	mixed venous oxygen
MVR	mitral valve replacement
NIH	National Institute of Health
NIRS	near-infrared spectroscopy
NO	nitric oxide

NTG	nitroglycerin
NTP	nitroprusside
NYHA	New York Heart Association
OM	obtuse marginal
OR	odds ratio
OR	operating room
Pa	arterial pressure
PA	pulmonary artery
PAC	pulmonary artery catheter
Paf	femoral arterial pressure
PAF	platelet activating factor
PAP	pulmonary artery pressure
Par	radial arterial pressure
PCWP	pulmonary capillary wedge pressure
PEEP	positive end-expiratory pressure
PFO	patent foramen ovale
PGE_1	prostaglandin E_1
PGI_2	prostacyclin
PH	pulmonary hypertension
PML	posterior mitral leaflet length
Pms	mean systemic pressure
PMV	prosthetic mitral valve
PN	pseudonormal
Ppa	pulmonary artery pressure
PPM	patient-prosthesis mismatch
Pra	right atrial pressure
Prv	right ventricular pressure
PVF	pulmonary venous flow
PVR	pulmonary vascular resistance

PVRI	indexed pulmonary vascular resistance
PW	pulsed-wave
QHLI	Quebec Heart and Lung Institute
Ra	arterial resistance
RA	relaxation abnormality
RA	right atrium
Rad	Radial
RADt	right atrial transverse diameter
RBC	red blood cell;
RCA	right coronary artery
RCT	randomized controlled trial
ROC	receiver operating characteristics
RPA	right pulmonary artery
Rrv	resistance to venous return
RV	residual volume
RV	right ventricle or right ventricular
RVAD	right ventricular assist device
RVDD	right ventricular diastolic dysfunction
RVED	right ventricular end-diastolic volume
RVEDA	right ventricular end-diastolic area
RVEF	right ventricular ejection fraction
RVES	right ventricular end-systolic volume
RVESA	right ventricular end-systolic area
RVFAC	right ventricular fractional area change,
RVMPI	right ventricular myocardial performance index
RVOT	right ventricular outflow tract
RVOTO	right ventricular outflow tract obstruction
Rvr	resistance to venous return
RWMA	regional wall motion abnormalities

RWMSI	regional wall motion score index
S	systolic
SAM	systolic anterior motion
SAP	systemic arterial pressure
ScO_2	cerebral oxygen saturation
SCV	subclavian vein
SD	standard deviation;
SE	standard error
Sec	seconds
SLCL	septal to leaflet coaptation length
Sm	systolic mitral annular velocity
SPAP	systolic pulmonary artery pressure
St	systolic tricuspid annular velocity
STS	Society of Thoracic Surgeons
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVRI	indexed systemic vascular resistance
TAPSE	tricuspid annular plane systolic excursion
TAV	tricuspid annular velocity
TD	thermodilution
TDI	tissue Doppler imaging
TEE	transesophageal echocardiography
TLC	total lung capacity
TMF	transmitral flow
TNF	tumor necrosis factor
TO_2	oxygen transport
TTF	transtricuspid flow
TV	tricuspid valve

UK	United Kingdom
USA	United States of America
VAD	ventricular assist device
Vp	velocity of propagation
VR	venous return

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Foreword

Every year, 1 million to 1.25 million patients worldwide undergo cardiac surgery. [1] Up to 36,000 cardiac surgeries are performed each year in Canada and close to 8000 in Quebec (www.ccs.ca). With the aging of the population, cardiac surgery will increasingly be offered to patients at a higher risk of complications. Elderly patients have increased co-morbidities and aging is also a significant risk factor in the prevalence of coronary artery disease. [2] The consequence is a reduced physiologic reserve. These issues will have a significant impact on future healthcare costs, because our population undergoing cardiac surgery will be older and more likely to develop postoperative complications. The relation between these postoperative complications and the impact of cardiac surgery has been the object of intensive research performed by several pioneers at the Montreal Heart Institute (MHI) [8] at large, and in the anesthesia department in particular by Dr. Raymond Martineau.

Dr. Raymond Martineau, anesthesiologist at the MHI, played a pivotal role in the creation of a database compiling the data of all patients operated in this institution between 1995 and 1999. Unfortunately, Dr. Martineau was unable to sustain that very important activity and the Department of Anesthesia was saddened when he passed away in 2005. I had the privilege to work with Dr. Martineau and, in collaboration with the Department of Cardiac Surgery, we published several reports using this database. [9-11] When I was recruited by the Department of Anesthesiology of the MHI in 1999, my duty was to develop the use of transesophageal echocardiography (TEE) in the operating room. To do so, Dr. Pierre Couture and I trained our colleagues, developed a database, published in collaboration with Drs. Jean Buithieu and Jean-Claude Tardif a textbook on TEE, [12] the second edition with the collaboration of Dr. Annette Vegas, [13] and performed several research projects regarding the use of TEE in the operating room and in the intensive care unit. [10-12;14-50] In 2006, I enrolled in a PhD program at the University of Montreal. My objective was to improve my research skills in order to perform clinical studies tackling a

problem I felt was important in clinical medicine, namely the issue of hemodynamic instability. When this phenomenon occurs in the setting of cardiac surgery, namely between the initiation of the weaning process of cardiopulmonary bypass (CPB) and the moment when the patient leaves the operating room, we have been calling it difficult separation from CPB. Since the beginning of my PhD in 2006, in collaboration with other investigators and as the supervisor of residents as well as fellow, master and PhD students, we conducted several investigations regarding the issue of difficult weaning from CPB. [10;11;38-44;46;47;51-53] The results of four of these investigations will be presented in this work. Firstly, we will define difficult weaning from CPB and explore its consequences. Secondly, the mechanism of difficult weaning from CPB will be presented based on the physiological concept of venous return described by Guyton [54] and our experience using TEE since 1992 in more than 15,000 patients. Finally, the rationale and the preliminary studies of a novel approach using inhaled milrinone will be presented.

Introduction

One of the dreaded complications in cardiac surgery is difficult separation from CPB. In the setting of cardiac surgery, we define difficult separation from CPB as the process that may take place between the beginning of the weaning process of CPB and the moment the patient leaves the operating room. When difficult separation from CPB is associated with right ventricular (RV) failure, the mortality rate will range from 44% to 86%. [3-7] For this reason the diagnosis, the preoperative prediction, the mechanism, prevention and treatment of difficult separation from CPB will be crucial in order to improve the selection and care of patients and to prevent complications for the cardiac surgical population.

The hypotheses of this thesis are the following: 1) difficult separation from CPB is independently associated with an increased risk of morbidity and mortality, 2) the mechanism of difficult separation from CPB can be understood through a systematic approach based on the concept of venous return, 3) inhaled milrinone is a preventive and therapeutic approach in the patient at risk of difficult weaning from CPB after cardiac surgery.

The thesis will include four key studies. The first study will demonstrate the prognostic importance of difficult weaning from CPB in a multicentered Canadian study in 2331 patients [55] in which the MHI participated. The second and third studies are part of a single-centered randomized controlled trial [56] in which we explore the natural hemodynamic and echocardiographic evolution of 120 patients undergoing valvular surgery and describe the characteristics of patients randomized to amiodarone and those requiring inotropes to be weaned from CPB. Finally, the fourth study is the first randomized controlled trial on the intraoperative use of inhaled milrinone for the prevention of difficult separation from CPB.

Chapter 1 Definition and importance of difficult separation from CPB

In this first chapter, we will define difficult separation from CPB, review the predictors, the significance and the consequences of this important complication in cardiac surgery. Finally, we will present the research performed by the candidate and his collaborators on this issue since the beginning of his PhD program in 2006.

1.1 Definition of difficult separation from CPB

The time sequence in a cardiac surgical procedure is illustrated in Figure 1. In the preoperative period, the patient will be evaluated by several members of the cardiac team, mainly the cardiac surgeon and the cardiac anesthesiologist, to determine the precise surgical procedure to be performed and also for risk stratification. This will be discussed in more detail in section 1.2. After the preoperative evaluation, the patient is brought in the operating room where the surgical procedure is performed. Following the cardiac surgical procedure, the patient is then transferred to the intensive care unit for 24 to 48 hours and to the postoperative ward for 5 to 10 days before being discharged home or to a recovery facility. The operating room time is divided in three periods: before, during and after CPB. Cardiopulmonary bypass is the term used to describe an extracorporeal circuit used during cardiac surgery. The CPB maintenance is under the supervision of a professional called the perfusionist.

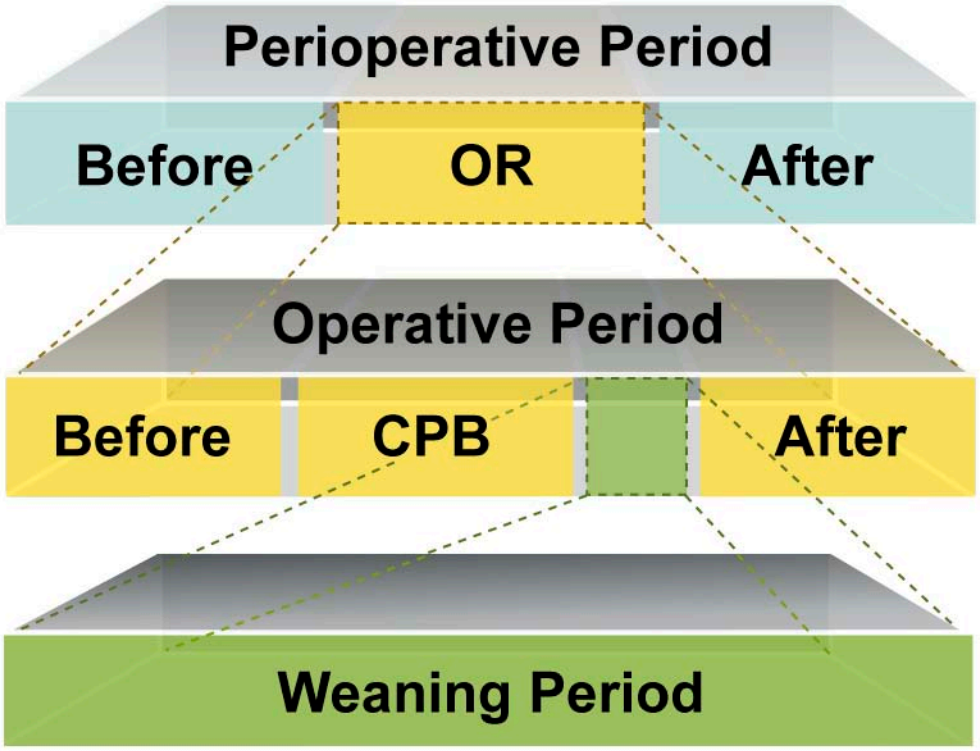

Figure 1 Time sequence of a cardiac surgical procedure

A cardiac surgical procedure can be divided into three periods: before, in the operating room (OR) and after the procedure. The time after the procedure includes the time spent in the intensive care unit (ICU) and in the hospital. In the OR, there are three periods, before, during and after cardiopulmonary bypass (CPB). The event at the end of CPB, when the extracorporeal circulation is gradually withdrawn, corresponds to the weaning from CPB. In this thesis, the expression "difficult separation from CPB" is related to both the weaning period and the operative period following CPB.

The role of CPB is to temporarily replace the heart and lungs[1] which are not functional during the cardiac procedure. The role of CPB is to provide oxygen transport to the body and all the vital organs, except the heart and lungs. The majority of cardiac

[1] The term extracorporeal circuit or heart-lung machine is also used as a synonym of CPB.

surgeries are performed using CPB.[2] The use of CPB can be associated with specific complications that will be discussed in more details in section 1.2.5. At the end of CPB, when the cardiac surgery is completed, the cardiac team will gradually withdraw the extracorporeal support. This process is called weaning or separation from CPB. Weaning from CPB begins when the surgeon decides to gradually reduce the venous return from the CPB and derives it back to the patient. This will be performed only if the cardiac team considers that the patient is stable enough to maintain his oxygen transport. Weaning from CPB is considered complete when the cardioplegia, venous and arterial cannulae are removed. This is followed by the administration of protamine. In this thesis, the expression "difficult separation from CPB" is related to both the weaning period and the operative period following CPB. This period ends when the patient leaves the operating room.

Normally, when CPB is gradually withdrawn, the heart resumes normal mechanical and electrical activity. The CPB is then turned off and removed from the patient. However in some patients, vasoactive drugs such as intravenous noradrenaline are required to maintain an adequate arterial pressure and thus sustain cardiac function and oxygen transport. The dosage of this vasoactive medication can vary from one patient to another. If one vasoactive agent is not sufficient, typically additional medications such as inotropes like intravenous milrinone will be added to wean the patient from CPB. If this pharmacological strategy does not produce the desired effect, the weaning process will fail and the cardiac surgeon will have to reinstitute full CPB. This is called "return on CPB". As the pharmacological approach is insufficient, mechanical devices used to temporarily support ventricular function such as an intra-aortic balloon pump (IABP) or ventricular assist device (VAD) will be used. There are several reasons or mechanisms to explain this failure to wean from CPB and they will be detailed in Chapter 3. However, the anesthesiologist using TEE will have an important role to play if difficult weaning from CPB occurs. His role will be to rule out any unexpected surgical complication resulting for instance from a dysfunctional prosthesis. In the largest series published so far on the role of

[2] Some cardiac surgeries, for instance coronary revascularization, can be performed without CPB. This is called off-pump cardiac surgery. These procedures and their impact will not be discussed in the thesis.

TEE in 12,566 patients undergoing cardiac surgery, Eltzschig *et al.* [57] observed that TEE influenced cardiac surgical decisions in 9% of all cases. This has also been our experience. [16] In some of these cases, the surgeon will have to revise his procedure. Finally, in rare instances, the CPB weaning process will not be possible and the patient will die in the operating room. Therefore, the process of CPB weaning is a critical moment during cardiac surgery. It is the earliest period after cardiac surgery where the patient is at increased risk of morbidity and mortality. It does not represent a "yes or no" process but a complex situation that requires a comprehensive approach and definition. How has difficult separation from CPB been defined in the literature?

The literature confirms that difficult separation from CPB is a life-threatening condition because, if unsuccessful, it can lead to intraoperative mortality. [58] Several authors have studied and defined difficult separation from CPB. These definitions are summarized in Table 1. [10;17;19;51;59-73]

Butterworth *et al.* [64] defined difficult weaning from CPB as postoperative hemodynamic instability requiring the use of positive inotropic support such as infusions of dobutamine, epinephrine, or amrinone. Dopamine was considered a positive inotropic drug only if it was infused at rates of 5 μg/kg/min or greater. Patients received inotropic drugs based on the observation of reduced cardiac contractility during weaning from CPB, by measurement of a reduced cardiac index (< 2.2 liters/min/m^2), or both. The right ventricle (RV) was directly inspected in the surgical field. The left ventricle (LV) was evaluated using TEE. Duration of drug use was not mentioned and TEE-related definition of RV or LV dysfunction was not identified. Surgenor *et al.* [74] defined heart failure after cardiac surgery as hypotension or low cardiac index requiring return under CPB, inotropic support or requirement for an IABP. Muller *et al.* [69] defined hemodynamic instability after cardiac surgery as ventricular dysfunction requiring the use of vasoactive agents based on direct visual inspection of the heart or through TEE examination or a cardiac index < 2 liters/min/m^2. The term post-bypass inotropic support has been used as a synonym of difficult separation from CPB and defined as the use of dopamine, dobutamine or epinephrine for at least 12 hours in the intensive care unit. [17;58] The use of dopamine

from 0.5-3.0 µg/kg/min to increase urine output was not considered in the definition of inotropic support. [58] Finally, the term "low cardiac output syndrome" (LCOS) has been used in several studies [75-77] to describe the consequence of difficult separation from CPB. The term LCOS also covers the period in the intensive care unit. It is defined as a postoperative condition: 1) requiring an IABP to be weaned from CPB or in the intensive care unit because of hemodynamic compromise, or 2) requiring inotropic medication (dopamine, dobutamine, milrinone, or epinephrine) to maintain the systolic blood pressure at 90 mmHg and the cardiac output at 2.2 L/min/m² for 30 minutes in the intensive care unit after correction of all of the electrolyte and blood gas abnormalities and after adjusting the preload to its optimal value. The dosage of vasoactive drugs is not mentioned. The term LOF for low output failure has also been used to describe the need for one of the following: an IABP, return to CPB after initial separation inotropes at 48 hours postoperatively. [78]

To summarize, in several of these studies, investigators have used variables such as 1) arterial pressure, 2) cardiac index, 3) filling pressures, 4) TEE findings, 5) amount and duration of vasoactive drugs, 6) subjective intraoperative assessment of reduced RV and LV contractility, 7) the need to return on CPB and 8) the use of mechanical devices to wean from CPB in their definition of difficult separation from CPB. There is also some overlapping in terms of the timing understood when using the phrase difficult separation from CPB. Some consider it to be an intraoperative event only, others a postoperative one, while other investigators include both periods in their definition (Table 1). In the setting of cardiac surgery and in this thesis, we define difficult separation from CPB as the process that may take place between the beginning of the weaning process of CPB and the moment the patient leaves the operating room.

Each of these elements requires consideration and should be carefully analyzed.

Table 1 Various definitions of difficult separation from CPB proposed in the literature

Author and references	Year of publication	Number of patients	Type of study	Population	Difficult separation from cardiopulmonary bypass (CPB) definitions
Boldt J, *et al.* [59]	1990	30	Prospective, open-labeled study.	Elective cardiac surgery patients. CABG only. Fractional area change (FAC) < 50%.	Weaning from CPB not possible without pharmacological support.
Hardy JF, *et al.* [60]	1993	19	Prospective, open-labeled, phase IV study.	Elective cardiac surgery patients.	Diastolic pulmonary artery pressure (DPAP) > 15 mmHg or CVP > 15 mmHg.
Butterworth JF, *et al.* [62]	1993	39	Prospective, randomized, double-blind study.	33 elective CABG patients, 6 valve surgery patients.	CI < 2.2 L/min/m^2.
De Hert SG, *et al.* [63]	1995	20	Prospective, randomized, double-blind study.	Elective cardiac surgery patients. CABG only.	CI < 2 L/min/m^2.
Butterworth JF, *et al.* [64]	1998	149	Ancillary analysis of a prospective, randomized, double-blind study.	Elective cardiac valve surgery patients.	Observation of reduced cardiac contractility during weaning, and/or CI < 2.2 L/min/m^2.
Kikura M, *et al.* [65]	1998	28	Prospective study, non-randomized nor blinded.	CABG and valve surgery patients.	CI < 2.2 L/min/m^2 despite NTG and inotropes infusions.
Yamada T, *et al.* [66]	2000	48	Prospective, randomized, double-blind study.	Elective cardiac surgery patients. CABG only.	CI < 2.5 L/min/m^2, SAP < 90 mmHg.

Author and references	Year of publication	Number of patients	Type of study	Population	Difficult separation from cardiopulmonary bypass (CPB) definitions
Suematsu Y, *et al.* [67]	2000	167	Retrospective analysis.	Elective cardiac surgery patients requiring CPB.	Intraoperative need for epinephrine and/or norepinephrine exceeding 0.2 ug/kg/min.
Bernard F, *et al.* [17]	2001	66	Prospective observational cohort study.	52 elective CABG alone, 14 combined procedures, valvular surgeries and re-operations.	SAP < 80 mmHg, DPAP > 15 mmHg during weaning from CPB, reinstitution of CPB or an IABP. Presence of significant vasopressor and/or inotropic support.
Van der Maaten JM, *et al.* [68]	2001	34	Prospective, non-randomized clinical study.	Elective cardiac surgery patients. CABG only.	CI < 2.4 L/min/m^2 and/or MAP < 60 mmHg.
Muller M, *et al.* [69]	2002	1471	Retrospective analysis.	Elective cardiac surgery patients, including CABG, valve and combined procedures.	Observation of reduced cardiac contractility during or after weaning (either by direct observation of the right ventricle or with TEE) and/or CI < 2.0 L/min/m^2.
Groban L, *et al.* [70]	2002	381	Post-hoc analysis of a randomized, masked clinical trial of insulin therapy.	Elective cardiac surgery patients. CABG only.	Inotropic, vasoactive and mechanical support (IABP, if needed) initiated if CI < 2.2 L/min/m^2, DPAP > 20 mmHg and/or SAP < 90 mmHg.

Author and references	Year of publication	Number of patients	Type of study	Population	Difficult separation from cardiopulmonary bypass (CPB) definitions
Wagner F, *et al.* [71]	2003	40	Prospective, randomized, double-blind study.	Elective cardiac surgery patients. CABG only. FAC < 35% preoperatively.	Moderate to high dose inotropic and/or vasopressor therapy, or the need of a mechanical support (IABP).
Tsukui H, *et al.* [72]	2004	151	Retrospective analysis.	Elective cardiac surgery patients including ischemic heart disease, valvular and congenital pathologies, along with miscellaneous procedures.	Epinephrine, norepinephrine, dopamine, dobutamine and milrinone were used if hemodynamic instability during weaning from CPB. IABP was installed if instability persisted despite medical treatment.
McKinlay KH, *et al.* [73]	2004	1009	Retrospective analysis.	Elective cardiac surgery patients. CABG and complex procedures.	Inotropic support in the form of dopamine (> 5 ug/kg/min) or any dose of epinephrine, norepinephrine, dobutamine or milrinone, along with IABP *vs*. hypotension, low cardiac output and inability to separate from bypass.

Author and references	Year of publication	Number of patients	Type of study	Population	Difficult separation from cardiopulmonary bypass (CPB) definitions
Surgenor SD *et al.* [78]	2006	8004	Prospective analysis	CABG	Low output failure: the need for one of the following: an IABP, return to CPB after initial separation or ≥ 2 inotropes at 48 hours postoperatively
Robitaille A, *et al.* [10]	2006	1498	Retrospective analysis.	Elective cardiac surgery patients, all types combined (CABG, valve, complex and miscellaneous procedures).	SAP < 80 mmHg, DPAP or wedge pressure > 15 mmHg during weaning from CPB, reinstitution of CPB or an IABP. Presence of significant vasopressor and/or inotropic support.

CABG, coronary artery bypass graft; CI, cardiac index; CPB, cardiopulmonary bypass; DPAP, diastolic pulmonary artery pressure; FAC, fractional area change; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; NTG, nitroglycerin; SAP, systolic arterial pressure; TEE, transesophageal echocardiography.

The first element of the definition is the systolic arterial pressure. Systolic pressure is routinely used and monitored in the operating room and the intensive care unit. It is used as an index of organ perfusion pressure and, therefore, tissue perfusion pressure. However the site of measurement of this parameter is very important. Systolic arterial pressure, when reduced in the hemodynamically unstable patient, has to be confirmed by central measurement, aortic or femoral. [79;80] This is a very important point and illustrated in Figure 2.

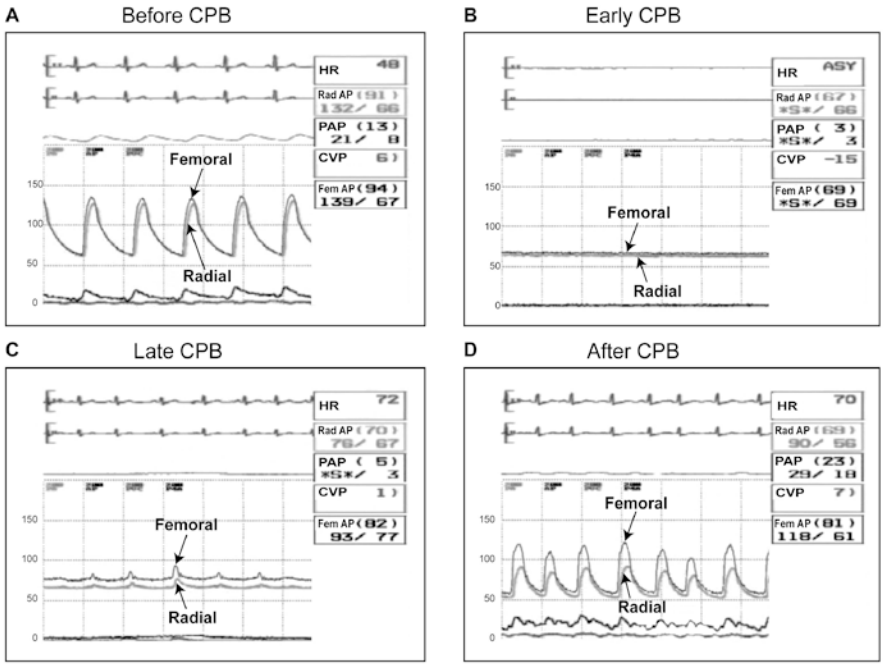

Figure 2 Radial to femoral artery pressure gradient during cardiac surgery

(A) Before cardiopulmonary bypass (CPB) a normal gradient between the radial (Rad) and femoral (Fem) artery was observed. (B) During the early part of CPB, no abnormality in gradient was observed. (C) The gradient appears during the later part of CPB. (D) After CPB, the systolic and mean femoral artery pressures were 118 mmHg and 81 mmHg, respectively. The systolic and mean radial artery pressures were 90 mmHg and 69 mmHg, respectively. (HR, heart rate; AP, arterial pressure; PAP, pulmonary artery pressure; CVP, central venous pressure) (With permission of Denault *et al.* [80]).

The appearance of a pressure gradient between the radial and femoral arteries can be commonly observed both in the cardiac operating room and in the intensive care unit in

patients who are thought to be hemodynamically unstable. Despite previous descriptions of this observation [79;81] in the literature, the mechanisms responsible for this gradient remain poorly understood [82] and its presence is not routinely recognized. The pressure gradient is normally < 20 mmHg between the aortic root and radial artery, being higher in the distal arteries. [83] In our clinical experience involving a large series of patients undergoing cardiac surgery, radial artery-aortic root systolic pressure gradients > 25 mmHg (the radial being lower than the aortic) occur in approximately 30-50% of cardiac procedures (Section 1.4.1). Maximum gradients are usually observed just after separation from CPB. In some patients, these gradients resolve towards the end of the procedure, but there is limited predictability regarding their dynamic variations. Transesophageal echocardiography and transthoracic echocardiography can also be used to detect an abnormal arterial gradient when clinically significant mitral regurgitation is present. [80] Early recognition of an abnormally wide aortic-radial arterial pressure gradient is therefore the first and most important step in excluding intraoperative hemodynamic instability as a cause of persistent hypotension in cardiac surgery.

The second element of the definition is cardiac filling pressure such as central venous pressure, diastolic pulmonary artery pressure and pulmonary capillary wedge pressure. As difficult separation from CPB represents cardiac dysfunction (either systolic, diastolic or both), filling pressures will be elevated in the presence of reduced systemic pressure. Elevated filling pressures are usually defined as either diastolic pulmonary artery pressure or pulmonary capillary wedge pressure >15 mmHg [60] or 20 mmHg. [70] This value is somehow arbitrary because it can depend on several factors, the most common being diastolic function or ventricular compliance. Ventricular compliance is unique to each surgical patient and is almost invariably altered after cardiac surgery. [39] Alteration in ventricular compliance after cardiac surgery has been described using echocardiography since the early 1990s. [84-92] If ventricular compliance is reduced after cardiac surgery, ventricular filling pressures will increase in order to maintain an appropriate preload and cardiac output. This observation explains why Reichert *et al.* [93] defined post-cardiac surgery hypovolemia as a pulmonary capillary wedge pressure value less than the

preoperative wedge pressure +10 mmHg. The "+ 10 mmHg" is a correcting factor based on the experience and observations of the authors, who noted that higher filling pressures were required after CPB in order to maintain an adequate preload and consequently an adequate cardiac output. Several of the studies pertaining to filling abnormalities or diastolic dysfunction after CPB examined a single echocardiographic parameter often limited to the left ventricle, [68;88;90;92;94-98] as opposed to biventricular systolic and diastolic evaluation. [40;43] This limitation could result in a misinterpretation of the actual change in cardiac function. This will be discussed in section 1.4.2.

The third element in the definition of difficult separation from CPB is the pharmacological intervention. The dosage and amount of vasoactive agents required for weaning from CPB needs to be quantified. The pharmacological approach on the use of vasoactive medication differs significantly from center to center, even in the same country. [99] At the MHI, significant vasopressive and/or inotropic support is defined by the use of norepinephrine > 0.06 μg/kg/min, epinephrine > 0.06 μg//kg/min, dobutamine > 2 μg/kg/min or the use of milrinone. [52] Returning on CPB can be secondary to hemodynamic or mechanical complications and is a severity criterion. The use of an IABP and VAD to wean from CPB implies a severe mechanical problem most likely related to the patient's underlying condition. Finally, in order to standardize the vasoactive management during CPB (Appendix 2) and the weaning process, (Appendix 3) we developed algorithms to be applied in studies dealing with separation from CPB. [50;52;56]

In summary, the definition used to describe difficult separation from CPB varies significantly among investigators. Cleary defined hemodynamic variables, particularly the site of measurement of the arterial pressure, seem essential in detecting the true presence of difficult separation from CPB. Filling pressure indices have to be evaluated in relation with baseline measurements, as each patient can serve as his own control. A systematic echocardiographic approach would be useful to identify the mechanism at work in difficult separation from CPB. The use of vasoactive agents should follow a logical algorithm based on hemodynamic and echocardiographic information. Finally, a classification could be used as it appears that different grades of severity in separation from CPB can be present. The

worst form of difficult separation from CPB would be the one associated with the requirement for mechanical devices.

1.2 Predictors of difficult separation from CPB

Patients at risk of complications and death after cardiac surgery can be identified through the use of scores developed in several large-scale studies in which multivariate analysis identified variables associated with an increased risk of morbidity and mortality. Some of these scores include for instance the MHI score, [8] the Parsonnet score, [100] the EuroSCORE, [101] the Cardiac Anesthesia Risk Evaluation (CARE) score [102] and the Society of Thoracic Surgeons (STS) score. [103] These scores are useful because they can provide an estimation of mortality and morbidity. There is so far no score that enables the identification of patients at risk of difficult separation from CPB. It is likely that similar variables associated with an increased risk of morbidity and mortality will be associated with difficult separation from CPB. These variables can be classified as demographic, surgical, biochemical, hemodynamic and echocardiographic.

1.2.1 Demographic and surgical variables

Several demographic variables in relation with the type of surgery have been identified as important predictors of difficult weaning from CPB.

1.2.1.1 Coronary revascularization

In patients undergoing coronary revascularization, Surgenor *et al.* [74] identified reoperation, urgent surgery, peripheral vascular disease, diabetes and renal failure requiring dialysis as demographic and surgical variables associated with an increased mortality from heart failure. Other predictors of difficult separation from CPB in coronary bypass surgery are older age and female gender, [58] previous myocardial infarction and chronic pulmonary obstructive disease. [69] Rao *et al.* [75] retrospectively analyzed the risk of LCOS from a database of 4558 patients operated for coronary revascularization in Toronto between 1990 and 1993. The independent predictors of LCOS were determined by stepwise

logistic regression analysis. The prevalence of LCOS was 9.1%. The independent predictors were (odds ratio in parenthesis) left ventricular ejection fraction < 20% (5.7), repeat operation (4.4), emergency operation (3.7), female gender (2.5), diabetes (1.6), age > 70 year-old (1.5), left main coronary artery stenosis (1.4), recent myocardial infarction (1.4) and triple-vessel disease (1.3).

1.2.1.2 Valvular surgery

Valvular surgery is typically longer and more complex than coronary revascularization. It is not surprising that it is associated with an increased risk of postoperative inotropic requirement. In a study involving 1009 patients undergoing cardiac surgery, McKinlay *et al.* [73] identified coronary revascularization in association with mitral valve repair or replacement as an independent risk factor for postoperative inotropic support. Maganti *et al.* [77] retrospectively analyzed the risk of LCOS from a database of 2255 patients operated for isolated aortic valve replacement in Toronto between 1990 and 2003. The independent predictors were determined by stepwise logistic regression analysis. The prevalence of LCOS was 3.9%. The independent predictors were (odds ratio in parenthesis): renal failure (5.0), earlier year of operation (4.4), left ventricular ejection fraction < 40% (3.6), shock (3.2), female gender (2.8), and increasing age (1.02). Overall operative mortality was 2.9%. An additional factor associated with the requirement for inotropic drugs after valvular surgery is the anesthesiologist's preference for the use of vasoactive medications. [64] In a study involving aortic valve replacement in combination with revascularization, Ahmed *et al.* [104] identified preoperative renal disease, elevated left ventricular end-diastolic pressure (≥ 20 mmHg), reduced left ventricular ejection fraction (≤ 40%) and low cardiac index (≤ 2.5 L/m/m? as predictors of postoperative inotropic requirements.

1.2.1.3 Duration and utilization of cardiopulmonary bypass

Both the duration of CPB and cross-clamping are surgical variables that predict hemodynamic complications in several studies. [10;17;58;69;70;72;73;105;106] We have also documented that hemodynamic complications in patients undergoing coronary

revascularization were observed in 53% of patients in whom CPB was used, as opposed to 14% of patients undergoing surgery with off-pump bypass. [10] The use of CPB was indeed an independent predictor of hemodynamic complications ($p < 0.0001$), and this finding was also observed by other authors. [58;72;107] As suggested by Butterworth *et al.*, [64] a longer CPB time can be associated with technical or mechanical difficulties or associated procedures, including valvular surgery and coronary revascularization. As the CPB is longer, the patient and the myocardium are exposed to the effect of the inflammatory response with a potentially greater need for blood products. The latter is not only associated with LOF but also with increased mortality. [72;78]

1.2.2 Biochemical variables

Among the biochemical variables, our group observed that an elevated veno-arterial PCO_2 gradient before the cardiac surgical procedure was an independant variable associated with an increased risk of difficult separation from CPB. [105] Elevated veno-arterial PCO_2 gradient is a marker of ischemia, [108] in the same manner as lactate. Not surprisingly, the intraoperative lactate level obtained during CPB has also been shown to correlate with difficult separation from CPB and mortality (Figure 3). [9]

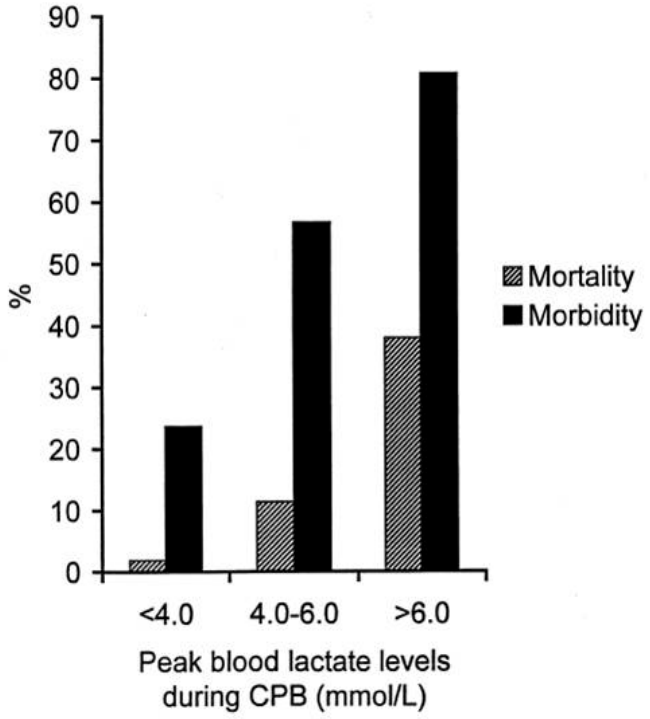

Figure 3 Mortality and morbidity in relation with lactate level during CPB

Positive correlation in 1376 cardiac surgical patients between peak blood lactate levels during cardiopulmonary bypass (CPB) and the rate of postoperative morbidity and mortality ($p < 0.001$). (With permission of Demers *et al.* [9])

These two studies, conducted at the MHI, tend to support that measures of reduced oxygen transport or hypoperfusion before or during CPB could either be markers or determinants of hemodynamic instability and mortality after cardiac surgery. In that regard, Rao *et al.* [76] documented that, in 623 patients undergoing coronary revascularization, the only predictor of LCOS was the myocardial lactate release after 5 minutes of cross-clamping. Age and reduced left ventricular ejection fraction were the only two predictors of this metabolic abnormality after CPB. The rise in creatinine kinase (CK) was not a predictor of LCOS. Other authors have also confirmed that reduced myocardial pH [109] (Figure 4) or increased myocardial lactate measured during CPB [110] have been shown to be predictors of increased postoperative inotropic support and mortality. This abnormal lactate release could imply delayed recovery of normal aerobic myocardial metabolism. As

the myocardial metabolism is altered, myocardial function will be abnormal. Therefore, the risk of difficult separation from CPB is likely to correlate with indices of global or regional myocardial tissue hypoperfusion. In that regard, a recent paper by Turer *et al.* [111] explored the new field of metabolomics in cardiac surgery. The measurements of several metabolites produced from ischemia/reperfusion during retrograde cardioplegia were analyzed. An association between the duration of inotropic support and myocardial lactate was observed. This study suggests that patients with left ventricular dysfunction have limited myocardial metabolic reserve and flexibility after global ischemia/reperfusion stress.

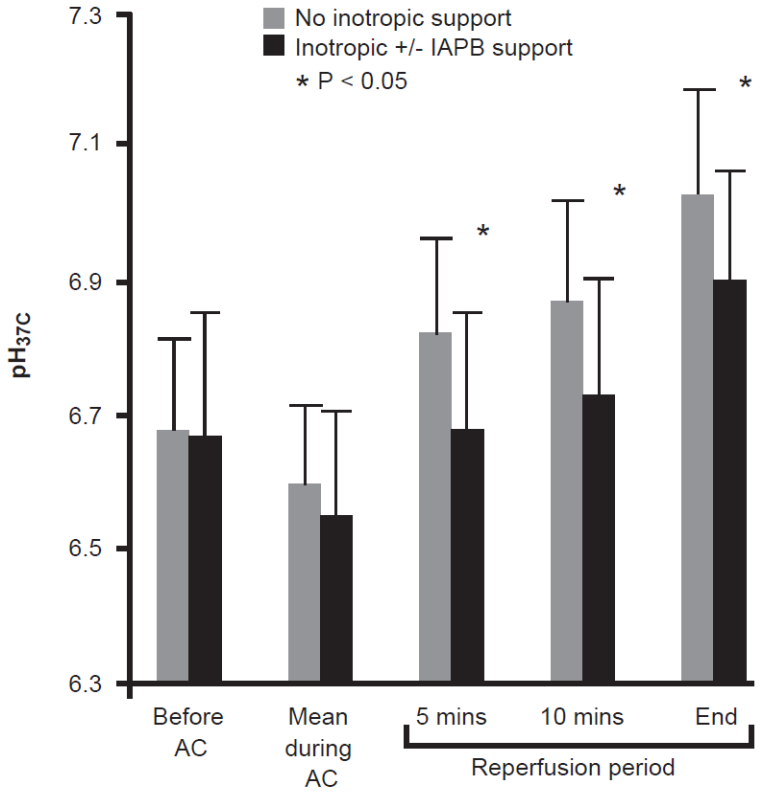

Figure 4 Intramyocardial acidosis and inotropic requirement

Comparison of myocardial tissue pH_{37C} between patients who needed inotropic support versus those who did not at 5 time points during surgery: Before aortic occlusion (AC), mean during AC, at 5 minutes of reperfusion, at 10 minutes of reperfusion, and at the end of reperfusion. (IABP, intra-aortic balloon pump).(Adapted from Kumbhani *et al.* [109])

1.2.3 Hemodynamic and echocardiographic variables

Among the hemodynamic data predicting post-CPB inotropic support and mortality after cardiac surgery, left ventricular systolic dysfunction is frequently found as the most important and frequently reported variable. [58;64;69;70;73;75;77;78;104;106;109] Left ventricular dysfunction is either defined by a history of congestive heart failure, by a cardiac variable such as reduced left ventricular ejection fraction (LVEF) or ventricular enlargement, or as its consequence on daily living, such as the New York Heart Association (NYHA) classification. All these definitions have been associated with postoperative inotropic requirement. [10;58;64;69;78] Left ventricular dysfunction will be associated with echocardiographic evidence of abnormal regional or global wall motion and can also be associated with an elevated left ventricular end-diastolic pressure (LVEDP). This parameter has also been reported as an independent predictor of inotropic requirement [58;104] and mortality. [11]

Right ventricular systolic and diastolic dysfunction may also be a predictor of mortality and morbidity. Maslow *et al.* [112] studied patients with reduced left ventricular systolic function (LVEF $\leq$ 25%) before coronary revascularization. Those without right ventricular dysfunction prior to surgery had less inotropic requirement after revascularization and a mortality rate of 9.7%. In contrast, patients with reduced LVEF associated with reduced right ventricular dysfunction experienced more frequent difficult separation from CPB and a mortality rate of 100% within 18 months. This study supports the hypothesis that preoperative right ventricular systolic dysfunction is a predictor of difficult weaning from CPB and mortality before cardiac surgery. However, right ventricular diastolic dysfunction may also be an important criterion to be evaluated. In a pilot study of 121 patients undergoing cardiac surgery, Carricart *et al.* [34] observed that preoperative abnormal hepatic venous flow, as a marker of right ventricular diastolic dysfunction, [113;114] was associated with difficult weaning from CPB. In a subset of patients undergoing valvular surgery only, abnormal hepatic venous flow before surgery was associated with a higher Parsonnet score, more atrial fibrillation, pacemaker

requirement, mitral valve replacement, reoperation, a lower systemic mean arterial (MAP) to mean pulmonary artery pressure (MPAP) ratio, a higher wall motion score index, a higher incidence of abnormal right ventricular systolic function and more frequent use of intravenous milrinone. However, abnormal hepatic venous flow before cardiac surgery was not found to be an independent predictor of difficult separation from CPB and worse outcome. In that study, pulmonary hypertension defined using the MAP/MPAP ratio was the best predictor of hemodynamic complications.

Pulmonary hypertension is another hemodynamic variable associated with an increased risk of difficult weaning from CPB, morbidity and mortality in cardiac surgery. [8;100;115-117] However, few studies have reported an association between pulmonary hypertension and difficult weaning from CPB. [10;34;46] This will be discussed in more detail in Chapter 6.

1.2.4 Patient-prosthesis mismatch

Aortic patient-prosthesis mismatch (PPM) is the result of a prosthesis too small for the patient's body surface area (BSA). [118-125] The selection of the type and size of prosthetic valve is also very important, because it has been shown that, if the effective orifice area (EOA) of the valve is too small in relation to body size, then occurs a so-called PPM, which increases intraoperative and long-term mortality (Figure 5). [118-125]

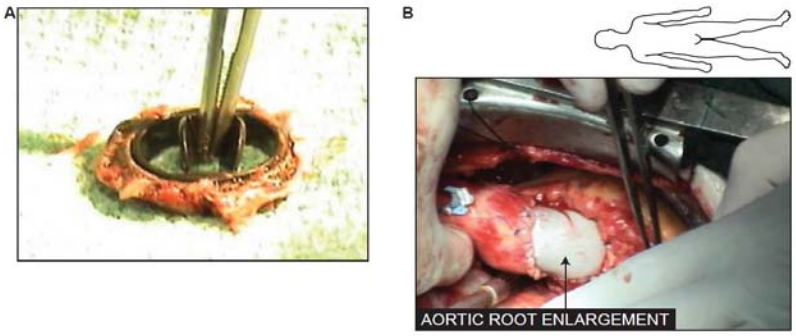

Figure 5 Patient–prosthesis mismatch

A 71-year-old man with a body surface area of 1.89 m² was re-operated for symptoms of severe aortic valve stenosis (severe dyspnea, NYHA class IV and pulmonary hypertension of 60/15 mmHg). He had aortic valve replacement (AVR) 4 years ago with a Carbomedics #19 mechanical bileaflet prosthesis (effective orifice area (EOA) = 1.06 cm²). The preoperative mean gradient was 41 mmHg. The intraoperative aspect of the prosthetic valve was completely normal. (B) Example of an aortic root enlargement procedure in a 69-year-old patient with a reduced aortic diameter requiring AVR. (Courtesy of Dr. Michel Carrier with permission of Denault *et al.* [12])

From various studies, PPM can be found in 19-70% of patients undergoing aortic valve replacement (AVR). [119-122] In a study including 1266 patients who underwent AVR at the Quebec Heart and Lung Institute (QHLI), the prevalence of moderate PPM defined as an index EOA (iEOA) $\leq$ 0.85 cm^2/m^2 was 38%, and that of severe PPM (iEOA $\leq$ 0.65 cm^2/m^2) was 2%. After adjusting for other risk factors, moderate and severe PPM were associated with a 2.0-fold (95% confidence interval: 1.1-3.7) and 12.6-fold (95% confidence interval: 4.3-37.0) increase in mortality, respectively. It is possible that the increased LVEDP and left ventricular afterload with associated reduced coronary flow reserve [126] with PPM may predispose to difficult separation from CPB. In a study of 156 patients undergoing AVR and followed-up for a median period of 3.5 years, Brown *et al.* [127] observed that postoperative events and survival after AVR were more related to the severity of LV diastolic function than PPM. Finally, the link between aortic PPM and difficult separation from CPB has not been described.

PPM of the mitral valve has recently been described [128] and defined as an iEOA ≤ 1.2 cm²/m². In a study which included 929 consecutive patients undergoing mitral valve replacement, severe PPM was associated with a 3-fold increase in postoperative mortality after adjustment for other risk factors. As mitral PPM will be associated with postoperative pulmonary hypertension, right ventricular failure and consequently difficult separation from CPB could result from this condition. The relation between mitral PPM and difficult separation from CPB has not been described.

1.2.5 Other factors involved in the risk of difficult separation from CPB

Other factors could predispose to difficult separation from CPB in cardiac surgery. For instance, aberrant positioning of the cardioplegia cannula could be associated with inadequate myocardial protection (Figure 6).

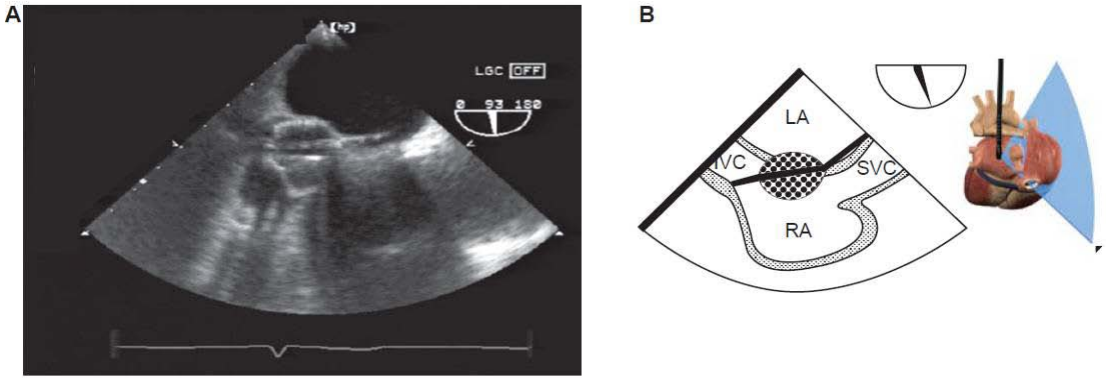

Figure 6 Retrograde cardioplegia cannula

(A, B) Bicaval view showing the retrograde cardioplegia cannula positioned toward the atrial septum through the patent foramen ovale. (IVC, inferior vena cava; LA, left atrium; RA, right atrium; SVC, superior vena cava). (Photo courtesy of Dr. Baqir Qizilbash with permission of Denault *et al.* [13]).

Coronary embolization from air or residual debris that can occur after CPB (Figure 7) could also be associated with difficult weaning from CPB.

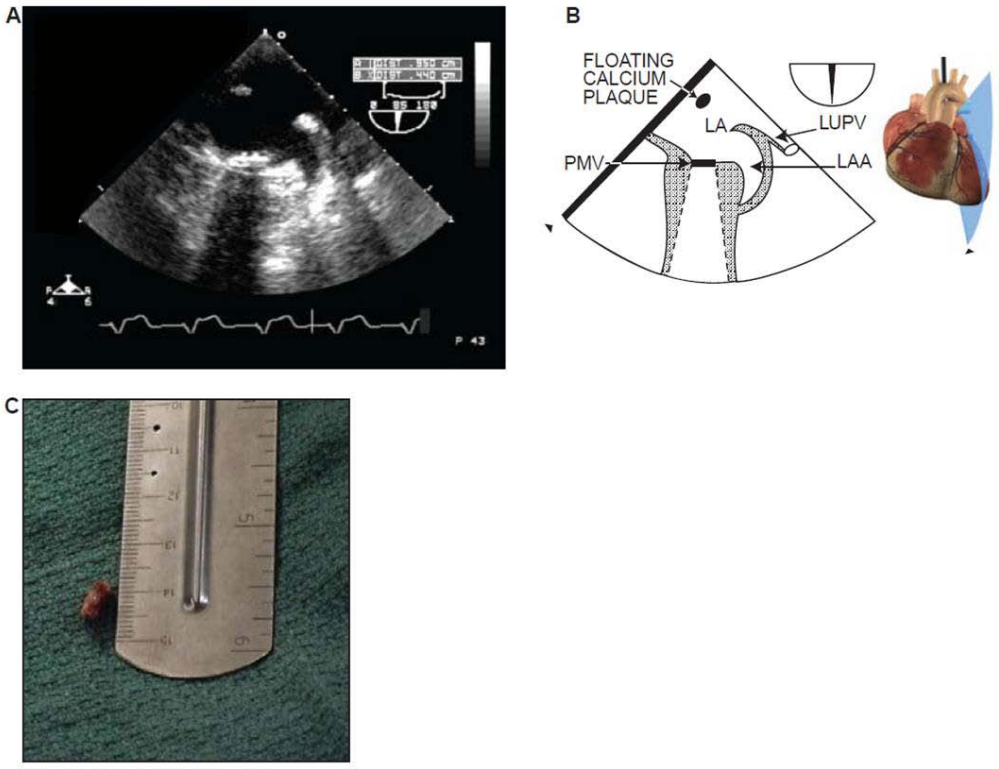

Figure 7 Calcium emboli in valvular surgery

A 70-year-old man who underwent coronary revascularization and combined aortic and mitral valve replacement. (A,B) As weaning from cardiopulmonary bypass (CPB) proceeded, floating material was detected in the left atrium (LA) from this mid-esophageal two-chamber view. The attending surgeon went back immediately to full CPB. (C) This material was a 4 x 1 mm floating calcium plaque which was removed. The patient had no postoperative neurological complications (LAA, left atrial appendage; LUPV, left upper pulmonary vein; PMV, prosthetic mitral valve) (With permission of Denault *et al.* [13]).

Additionally, technical problems such as a residual paravalvular leak or dysfunctional prosthesis (Figure 8) could also contribute to difficult weaning from CPB.

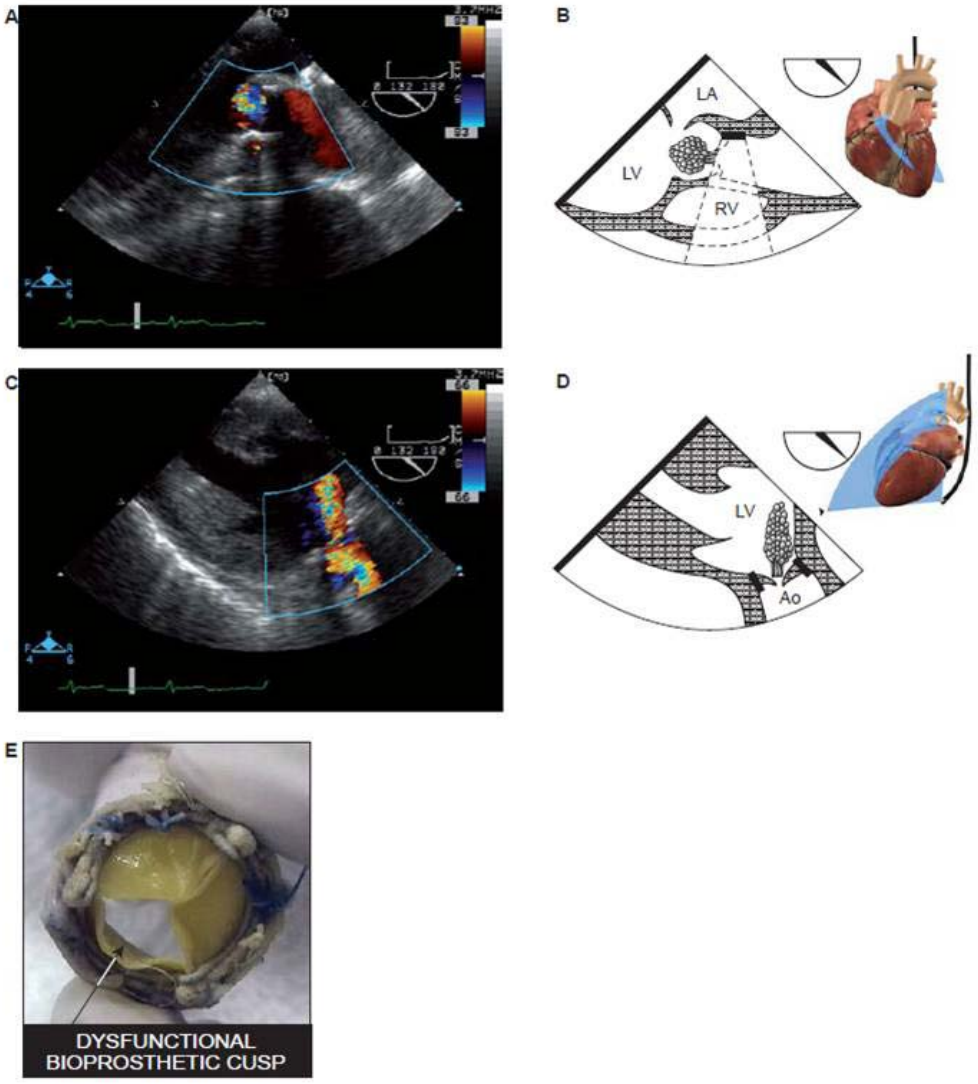

Figure 8 Dysfunctional AoV bioprosthesis after AVR

A 60-year-old man was reoperated after valve replacement (AVR) for periprosthetic aortic regurgitation (AR). (A–D) After the procedure, abnormal significant AR is still visible on the mid-esophageal long-axis and deep transgastric views. The new bioprosthesis was removed and replaced by another one. (E) Upon examination of the defective bioprosthesis, abnormal motion of one of the leaflets was noted (Ao, aorta; AoV, aortic valve; LA, left atrium; LV, left ventricle; RV, right ventricle). (Photo E courtesy of Dr. Tack Ki Leung, with permission of Denault *et al.* [13]).

All these conditions can be diagnosed and prevented with TEE. Finally, the reperfusion syndrome could also be associated with unexpected pulmonary hypertension upon weaning from CPB. This will be discussed in Chapter 6.

To summarize, there are several demographic, surgical, biochemical, hemodynamic and echocardiographic preoperative variables that can be associated with hemodynamic instability and difficult weaning from CPB after cardiac surgery. They are important to document if a new therapy is introduced, so that similar groups can be compared. Few of the demographic and surgical variables can be modified before planning cardiac surgery. The inclusion of left and right ventricular systolic and diastolic dysfunction, PPM and pulmonary hypertension as predictors of difficult separation from CPB is new and interesting because these variables could possibly be modified before and during cardiac surgery. Furthermore, the role of TEE is to monitor and to diagnose conditions that could result in difficult separation from CPB and could be modified through a medical or surgical approach. Table 2 and Table 3 summarize studies in which the primary endpoint was hemodynamic instability or difficult weaning from CPB after cardiac surgery.

Table 2 Studies on difficult separation from CPB and postoperative inotropes

Author	Year	N	Death	Population	Single vs multicentered	Timing of inotropic administration	Method	Primary endpoint	Prevalence
Royster *et al.* [58]	1991	128	5 (3.9)	CABG	S	OR & ICU	Retrospective	Inotropic support	58 (45%)
Davila-Roman *et al.* [4]	1995	75	34 (44%)	LCOS	S	> 48 hours after OR	Retrospective	LCOS	NA
Rao *et al.* [75]	1996	4558	109 (2.4)	All	S	ICU	Retrospective	LCOS	412 (9.1%)
Butterworth *et al.* [64]	1998	149	9 (6%)	Valve	S	OR & ICU	RCT post hoc	Inotropic support	78 (52%)
Groban *et al.* [70]	2002	381	7 (1.8%)	CABG	S	OR & ICU	RCT post hoc	Inotropic support	142 (37.2%)
Muller *et al.* [69]	2002	1471	33 (2.2%)	All	S	OR & ICU	Retrospective	Inotropic support	476 (32,4%)
McKinlay *et al.* [73]	2004	1009	NA	All	S	OR	Retrospective	Inotropic support	50 (52%)
Tsukui *et al.* [72]	2004	151	3 (1.9)	All	S	OR & ICU	Prospective	Inotropic support	71 (47%)
Kumbhani *et al.* [109]	2005	247	9 (3.6)	All	S	OR	Retrospective	Inotropic support	50 (20.2%)
Heringlake *et al.* [110]	2005	20	NA	CABG	S	OR	Microdialysis	Inotropic support	6 (30%)
Maganti *et al.* [77]	2005	2255	66 (2.9%)	AVR	S	OR & ICU	Retrospective	LCOS	87 (3.9%)
Robitaille *et al.* [10]	2006	1439	50 (3.5%)	All	S	OR & ICU	Retrospective	Inotropic support	876 (61%)
Surgenor *et al.* [78]	2006	8004	NA	CABG	M	OR & ICU	Prospective	LOF	644 (8.1%)
Weis *et al.* [106]	2006	1558	34 (2.2%)	All	S	ICU	Prospective	Vasopressor dependence	425 (27%)
Ahmed *et al.* [104]	2009	97	10 (10.3)	CABG-AVR	S	OR	Retrospective	Inotropic support	50 (52%)

AVR, aortic valve replacement; CABG, coronary revascularization; ICU, intensive care unit; LCOS, low cardiac output state; LOF, low output failure; M, multicenter study; N, number; NA, not available; OR, operating room; RCT, randomized controlled trial; S. single center study;

Table 3 Risk factor for difficult separation from CPB and postoperative inotropes

Author	Age	Gender	CHF	Renal disease	CAD	Re-operation	Urgent/ emergency	LVEDP	LVEF	CPB or CX duration	Transfusions	Other factors
Royster *et al.* [58]	X	X	Cardiac enlargment					X	X	X		
Davila-Roman *et al.* [4]					Recent MI							
Rao *et al.* [75]	X	X			Previous MI, left main	X	X		X			Left main CAD and triple Vx, diabetes
Butterworth *et al.* [64]	X		CHF						X			Anesthesiologist
Groban *et al.* [70]	X	X			Hx angina				X	X		
Muller *et al.* [69]	X		CHF and NYHA > 2		No of MI					X		COPD, CABG
McKinlay *et al.* [73]						X			X	X		WMSI by TEE, CABG + MVR, MR 3-4/4
Tsukui *et al.* [72]										X	X	Use of IABP
Kumbhani *et al.* [109]									X			pH_{37c} at 5 or 10 min of reperfusion
Heringlake *et al.* [110]												Myocardial lactate
Maganti *et al.* [77]	X	X		X					X			Year of operation, pre-op shock
Robitaille *et al.* [10]	X	X	CHF							X		Pre-op neurological disease, IABP, MAP/MPAP
Surgenor *et al.* [78]		X	CHF	X		Prior CABG	X		X		X	Reduced hematocrit, WBC ≥ 12
Weis *et al.* [106]									X	X		Interleukin 6 concentration
Ahmed *et al.* [104]				X				X	X			Cardiac index

CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CX, cross-clamping; Hx, history; IABP; intra-aortic balloon pump; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MI, myocardial infarction; MPAP, mean pulmonary artery pressure; MR, mitral regurgitation; MVR, mitral valve replacement or repair; No, number; NYHA, New York Heart Association; TEE, transesophageal echocardiography; Vx, vessels; WBC, white blood cell; WMSI, wall motion score index

1.3 The significance and consequence of difficult separation from CPB

Why is difficult separation from CPB a potentially significant complication in cardiac surgery? If the CPB weaning process requires the presence of significant vasoactive support, this may lead to insufficient oxygen transport and hypoperfusion. In fact, hemodynamic instability after cardiac surgery is associated with an increased risk of morbidity and mortality. In the study of Surgenor *et al.* [74] in 8641 patients undergoing coronary revascularization, 64.8% of deaths were attributed to post-CPB heart failure. The mortality is significantly higher if the hemodynamic instability is secondary to severe right ventricular systolic dysfunction, a known factor for negative outcome after cardiac surgery, [3;4;112] with mortality ranging from 44% to 86%. [3;4] Mortality is also associated with an increase in the use of vasoactive drugs. Muller *et al.* [69] studied 1471 patients undergoing various types of cardiac surgery and found that 81.2% of the non-survivors received inotropes compared to 18.2% of survivors ($p < 0.01$). In the 2 studies from Toronto that included 4558 patients undergoing coronary revascularization and 2255 isolated AVR patients, [75;77] the operative mortality for coronary revascularization was 19 times higher (16.9% *vs.* 0.9%; $p = 0.001$) in patients undergoing coronary revascularization and 25 times higher in patients with AVR (38% *vs.* 1.5%; $p < 0.001$) who experienced LCOS. Therefore, if difficult separation from CPB results from an imbalance between circulatory reserve and demand, continuous monitoring of this imbalance could be used to detect and potentially evaluate the effect of any intervention. This tissue perfusion monitoring can be obtained using near-infrared spectroscopy (NIRS) and has been shown to be of prognostic value in septic shock. [129]

Near-infrared spectroscopy (NIRS) can be used to monitor local tissue perfusion during cardiac surgery [130] but has also been used as a monitor of tissue perfusion in various types of shock states. [129;131;132] Monitoring with NIRS provides a non-invasive measure of local tissue perfusion. It is particularly useful during non-pulsatile flow conditions such as CPB or cardiac arrest. In two recent randomized trials, cerebral oximetry monitoring has been associated with shorter recovery room and hospital stays following

non-cardiac surgery, [133] and with a decrease in major organ dysfunction and in intensive care unit length of stay after cardiac surgery, [134] thus providing the rationale for its use. Significant brain desaturation (Figure 9) can be observed in hemodynamically unstable patients or those experiencing difficult separation from CPB. Brain desaturation is a marker of the imbalance between oxygen transport and oxygen supply that occurs during hemodynamic instability or difficult separation from CPB. [135] Transient hypoperfusion following low flow state may cause injury to the gut mucosa, allowing bacterial translocation and endotoxemia. [136] In some patients, if this condition persists, it can further develop into shock and multiorgan failure. [137] This mechanism could explain the observed association between brain desaturation and multiorgan dysfunction. [134]

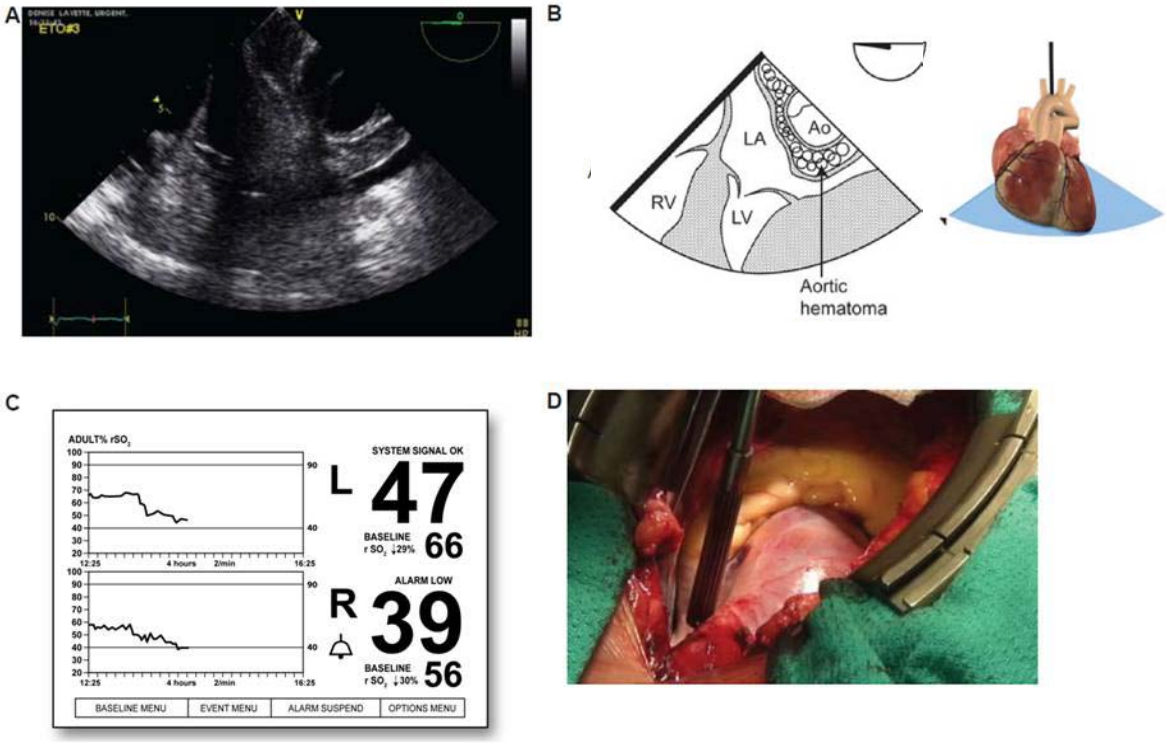

Figure 9 Hemodynamic instability and brain desaturation

(A,B) Mid-esophageal view showing an aortic hematoma compressing the left atrium (LA), creating an acute localized tamponade. (C) The onset of the hematoma was associated with hemodynamic instability and an abrupt reduction in the brain oximetry signal (arrow). (D) Intraoperative aspect of the aortic dissection (Ao, aorta; AoV, aortic valve; LV, left ventricle, RV, right ventricle)(With permission of Denault *et al.* [13]).

1.4 Research and development since the beginning of the PhD in 2006 at the MHI

Since 2006, several studies have been performed at the MHI regarding the definition, the predictors and the outcome of difficult separation from CPB. These are summarized below.

1.4.1 Studies on arterial pressure and separation from CPB

Su *et al.* performed a retrospective analysis of the MHI TEE database that included 129 consecutive patients undergoing cardiac surgery and monitored with both radial and femoral artery catheters. The maximal difference between the MAP from the femoral and the radial catheter was recorded. The authors identified the presence of a MAP gradient of 10 mmHg or more in 54% of these patients (presented at the CAS 2008 Meeting in Halifax). A small BSA was found to be the strongest independent predictor of this gradient (OR: 0.06; 95% CI: 0.01-0.37, $p = 0.003$). In order to confirm these findings, Fuda *et al.* performed a prospective study using the same definition; the authors observed a significant arterial gradient in 45% of 73 consecutive cardiac surgical patients (presented at the 2009 Cardiac Team Meeting in Tremblant). The same risk factor was found in addition to a small diameter of the radial artery (OR: 0.695; 95% CI: 0.57-0.847, $p < 0.0001$). These two studies highlight the importance of the site of measurement of the arterial pressure. Such pressure gradients typically manifest during CPB (Figure 2).

1.4.2 Studies on diastolic function and separation from CPB

In 49 patients undergoing coronary revascularization, Shi *et al.* [40] performed transthoracic echocardiography the day before surgery and repeated the examination 48 hours and 6 months later. The examination included the evaluation of both the left and right ventricular systolic and diastolic function. The results are summarized in Figure 10.

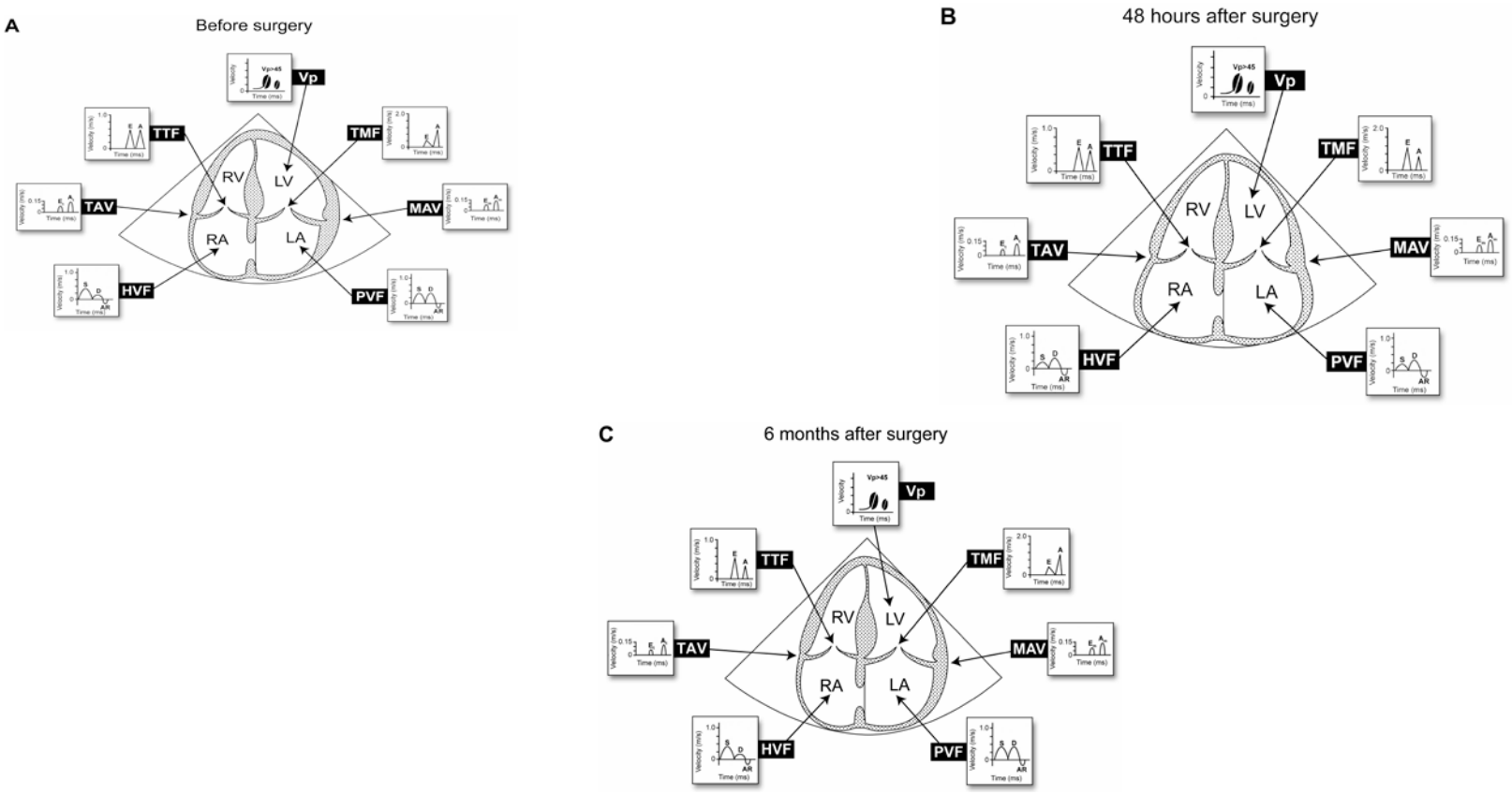

Figure 10 Biventricular cardiac dimensions and Doppler during CABG

Changes observed in biventricular cardiac dimensions and in Doppler profiles before coronary revascularization (**A**), at 48 hours (**B**) and 6 months (**C**) after coronary revascularization. At 48 hours, an increase in both the left and right atrial size is observed. This is associated with

deterioration in both the left and right ventricular diastolic parameters. At 6 months, no significant difference is seen compared to the preoperative echocardiographic parameters. (CABG, coronary artery bypass grafting; HVF: hepatic venous flow, MAV: mitral annular velocities, PVF: pulmonary venous flow, TMF: transmitral flow, TTF: transtricuspid flow, Vp: velocity of propagation) (With permission of Shi *et al.* [40]).

The prevalence of moderate and severe left ventricular diastolic dysfunction increased from the preoperative period to 48 hours after coronary revascularization from 8.2% to 53.7%, and from 2.0% to 9.7%, respectively ($p < 0.0001$, 48 hours *vs*. pre- for both). The patterns at 6 months were similar to those observed preoperatively. A similar evolution over time was found for right ventricular diastolic dysfunction. The same evaluation was done using TEE by Couture *et al.* [50] in 50 patients undergoing coronary revascularization (Table 4). Similar observations were made. In patients undergoing coronary revascularization, deterioration of left and right diastolic function was observed after CPB regardless of the use of intravenous milrinone. These observations have not been made in patients undergoing valvular surgery.

Table 4 Left and right ventricular diastolic function

Time	Score	Milrinone (*n* (%))	Placebo (*n* (%))	Group x time interaction *p* value	Group *p* value	Time *p* value
LVDD				0.2029	0.1989*	0.2834*
Pre-bolus	1	0 (0)	0 (0)			
	2	14 (58)	6 (25)			
	3	7 (29)	15 (63)			
	4	3 (13)	2 (8)			
	5	0 (0)	1 (4)			
Post-bolus	1	0 (0)	0 (0)			
	2	7 (33)	11 (46)			
	3	14 (67)	9 (37)			
	4	0 (0)	4 (17)			
	5	0 (0)	0 (0)			
Post-CPB	1	0 (0)	2 (9.5)			
	2	8 (33)	4 (19)			
	3	14 (58)	9 (43)			
	4	2 (8)	4 (19)			
	5	0 (0)	2 (9.5)			
RVDD						
Pre-bolus	1	1 (5)	0 (0)			
	2	18 (95)	17 (90)			
	3	0 (0)	2 (10)			
	4	0 (0)	0 (0)	-	0.0407**	-
	5	0 (0)	0 (0)			

Post-bolus	1	0 (0)	0 (0)			
	2	19 (91)	15 (75)			
	3	2 (9)	5 (25)	-	0.1827**	-
	4	0 (0)	0 (0)			
	5	0 (0)	0 (0)			
Post-CPB	1	0 (0)	0 (0)			
	2	6 (32)	10 (43.5)			
	3	10 (52)	10 (43.5)	-	0.4664**	-
	4	3 (16)	3 (13)			
	5	0 (0)	0 (0)			

* Overall *p* value in case of a non-significant group x time interaction;
** Generalized estimating equation (GEE) model including group as independent variable was performed at each time point because patients were not evenly distributed among the five-scale score, and the model including time, group and group*time did not converge. LVDD score: left ventricular diastolic dysfunction score; RVDD score: right ventricular diastolic dysfunction score (With permission of Couture *et al.* [50])

1.4.3 Studies on predictors of difficult separation from CPB

Hemodynamic instability after CPB will vary according to the type of procedure. In a study by Robitaille *et al.,* [10] hemodynamic complications after cardiac surgery were more common in patients undergoing valvular ($p < 0.0001$), complex surgeries ($p < 0.0001$) and repeat surgery ($p = 0.0005$).

1.4.4 Studies on the outcome of difficult separation from CPB

A study by Robitaille *et al.* [10] was performed to explore the role of the hemodynamic profile as a predictor of hemodynamic complications after cardiac surgery. A total of 1439 consecutive adult patients having undergone a cardiac surgical procedure in 1999 were included (96% of the population operated in 1999). Hemodynamic parameters were collected before the beginning of the procedure but after the induction of general anesthesia and were then analyzed to assess their ability to predict mortality and

hemodynamic complications, defined as a composite index including death, unexpected cardiac arrest, presence of vasoactive drugs for more than 24 hours postoperatively or the use of an IABP that was not inserted preoperatively. There were 50 deaths, 33 (66%) of which were secondary to hemodynamic complications. Patients with postoperative hemodynamic complications had more frequent difficult separation from CPB (84% *vs.* 55%, $p < 0.001$). Stepwise multiple logistic regression analysis showed that the preoperative use of an IABP (OR: 2.2, CI 1.2-3.9, $p = 0.101$) and difficult separation from CPB (OR, 3.5, CI 2.5-5.1, $p < 0.0001$) were independent predictors of hemodynamic complications. In the second study by Chagnon *et al.* [35] that included 243 patients operated between 2001 and 2004, we were able to reconfirm our findings: difficult separation from CPB was the most important factor related to the composite index of hemodynamic instability as previously defined (OR: 3.5, CI 2.5-5.1, $p < 0.0001$)(Table 5). In a third study exploring the role of LVEDP as a predictor of mortality in 3024 adult patients from 1996 to 2000, hemodynamic instability after cardiac surgery was found in 57% of patients who did not survive. [11] The two most common complications were difficult separation from CPB in 45% of patients and postoperative hemodynamic complications in 13% of patients. These three studies imply that difficult separation from CPB leading to postoperative hemodynamic instability is a significant contributing factor involved in 57-66% of patients who die after cardiac surgery. In addition, morbidity and mortality will increase if difficult separation from CPB is present, even if the duration of CPB is short.

Table 5 Univariate and multivariate analysis for hemodynamic complications

Variables	**Odd**	**95% CI**	***P* value**
Univariate Analysis			
Age	1.00	0.97-1.03	0.8481
Female vs. Male	1.35	0.70-2.59	0.3713
CPB time	1.02	1.01-1.02	<0.0001
Aortic cross-clamp time	1.01	1.01-1.02	0.0008
Vasopressor preoperatively	0.92	0.10-8.38	0.9373
IABP preoperatively	0.91	0.19-4.45	0.9103
DSB	5.86	2.60-13.25	<0.0001
CI	0.94	0.44-2.00	0.8657
MAP/MPAP	0.75	0.56-1.01	0.0615
LVEF <35% vs. ≥50%	2.05	0.82-5.13	0.1274
LVEF 35-50% vs. ≥50%	0.56	0.17-1.78	0.3223
LVWMSI	2.00	1.02-3.90	0.0453
LV diastolic function profile			
PN or RE vs. N or RA	1.81	0.81-4.03	0.1467
RV diastolic function profile			
PN or RE vs. N or RA	0.75	0.24-2.33	0.6130
Multiple Stepwise logistic Regression			
CPB time *	1.01	1.01-1.02	0.0003
Difficult separation from CPB	4.73	2.04-10.97	0.0003

Univariate and multivariate analysis for hemodynamic complications in 243 patients operated at the Montreal Heart Institute (MHI) from 2001-2004

CPB, cardiopulmonary bypass; DSB, difficult separation from bypass; IABP, intra-aortic balloon pump; CI, cardiac index; CI, confidence interval; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; LVWMSI, left ventricular wall motion score index; N, normal; RA, relaxation abnormality; PN, pseudo-normal; RE, restrictive. * CPB time and aortic cross-clamp time are correlated, therefore only CPB time is included in the multivariate model.

The next step after these three preliminary studies was to retrospectively confirm our hypothesis in a larger population and in another institution. In a combined database (1994-2004) from both the Montreal Heart Institute (MHI) ($n = 4993$) and the Quebec

Heart and Lung Institute (QHLI) ($n = 4920$), we observed that difficult separation from CPB was associated with an increased mortality (MHI: OR 3.1, CI, 1.9-5.2, $p < 0.0001$ and QHLI: OR 2.1, CI, 1.4-3.2, $p = 0.0001$). [51] The overall hospital mortality in both groups was 3.9%. A doubling of the mortality rate (316 deaths/4039 patients = 7.8%) was observed in patients with difficult separation from CPB.

Finally, to explore the relation between difficult separation from CPB, mortality and morbidity, we analyzed 6120 consecutive patients from 1995-1999 operated at the MHI. Separation from CPB was defined as difficult if there was a requirement for significant vasoactive support according to a previous definition [10;52] and very difficult if return to CPB was necessary or if a new IABP or any mechanical device was required to wean the patient from CPB. Hospital mortality and life-threatening or serious adverse clinical events, including pulmonary, infectious, renal, hemodynamic, gastrointestinal and neurological complications and myocardial infarction during the 30-day study period, were noted.

Neurological complications were defined as postoperative coma, seizures or a transient or permanent focal neurologic deficit. The diagnosis of myocardial infarction was based on the presence of an increase in CK-MB of more than 100 units, new Q waves in two contiguous electrocardiogram leads or confirmed graft occlusion within the first 30 days after surgery. Hemodynamic complications were defined as the requirement of a new IABP, postoperative cardiac arrest or vasoactive requirements for more than 24 hours. Respiratory failure was defined as duration of intubation of more than 48 hours or reintubation for a pulmonary cause. Renal complications were defined as the requirement for dialysis. Gastrointestinal complications were defined as upper or lower gastrointestinal bleeding, hepatic dysfunction, requirement for laparotomy, acute cholecystitis, pancreatitis or mesenteric ischemia. Infectious complications were defined as one or more infections except urinary tract or lower extremity wound infection. Duration of stay in the intensive care unit and the hospital was noted.

Using these definitions, 3253 (53.1%), 2466 (40.3%) and 401 (6.6%) patients were classified as easy, difficult and very difficult separation from CPB. Their mortality was

0.7%, 4.5% and 22.4% ($p < 0.001$), respectively. The neurological, cardiac, hemodynamic respiratory, renal, gastrointestinal and infectious complications were all significantly increased as well as the duration of stay in the intensive care unit and the hospital in patients with difficult and very difficult separation from CPB ($p < 0.0001$) (Table 6).

The next step of this study is to confirm these findings in a multicentered trial and to determine the extent through which difficult separation from CPB is or not an independent predictor of mortality.

Table 6 Outcome and degree of separation from CPB at the Montreal Heart Institute

Variable	Easy (n=3253) n (%) or mean ± SD	Difficult (n=2466) n (%) or mean ± SD	Very difficult (n=401) n (%) or mean ± SD	*P*
Age (years)	61 ± 10	64 ± 11	65 ± 11	< 0.0001
Gender				< 0.0001
Male	2505 (58)	1554 (36)	236 (5)	
Female	748 (41)	912 (50)	165 (9)	
Weight (kg)	77 ± 14.4	72.9 ± 15.2	70.3 ± 14.3	< 0.0001
Height (cm)	166.1 ± 8.8	163.9 ± 9.7	162.3 1 ± 9.3	< 0.0001
Body surface area(cm^2/m^2)	1.88 ± 0.21	1.82 ± 0.22	1.77 ± 0.22	< 0.0001
Cardiovascular risk factors				
Hypertension	1495 (46)	1173 (48)	196 (49)	0.33220
Severe obesity	901 (57)	585 (37)	89 (6)	0.0007
Smoking	741 (28)	501 (26)	85 (6)	
History of smoking	896 (33)	613 (32)	104 (6)	0.21180
Ischemic heart disease risk factors				
Angina	1807 (56)	1159 (36)	218 (7)	< 0.0001
Previous myocardial infarction < 6 months	448 (49)	399 (44)	67 (7)	0.02390
Previous cardiac surgery	197 (25)	462 (60)	114 (15)	< 0.0001
Poor left ventricular function	64 (25)	161 (62)	34 (13)	< 0.0001
History of congestive heart failure	537 (30)	1066 (59)	197 (11)	< 0.0001
Coexisting illness				
Disabling stroke	69 (45)	72 (47)	12 (8)	0.12850

Severe lung disease	245 (42)	273 (47)	61 (11)	< 0.0001
Diabetes mellitus	614 (53)	480 (41)	68 (6)	0.49060
Preoperative drug therapy				
ACE inhibitor	738 (41)	939 (52)	134 (7)	< 0.0001
Nitrates	1901 (58)	1167 (35)	218 (7)	< 0.0001
Beta-blockers	2014 (57)	1304 (37)	205 (6)	< 0.0001
Digitalis	250 (30)	489 (59)	92 (11)	< 0.0001
Calcium-channel blockers	1519 (57.3)	965 (36.4)	168 (6.3)	< 0.0001
Diuretics	642 (35)	1044 (56)	176 (9)	< 0.0001
Other antiarrhythmic agents	131 (32)	233 (57)	44 (11)	< 0.0001
Anticoagulants				
Heparin	1245 (51)	994 (41)	198 (8)	< 0.0001
Aspirin	649 (56)	439 (38)	77 (6)	
Laboratory parameters				
Hemoglobin(g/L)	138 ± 16	132 ± 18	131 ± 17	< 0.0001
Creatinine (umol/L)	102 ± 37	107 ± 48	113 ± 62	< 0.0001
Intraoperative				
Duration of surgery (min)	257 (53)	287 (69)	336 (102)	< 0.0001
Duration of CPB (min)	74 (27)	97 (40)	127 (67)	< 0.0001
Type of surgery				< 0.0001
Elective	35 (24)	93 (64)	17 (12)	
Urgent	925 (60)	554 (36)	68 (4)	
Emergency	1739 (53)	1310 (40)	246 (7)	
Type of procedure				< 0.0001
Complex valves	73 (2)	226 (9)	42 (11)	

	Combined + CABG	119 (4)	380 (15)	77 (19)	
	Isolated CABG	2669 (82)	1288 (52)	209 (52)	
	Isolated valves	392 (12)	572 (23)	73 (18)	
Antifibrinolytics					0.4509
	Aprotinin	300 (9.2)	789 (32)	140 (34.9)	< 0.0001
	Tranexamic acid	38 (1.2)	38 (1.5)	6 (1.5)	
	Aminocaproic acid	1396 (42.9)	799 (32.4)	151 (37.6)	
Postoperative outcome					
	Mortality	21 (1)	110 (4)	90 (22)	< 0.0001
	Neurological complications	65 (2)	98 (4)	31 (8)	< 0.0001
	Myocardial infarction	166 (5)	355 (15)	127 (34)	< 0.0001
	Hemodynamic complications	160 (5)	472 (19)	276 (71)	< 0.0001
	Respiratory failure	78 (2)	202 (8)	68 (18)	< 0.0001
	Renal complications	23 (1)	53 (2)	27 (7)	< 0.0001
	Gastrointestinal complications	85 (2)	165 (4)	77 (8)	< 0.0001
	Infectious complications	78 (2)	182 (7)	59 (16)	< 0.0001
	ICU length of stay (days)	3.3 ± 3.6	4.3 ± 5.3	7.1 ± 8.1	< 0.0001
	Hospital length of stay (days)	6.8 ± 4.8	9.4 ± 8.8	12.2 ± 12.1	< 0.0001

CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; SD, standard deviation

Chapter 2 Manuscript #1

Foreword to Manuscript #1

The first manuscript is part of a Canadian national multicentered randomized controlled trial on the use of antifibrinolytics during cardiac surgery. The results were published in the *New England Journal of Medicine* in 2008. [55] The study was also designed to explore several issues in this particular population of 2331 high-risk cardiac surgical patients. As a co-investigator, my interest and responsibility were to explore the significance of difficult separation from CPB in this population. Therefore, in collaboration with the other investigators, we analyzed the data from this cohort and are presenting the results in the current manuscript. The results of this study will be submitted to *Anesthesiology*.

Intraoperative hemodynamic instability during and after separation from cardiopulmonary bypass

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Abstract

Background: Prediction of mortality in cardiac surgery is commonly based on preoperative variables. However, intraoperative variables may play a significant role in postoperative outcome. Among these variables, the pharmacological and mechanical support required during separation from cardiopulmonary bypass (CPB) could represent the earliest manifestation of a reduced capacity to sustain cardiac surgery and could significantly impact survival after cardiac surgery. Our hypothesis is that the stratification of separation from CPB into 3 categories (easy, difficult and very difficult) will be independently associated with life-threatening complications and survival after cardiac surgery.

Objectives: To document the prevalence of difficult and very difficult separation from CPB and their impact on postoperative outcome.

Methods: Prospective study in 19 Canadian tertiary care hospitals of high-risk cardiac surgical patients involved in the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study. Separation from CPB was stratified as easy when only vasoactive agents or inotropes were required, difficult when both drugs were used and very difficult when the first weaning process failed or the patient required mechanical devices to be weaned from CPB. Backward logistic regression was performed to determine predictors of difficult or very difficult separation from CPB, life-threatening complications and mortality.

Results: There were a total of 2331 patients in the BART study with a mean age of 66±11 and 71.8% were male. There were 1158 (49.7%), 835 (35.8%) and 338 (14.5%) patients in the easy, difficult and very difficult categories, respectively. A total of 108 patients died (4.6%), from which 84 (77.8%) experienced difficulty in weaning from CPB. Very difficult separation from CPB was found to be an independent predictor of mortality (odds ratio 3.091; 95% confidence interval 1.706-5.601). Predictors of very difficult separation from CPB were age (10 units) (OR, 1.222; 95% CI, 1.071-1.4201), reduced left ventricular function (OR 1.718; 95% CI, 1.098-2.689), previous myocardial infarction (OR, 1.491; 95% CI, 1.106-2.011), mitral valve regurgitation (OR, 1.535; 95% CI, 1.154-2.041),

previous cardiac surgery (OR, 1.527; 95% CI, 1.108-2.105), higher preoperative prothrombin time (10 units) (OR, 1.090; 95% CI, 1.027-1.170) and longer CPB duration (60 units)(OR, 2.150; 95% CI, 1.870-2.490). Both difficult and very difficult separation from CPB were independent predictors of myocardial infarction within 30 days (OR, 2.191, 95% CI, 1.244-3.857 and OR, 4.151, 95% CI, 2.210-7.795), cardiogenic shock (OR, 2.152, 95% CI, 1.599-2.895 and OR, 3.677, 95% CI, 2.587-5.226), respiratory failure (OR, 1.697, 95% CI, 1.246-2.313 and OR, 2.911, 95% CI, 2.026-4.181), new onset renal failure (OR, 1.691, 95% CI, 1.240-2.304 and OR, 2.946, 95% CI, 2.051-4.231) and massive bleeding (OR, 1.381, 95% CI, 1.018-1.873 and OR, 1.727, 95% CI, 1.190-2.507).

Conclusion: Difficulty in the process of separation from CPB is an independent predictor of mortality and adverse outcome after cardiac surgery. As a surrogate endpoint, strategies to facilitate separation from CPB could represent new approaches in improving outcome in cardiac surgery. (Current Controlled Trials number, ISRCTN15166455).

Keywords: Cardiac surgery; Mortality; Morbidity; Cardiopulmonary bypass; Outcome.

Introduction

Several risk factors have been proposed to predict mortality in cardiac surgery. The evaluated risk factors are typically those present before the cardiac surgical procedure. [100;101] Predicting models are however insufficient to explain all the mortality observed in cardiac surgery. [138] This limitation in the prediction models may be secondary to other intraoperative factors that could play a significant role in the postoperative outcome of a patient undergoing cardiac surgery. However, these intraoperative factors are not routinely considered in risk stratification but their inclusion has shown potential to improve outcome prediction. [139] Among these risk factors, the amount of pharmacological and mechanical support during cardiopulmonary bypass (CPB) has been shown to play a key role in survival after cardiac surgery in several centers. [69;73;75;77] At the end of a cardiac surgical procedure using CPB, the period during which the extra-corporeal circulation is gradually removed corresponds to the weaning period. During that critical period, if significant vasoactive or inotropic support is necessary or if the introduction of new onset mechanical assistance or return on CPB prove necessary, then the term difficult separation from CPB is used. [61] This represents a significant complication that can persist until transfer to the intensive care unit (ICU) with an increased risk of morbidity and mortality. [10;58;69;73-75;77;78] However, in several studies on CPB weaning, the inotropic requirement has been the main focus; [69;73] several of these studies were single-centered, [69;73;75;77;139;140] and in those investigations, the differentiation between pharmacological and mechanical support and therefore the severity of separation from CPB, has not been stratified. Our hypothesis is that the weaning process from CPB is a critical intraoperative factor with an incremental value independently associated with increased morbidity and mortality in high-risk cardiac surgery.

Study Design

The data from this study were obtained from the Blood Conservation Using Antifibrinolytics in Randomized Trial (BART) study which a multicenter, blinded, randomized, controlled study was comparing three antifibrinolytic agents commonly used in high-risk cardiac surgery. [55] Enrolled patients from Canadian cardiac surgical centers underwent high-risk cardiac surgery. This was defined as a surgical intervention with an average mortality of at least twice the norm for isolated primary CABG and a risk of repeat surgery exceeding 5%. The study was approved by the Research Ethics Committee of each participating center and the central coordinating center. Written informed consent was obtained from all patients. The study was designed, conducted, and reported by the executive committee. From 2002 to 2007, patients who were at least 19 years of age from 19 Canadian cardiac surgical units were recruited. All the patients were undergoing one of the following high-risk cardiac surgical procedures for which CPB bypass was required. These included repeat cardiac surgery, isolated mitral valve replacement, combined valve and coronary artery bypass graft (CABG) surgery, multiple valve replacement or repair, and surgery of the ascending aorta or aortic arch. Patients who required either urgent or elective procedures were considered eligible. Patients were excluded when undergoing lower risk operations, such as isolated primary CABG with or without CPB, isolated mitral valve repair or aortic valve replacement, and infrequent procedures such as heart transplantation, implantation of a left ventricular assist device, and surgery to repair congenital heart defects. The research pharmacist at each center randomly assigned patients to receive one of the three antifibrinolytic medications, which included aprotinin, aminocaproic acid and tranexamic acid, as previously published. [55]

Definition of pre- and intraoperative data

Preoperative data were collected for the following variables: patient age, gender, weight, height, body surface area, cardiovascular risk factors (hypertension, dyslipidemia, severe obesity, smoking), ischemic heart disease risk factors (angina, previous myocardial infarction and cardiac surgery), valvular heart disease, congestive heart failure, reduced left

ventricular function, New York Heart Association classification, coexisting illness (disabling stroke, previous thromboembolism, severe lung disease, chronic renal dysfunction, diabetes mellitus), medical treatment and cardiac medications and laboratory parameters (hemoglobin, platelets, white blood cells, creatinine, coagulogram). The intraoperative data included the American Society of Anesthesia classification, duration of surgery and CPB, elective, urgent or emergency surgery, type of procedure and antifibrinolytics, heparin dosages, as well as blood losses in the CPB circuit or through the chest tube. (See Appendix 1 for definitions of variables)

Study Outcomes

Our primary study outcome was to assess the relationship between the severity of weaning from CPB and mortality defined as death from any cause within 30 days. Two definitions were used to stratify the severity in weaning from CPB and were exclusive. Difficult separation from CPB was defined as the requirement for both vasoactive and inotropic agents from the end of CPB until the end of the operation. Very difficult separation from CPB was defined as one or more failures of the first weaning attempt or the requirement for intra-aortic balloon pump (IABP) or a ventricular assist device to leave the operating room. Secondary outcomes included life-threatening or serious adverse clinical events such as stroke, myocardial infarction, cardiogenic shock, respiratory failure, new onset renal failure and massive bleeding during the 30-day study period. (See definitions in Appendix 1)

The length of ICU and hospital stay was noted. Patients who were not admitted to an ICU were assigned an ICU length of stay of 0. We defined the length of hospital stay as the discharge date minus the surgery date plus 1 day. All the variables entered in the BART study were verified by at least two investigators. Built-in logic and range checks were used and chart audits by the data entry coordinator were performed at each site.

Statistical analysis

Baseline characteristics of patients in the 3 groups (easy, difficult and very difficult separation from CPB) and those who died were described with the use of frequency distributions and univariable descriptive statistics, including measures of central tendency and dispersion. We used multiple logistic regression models to further elucidate the relationship between severity of separation from CPB classes and intraoperative parameters while adjusting for preoperative parameters considered as potentially confounding variables. The same approach was used for mortality and secondary outcomes. We calculated odds ratios (OR) with 95% confidence intervals (CI) for each of the three comparisons. $P < 0.05$ was considered significant.

Results

A total of 2331 patients were recruited from 2002 to 2007 and included in the analysis. There were 1674 males (71.8%) and 657 females (28.2%) with a mean age of 66 ± 11.0 years. The characteristics of the studied population are shown in Table 7. A total of 1158 (49.7%), 835 (35.8%) and 338 (14.5%) patients were included in the easy, difficult and very difficult separation from CPB category, respectively. A total of 108 patients (4.6%) died. As the difficulty in separation from CPB increased, there was a proportional increase in mortality (easy, $n = 24$ (2.1%); difficult, $n = 39$ (4.7%); very difficult, $n = 45$ (13.4%)).

Independent risk factors for difficult and very difficult separation from CPB are shown in Table 8. The risk factors for difficult versus easy separation from CPB were: reduced left ventricular function (OR 1.859; 95% CI, 1.324-2.634), regurgitation of the mitral valve (OR, 1.388; 95% CI, 1.104-1.744), the aortic valve (OR, 1.322; 95% CI, 1.075-1.626), and the tricuspid valve (OR, 1.5558; 95% CI, 1.245-1.949), urgent or emergency versus elective surgery (OR, 1.755; 95% CI, 1.366-2.253) and longer CPB duration (60 units) (OR, 1.380; 95% CI, 1.209-1.578). Aortic stenosis (OR, 0.720; 95% CI, 0.588-0.884) and CPB blood losses (100 units) (OR, 0.971; 95% CI, 0.950-0.992) reduced the risk for difficult separation from CPB.

Similar risk factors for very difficult versus easy separation from CPB included left ventricular function (OR 1.718; 95% CI, 1.098-2.689), mitral valve regurgitation (OR, 1.535; 95% CI, 1.154-2.041) and longer CPB duration (60 units)(OR, 2.150; 95% CI, 1.870-2.490). Age (10 units) (OR, 1.222; 95% CI, 1.071-1.4201), previous myocardial infarction (OR, 1.491; 95% CI, 1.106-2.011), previous cardiac surgery (OR, 1.527; 95% CI, 1.108-2.105), and higher preoperative prothrombin time (10 units) (OR, 1.090; 95% CI, 1.027-1.170) were preoperative factors associated with very difficult separation from CPB. Among patients with very difficult separation from CPB, 223 (65.9%) required both vasopressors and inotropes, 38 of which died. Therefore 84.4% of the mortality in this group was associated with criteria for both difficult and very difficult separation from CPB.

Some of the predictors of mortality (Table 9) were the same as those predicting difficult and very difficult separation from CPB. These include age (10 units) (OR, 1.557; 95% CI, 1.213-2.028), prothrombin time (10 units) (OR, 1.096; 95% CI, 1.024-1.164) and CPB duration (60 units) (OR, 1.788; 95% CI, 1.529-2.103). Renal disease (OR, 1.921; 95% CI, 1.029-3.585), the use of diuretics (OR, 1.758; 95% CI, 1.108-2.790) and reduced hemoglobin (1 unit) (OR, 0.985; 95% CI, 0.972-0.999) were associated with increased mortality. Very difficult separation from CPB (OR 3.091, 95% CI, 1.706-5.601) was found to be an independent predictor of mortality. Figure 11 summarizes the risk factors associated with the severity of CPB weaning and mortality.

Secondary outcomes and the severity of CPB weaning are shown in Table 10. Both difficult and very difficult separation from CPB were independent predictors of myocardial infarction within 30 days (OR, 2.191, 95% CI, 1.244-3.857 and OR, 4.151, 95% CI, 2.210-7.795, respectively), cardiogenic shock (OR, 2.152, 95% CI, 1.599-2.895 and OR, 3.677, 95% CI, 2.587-5.226), respiratory failure (OR, 1.697, 95% CI, 1.246-2.313 and OR, 2.911, 95% CI, 2.026-4.181), new onset renal failure (OR, 1.691, 95% CI, 1.240-2.304 and OR, 2.946, 95% CI, 2.051-4.231) and massive bleeding (OR, 1.381, 95% CI, 1.018-1.873 and OR, 1.727, 95% CI, 1.190-2.507).

Discussion

In this multicentered study conducted in 19 centers across Canada, we observed an association between the amount of pharmacological and mechanical support during separation from CPB, life-threatening or serious adverse clinical events, length of ICU and hospital stay, and mortality. A total of 108 patients died and 77.8% experienced difficulty in the process of separation from CPB. Furthermore, those failing to be weaned on the first attempt and requiring additional surgical intervention or mechanical devices experienced an increased mortality, independently of their underlying condition. Both difficult and very difficult separation from CPB were also related. In patients with very difficult separation from CPB, 84.4% also presented pharmacological criteria for difficult separation from CPB. In addition, we observed that predictors of difficult and very difficult separation from CPB were different. These variables were also different from those predicting mortality (Figure 11). This could explain why preoperative risk factors alone do not completely predict mortality and morbidity. [141] As the patient is admitted to the ICU, the inclusion of intraoperative factors would allow to reset risk stratification in terms of predicting morbidity and mortality. Furthermore, as the process of weaning from CPB can influence postoperative outcome, the potential identification and correction of factors associated with difficult separation from CPB could represent a new field of research or a surrogate endpoint in cardiac surgery.

Predictors and mechanism of difficult separation from CPB

Several variables were identified as independent predictors of difficult and very difficult separation from CPB. The mechanism of difficult separation from CPB can be explained by an imbalance between circulatory reserve and demand (Figure 12). This imbalance can occur at a systemic or at a specific organ level. Such supply and demand mismatch will result in ischemic tissue injury and consequently lactic acidosis. Global lactate level during CPB [9] and reduced myocardial pH [109] or increased myocardial lactate measured during CPB [76;110] have been shown to be predictors of increased

postoperative inotropic support and mortality. Therefore the risk of difficult separation from CPB is likely to correlate with indices of global or regional myocardial tissue hypoperfusion.

Hypoperfusion will occur if the circulatory reserve is reduced in relation to circulatory demand. Circulatory reserve is defined as the ability to deliver oxygen to the periphery. This ability is a function of arterial oxygen content and cardiac output. Arterial oxygen content depends on oxygen saturation and hemoglobin. In this study, we observed that reduced hemoglobin and elevated prothrombin time (PTT) were associated with an increased mortality. Both conditions are likely to be associated with an increased risk of transfusion, which has been shown to be an independent predictor of postoperative low output failure. [78]

The mechanism of reduced cardiac output after CPB can be approached using the concept of venous return [54] because several of the determinants of venous return can be measured or estimated at the bedside using both hemodynamic monitoring and transesophageal echocardiography (TEE). Venous return and consequently cardiac output are determined by three variables, which are the mean systemic pressure, the right atrial pressure and the resistance to venous return (Figure 2). Difficult separation from CPB will be present when one or more of these factors is altered before or during the weaning process.

First venous return will be reduced if there is a reduction in the mean systemic pressure secondary to a loss of blood volume or an increase in venous compliance. Factors associated with an increased risk of bleeding such as reoperation, [73;75;100] higher preoperative PTT and reduced hemoglobin will predispose to a reduction in mean systemic pressure. These factors were associated with very difficult separation from CPB and mortality. The increase in venous compliance can be linked to the duration of CPB. Longer CPB duration will be associated with increased inflammatory reaction, [142] vasoplegia [106] and, consequently, an increased requirement for vasopressors. [69;73] We observed lower CPB blood losses in patients with difficult separation from CPB. This could

be related to the reduced level of retransfusion of CPB blood in the systemic circulation and the deleterious effect of transfusion. [143] The amount was not clinically significant and the processing of blood uncontrolled. Unprocessed retransfused blood is a source of inflammatory mediators [144] and could offset the benefits of increased hemoglobin.

An increase in right atrial pressure is another mechanism predisposing to difficult separation from CPB. Factors associated with elevation in right atrial pressure such as previous myocardial infarction and reduced left ventricular systolic function were associated with an increased risk of difficult weaning from CPB. These factors have been shown to be associated with increased inotropic requirements [58;64;69;70;73;75;77;104] and mortality in cardiac surgery. [141] Both valvular regurgitation and advanced age are commonly associated with elevated filling pressure, [11] diastolic dysfunction [145] and pulmonary hypertension. Pulmonary hypertension is associated with an increased risk of vasoactive support requirement after CPB [10;46] and mortality. [10;100;101;115] Pulmonary hypertension is typically secondary to left heart disease but can be exacerbated after CPB because of the reperfusion syndrome, [146] dysfunctional prosthesis or inadequate revascularization and, in some cases, in patients with aortic or mitral patient-prosthesis mismatch. [120;128] However, preoperative right ventricular dysfunction seems to be an even more important risk factor in cardiac surgery [46;112] than the severity of pulmonary hypertension. The observed increased difficulty of weaning from CPB in patients with tricuspid regurgitation could be related to this factor. When difficult separation from CPB is associated with postoperative right ventricular failure, the mortality can be as high as 86%. [3] Renal disease is a known factor associated with increased mortality in cardiac surgery, [115;147] and the use of diuretics could be related to worse cardiac conditions. Any factor increasing right atrial pressure can result in increased requirements for inotropic and vasoactive agents. We observed that aortic stenosis reduced the risk of difficult separation from CPB. In these high-risk patients compared with valvular regurgitation, aortic stenosis is the most benign valvular disease and has little or no incremental prognostic value. [100]

Finally, the third mechanism is an increase in resistance to venous return resulting from an external or internal extracardiac flow obstruction such as tamponade, pneumothoraces, and thoracic or abdominal compartment syndrome. [148] This third mechanism is uncommon and poorly documented in the period immediately following CPB during open chest surgery, except in cases where the inferior vena cava flow is accidentally interrupted. [149] The treatment of this condition relies on the recognition and correction of the underlying mechanical cause. Finally, multiple determinants of venous return can often be altered. Blais *et al.* [121] observed that the combination of aortic valve patient-prosthesis mismatch and reduced left ventricular ejection increased perioperative mortality up to 67%. Recognition and correction of these factors when possible could play a significant role in reducing the prevalence of difficult separation from CPB.

The association between mortality and difficult weaning from CPB

Several preoperative variables have been associated with increased mortality in cardiac surgery and are used in risk stratification. [74;100-102] These studies differ regarding the type of procedure (CABG, valvular or not), the specific population and age group, the inclusion of a single or multiple centers, the duration of follow-up and the inclusion of mortality and postoperative morbidities as primary and secondary endpoints. Nilsson *et al.* [141] applied 19 preoperative risk stratification models to 6222 patients undergoing open heart surgery. The highest discriminatory power using a receiver operating curve (ROC) was 0.84 in predicting 30-day mortality. The absence of a higher discriminatory score could be explained by other factors that can influence postoperative survival such as intraoperative and postoperative variables. In a study of 1157 elderly patients from a single institution, Rady *et al.* [139] combined the use of preoperative, intraoperative and postoperative factors to predict postoperative mortality. The mortality ROC area increased to 0.90 by the inclusion of all these criteria. In that study, the use of inotropic agents upon admission to the ICU was significantly related to mortality. However, the extent to which difficult separation from CPB can be seen as an independent

predictor of mortality had not been demonstrated before the conducting of a prospective multicentered study.

Several definitions of post-CPB hemodynamic instability have been used and studied as postoperative outcome. Difficult separation from CPB, [10;11;60] postoperative inotropic dependency, [58;64;69] low cardiac output state [4;75;77] and low output failure [78] are some of the terms used. This association between difficult separation from CPB and mortality is much more established [69;75;77;109] than the independent value of difficult separation from CPB in predicting mortality. Only two single-center studies have demonstrated that the use of inotropes after cardiac surgery was an independent predictor of increased mortality. [139;140]

Difficult separation from CPB is the earliest period after cardiac surgery when inappropriate oxygen supply can be observed. It occurs in the operating room while the chest is still open. When difficult separation from CPB is present, it requires not only rapid pharmacological and mechanical interventions but also a careful search for potential reversible factors and therefore a quest for the underlying mechanism. The understanding of this condition has been greatly improved since the introduction of intraoperative transesophageal echocardiography (TEE), which can lead to medical and surgical interventions before chest closure. [16;57;150-153] In the setting of difficult separation from CPB resulting in hemodynamic instability, TEE is considered a type I indication. [154]

Limitations

In predicting mortality, the difficulty in separating from CPB is unknown when the patient is seen before a cardiac surgical operation. This predictor will only be made manifest later in the operating room. Preoperative risk stratification models are still useful. Knowing the difficulty in separation from CPB is an advantage in the postoperative period only. For the critical care physician, resources allocation and outcome will be influenced by how well separation from CPB went. The goal of this study was to document the

importance of difficult separation from CPB in a multicentered national study. However the precise mechanism leading to this condition was not identified for each patient. Intraoperative echocardiography was used in 2075 (89.1%) patients but the exam was not standardized and the final report not collected. There are also other variables associated with difficult separation from CPB such as pulmonary artery pressure, [10;100;101;115] left ventricular end-diastolic pressure, [11] diastolic function parameters, [155] right ventricular function indices, [46;112] and myocardial pH and lactate [76;109;110] which were not routinely used and consequently unavailable. Further studies using a systematic approach for the diagnosis of conditions resulting in difficult separation from CPB are needed to gain more insight on the mechanism of this critical condition.

Conclusion

In summary, in patients undergoing high-risk cardiac surgery, significant pharmacological and mechanical support during weaning from CPB is independently associated with increased morbidity and mortality. Difficult separation from CPB could be viewed as a surrogate endpoint in cardiac surgery. Strategies to identify and understand the mechanism using TEE [48] or metabolic markers [111] could reduce the prevalence of this complication and could lead to the introduction of new pharmacological strategies or mechanical devices that would greatly improve the care provided to the cardiac surgical patient.

Table 7 Outcome and degree of separation from CPB in the BART study

Variable	Population (n = 2331) n (%) or mean ?SD	Easy (n=1158) n (%) or mean ?SD	Difficult (n=835) n (%) or mean ?SD	Very difficult (n=338) n (%) or mean ?SD	Mortality (n=108) n (%) or mean ?SD
Age	66 ?11.0	66.2 ?11.3	67.2 ?10.9	68.1 ?9.9	71 ?10.1
Gender					
Male	1674 (71.8)	845 (73.0)	594 (71.1)	235 (69,5)	67 (62.0)
Female	657 (28.2)	313 (27.0)	241 (28.9)	103 (30,5)	41 (38.0)
Weight (kg)	81.4 ?17.3	81.9 ?17.3	81.1 ?17.4	80 ?17.4	78.1 ?18.1
Height (cm)	167.9 ?15.4	168.7 ?14.7	167.4 ?15.8	166.8 ?16.3	166 ?14.4
Body surface area (cm?m?	1.94 ?0.26	1.95 ?0.26	1.93 ?0.26	1.91 ?0.26	1.88 ?0.22
Cardiovascular risk factors					
Hypertension	1456 (62.5)	731 (63.1)	503 (60.2)	222 (65.7)	82 (75.9)
Dyslipidemia	1468 (63.0)	722 (62.3)	516 (61.8)	230 (68.0)	75 (69.4)
Severe obesity	687 (29.5)	342 (29.5)	241 (28.9)	104 (30.8)	27 (25.0)
Smoking	343 (14.7)	163 (14.1)	136 (16.3)	44 (13.0)	11 (10.2)
History of smoking	1587 (68.1)	790 (68.2)	571 (68.4)	226 (66.9)	70 (64.8)
Ischemic heart disease risk factors					
Angina	1195 (51.3)	602 (52.0)	387 (46.3)	206 (60.9)	64 (59.8)
Canadian Cardiovascular Society Class					
0	1055 (50.7)	503 (43.4)	431 (51.6)	121 (35.8)	42 (42.4)
I	66 (3.2)	36 (3.1)	20 (2.4)	10 (3.0)	1 (1.0)
III	314 (15.1)	174 (15.0)	96 (11.5)	44 (13.0)	9 (9.1)
III	485 (23.3)	254 (21.9)	157 (18.8)	74 (21.9)	28 (28.3)
IV	163 (7.8)	70 (6.0)	53 (6.3)	40 (11.8)	19 (19.2)
Previous myocardial infarction < 6 months	203 (8.8)	78 (6.7)	85 (10.2)	40 (11.8)	16 (14.8)
Previous myocardial infarction	659 (28.3)	277 (23.9)	258 (30.9)	124 (36.7)	40 (37.0)
Previous cardiac surgery	572 (24.5)	254 (21.9)	216 (25.9)	102 (30.2)	35 (32.4)

Variable	Population (n = 2331) n (%) or mean ?SD	Easy (n=1158) n (%) or mean ?SD	Difficult (n=835) n (%) or mean ?SD	Very difficult (n=338) n (%) or mean ?SD	Mortality (n=108) n (%) or mean ?SD
Valvular heart disease					
Tricuspid regurgitation	967 (45.7)	401 (34.6)	426 (51.0)	140 (41.4)	54 (55.1)
Aortic regurgitation	1136 (53.1)	515 (44.5)	454 (54.4)	167 (49.4)	58 (59.8)
Aortic stenosis	1282 (59.0)	682 (58.9)	427 (51.1)	173 (51.2)	55 (56.7)
Mitral regurgitation	1403 (65.4)	616 (53.2)	570 (68.3)	217 (64.2)	79 (80.6)
Mitral stenosis	256 (12.1)	122 (10.5)	104 (12.5)	30 (8.9)	15 (15.5)
Congestive heart failure	913 (39.2)	410 (35.4)	364 (43.6)	139 (41.1)	53 (49.1)
Admission for congestive heart failure	261 (11.8)	100 (8.6)	120 (14.4)	41 (12.1)	18 (18.0)
New York Heart Association class					
None	1411 (64.0)	669 (57.8)	445 (53.3)	185 (54.7)	55 (57.9)
1	49 (2.2)	21 (1.8)	20 (2.4)	8 (2.4)	1 (1.1)
2	202 (9.2)	104 (9.0)	72 (8.6)	26 (7.7)	5 (5.3)
3	456 (20.7)	212 (18.3)	178 (21.3)	66 (19.5)	25 (26.3)
4	85 (3.9)	35 (3.0)	27 (3.2)	23 (6.8)	9 (9.5)
Poor left ventricular function	230 (9.9)	75 (6.5)	109 (13.1)	46 (13.6)	15 (13.9)
Coexisting illness					
Disabling stroke	53 (2.3)	20 (1.7)	23 (2.8)	10 (3.0)	4 (3.7)
Previous thromboembolism	93 (4.0)	43 (3.7)	38 (4.6)	12 (3.6)	1 (0.9)
Severe lung disease	142 (6.1)	55 (4.7)	63 (7.5)	24 (7.1)	11 (10.2)
Chronic renal dysfunction	142 (6.1)	54 (4.7)	58 (6.9)	30 (8.9)	19 (17.6)
Diabetes mellitus	559 (24.0)	262 (22.6)	203 (24.3)	94 (27.8)	33 (30.6)
Preoperative drug therapy					
ACE inhibitor	1092 (47.0)	503 (43.4)	420 (50.3)	169 (50.0)	55 (51.0)
Nitrates	592 (25.7)	271 (23.4)	216 (25.9)	105 (31.1)	40 (37.4)

Variable	Population (n = 2331) n (%) or mean ?SD	Easy (n=1158) n (%) or mean ?SD	Difficult (n=835) n (%) or mean ?SD	Very difficult (n=338) n (%) or mean ?SD	Mortality (n=108) n (%) or mean ?SD
Beta-blocker	1246 (53.6)	594 (51.3)	460 (55.1)	192 (56.8)	69 (63.9)
Digoxin/Digitalis	253 (10.9)	104 (9.0)	110 (13.2)	39 (11.5)	21 (19.4)
Calcium-channel blocker	631 (27.2)	340 (29.4)	208 (24.9)	83 (24.6)	37 (34.3)
Diuretic	1009 (43.4)	445 (38.4)	401 (48.0)	163 (48.2)	67 (62.0)
Other antiarrhythmic agents	217 (9.4)	107 (9.2)	70 (8.4)	40 (11.8)	16 (14.8)
Anticoagulants					
Heparin-U/day					
≤ 10,000 yes	65 (2.8)	19 (1.6)	28 (3.4)	18 (5.3)	10 (9.3)
> 10,000 yes	223 (9.6)	83 (7.2)	108 (12.9)	32 (9.5)	16 (14.8)
Low-molecular weight	121 (5.2)	56 (4.8)	43 (5.1)	22 (6.5)	8 (7.4)
Warfarin	292 (12.6)	128 (11.1)	119 (14.3)	45 (13.3)	20 (18.7)
Antiplatelet agent					
Aspirin					
None	1205 (52.4)	628 (54.2)	427 (51.1)	150 (44.4)	48 (44.9)
≤ 325	1054 (45.7)	500 (43.2)	382 (45.7)	172 (50.9)	56 (52.3)
>325	43 (1.9)	18 (1.6)	15 (1.8)	10 (3.0)	3 (2.8)
Other agents	102 (4.4)	44 (3.8)	39 (4.7)	19 (5.6)	5 (4.9)
Laboratory parameters					
Hemoglobin (g/L)	136.3 ?16.3	137.5 ?15.6	135.1 ?16.9	135.3 ?16.8	127.4 ?17.6
Platelets (x 10^9/L)	230.8 ?66.5	233.5 ?66.8	229 ?66.1	226.2 ?66.2	234.5 ?76.3

Variable	Population (n = 2331) n (%) or mean ?SD	Easy (n=1158) n (%) or mean ?SD	Difficult (n=835) n (%) or mean ?SD	Very difficult (n=338) n (%) or mean ?SD	Mortality (n=108) n (%) or mean ?SD
White Blood Cells (x 10^9/L)	7.9 ?6.6	8.2 ?8.3	7.6 ?4.3	7.6 ?4.8	7.3 ?2.2
International Normalized Ratio	1.06 ?0.1	1.04 ?0.1	1.07 ?0.1	1.07 ?0.2	1.1 ?0.2
Prothrombin Time (sec)	34.2 ?19.2	32.6 ?16.1	35.2 ?17.0	37.6 ?30.1	42.7 ?41.3
Fibrinogen (g/L)	4.5 ?2.5	4.2 ?1.5	4.7 ?2.5	5.2 ?4.8	4.5 ?1.8
Creatinine (umol/L)	96.1 ?41.9	94.7 ?49.4	96.9 ?32.8	98.7 ?32.8	107.7 ?45.5
Intraoperative					
American Society of Anesthesiologist Class					
1	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0
2	35 (1.6)	21 (1.8)	10 (1.2)	4 (1.2)	1 (0.9)
3	971 (44.4)	478 (41.3)	352 (42.2)	141 (41.7)	34 (33.3)
4	1177 (53.8)	580 (50.1)	426 (51.0)	171 (50.6)	66 (64.7)
5	5 (0.2)	3 (0.3)	1 (0.1)	1 (0.3)	1 (0.9)
Duration of surgery (hours)	4.3 ?1.6	4.1 ?1.3	4.2 ?1.6	5.3 ?2.2	5.9 ?2.8
Duration of CPB (minutes)	139.1 ?60.7	128.5 ?47.6	135.3 ?53.7	184.8 ?91.1	203.8 ?116.2
Type of surgery					
Elective	1882 (80.8)	997 (86.1)	619 (74.1)	266 (78.7)	76 (70.4)
Urgent	446 (19.1)	160 (13.8)	215 (25.7)	71 (21)	32 (29.6)
Emergency	2 (0.1)	1 (0.1)	0 (0)	1 (0.3)	0 (0.0)
Type of procedure					
Complex	235 (10.1)	106 (9.2)	104 (12.5)	25 (7.4)	7 (6.5)
Combined + CABG	1282 (55.0)	636 (54.9)	448 (53.7)	198 (58.6)	64 (59.3)

Variable	Population (n = 2331) n (%) or mean ?SD	Easy (n=1158) n (%) or mean ?SD	Difficult (n=835) n (%) or mean ?SD	Very difficult (n=338) n (%) or mean ?SD	Mortality (n=108) n (%) or mean ?SD
Isolated aorta	59 (2.5)	37 (3.2)	13 (1.6)	9 (2.7)	0 (0.0)
Isolated CABG	259 (11.1)	139 (12)	76 (9.1)	44 (13.0)	16 (14.8)
Isolated valves	495 (21.2)	239 (20.6)	194 (23.2)	62 (18.3)	21 (19.4)
Antifibrinolytics					
Aprotinin	781 (33.5)	388 (33.5)	276 (33.1)	117 (34.6)	47 (43.5)
Tranexamic acid	770 (33.0)	365 (31.5)	287 (34.4)	118 (34.9)	30 (27.8)
Aminocaproic acid	780 (33.5)	405 (35.0)	272 (32.6)	103 (30.5)	31 (28.7)
Total heparine dosage (IU)	48559 ?40552	47369 ?42524	47811 ?41422	54497 ?29529	54861 ?30640
CPB blood losses (ml)	467 ?489.8	483.6 ?469.8	425.9 ?487.7	515.5 ?552.8	522.7 ?743.2
Postoperative outcome					
Mortality	108 (4.6)	24 (2.1)	39 (4.7)	45 (13.3)	
Stroke within 30 days	72 (3.1)	29 (2.5)	25 (3)	18 (5.3)	15 (13.9)
Myocardial infarction within 30 days	83 (3.8)	21 (1.8)	34 (4.1)	28 (8.3)	16 (14.8)
Cardiogenic shock	332 (14.2)	85 (7.3)	143 (17.1)	104 (30.8)	45 (41.7)
Respiratory failure	294 (12.7)	87 (7.5)	113 (13.5)	94 (27.8)	54 (50.0)
New onset renal failure	299 (12.9)	102 (8.8)	126 (15.1)	71 (21.0)	47 (43.5.)
Massive bleeding	261 (11.2)	94 (8.1)	102 (12.2)	65 (19.2)	45 (41.7)
Intensive care unit length of stay (days)	3.2 ?6.9	2.3 ?4.4	3.5 ?6.9	5.7 ?11.9	4.5 ?6.1
Hospital length of stay (days)	11.9 ?12.6	10.2 ?8.7	12.6 ?12.2	15.9 ?21.3	7.9 ?7.6

ACE, angiotensin converting enzyme; BART, Blood Conservation Using Antifibrinolytics in a Randomized Trial; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; IU, international unit; RBC, red blood cell; SD, standard deviation; sec, seconds

Table 8 Predictors of the degree of separation from CPB in the BART study

Variables	B ± SE	Odds ratio	95% CI	*P* value
Easy compared to difficult separation from CPB				
Reduced left ventricular function	0.6247 ± 0.1754	1.868	1.324-2.634	0.0004
Mitral valve regurgitation	0.3278 ± 0.1166	1.388	1.104-1.744	0.0049
Aortic valve regurgitation	0.2795 ± 0.1054	1.322	1.075-1.626	0.0080
Tricuspid valve regurgitation	0.4376 ± 0.1145	1.558	1.245-1.949	0.0001
Urgent/emergency *vs.* elective	0.5623 ± 0.1276	1.755	1.366-2.253	<0.0001
Aortic valve stenosis	-0.3267 ± 0.1039	0.721	0.588-0.884	0.0017
CPB blood losses (100 units)	-0.0003 ± 0.0001	0.971	0.950-0.992	0.0083
CPB duration (60 units)	0.0054 ± 0.0011	1.380	1.209-1.578	< 0.0001
Easy compared to very difficult separation from CPB				
Age (10 units)	0.0201 ± 0.00685	1.222	1.071-1.401	0.0034
Reduced left ventricular function	0.5411 ± 0.2286	1.718	1.098-2.689	0.0179
Previous myocardial infarction	0.3995 ± 0.1525	1.491	1.106-2.011	0.0088
Mitral valve regurgitation	0.4284 ± 0.1454	1.535	1.154-2.041	0.0032
Previous cardiac surgery	0.4236 ± 0.1637	1.527	1.108-2.105	0.0097
Prothrombin time (10 units)	0.0086 ± 0.0032	1.090	1.027-1.170	0.0076
CPB duration (60 units)	0.0128 ± 0.00122	2.150	1.870-2.490	< 0.0001

B, estimate; BART, Blood Conservation Using Antifibrinolytics in a Randomized Trial; CI, confidence interval; CPB, cardiopulmonary bypass; SE, standard error

Table 9 Predictors of mortality in the BART study

Variables	**B ± SE**	**Odds Ratio**	**95% CI**	***P* value**
Age (10 units)	0.0443 ± 0.0131	1.557	1.213-2.028	0.0007
Renal disease	0.6526 ± 0.3184	1.921	1.029-3.585	0.0404
Use of diuretics	0.5644 ± 0.2355	1.758	1.108-2.790	0.0165
Hemoglobin (1 unit)	-0.0147 ± 0.00692	0.985	0.972-0.999	0.0342
Prothrombin time (10 units)	0.0091 ± 0.00316	1.096	1.024-1.164	0.0039
Easy *vs.* difficult separation from CPB	0.5155 ± 0.2875	1.674	0.953-2.942	0.0730
Easy *vs.* very difficult separation from CPB	1.1285 ± 0.3033	3.091	1.706-5.601	0.0002
CPB duration (60 units)	0.0097 ± 0.0013	1.788	1.529-2.103	< 0.0001

B, estimate; BART, Blood Conservation Using Antifibrinolytics in a Randomized Trial; CI, confidence interval; CPB, cardiopulmonary bypass; SE, standard error

Table 10 Postoperative outcome in the BART study

Variables	B ± SE	Odds Ratio	95% CI	*P* value
Myocardial infarction within 30 days				
Easy *vs*. difficult separation from CPB	0.7843 ± 0.2886	2.191	1.244-3.857	0.0066
Easy *vs*. very difficult separation from CPB	1.4234 ± 0.3215	4.151	2.210-7.795	< 0.0001
Cardiogenic shock				
Easy *vs*. difficult separation from CPB	0.7662 ± 0.1513	2.152	1.599-2.895	< 0.0001
Easy *vs*. very difficult separation from CPB	1.3021 ± 0.1794	3.677	2.587-5.226	< 0.0001
Respiratory failure				
Easy *vs*. difficult separation from CPB	0.5291 ± 0.1579	1.697	1.246-2.313	0.0008
Easy *vs*. very difficult separation from CPB	1.0683 ± 0.1848	2.911	2.026-4.181	< 0.0001
New onset renal failure				
Easy *vs*. difficult separation from CPB	0.5251 ± 0.1580	1.691	1.240-2.304	0.0009
Easy *vs*. very difficult separation from CPB	1.0805 ± 0.1847	2.946	2.051-4.231	< 0.0001
Massive bleeding				
Easy *vs*. difficult separation from CPB	0.3227 ± 0.1556	1.381	1.018-1.873	0.0381
Easy *vs*. very difficult separation from CPB	0.5464 ± 0.1902	1.727	1.190-2.507	0.0041

B, estimate; BART, Blood Conservation Using Antifibrinolytics in a Randomized Trial; CI, confidence interval; CPB, cardiopulmonary bypass; SE, standard error

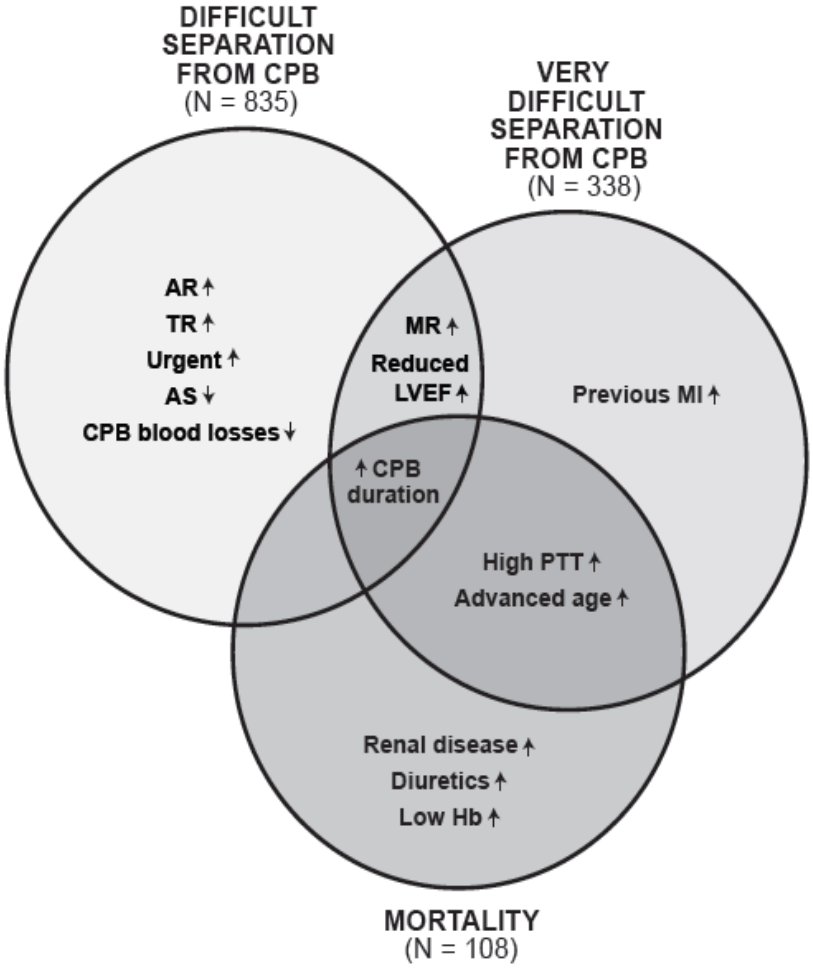


Figure 11 Interactions between risk factors

Summary of the multivariate analysis for difficult separation from cardiopulmonary bypass (CPB), very difficult separation from CPB and mortality. (AR, aortic regurgitation; AS, aortic stenosis; Hb, haemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; PTT, prothrombin time; TR, tricuspid regurgitation)

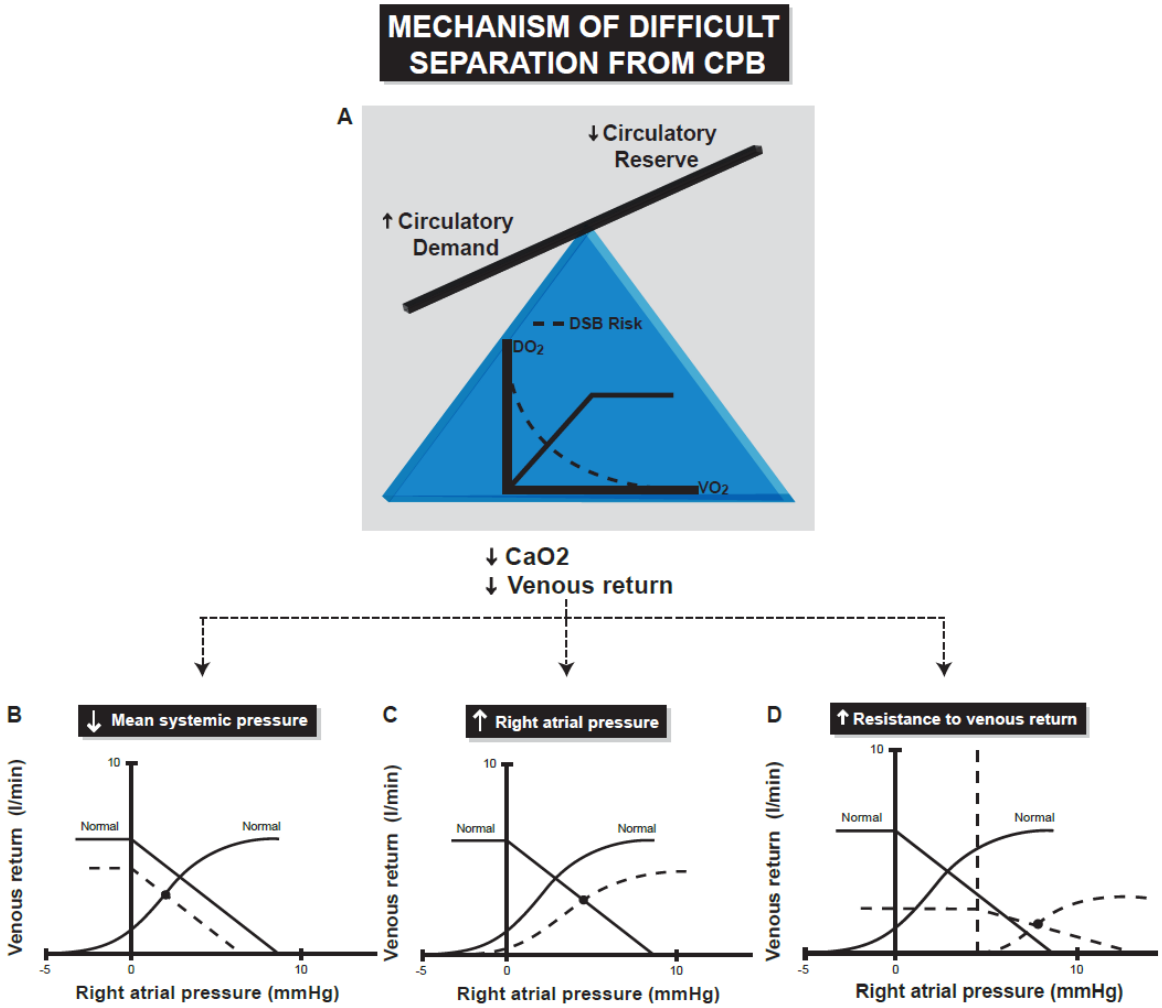


Figure 12 Mechanism of difficult separation from CPB

(A) Similarly to a shock state, difficult separation from bypass (DSB) results from an imbalance between circulatory demand and circulatory reserve. The risk of DSB will increase as global and myocardial oxygen transport (DO_2) is reduced in relation to oxygen consumption (VO_2). Determinants of circulatory reserve are the arterial oxygen content (CaO_2) and cardiac output or venous return. (B-D) The venous return and cardiac output (*y* axis) and its relation to right atrial pressure (*x* axis) are shown (solid line). The intersection of both curves will correspond to the right atrial pressure at which, in a steady state, an individual will have a unique venous return and cardiac output. The mean systemic pressure corresponds to the point where the venous return = 0 L/min. The slope of the venous return curve is linked to the resistance to venous return. Venous return will be reduced if the mean systemic pressure is reduced, if the right atrial pressure is increased or if resistance to venous return is increased. [54]

(B) Reduction in mean systemic pressure (dotted line) will result in a medial shift of the venous return curve. In such a situation, filling pressure, venous return and cardiac output will be reduced. There are two basic mechanisms: a reduction in the stressed volume and an increase in venous compliance. (C) An increase in right atrial pressure (dotted line) will

result in a reduction in venous return and consequently cardiac output. (D) Finally, in situations of increased resistance to venous return, (such as tamponade or pneumothorax), venous return and cardiac output are reduced. Right atrial pressure is increased. This is secondary to the rise in external cardiac pressure. Venous return will now be limited not by subatmospheric pressure but by the external pressure. As a result, venous return is now equal to the difference between mean systemic pressure and the external pressure divided by the resistance to venous return. The slope of the venous return curve is reduced from an increase in the resistance to venous return. A normal compensatory increase in mean systemic pressure will also be observed secondary to the activation of the autonomic nervous system. (CPB; cardiopulmonary bypass)

Chapter 3 Mechanisms of difficult separation from cardiopulmonary bypass

As we have previously observed, difficult separation from CPB is an important and independent cause of morbidity and mortality. Therefore, it is of crucial importance to understand that mechanism precisely in order to initiate appropriate treatment. Difficult separation from CPB will result in a reduction in cardiac output, which will in turn result in hemodynamic instability. In order to describe this mechanism, the use of the concept of venous return as described by Guyton, [54] combined with that of biventricular pressure-volume relationship, can help us understand this critical condition. The use of TEE has allowed us to document the various causes of hemodynamic instability, and examples from the MHI TEE database (n = 15,000 exams) will be used to illustrate this concept.

3.1 Mechanism of hemodynamic instability

The various components of hemodynamic instability can be explained using the classical concept of venous return as described by Guyton. [54] In simple terms, venous return (VR) is determined by a pressure gradient. This gradient corresponds to the difference between the mean systemic venous pressure (Pms) in the periphery and the right atrial pressure (Pra). This pressure gradient difference is divided by the resistance to venous return (Rvr).

$$VR = \frac{\mathbf{Pms - Pra}}{\mathbf{Rvr}} \qquad \text{(Equation 1)}$$

Therefore venous return and, consequently, cardiac output, will be reduced if: 1) the right atrial pressure is elevated, 2) the mean systemic pressure is low, and/or 3) the resistance to venous return is increased. There are several ways to illustrate this relationship. The classical approach to describe venous return and cardiac output is illustrated in Figure 13. [156]

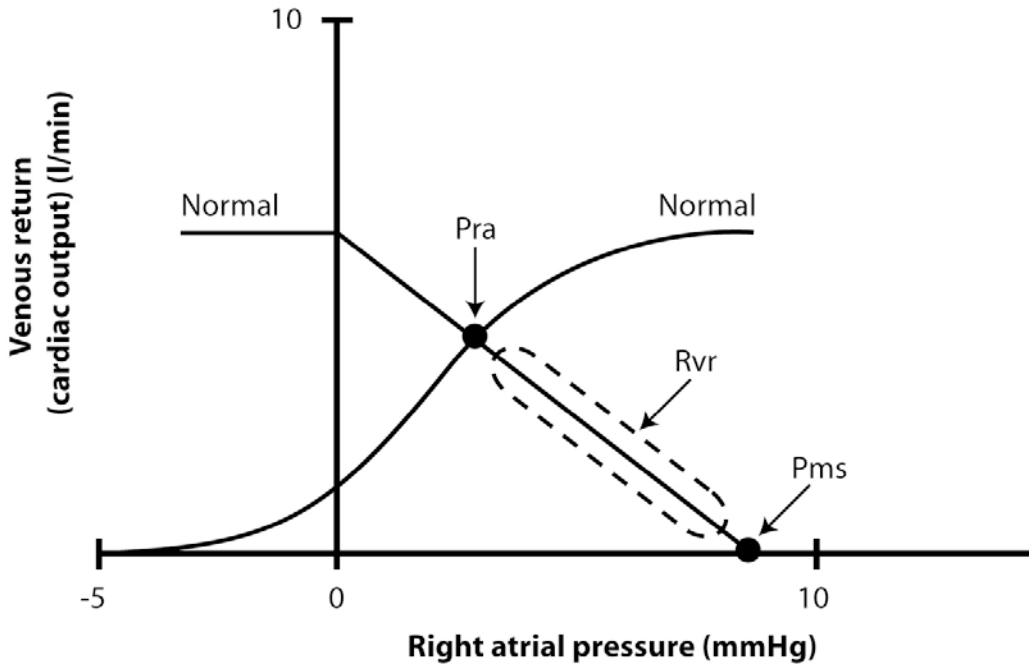


Figure 13 Venous return and cardiac output

The venous return and cardiac output (*y* axis) and its relation with right atrial pressure (*x* axis) is shown. The intersection of both curves will correspond to the right atrial pressure (Pra) at which, in a steady state, an individual will have an unique venous return and cardiac output. The mean systemic pressure (Pms) corresponds to the point where the venous return = 0. The venous return curve is linked to the resistance to venous return (Rvr) (dotted lines) (Adapted from Jacobsohn [156]).

The pressure-volume relationship is used to describe a single cardiac cycle (Figure 14).

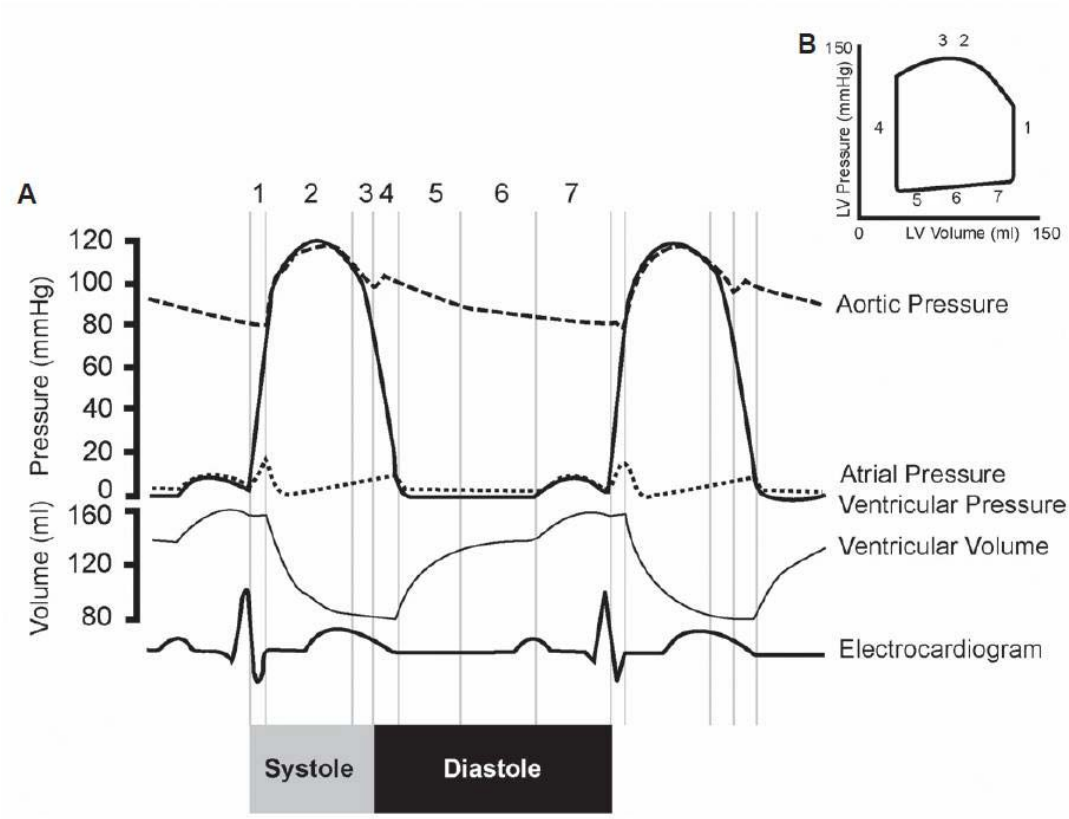


Figure 14 Pressure and volume during a cardiac cycle

(A) Changes in aortic, atrial, ventricular pressure, and ventricular volume in relation to the electrocardiogram. Left ventricular (LV) pressure and volume over time during a cardiac cycle is characterized by seven time-related events. Isovolumic contraction [1] is followed by early [2] and late [3] ejection. Diastole starts with isovolumic relaxation, [4] followed by the early filling phase after the opening of the mitral valve, [5] diastasis, [6] and atrial contraction. [7] (B) Corresponding LV pressure-volume relationship during one cardiac cycle (With permission of Denault *et al.* [12]).

The pressure-volume relationship is typically described for the left ventricle but has also been used to evaluate right ventricular function. [157] The major difference between both ventricles is the reduced pressure in the right compared to the left ventricle. [48] In order to integrate the pressure-volume relationship to the venous return concept, we used a simplified alternative approach illustrated in Figure 15.

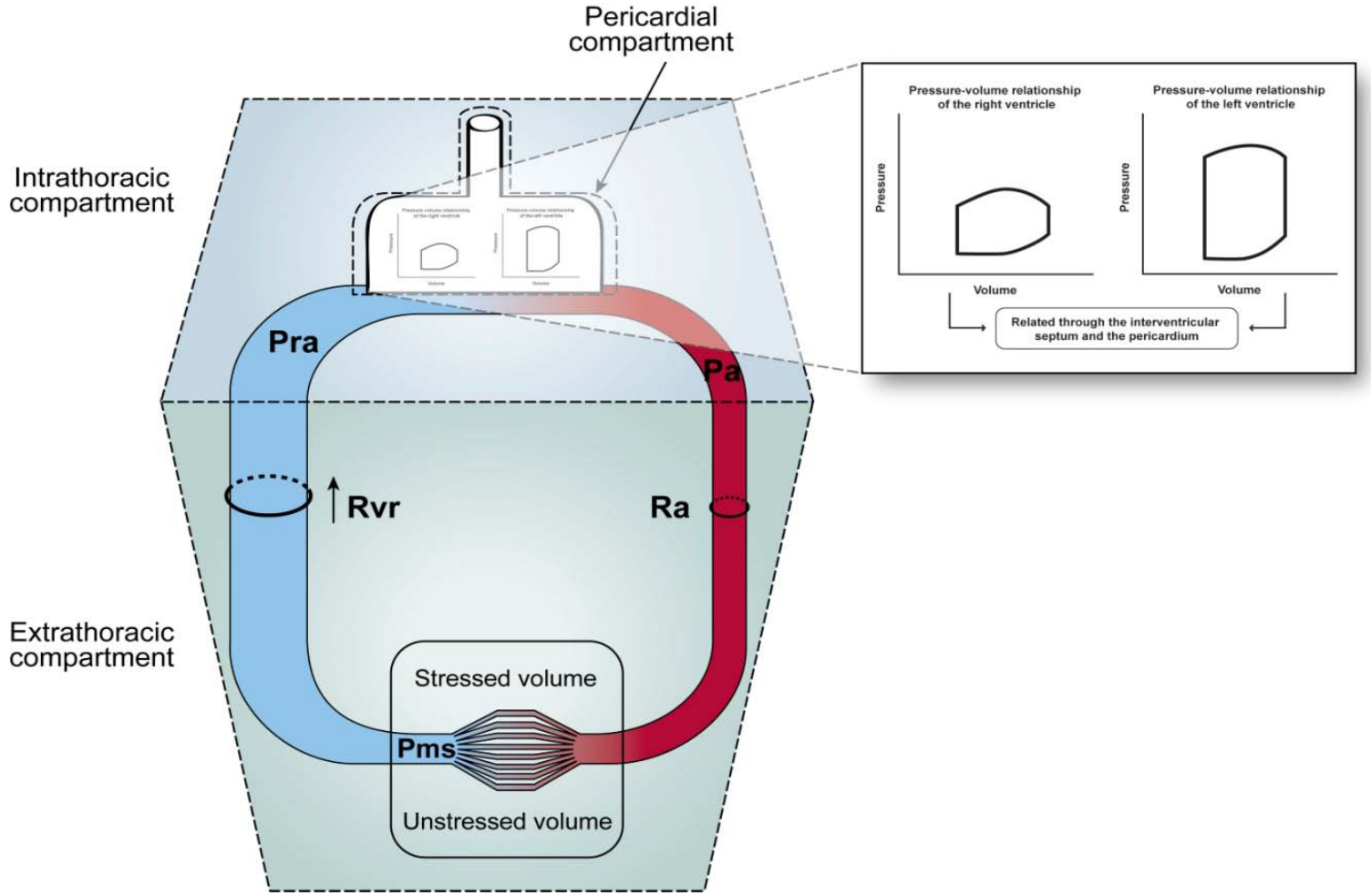


Figure 15 Venous return and pressure-volume loop concept

The circulatory system can be divided into an intrathoracic and an extrathoracic compartment. Illustrated in red is the arterial system and in blue, the venous system. Most of the blood volume (~70%) lies in the venous system. The mean systemic pressure (Pms) is determined by the stressed volume (~30% of blood volume). The cardiac pump has two components, the right and the left ventricles, defined by their respective pressure-volume loops (simplified). Both ventricles are connected together through the pericardium and the interventricular septum. The function and interaction between both ventricles will determine right atrial pressure (Pra). Blood returning back to the heart, i.e. venous return, will be dependent on the pressure gradient between the peripheral pressure, or Pms, and the central pressure, or Pra. Furthermore, any conditions increasing the resistance to venous return (Rvr), for instance compression of the inferior vena cava, will reduce venous return and consequently cardiac output. (Pa, systemic arterial pressure; Ra, arterial resistance) (With permission of Deslauriers *et al*. [158])

The combination of conventional hemodynamic monitoring and TEE allows the determination of the causes of hemodynamic instability. [44] However, so far, a systematic approach in the diagnosis of difficult separation from CPB using conventional hemodynamic and TEE has not been performed in cardiac surgery. This combined approach can be used to determine the causes of difficult separation from CPB. The causes of hemodynamic instability resulting in reduced venous return or cardiac output and leading to difficult separation from CPB are a reduction in Pms, an increase in Pra and an increase in Rvr (Table 11).

Table 11 Mechanism of hemodynamic instability in cardiac surgery

1) Reduction in mean systemic pressure:
- Reduction in stressed volume:
  - Hemorrhagic shock:
    - External hemorrhage
    - Internal: hemothorax, peritoneal hemorrhage, retroperitoneal hemorrrhage, gastrointestinal hemorrhage
- Increased in compliance
  - Sepsis and overwhelming shock [137]
  - Drug-induced vasodilation
  - Anaphylaxis
  - Vasoplegic syndrome
  - Adrenal insufficiency

2) Increased right atrial pressure
- Left and right ventricular systolic dysfunction
- Left and right ventricular diastolic dysfunction
- Left and right outflow tract obstruction
- Left and right embolism
- Aortic and mitral patient-prosthesis mismatch
- Hypoxemia and hypercapnia
- Pulmonary reperfusion syndrome

3) Increased resistance to venous return
- Compartment syndrome
  - Pericardial tamponade
  - Mediastinal: post cardiopulmonary bypass
  - Pleural: hemothorax and pneumothorax
  - Abdominal: intrinsic, extrinsic or parietal
- Vena cava syndrome
  - Inferior
  - Superior

3.1.1 Reduction in mean systemic pressure

The mean systemic pressure, or Pms, will depend on the amount of blood contributing to maintain a specific venous pressure. [156] This can be expressed by the following equation:

$$Pms = \frac{\mathbf{V - Vo}}{\mathbf{Compliance\ of\ the\ venous\ reservoir}}$$

$$Pms = \frac{\mathbf{V - V_0}}{\mathbf{Compliance\ of\ the\ venous\ reservoir}} \quad \text{(Equation 2)}$$

where V is the total volume of the venous reservoir and $\mathbf{V_0}$ the unstressed volume. The difference between V and V_0 is equal to the stressed volume. Consequently, a reduction in Pms will be caused by a loss of stressed volume, such as hemorrhagic shock, or an increase in compliance of the venous reservoir, such as can be the case following drug-induced vasodilation. Reduction of Pms results in a reduction in venous return and cardiac output from a parallel medial shift of the venous return curve. Pressure and volume of both ventricles will be reduced (Figure 16).

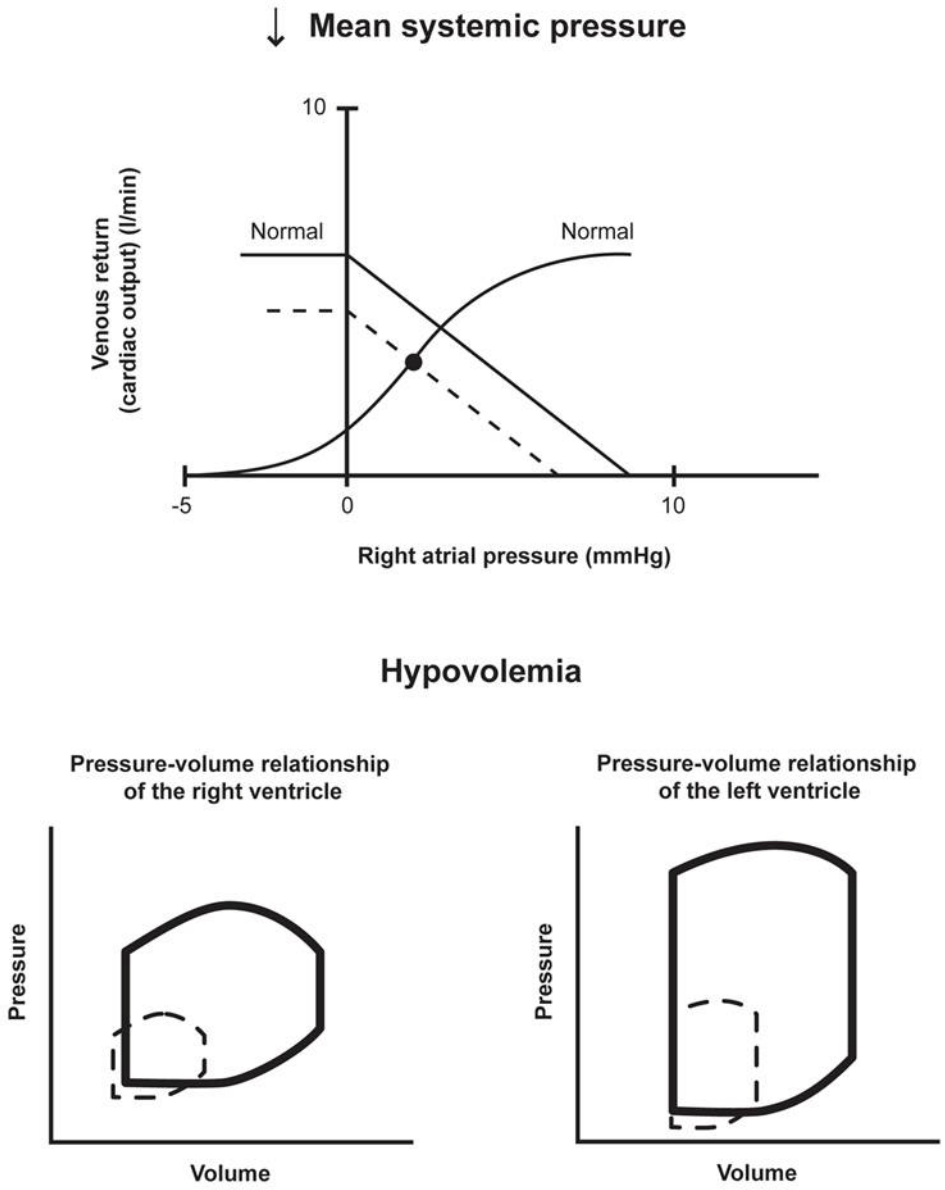


Figure 16 Reduction in mean systemic venous pressure

Reduction in mean systemic venous pressure will result in a medial shift of the venous return curve. In such a situation, pressure and volume of the right and left ventricles will be reduced. This diagnosis can be made with conventional hemodynamic monitoring alone. In such a situation, filling pressure, venous return and cardiac output will be reduced. There are two basic mechanisms: a reduction in the stressed volume and an increase in venous compliance. Both conditions will be associated with a reduction in both left- and right-sided cardiac dimensions; however, some specific echocardiographic findings can suggest rather one mechanism or the other.

3.1.1.1 Reduction in stressed volume

During cardiac surgery, hemorrhagic shock is a common mechanism of reduced Pms that occurs because of a loss of blood volume and, consequently, hemoglobin. Hemorrhagic shock can be defined as internal or external. The latter is easy to diagnose; the former can however prove more difficult to recognize. There are two conditions of internal blood losses that can be diagnosed during cardiac surgery. The first is massive pleural effusion secondary to a hemothorax. We have encountered this condition following traumatic perforation of the superior vena cava during the insertion of a central venous catheter. The diagnosis can easily be made using TEE, as both right and left pleural cavity can be seen using TEE). The mechanism of hemodynamic instability of a hemothorax can also result from an increase in the resistance to venous return, as will be discussed later. In such a situation, right atrial pressure might not be reduced, as the hemothorax can externally compress the right atrium.

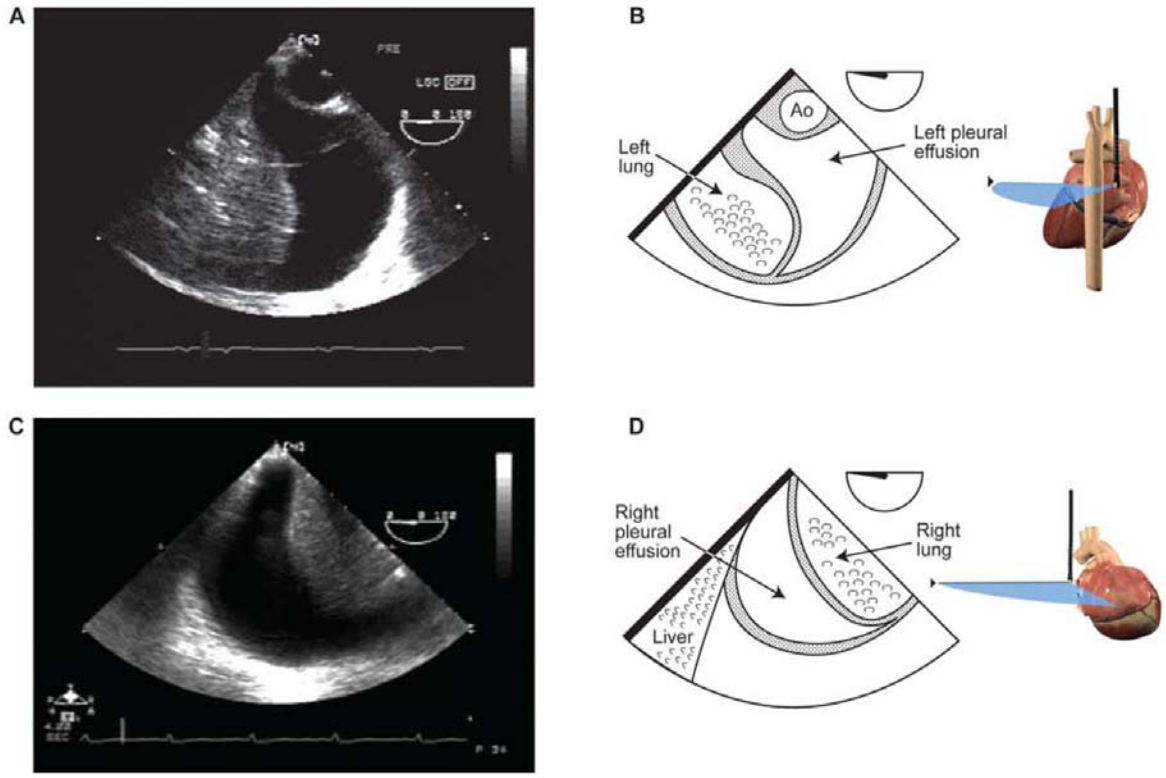


Figure 17 Bilateral pleural effusions

(A, B) The left pleural effusion is typically posterior to the descending aorta (Ao) and seen on the right side of the screen. (C,D) The right pleural effusion is on the left side of the screen where part of the liver can be seen. A total of 2500 mL of pleural fluid was removed from the right (900 mL) and left pleural (1400 mL) cavities (With permission of Denault *et al.* [13]).

Another cause of hemodynamic instability easily diagnosed in the operating room is peritoneal hemorrhage. This can result from abdominal aortic or iliac rupture, which can occur during manipulation of these structures. This situation has been encountered during the emergency insertion of an IABP. The diagnosis is based on the new onset of fluid collection in the abdomen. The echocardiographic image is similar to that of ascitis (Figure 18).

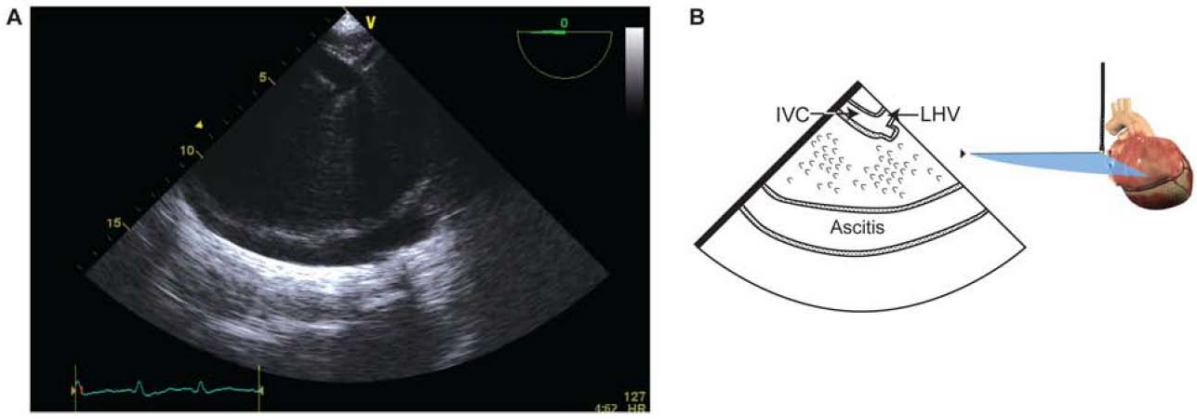


Figure 18 Abdominal examination using transesophageal echocardiography

(A,B) Presence of ascitis in a 58-year-old woman. (IVC, inferior vena cava, LHV, left hepatic vein) (Courtesy of Denault *et al.* [13]).

Other sites of bleeding include the gastrointestinal tract and the retroperitoneal space. Such a diagnosis would require other modalities, such as gastrointestinal endoscopy and computed tomography.

3.1.1.2 Increase in venous compliance

The second mechanism involved in a reduction in Pms is an increased compliance of the vascular system. This diagnosis can also be suggested by some specific echocardiographic signs evocative of an infectious process, for instance. Increased venous compliance can develop following the use of several drugs during cardiac surgery, during the vasoplegic syndrome and, in some cases, sepsis. [137]

The use of preoperative angiotensin-converting enzyme inhibitors has been associated with vasodilatory shock in cardiac surgery. [159] In such a case, vasopressin has been proposed as a drug of choice. [160;161] Drug-induced vasodilation can occur shortly following the induction of anesthesia and is often rapidly reversible. Anaphylactic reaction can also occur, particularly during the administration of blood products, aprotinin and protamine, and in patients previously exposed to these agents. Adrenaline or even vasopressin can be used in such a situation. [162] Similarly, the administration of protamine can be associated with acute pulmonary hypertension combined with right ventricular failure. [163] In these situations heparine, methylene blue [163] or inhaled prostacyclin [164] have been used to manage unstable patients. Patients exposed to or under corticosteroids can also present a predisposition to adrenal insufficiency, another cause of increased venous compliance. [165]

The term “vasoplegic syndrome” has been used to describe a severe systemic inflammatory response syndrome occurring after CPB [166] and, in rare instances, in patients without CPB. [136] Vasoplegic syndrome is defined as a mean arterial pressure < 60 mmHg, a cardiac output greater than 4.0 L/min, and low systemic vascular resistance (600 dyne/s/cm^5) under an intravenous norepinephrine infusion (0.5 µg/kg/min)[1]. [167] This condition can occur in up to 5% of patients undergoing cardiac surgery and is associated with an increased morbidity and mortality going up to 5.6%. Treatment with methylene blue has been shown to be effective in 94% of cases. [167] The mechanism of the vasoplegic syndrome is thought to be related to surgical trauma, contact of blood

[1] This is equivalent to 130 mL/hr of norepinephrine (4 mg/250 mL) for a 70 kg patient.

components with the artificial CPB circuit and lung reperfusion injury. [168] This effect will trigger a cytokine-mediated activation of platelets and leukocytes. Both tumor necrosis factor α (TNF-α) and interleukin-6 levels are related to the degree of surgical stress. [169] A high level of TNF-α will promote the secretion of nitric oxide (NO) and platelet-activating factor (PAF). The release of NO will reduce systemic vascular resistance and increase compliance; PAF is partially responsible for the increased permeability in sepsis and shock. [170]

Finally, emergency operation in patients already hemodynamically unstable on vasoactive medication is a well-known risk factor for LCOS [75;78] and mortality. [141] These patients may already show an increase in venous compliance from sepsis. Active endocarditis for instance, with the associated sepsis, is an important predictor of outcome in the Parsonnet score [100] and EuroSCORE. [101;141] In such conditions, the requirement for vasoactive medication can be the result not only of an increased venous compliance but is also often associated with other mechanisms.

3.1.2 Increased right atrial pressure

Increased right atrial pressure can result from left and right systolic dysfunction, diastolic dysfunction, outflow tract obstruction and embolism. In addition, certain biochemical conditions can increase pulmonary vascular resistance, such as hypoxemia, hypercapnia and the pulmonary reperfusion syndrome (see Chapter 6). Aortic and mitral patient-prosthesis mismatch are other factors that can contribute to an increase in right atrial pressure. These conditions, along with their definitions, mechanisms and echocardiographic signs, will be reviewed.

3.1.2.1 Left ventricular systolic dysfunction

One of the most common causes of elevated right atrial pressure is left ventricular systolic dysfunction. During cardiac surgery, left ventricular systolic dysfunction can result from ischemia, poor protection during CPB and air embolism. In a situation where systolic

dysfunction appears either to the left or the right, a right-sided (or lateral) shift of the pressure-volume relationship will be observed. Biventricular volumes will be increased, while ventricular pressure is typically normal or high (Figure 19).

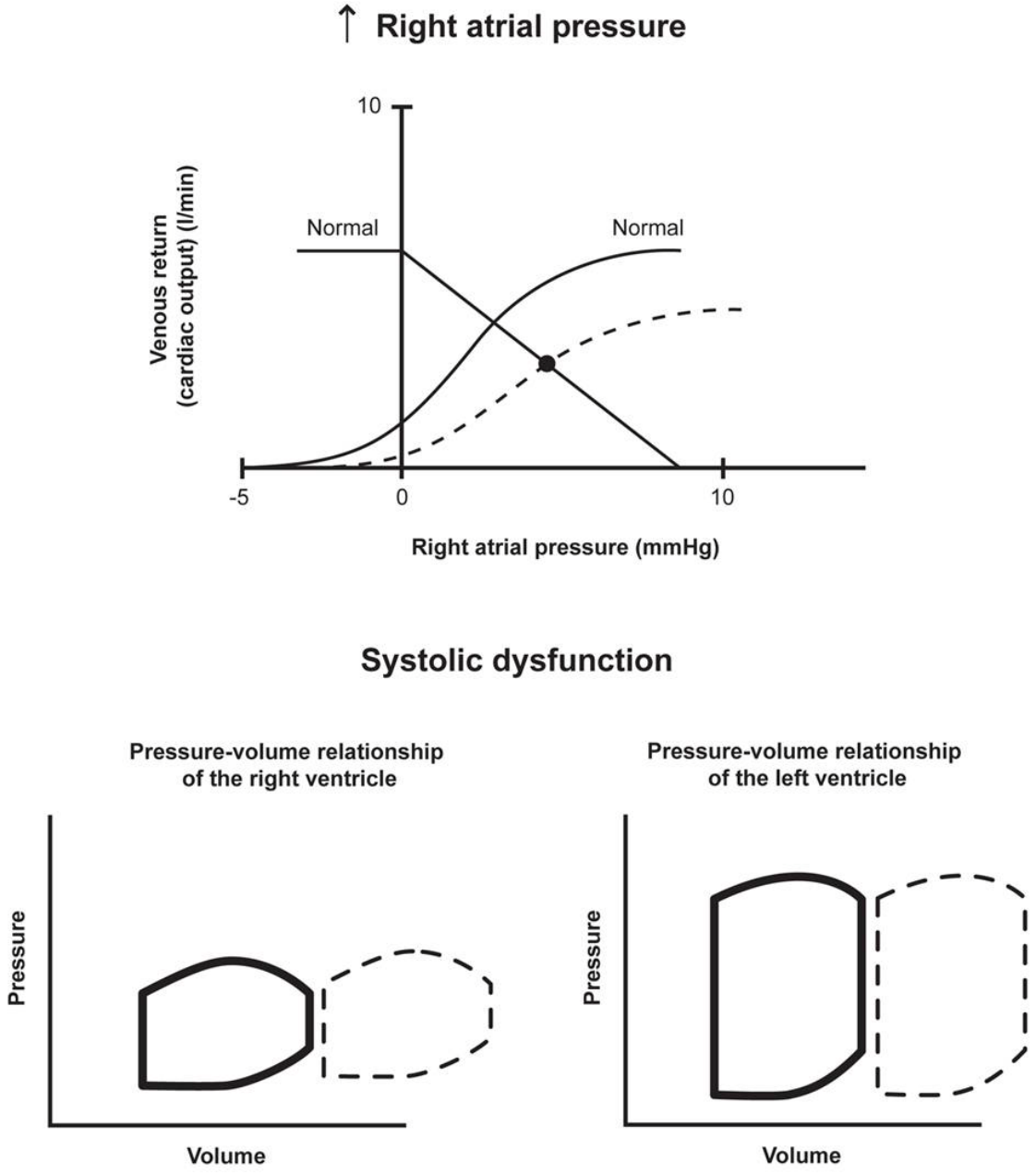


Figure 19 Biventricular systolic dysfunction

Biventricular systolic dysfunction will be associated with a reduction in venous return and cardiac output. The right atrial pressure will increase. In that situation, the pressure and volume of the right and left ventricles will shift laterally.

Echocardiographically, signs of left ventricular dysfunction include a reduced left ventricular ejection fraction measured either using a mid-esophageal view (Figure 20) or transgastric view (Figure 21).

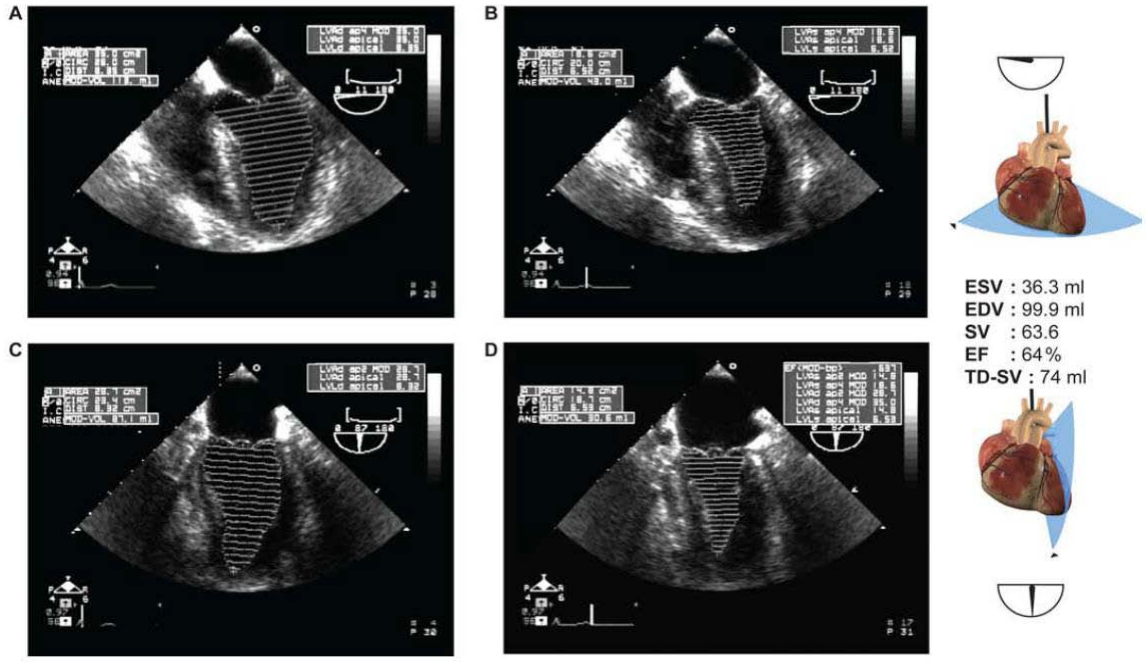


Figure 20 Simpson's method of discs

Measurement of left ventricular volumes by modified Simpson's biplane method using mid-esophageal four- (A,B) and two-chamber (C,D) views. The calculated echocardiographic stroke volume (SV) was slightly different from the SV measured with thermodilution (TD) (EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume). (With permission of Denault *et al.* [13])

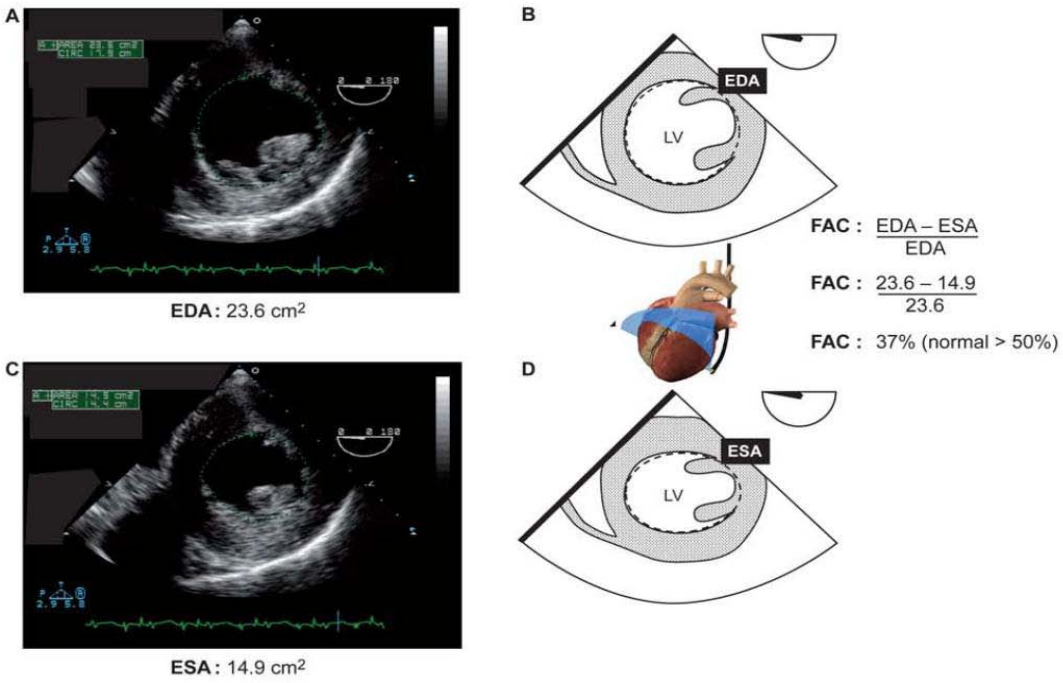


Figure 21 Left ventricular fractional area change

Measurement of fractional area change (FAC) in a 75-year-old man with unstable angina undergoing emergency revascularization. A transgastric mid-papillary view of the left ventricle (LV) in diastole (A,B) and in systole (C,D) provides the measurements to calculate the FAC, which was 26%. Note the exclusion of the papillary muscles during tracing of the areas. (EDA, end diastolic area; ESA, end systolic area). (With permission of Denault *et al.* [12])

Left ventricular systolic dysfunction originating from either coronary artery disease, cardiomyopathy, or associated with valvular heart disease, will be associated with an elevated left ventricular filling pressure and, consequently, post-capillary pulmonary hypertension. In cardiac surgery, left ventricular systolic dysfunction can be present before or after the procedure.

When present before the procedure, left ventricular systolic dysfunction, defined as reduced LVEF or associated with regional wall motion abnormalities (RWMA), is a known predictor of perioperative mortality in cardiac surgery. [73] This observation was well described in the Coronary Artery Surgery Study (CASS) in 1983. [171] This study

analyzed 7658 patients who underwent isolated coronary revascularization, irrespective of age, and examined whether an age of 65 years or older was an independent predictor of perioperative mortality. The variables selected, in order of significance, were: congestive cardiac failure score; left main coronary artery stenosis and a left-dominant circulation; age of 65 years or older; left ventricular wall motion score; gender; and history of unstable angina pectoris. [171] When left ventricular dysfunction before cardiac surgery is associated with mortality, the mechanism involved is most likely hemodynamic instability. Indeed, in a smaller study of 128 patients undergoing coronary revascularization, Royster *et al.*, [58] using logistic regression analysis, observed that LVEF was significantly lower and the most significant factor ($p = 0.0022$) associated with the requirements for inotropes after cardiac surgery.

Left ventricular dysfunction can occur after cardiac surgery and will be associated with a worse outcome. Leung *et al.* [172] found that postoperative RWMA, as demonstrated by TEE, was the most reliable predictor of operative outcome. Six of 18 patients with postoperative RWMA had an adverse outcome, defined as myocardial infarction, severe left ventricular dysfunction requiring inotropic therapy, or cardiac death, whereas none of the 32 patients without postoperative RWMA showed any adverse outcome.

In summary, reduced left ventricular dysfunction is associated with worse outcome after cardiac surgery when it is present before or after the procedure. Post-capillary pulmonary hypertension is the consequence of left ventricular dysfunction; however, an elevation of LVEDP will appear before elevated left atrial pressures reach the pulmonary circulation. In addition, elevated LVEDP can be present without reduced left ventricular systolic function. This condition is named left ventricular diastolic dysfunction.

3.1.2.2 Left ventricular diastolic dysfunction

Diastolic dysfunction is evaluated and diagnosed by an accepted classification and recommended guidelines (Figure 22). [173;174] These guidelines are based on Doppler signals obtained at the mitral valve leaflet, namely the transmitral flow (TMF) early (E) and

atrial (A) velocities, the pulmonary venous flow (PVF) systolic (S) and diastolic (D) velocities and the myocardial wall velocities measured at the mitral annulus, so-called the mitral annular velocities (MAV). The latter are composed of Em (early component of the MAV) and Am (late or atrial component of the MAV). In patients undergoing cardiac surgery, we have used the following criteria to define diastolic function: normal (TMF E/A >1, PVF S/D >1, MAV Em/Am >1), mild diastolic dysfunction (E/A < 1, S/D >1, MAV Em/Am <1), moderate diastolic dysfunction (E/A 1, S/D <1, MAV Em/Am <1), and severe diastolic dysfunction (E/A >2, S/D <1, MAV Em/Am < or >1).

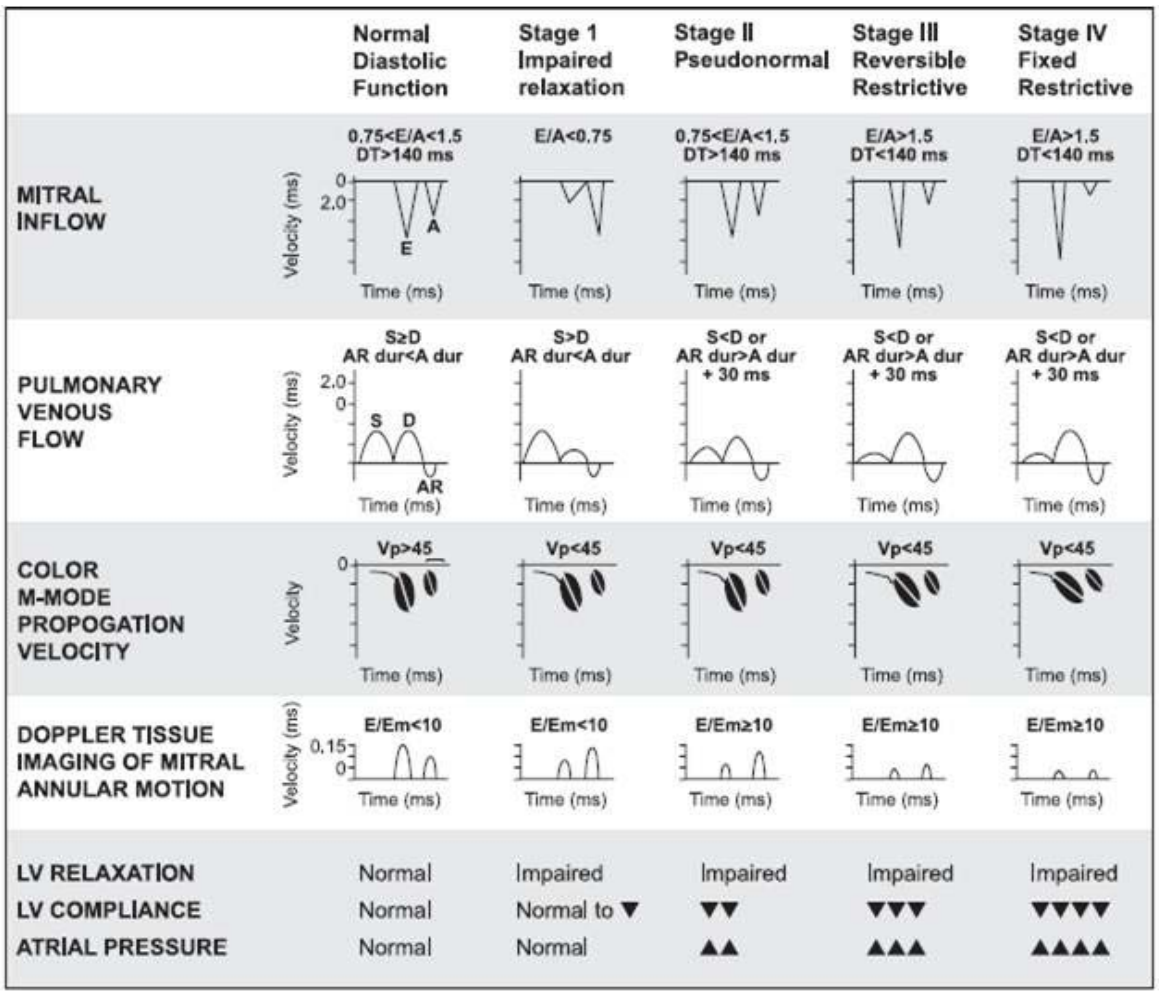


Figure 22 Echocardiographic classification of diastolic dysfunction

(A, peak late diastolic transmitral flow velocity; A dur, duration of mitral inflow A-wave; AR dur, peak pulmonary venous atrial reversal flow velocity duration; D, peak diastolic pulmonary venous flow velocity; DT, deceleration time; E, peak early diastolic transmitral flow velocity; Em, peak early diastolic myocardial velocity; LV, left ventricular; S, peak systolic pulmonary venous flow velocity; Vp, flow propagation velocity). (With permission of Denault *et al.* [12]).

Diastolic dysfunction of both the left and right ventricles will be associated with a normal or reduced volume requiring an increased filling pressure (Figure 23).

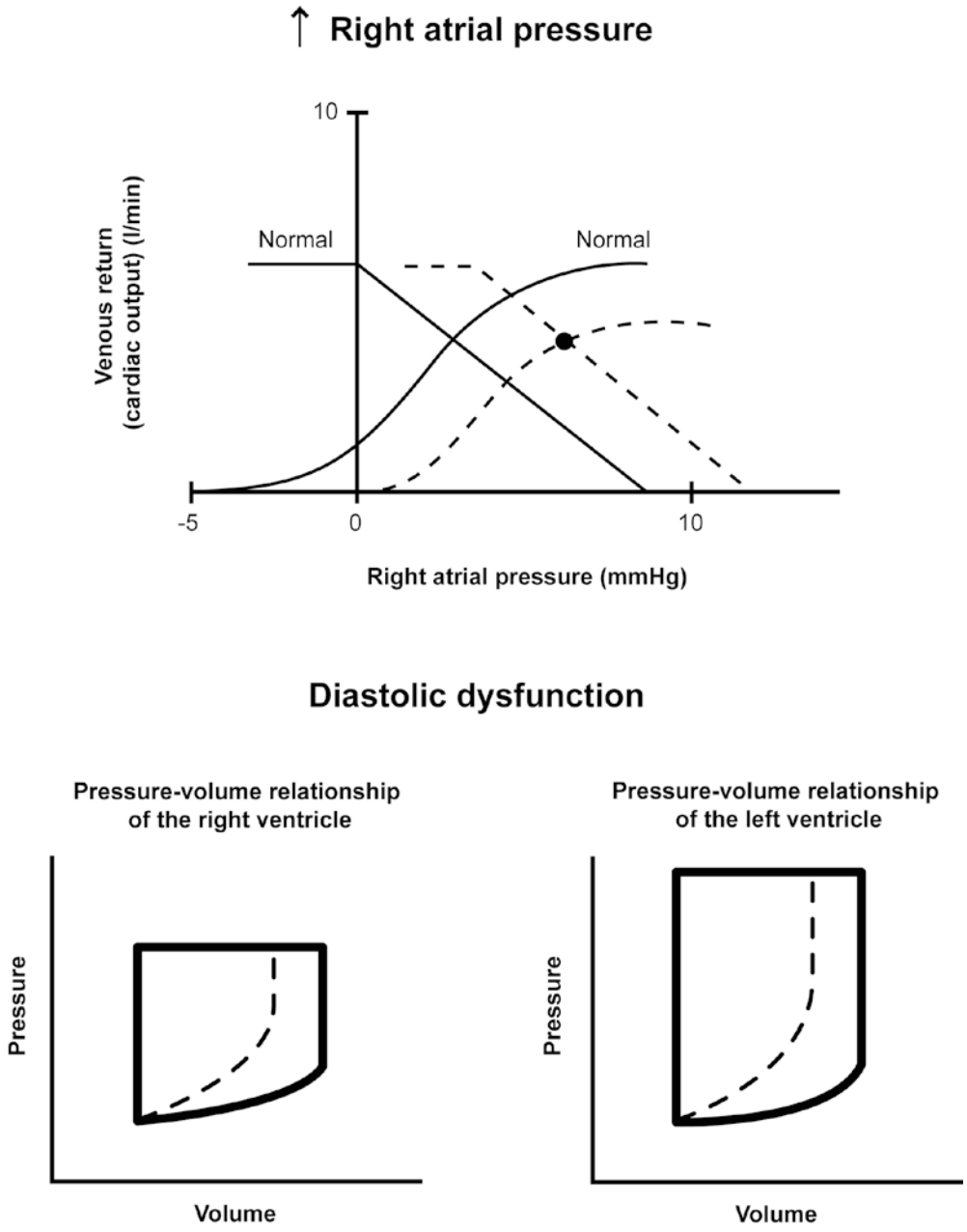


Figure 23 Biventricular diastolic dysfunction

Biventricular diastolic dysfunction will be associated with a maintained venous return and cardiac output. However, the right atrial pressure will increase from a parallel rightward shift of the venous return curve. In that situation, the filling pressure will increase and ventricular volume can be normal or reduced.

The recognition that left ventricular diastolic dysfunction plays a central role in the pathophysiology of cardiac disease has been compared to the discovery of the Rosetta Stone, which played a key role in understanding 1000 years of Egyptian history. [175] This new understanding was triggered by developments in echocardiography that allowed for a simple, rapid and non-invasive assessment of cardiac function. However, before echocardiography was routinely used in cardiology, several clinicians observed that elevated LVEDP *per se* was associated with mortality. In 1983, in the CASS study, Gersh *et al.* [171] reported their results on 1086 patients of 65 years of age or older who underwent isolated coronary artery bypass grafting. Using a stepwise linear discriminant analysis, the authors identified five variables predictive of perioperative mortality. The first was the presence of 70% or more stenosis of the left main coronary artery and a left-dominant circulation, and the second most important factor was LVEDP.

There is a growing interest in the evaluation of diastolic dysfunction. Diastolic dysfunction is associated with reduced survival in patients with congestive heart failure, [176;177;177-179] sepsis [180] and following acute myocardial infarction. [181;182] This is consistent with the observation that preoperative elevated LVEDP increases the incidence of postoperative inotropic support [58;104] and mortality. [8;11;183] It also supports the hypothesis that diastolic dysfunction before cardiac surgery could have an impact on survival and postoperative complications. [17;39;155;184;185]

The hypothesis that patients with diastolic dysfunction are at higher risk of hemodynamic instability after cardiac surgery is supported by a study by Bernard *et al.* [17] that included 66 patients, of whom 52 underwent coronary revascularization alone. The factors associated with an increased need for vasoactive support after CPB were: female gender, diastolic dysfunction and prolonged duration of CPB. Diastolic dysfunction was more significant than systolic dysfunction in predicting difficult separation from CPB and vasoactive requirement after surgery. The importance of preoperative diastolic dysfunction as an independent predictor of hemodynamic complications and survival in cardiac surgery was reconfirmed by four other investigations. [39;155;184;185]

In summary, diastolic dysfunction will predispose to hemodynamic instability because the impairment of the left ventricle to accommodate volume and the consequent elevated LVEDP can predispose to pulmonary edema, pulmonary hypertension and right ventricular dysfunction. Finally, when hemodynamic instability occurs after cardiac surgery, it is almost invariably associated with filling abnormalities. [19]

3.1.2.3 Right ventricular systolic dysfunction

There are several ways to evaluate right ventricular function, and these methods were reviewed by Haddad *et al.* [48] Right ventricular function is commonly measured with 2D or Doppler echocardiography following published guidelines. [186] Right ventricular fractional area change (normal > 35%) (Figure 24), right ventricular myocardial performance index (Figure 25) and tricuspid annular plane systolic excursion (Figure 26) [44] can be obtained to evaluate right ventricular function. The right ventricular myocardial performance index is stratified as ≤ or 50%, as previously described. [187;188]

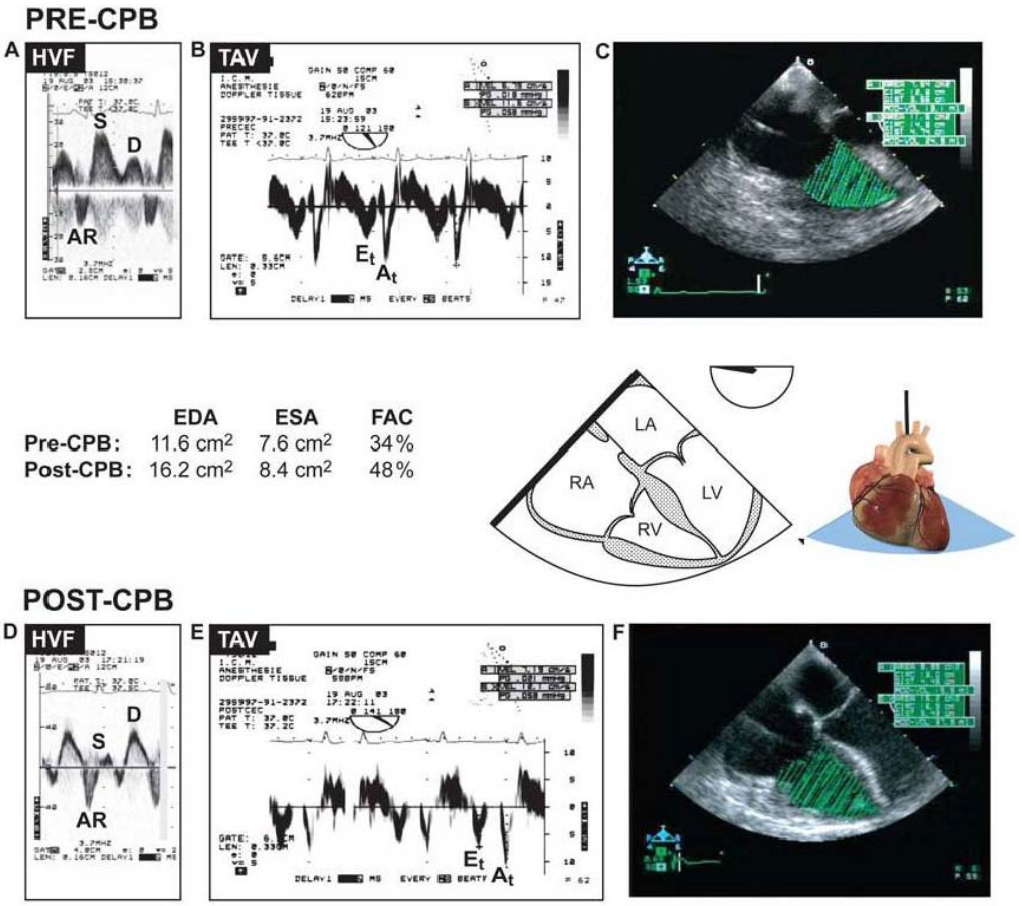
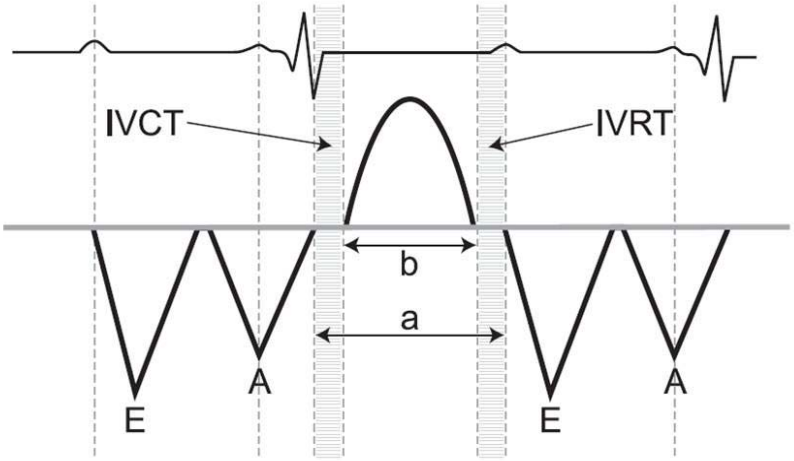


Figure 24 Right ventricular systolic and diastolic function

A 65-year-old man with previous inferior myocardial infarction scheduled for coronary revascularization. (A–C) Before cardiopulmonary bypass (CPB) the ejection fraction of the left ventricle (LV) is 20% with a low cardiac index of 1.5 L/min per m². (A) Pulsed wave Doppler hepatic venous flow (HVF) shows systolic flow (S) predominance. (B) Tricuspid annular velocities (TAV) by tissue Doppler shows a E_t/A_t ratio < 1 (E_t = 5.7 and A_t = 11.5 cm/sec). Both suggest mild diastolic dysfunction of the RV. (C) The fractional area change (FAC) of the RV is 34%. (D–F) Post-CPB. (D) The HVF showed new blunting of the systolic flow. (E) The TAV are increased with a similar ratio (E_t = 7.1 and A_t = 12.1 cm/sec). This suggests decreased RV compliance. (F) Right ventricular FAC increased to 48% consistent with the surgeon's visual appreciation of improved right ventricular function. Upon arrival to the intensive care unit, the cardiac index was 3.0 L/min per m² (AR, atrial reversal; EDA, end-diastolic area; ESA, end-systolic area; LA, left atrium; RA, right atrium). (With permission of Denault *et al.* [12])



$a = IVRT + IVCT + ET$

$b = ET$

$$MPI = \frac{a - b}{b} = \frac{IVRT + IVCT}{ET}$$

Normal value: LV = 0.39 ± 0.05
RV = 0.28 ± 0.04

Figure 25 Myocardial performance index (MPI)

Measurement of MPI or Tei index. (1) For the MPI of the left ventricle (LV), the transmitral inflow is used for measurement of the duration "a" from the end of atrial contraction (A-wave) to the beginning of LV filling (E-wave). (2) The ejection time (ET) or "b" is measured from a deep transgastric long-axis view Doppler interrogation of the left ventricular outflow tract. The MPI of the right ventricle (RV) is similarly obtained using the transtricuspid flow and the mid-esophageal ascending aorta short-axis view for the right ventricular outflow tract (IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time). (With permission of Denault *et al.* [12])

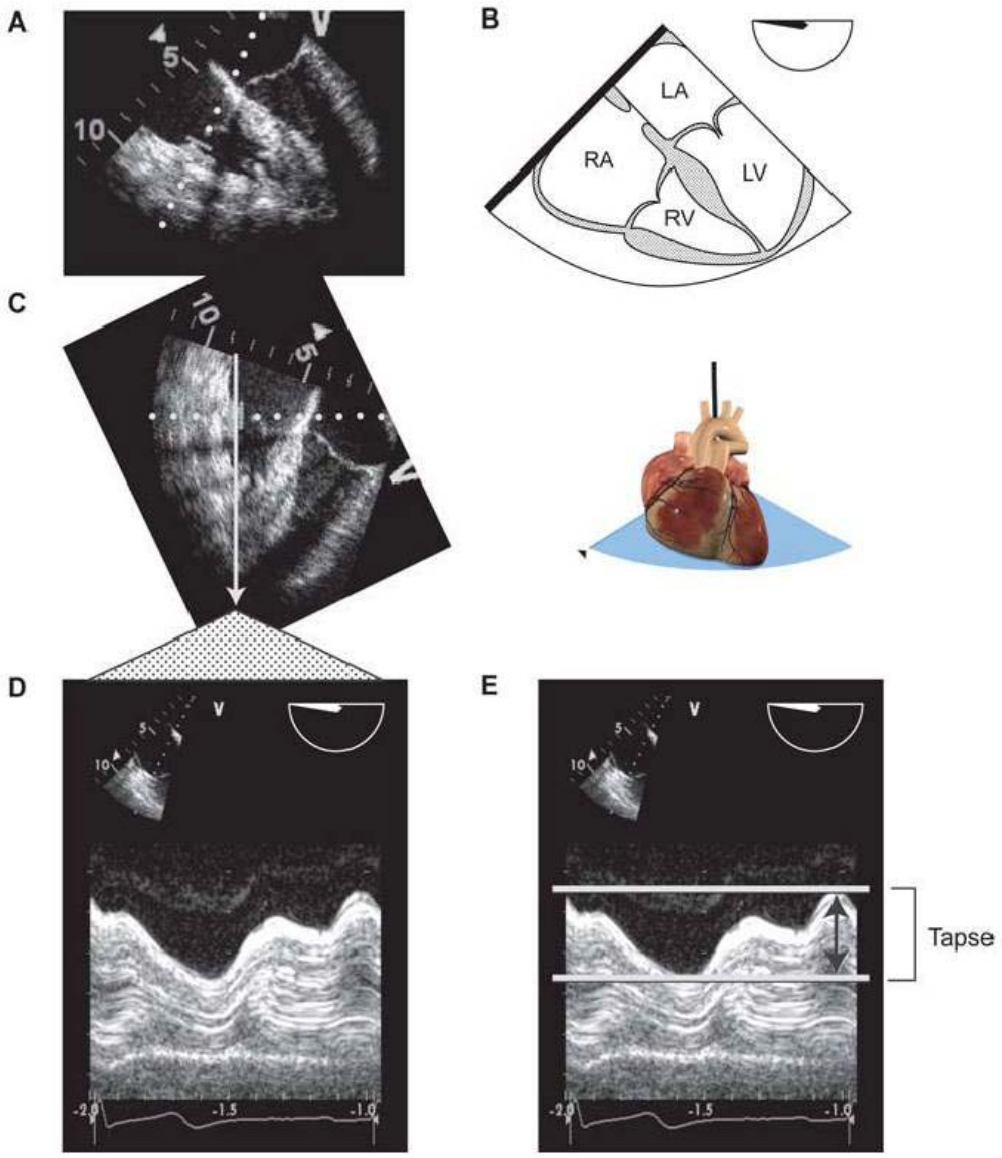


Figure 26 Tricuspid annular plane systolic excursion (TAPSE)

Steps in the measurement of the TAPSE measured using anatomic M-mode. First a four-chamber view is obtained (A-B). Then the M-mode cursor is positioned along the plane of the TAPSE motion (C). An M-mode figure of this excursion or displacement is obtained (D). The lower point corresponds to the maximal systolic excursion and the upper point is the atrial contraction. The TAPSE is equal to the total systolic excursion of the tricuspid annulus (E). Normal TAPSE should be 20-25 mm. (With permission of Denault *et al.* [12])

Right ventricular systolic dysfunction can be associated or not with left ventricular systolic dysfunction. The mechanism of biventricular systolic dysfunction was illustrated in Figure 27 However, isolated right ventricular systolic dysfunction can lead to left ventricular diastolic dysfunction and left ventricular outflow tract obstruction (Figure 27). In severe cases, this can lead to the opening of a patent foramen ovale and worsening hypoxemia. Hypoxemia will further increase pulmonary hypertension and thus lead to a deterioration of the right ventricular function if the cycle is uninterrupted.

There is growing evidence that morbidity and mortality associated with pulmonary hypertension (discussed in more detail in Chapter 6) are dependent on right ventricular adaptation to disease rather than on the absolute value of pulmonary arterial pressure. [46;189-191] Survival and outcome in idiopathic pulmonary arterial hypertension are more related to elevated mean right atrial pressure and reduced cardiac output than to pulmonary arterial pressure values alone. [189;192]

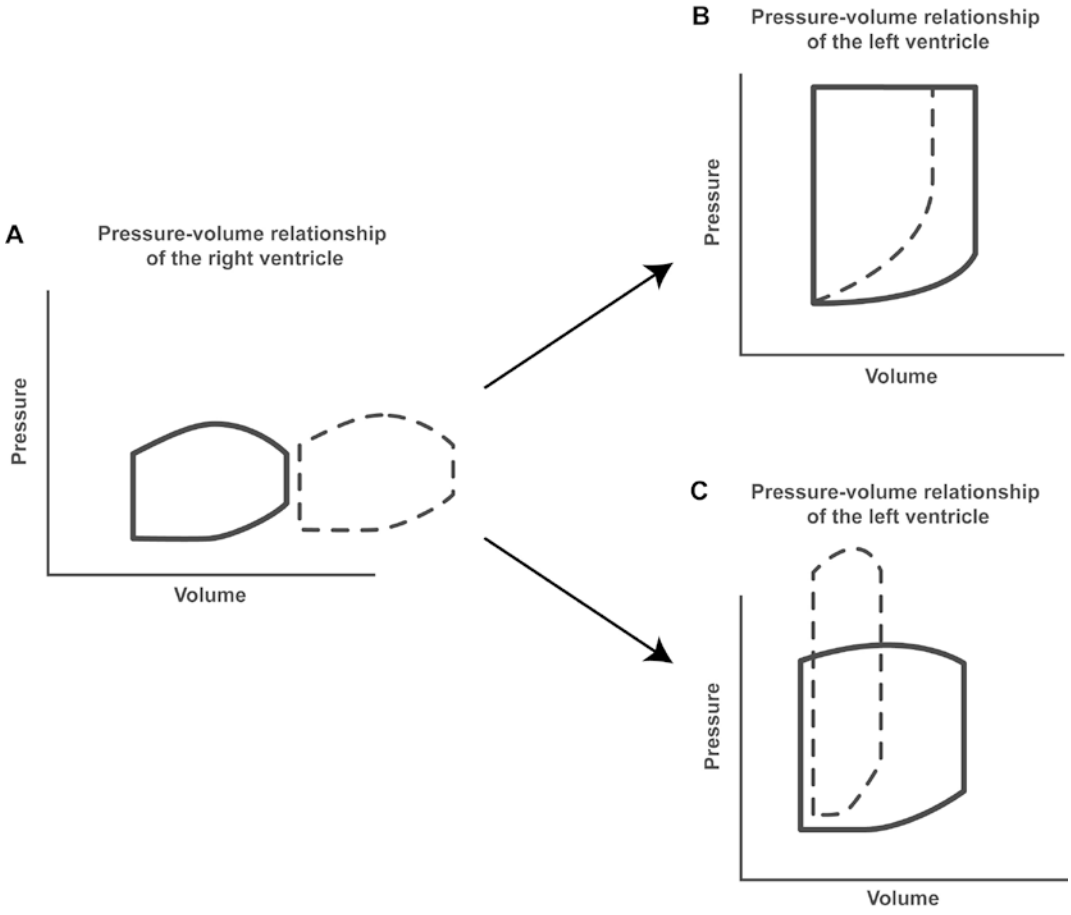


Figure 27 Isolated right ventricular systolic dysfunction

Isolated right ventricular systolic dysfunction (A) can alter the geometry of the left ventricle via the common pericardium and the interventricular septum through 2 mechanisms. The most frequent is a filling abnormality (B). This is associated with a reduction in left ventricular volume and an increase in left ventricular pressure. The second mechanism can appear in very severe right ventricular dysfunction. This will also be associated with a reduction in left ventricular volume, an increase in left ventricular pressure but also left ventricular outflow tract obstruction (C). In the latter situation, the use of inotropes could exacerbate the left ventricular outflow tract obstruction.

The importance of right ventricular function in cardiac surgery has been demonstrated in a variety of clinical settings such as high risk coronary or valvular heart disease, congenital heart disease, heart transplantation, in patients requiring mechanical assist devices and in the unstable postoperative patient (Table 12).

Table 12 Prognostic value of right ventricular function in cardiac surgery

Study	Population	Study Design	RV dysfunction	Results
Reitchert *et al.* [3]	Unstable postoperative patients	Prospective *n* = 60	RVFAC < 35%	RV dysfunction associated with high mortality rates
Pinzani *et al.* [193]	Mitral and combined mitro-aortic surgery	Retrospective *n* = 382	Clinical definition	Postoperative RV failure is the strongest predictor of postoperative mortality
Cullen *et al.* [194]	Tetralogy of Fallot	Prospective *n* = 35	Restrictive RV physiology	Restrictive physiology predicts longer intensive care unit stay post repair and lower cardiac output
Gatzoulis *et al.* [195]	Tetralogy of Fallot	Prospective *n* = 41	Restrictive RV physiology	Restrictive physiology predicts smaller RV and better exercise tolerance
Kromos *et al.* [196]	LVAD and RV failure	Retrospective *n* = 31	Clinical mean RVEF = 11.8%	Preoperative clinical factors such as fever, pulmonary edema, and intraoperative blood transfusions were associated with RVAD need
Hosenpud *et al.* [197]	Heart Transplantation	Retrospective International Society for Heart & Lung transplantation *n* = 69,205	RV failure associated with circulatory failure	RV failure accounts for up to 20% of early deaths

Study	Population	Study Design	RV dysfunction	Results
Oehiai *et al.* [6]	LVAD	Retrospective *n* = 245	RV failure requiring RVAD	23 patients (9%) required RVAD. The need for circulatory support, female gender, and non-ischemic etiology were predictors of RVAD need.
Maslow *et al.* [112]	CAD undergoing coronary bypass surgery with LVEF < 25%	Retrospective *n* = 41	RVFAC < 35%	RV dysfunction is associated with decreased long term survival
Therrien *et al.* [198]	Tetralogy of Fallot	Prospective *n* = 17	RV remodeling	Severe RV dilatation (RVEDV >170 mL/m² or RVESV > 85 mL/m²) associated with incomplete RV remodeling
Webb *et al.* [199]	Atrial septal defect	Retrospective series	RV remodeling	Older age at repair and abnormal RV myocardial relaxation were associated with incomplete RV remodeling
Denault *et al.* [38]	Patients undergoing bypass surgery	Retrospective and prospective *n* = 800	Dynamic obstruction of RVOT (Gd > 25 mmHg)	Incidence: 4%, dynamic obstruction of RVOT was associated with a higher incidence of difficult weaning from bypass
Haddad *et al.* [46]	High-risk valvular surgery	Prospective *n* = 50	RVFAC < 32% or RVMPI > 0.50	Preoperative RV dysfunction was associated with a higher incidence of postoperative circulatory failure

CAD: coronary artery disease, Gd: gradient, LV: left ventricular, LVAD: left ventricular assist device, RV: right ventricular, RVAD: right ventricular assist device, RVES: right ventricular end-systolic volume, RVED: right ventricular end-diastolic volume, RVEF: right ventricular ejection fraction, RVFAC: right ventricular fractional area change, RVMPI: right ventricular myocardial performance index, RVOT: right ventricular outflow tract obstruction (From Haddad *et al.* [49])

However, most of the evidence that supports the importance of right ventricular function is based on retrospective or small prospective studies. To date, parameters of right ventricular function have not been included in large-scale risk stratification models and therefore their incremental value to the Parsonnet score or the EuroSCORE have not been well established. [100;103;200;201] A recent panel from the National Institutes of Health has stressed the importance of research in the understanding of right ventricular failure. [191] Right ventricular dysfunction can be present before or after the surgical procedure.

In patients presenting with severe aortic stenosis, Boldt *et al.* [202] have demonstrated that preoperative right ventricular dysfunction was associated with a greater requirement of postoperative inotropic support. In a retrospective study including patients undergoing mitral and mitral-aortic valvular surgery, Pinzani *et al.* [193] demonstrated that preoperative right ventricular failure was associated with perioperative mortality. In this same study, postoperative right ventricular failure was the most important independent predictor of late survival. In a small prospective study of 14 patients with severe non-ischemic mitral regurgitation and high-risk descriptors (LVEF $\leq$ 45% or RV ejection fraction (RVEF) $\leq$ 20%), Wencker *et al.* [203] found that preoperative RVEF $\leq$ 20% predicted late postoperative death. In patients undergoing coronary revascularization, Maslow *et al.* [112] showed that right ventricular dysfunction defined by a right ventricular fractional area change (RVFAC) of less than 35% in the context of severe left ventricular systolic dysfunction (LVEF $\leq$ 25%) and non -emergent coronary revascularization was associated with an increased risk of postoperative morbidity and mortality. In this retrospective study ($n = 41$), patients with right ventricular dysfunction had a higher prevalence of diabetes mellitus and renal disease, as well as a higher incidence of postoperative inotropic or mechanical support, longer intensive care unit and hospital stay and a decreased short-term and long-term survival.

The presence of right ventricular failure after CPB is associated with a mortality rate ranging from 44% to 86%. [4] The incidence of post-cardiotomy acute refractory right ventricular failure ranges from 0.04 to 0.1%. Acute refractory right ventricular failure has also been reported in 2-3% patients after a heart transplant and in almost 20-30% patients

who received a left ventricular assist device support, with a reported initial salvage rate of only 25-30%. [5]

3.1.2.4 Right ventricular diastolic dysfunction

The mechanism of right ventricular diastolic function was illustrated in Figure 23. Normal right ventricular diastolic function [204] is defined using normal values reported for Doppler transtricuspid flow early (E) and atrial (A) velocities, [205] hepatic venous flow (HVF) systolic (S), diastolic (D) and atrial reversal (AR) velocities [113;114;206] and tissue Doppler imaging (TDI) of the tricuspid annulus. [207;208] The latter are composed of the Et (early component of the TDI) and At (late or atrial component of the TDI). Right ventricular diastolic function is classified as normal (TTF E/A >1, HVF S/D >1, Et/At >1), mild diastolic dysfunction (E/A <1, or reversed AR >50% of S wave measured on HVF, or Et < At when both E/A and S/D >1), moderate diastolic dysfunction (E/A ≥1, S/D <1, Et/At <1), and severe diastolic dysfunction (S wave reversal on HVF, irrespective of the E/A and S/D ratio).

Right ventricular diastolic dysfunction could constitute an additional marker to identify populations at higher risk of requiring vasoactive support, and potentially other clinical outcomes. We have previously documented that in hemodynamically unstable patients in the intensive care unit, abnormal right ventricular filling abnormalities were the most common echocardiographic observation. [19] We also noted, in a pilot study, that abnormal hepatic venous flow, when present before cardiac surgery, was associated with an increased need for vasoactive support after cardiac surgery. [34] In these two previous studies, patients were also not graded according to the severity of right ventricular diastolic dysfunction; however, in a recent study, [39] we were able to confirm that moderate to severe right ventricular diastolic dysfunction is associated with lower cardiac index and an increased risk of difficult separation from CPB.

3.1.2.5 Left ventricular outflow tract obstruction

With the increasing use of echocardiography, both in the operating room and in critically ill patients, left ventricular outflow tract obstruction (LVOTO) is being diagnosed more frequently. Left ventricular outflow tract obstruction can be defined as an obstruction to blood flow, either fixed or dynamic, usually located below the aortic valve but sometimes involving regions up to the ventricular apex. The term mid-cavitary or apical obstruction is then used. [209;210]

The diagnosis of LVOTO is critical because although the clinical manifestations are similar to those of left ventricular systolic dysfunction, the treatment and management are based on a completely different rationale. [211] Indeed, inotropic support, pharmacological or mechanical afterload reduction, and volume restriction used in heart failure would significantly deteriorate the hemodynamics of a patient presenting with a low output state resulting from LVOTO. Despite known risk factors for LVOTO, such as ventricular septal thickness > 13 mm, long posterior mitral leaflet, anteriorly displaced coaption point and mitro-aortic angle > 90 degrees, [212] we have seen this condition in numerous scenarios and believe that it has the potential to occur in almost every type of hemodynamically unstable patient presenting with a significantly reduced left ventricular preload. In LVOTO, elevated left ventricular filling pressure will be present with flow turbulence in the left ventricular outflow tract. In some patients, this turbulence can lead to a suctioning (Venturi effect) or drag effect [213] of the anterior leaflet of the mitral valve into the left ventricular outflow tract, the so-called SAM: systolic anterior motion. This will lead to mitral regurgitation, which is typically excentric (Figure 28).

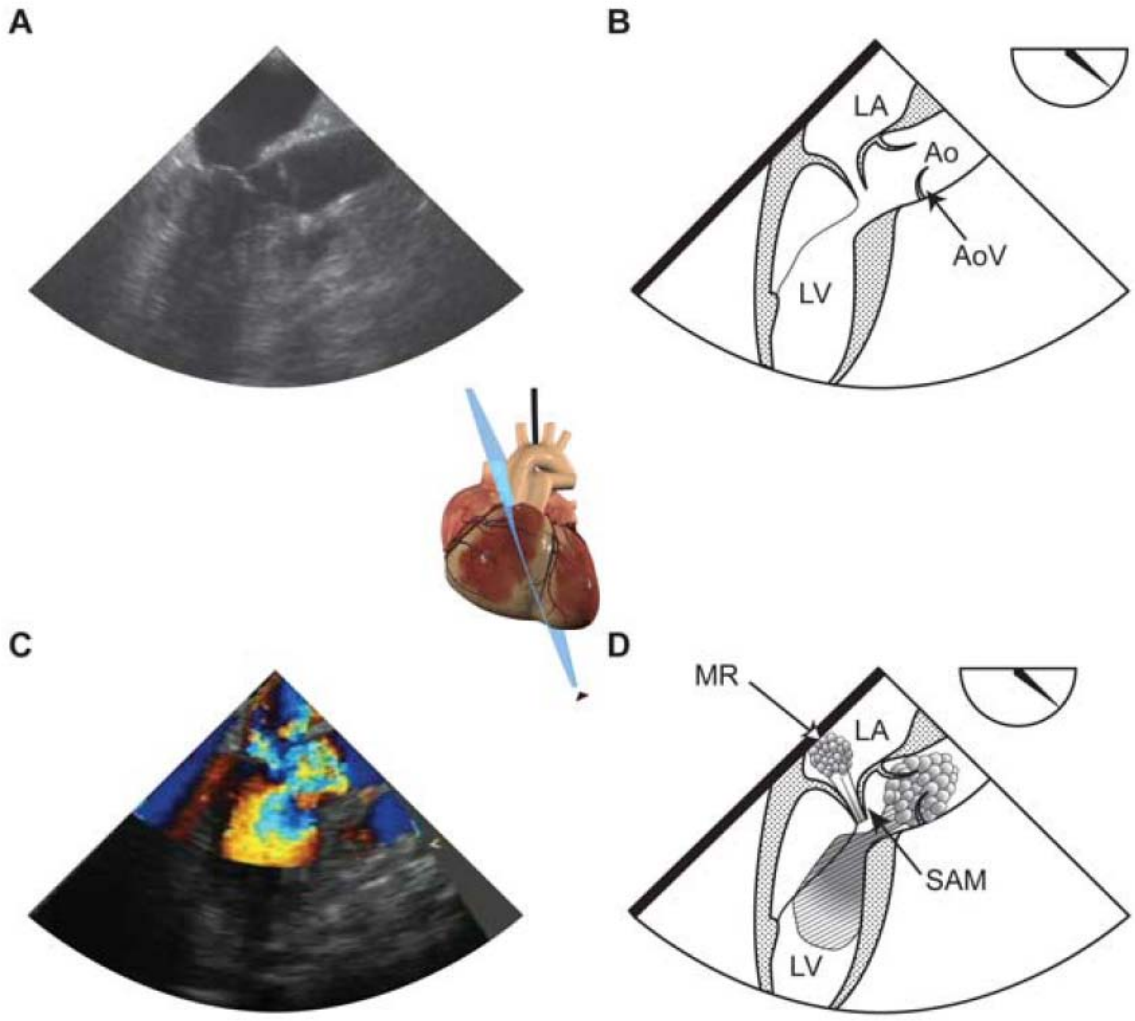


Figure 28 Dynamic left ventricular outflow tract (LVOT) obstruction

Mid-esophageal long-axis view in a 38-year-old man with hemodynamic instability. (A, B) Part of the anterior mitral valve leaflet is obstructing the LVOT. (C, D) This was associated with mitral regurgitation (MR). His hemodynamic condition improved with fluid and ß-blockade (Ao, aorta; AoV, aortic valve; LA, left atrium; LV, left ventricle; SAM, systolic anterior motion). (With permission of Denault *et al.* [12])

The consequence of a left or right ventricular outflow tract obstruction will be a reduction in stroke volume and cardiac output with an elevated filling pressure (Figure 29).

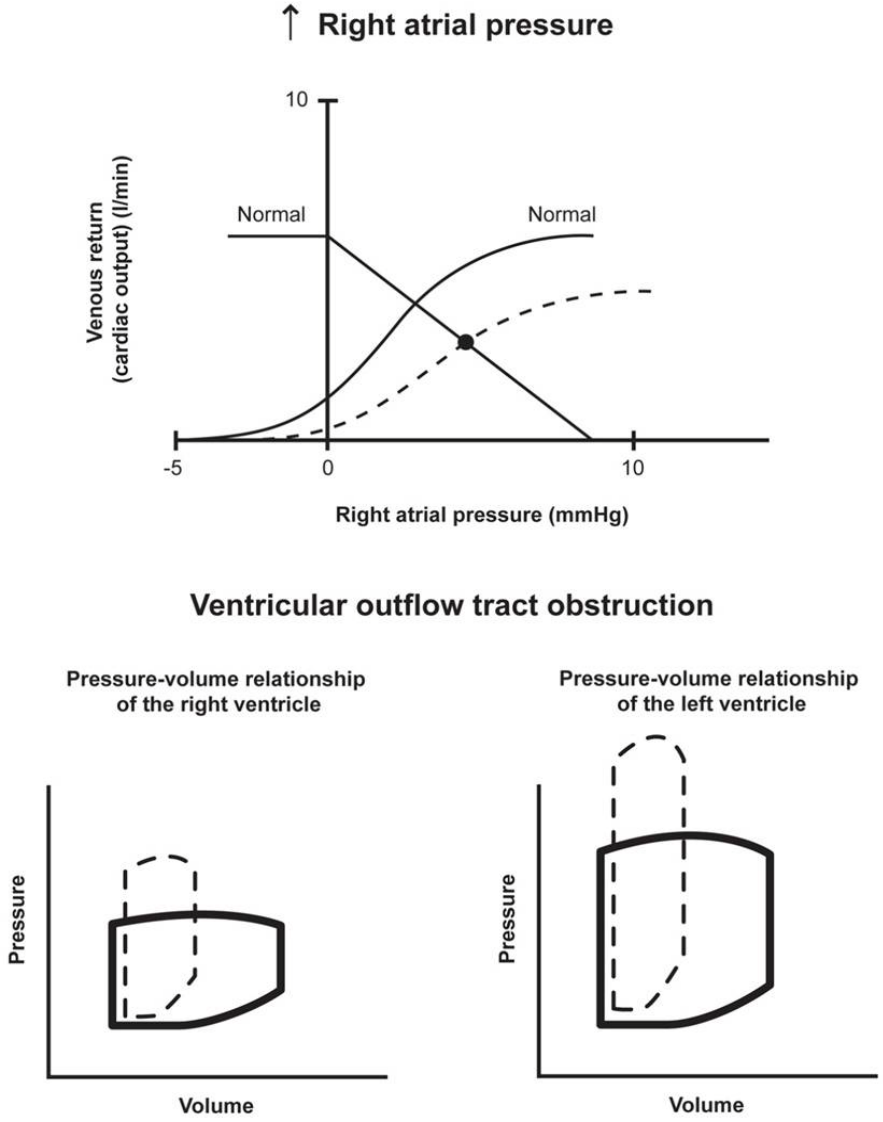


Figure 29 Ventricular outflow tract obstruction

Ventricular outflow tract obstruction of the right or left ventricle will be associated with a reduced venous return and cardiac output. The right atrial pressure will increase along the axis of the venous return curve. In that situation, the filling pressure will increase significantly and the ventricular stroke volume will be reduced.

Two types of LVOTO can be clinically present: one is dynamic and the other will have underlying structural anatomical abnormalities such as those observed in hypertrophic obstructive cardiomyopathy or extrinsic mechanical compression. In the dynamic form,

tachycardia and preload reduction will predispose to LVOTO. The dynamic form has been observed in aortic valve replacement, in mitral valve repair and in the critically ill patient (Figure 28).

In aortic stenosis, abnormal systolic intraventricular flow velocities can be observed reaching 14% and are aggravated with inotropes and vasodilators. [214] Aortic valve replacement for aortic stenosis in a patient with pre-existing left ventricular hypertrophy can cause significant SAM in the postoperative period. This results from the acute reduction in afterload, which allows increased left ventricular ejection in a small left ventricular outflow tract, thereby producing subvalvular stenosis or mid-ventricular obstruction. [12] This is usually transient and responds well to volume loading and cessation of inotropic drugs. However, in certain cases, surgical correction may be required (Figure 30). [215]

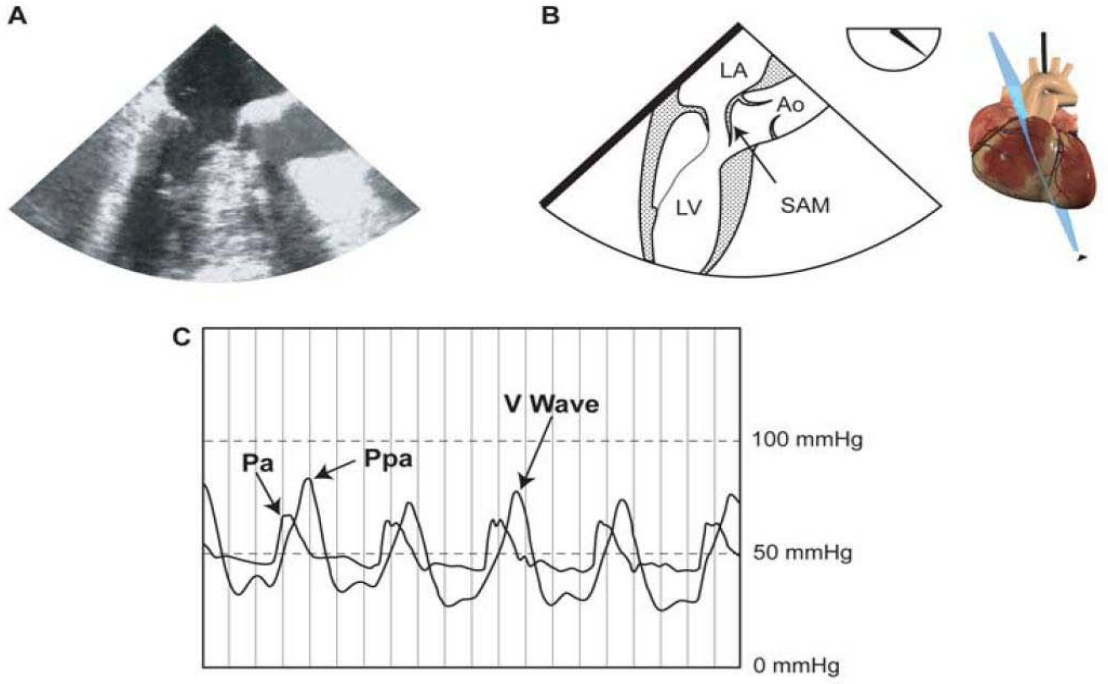


Figure 30 Left ventricular outflow tract obstruction (LVOTO).

A 53-year-old man with LVOTO after aortic valve replacement. (A,B) The mid-esophageal long-axis view showed the LVOTO secondary to left ventricular septal hypertrophy. (C)

Systemic hypotension was associated with the appearance of a giant "V" wave on the wedged pulmonary artery pressure (Ppa); tracing occurred as the patient was weaned from cardiopulmonary bypass. The "V" wave was secondary to mitral regurgitation from abnormal systolic anterior motion (SAM). This patient did not respond to medical therapy and underwent mitral valve replacement (Ao, aorta; LA, left atrium; LV, left ventricle; Pa, arterial pressure). (With permission of Denault *et al.* [12])

Systolic anterior motion can also occur after MV repair for prolapse. This complication must be specifically looked for while in the operating room after surgery. The incidence of LVOTO after mitral valve repair varies from 2% to 14% [216] and is more frequent with myxomatous changes involving both leaflets. The underlying mechanisms include the anterior displacement of the coaptation point, as well as a longer and redundant posterior leaflet (with or without a more acute mitro-aortic angle), causing the mitral valve apparatus to be displaced toward the LVOT and be dragged by the outflow, provoking a typical SAM and subsequent subvalvular obstruction. Preoperatively, a longer posterior leaflet compared to the anterior leaflet (anterior/posterior length ratio ≤ 1.3) and a shorter distance (≤ 2.5 cm) between the coaptation point and the septum are predictors of SAM development post-repair (Figure 31). [212] For some patients, the problem can be alleviated by increasing LV filling or reducing inotropic support. However, other patients require mitral valve replacement or subsequent repair. The sliding technique has been developed to decrease the incidence of this complication by reducing the posterior leaflet redundancy. [217]

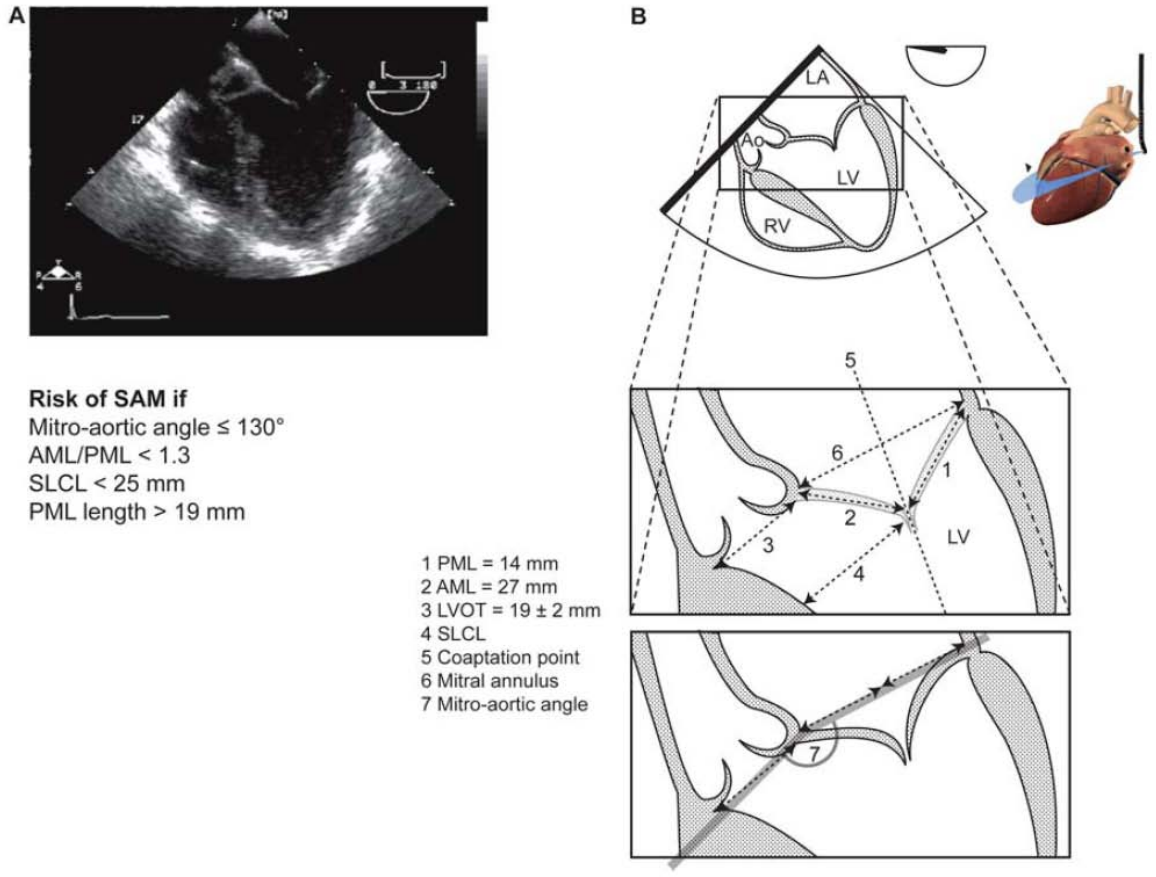


Figure 31 Risk factors of systolic anterior motion (SAM)

(A,B) Measurements to assess the risk for postoperative systolic anterior motion (SAM) after septal resection from a mid-esophageal four-chamber view (AML, anterior leaflet length; Ao, aorta; LA, left atrium; LV, left ventricle; PML, posterior leaflet length; RA, right atrium; RV, right ventricle; SAM, systolic anterior motion; SLCL, septal to leaflet coaptation length). (Adapted with permission of Denault *et al.* [12])

Finally, when using TEE in a series of 61 adults with unexplained hypotension for more than one hour in the intensive care unit, Heidenreich *et al.* [218] observed that LVOTO was present in 3% of patients.

Among the mechanical or extrinsic etiology of LVOTO, in some patients, right ventricular failure can predispose to LVOTO, as previously discussed (Figure 27). In this situation, right ventricular dilatation will reduce the filling of the left ventricle, thus leading

to LVOTO. This is a very difficult situation to manage, as right ventricular dysfunction is associated with poor outcome in numerous scenarios. Inotropic therapy to improve right ventricular function may worsen LVOTO. In such a situation, to improve right ventricular function, we have been using inhaled pulmonary vasodilators, such as prostacyclin or nitric oxide, with good results. [18] Finally, we have also observed extrinsic cardiac obstruction leading to LVOTO in cases such as regional tamponade after cardiac surgery. [12] In these situations, LVOTO will resolve as soon as the underlying cause is removed.

3.1.2.6 Right ventricular outflow tract obstruction

Right ventricular outflow tract obstruction (RVOTO), which can also be due to extrinsic [219-221] or intrinsic causes, [222-224] can also result in hemodynamic instability. According to time-honoured hemodynamic criteria, RVOTO is defined as "significant" when the peak right ventricular to pulmonary artery systolic gradient exceeds 25 mmHg. [225-227] Furthermore, when observed via TEE, significant RVOTO is defined as "fixed" if there is no change in RV outflow tract (RVOT) dimensions during the cardiac cycle with an anatomic substrate for obstruction, and as "dynamic" if RVOT dimensions increase appreciably in diastole. Dynamic RVOTO has been observed in hypertrophic cardiomyopathy [228] and after lung transplantation, [229;230] but it has rarely been described during cardiac surgery. [231]

3.1.2.7 Patient-prosthesis mismatch (PPM)

The indexed effective orifice area for each prosthesis is derived from normal reference values of effective orifice area published in the literature divided by the patient's BSA, as previously described and validated. [120;123;232] Aortic PPM is defined as not clinically significant if the indexed effective orifice area is > 0.85 cm^2/m^2, as moderate if it is > 0.65 cm^2/m^2 and ≤ 0.85 cm^2/m^2, and as severe if it is ≤ 0.65 cm^2/m^2. Mitral PPM is defined as not clinically significant (i.e. mild or no PPM) if the indexed effective orifice area is > 1.2 cm^2/m^2, as moderate if it is > 0.9 cm^2/m^2 and ≤ 1.2 cm^2/m^2, and as severe if it is ≤ 0.9 cm^2/m^2. [128] Moderate to severe aortic or mitral PPM can lead to increased LVEDP, filling

abnormalities (Figure 23), reduced coronary flow reserve, [126] pulmonary hypertension and right ventricular failure (Figure 27). This might explain why patients with PPM show an increase in mortality; however, the link between difficult separation from CPB and PPM has not yet been described.

3.1.2.8 Embolism

Embolism can be directed in the right or the left-sided cardiac chambers. It can be caused by thrombus, air, carbon dioxide or other materials (Figure 7). Right-sided embolism rarely occurs during cardiac surgery but can lead to acute right ventricular failure (Figure 27). Pulmonary embolism secondary to venous thrombus originating from the lower extremity is unusual during cardiac surgery because of the use of heparin. However, after heparin reversal using protamine and with mobilization, patients with predisposing conditions could develop this complication. The presence of mobile thrombus in the right atrium, right ventricle or pulmonary artery is pathognomonic of this condition (Figure 32).

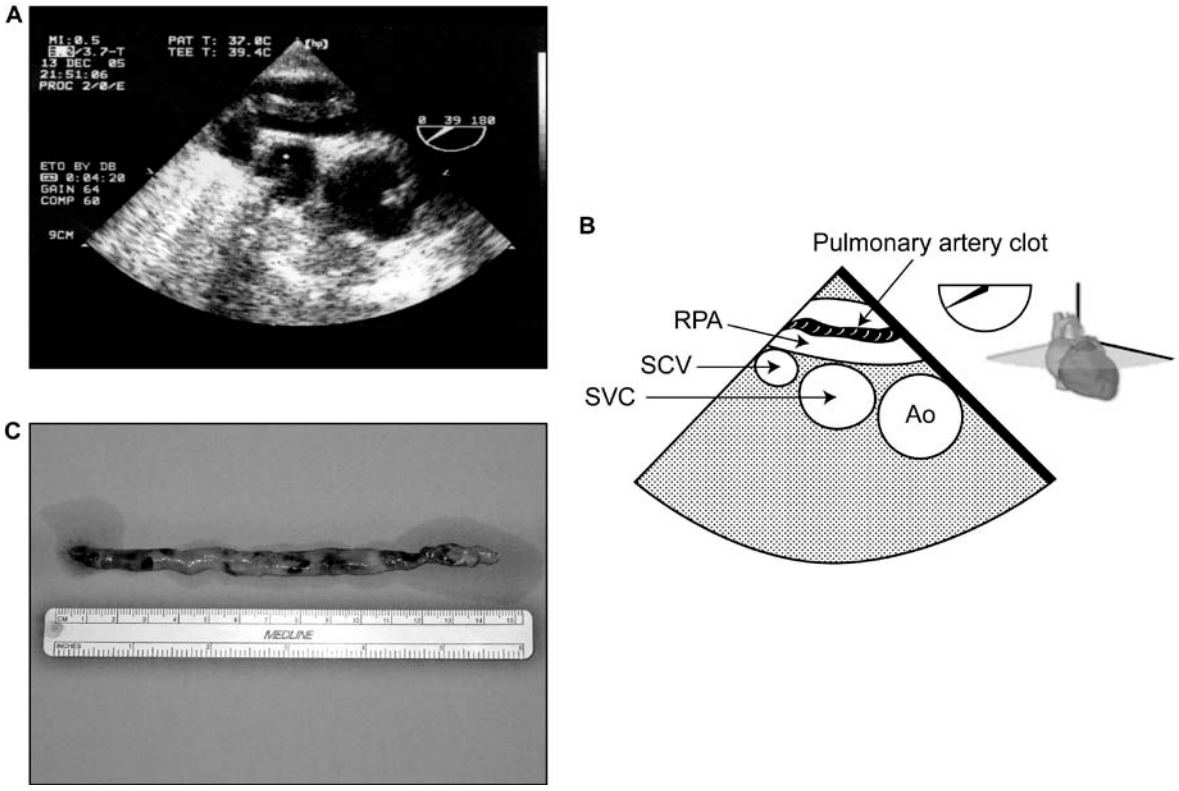


Figure 32 Pulmonary embolism immediately after coronary revascularization

This patient was hospitalized and waiting for more than a week before the procedure could take place. At the end of the procedure, while she was transferred in her bed, she became hemodynamically unstable. A transesophageal echocardiographic exam was immediately performed and showed the appearance of a clot in the right pulmonary artery (A-B). She was brought back to the operating room for urgent embolectomy and the clot was removed (C). She was discharged from the hospital in good condition. (Ao: aorta, RPA: right pulmonary artery, SCV: subclavian vein, SVC: superior vena cava) (Courtesy of Dr. David Bracco and Dr. Nicolas Noiseux).

Air embolism is frequently observed during cardiac surgery and usually has minimal or no consequence when present on the right-sided chambers, unless massive. In such a situation, the diagnosis is based on the appearance of an hyperechoic mobile signal in the right-sided chambers and pulmonary artery. Air will tend to accumulate in the most anterior portion of the right ventricle, i.e. the anterior leaflet of the pulmonic valve (Figure 33).

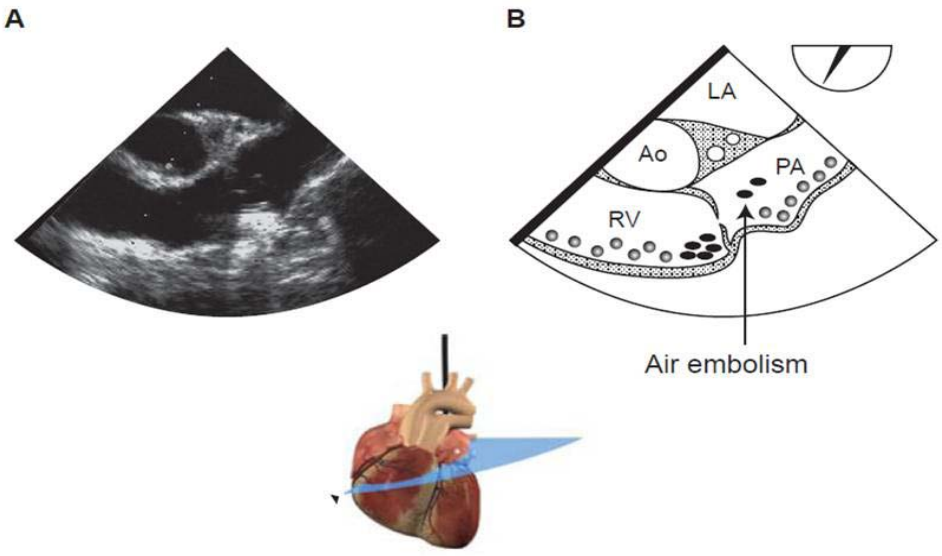


Figure 33 Air embolism

Air embolism in a 46-year-old woman hemodynamically unstable during spinal surgery in a ventral position. (A,B) She was turned back to a supine position and a mid-esophageal right ventricular outflow view revealed the residual presence of air bubbles on the most anterior aspect of the right ventricle (RV), pulmonary artery (PA) and on both sides of the anterior pulmonic valve (Ao, aorta; LA, left atrium). (Adapted with permission of Denault *et al.* [12])

The presence of air in the left-sided chambers is also common during valvular or open heart surgery. When present, it can lead to right ventricular dysfunction through air embolisation of the right coronary artery. This explains why the de-airing process of the left-sided chambers is of significant importance in valvular surgery (Figure 34).

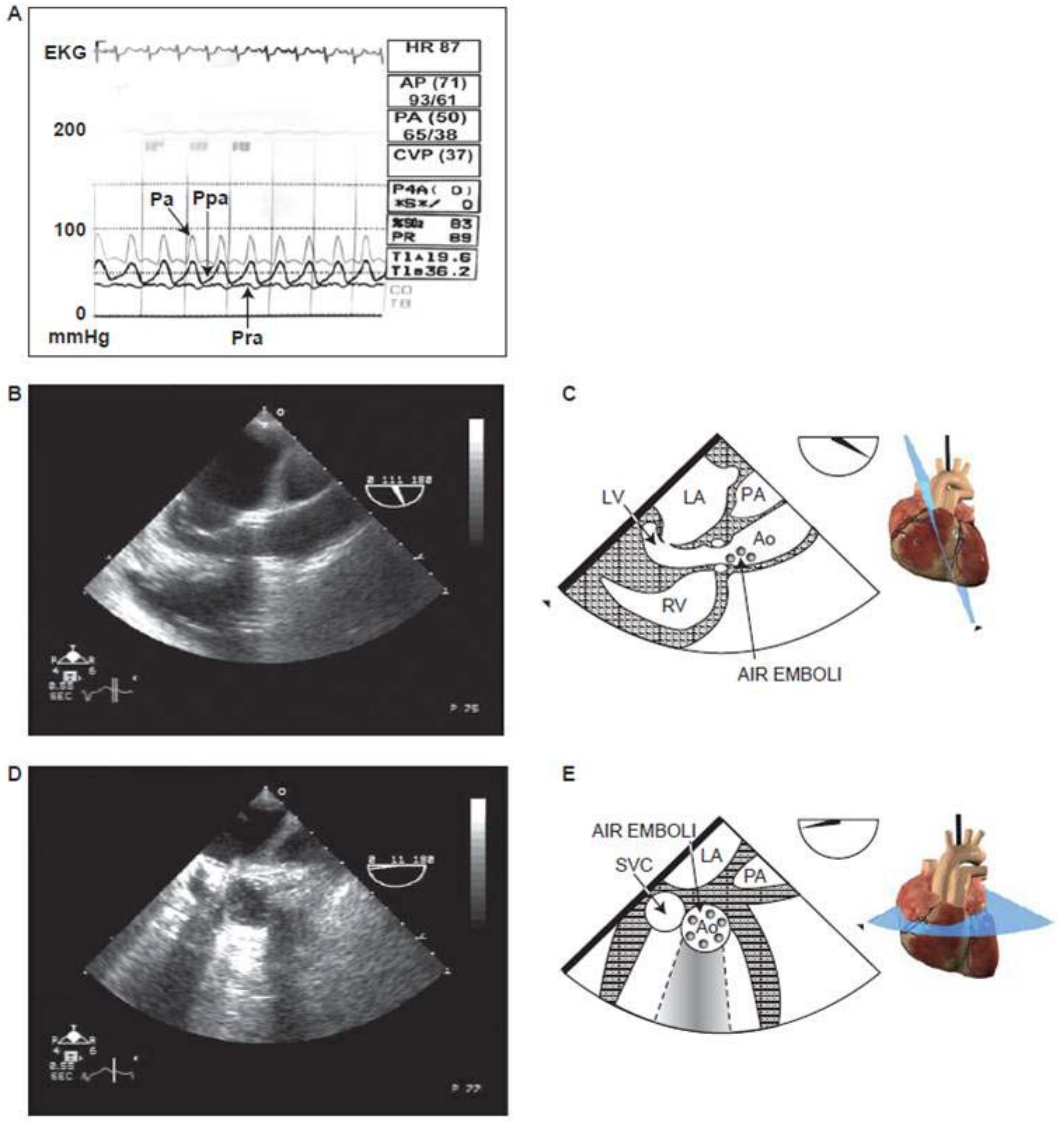


Figure 34 Air embolism

A 61-year-old woman underwent aortic valve replacement. She was easily weaned from cardiopulmonary bypass (CPB). As she was transferred onto the transportation bed, she developed acute pulmonary hypertension (A) followed by ventricular fibrillation. (B–E) She was resuscitated and a transesophageal echocardiographic exam was performed. A mid-esophageal aortic valve long-axis and short-axis view revealed strong echogenic material close to the prosthetic valve, consistent with air emboli dislodged during mobilization of the patient (Ao, aorta; EKG, electrocardiogram; LA, left atrium; LV, left ventricle; Pa, arterial pressure; PA, pulmonary artery; Ppa, pulmonary artery pressure; Pra,

right atrial pressure; RV, right ventricle; SVC, superior vena cava). (Adapted with permission of Denault *et al.* [12])

Carbon dioxide used during saphenectomy can also inadvertently be directed into the systemic circulation. Carbon dioxide embolism should be suspected when an increase in end-tidal carbon dioxide is followed by a decrease in cardiac output and hypotension. TEE is the most sensitive method to detect gas embolism [233] (Figure 35). We have observed such cases on two occasions. [28;234] Acute right ventricular failure requiring emergency CPB was the consequence of the first case. However, in the second case, the use of inhaled prostacyclin prevented us from using CPB. [28]

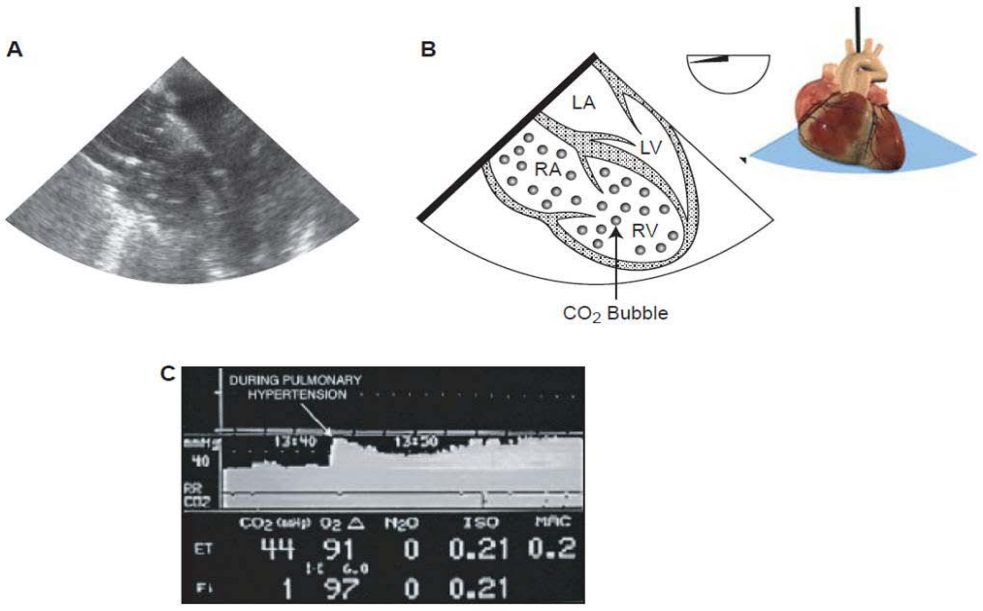


Figure 35 Carbon dioxide (CO_2) embolism

Mid-esophageal four-chamber view showing CO_2 embolism in a 69-year-old man undergoing laparoscopic saphenectomy who suddenly became hemodynamically unstable. (A, B) A mid-esophageal four-chamber view showed the appearance of bubbles in the right atrium (RA) and right ventricle (RV) originating from the inferior vena cava. This was associated with right cardiac chamber dilatation. (C) The hemodynamic instability coincided with an abrupt rise in end-tidal CO_2 (LA, left atrium; LV, left ventricle). (Adapted from Martineau *et al.* [28])

3.1.2.9 Hypoxemia and hypercapnia

Both hypoxemia and hypercapnia will lead to pulmonary vasoconstriction, pulmonary hypertension and increased right atrial pressure. This is consistent with the rationale for the Airway-Breathing-Circulation (ABC) method in resuscitation. Airway management and breathing remain the two initial and essential steps in the management of any hemodynamically unstable patient. The effect of hypoxemia is illustrated in Figure 36.

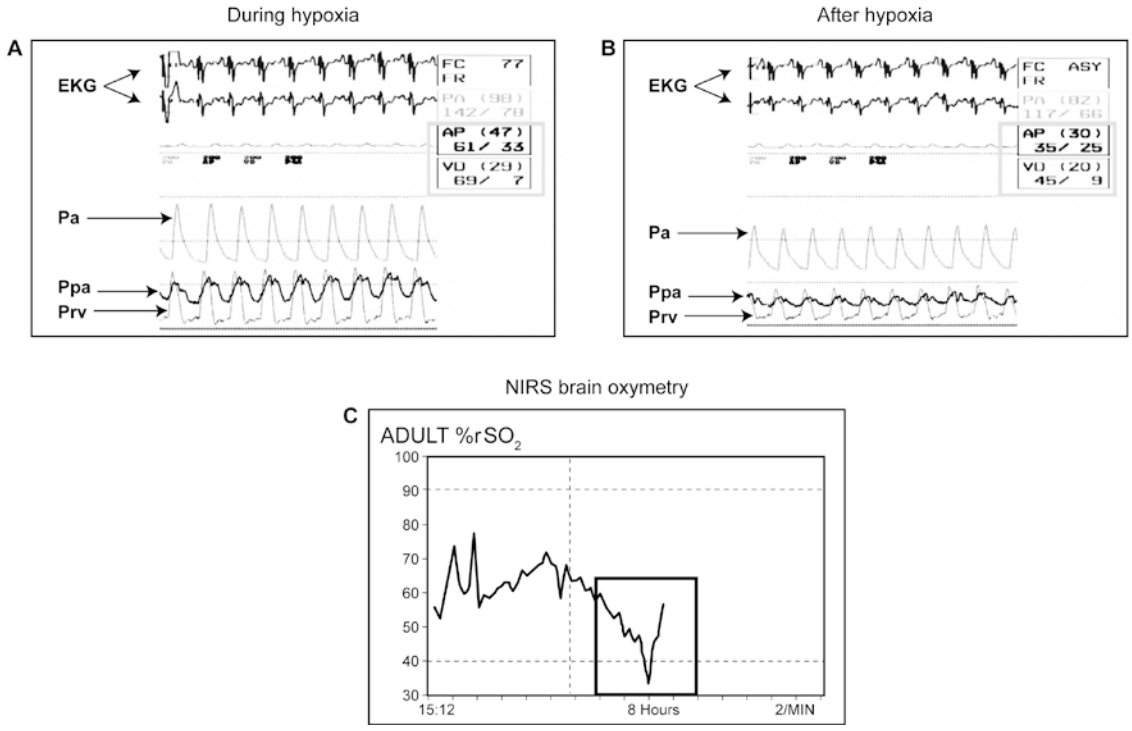


Figure 36 Hemodynamic effect of hypoxemia

Severe hypoxemia in a 48-year-old man observed after coronary revascularization. (A) During the hypoxic episode, the pulmonary artery pressure increased to 61/33 mmHg. (B) Using positive end-expiratory pressure, the hypoxic episode was corrected and the pulmonary artery pressure decreased to 35/25 mmHg. (C) Using near-infrared spectroscopy, the hypoxemia was associated with a reversible reduction in the brain oximetry signal.

Hemodynamic instability through hypoxemia will lead to right ventricular failure and its consequences on left ventricular function (Figure 27). During cardiac surgery, hypoxemia can result from a ventilation-perfusion mismatch or through a right to left shunt. In the latter case, the shunt is typically through a patent foramen ovale. (PFO or "*Trou de Botal*") present in 20% of the adult population (Figure 37).

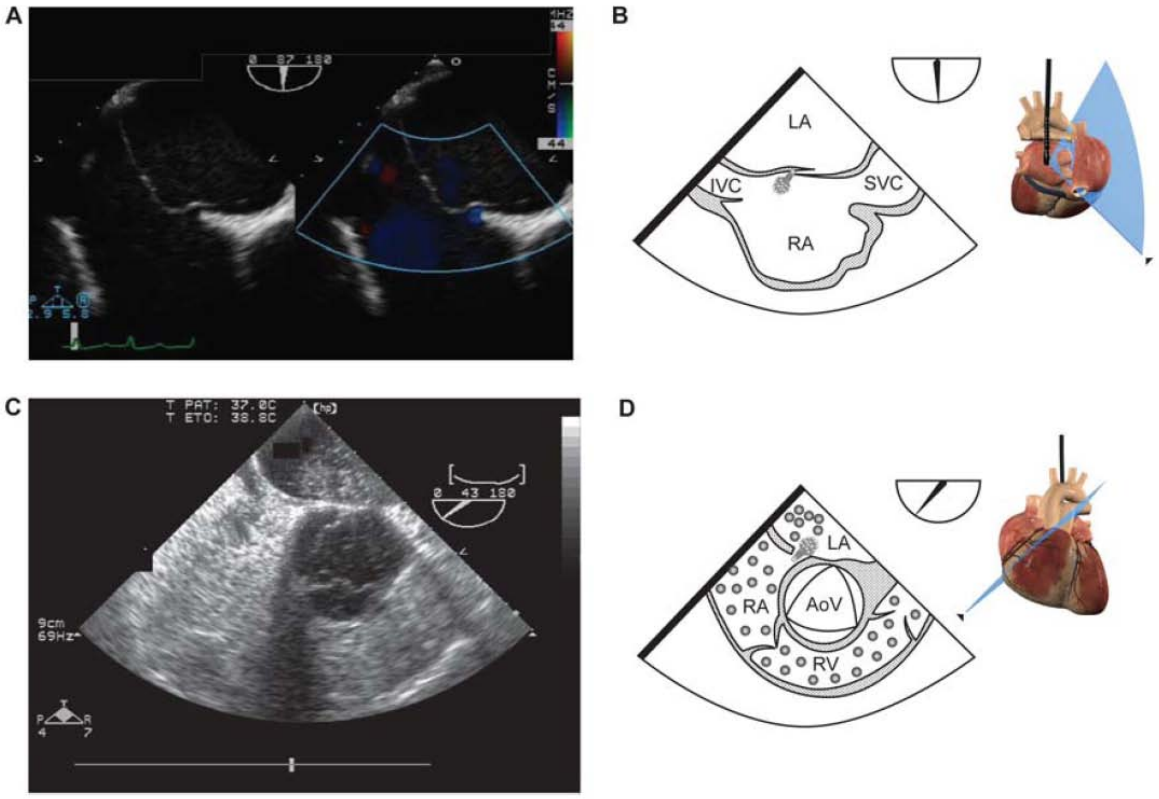


Figure 37 Patent foramen ovale (PFO)

(A,B) A PFO demonstrated by color flow Doppler in a mid-esophageal bicaval view. (C,D) Opacification of the right-sided cardiac chambers by intravenous injection of agitated normal saline. During the release phase of the Valsalva maneuver, microbubbles are seen crossing to the left atrium (LA) through a PFO. (With permission of Denault *et al.* [12])

A PFO has a normal amount of tissue when the septum primum is complete, but it does not fuse with the septum secundum to obliterate the foramen ovale. A right to left shunt can be elicited with a Valsalva maneuver. Patency of the foramen ovale can be

anatomically demonstrated with a probe. It usually has no consequences unless it is responsible for a cerebrovascular accident through paradoxical emboli (Figure 38). Some authors, however, suggest that it should be closed if found in a patient in whom a cardiac surgical procedure is performed, [235] but recent evidence suggest no survival benefit. [236] The presence of a PFO may alter the method of venous cannulation in the case of left-sided valve surgery or the need for cardioplegia in right-sided valve surgery. In cases where the patient is at a high risk of hypoxemia post-bypass, such as LVAD insertion and heart transplant, closure of the PFO is warranted.

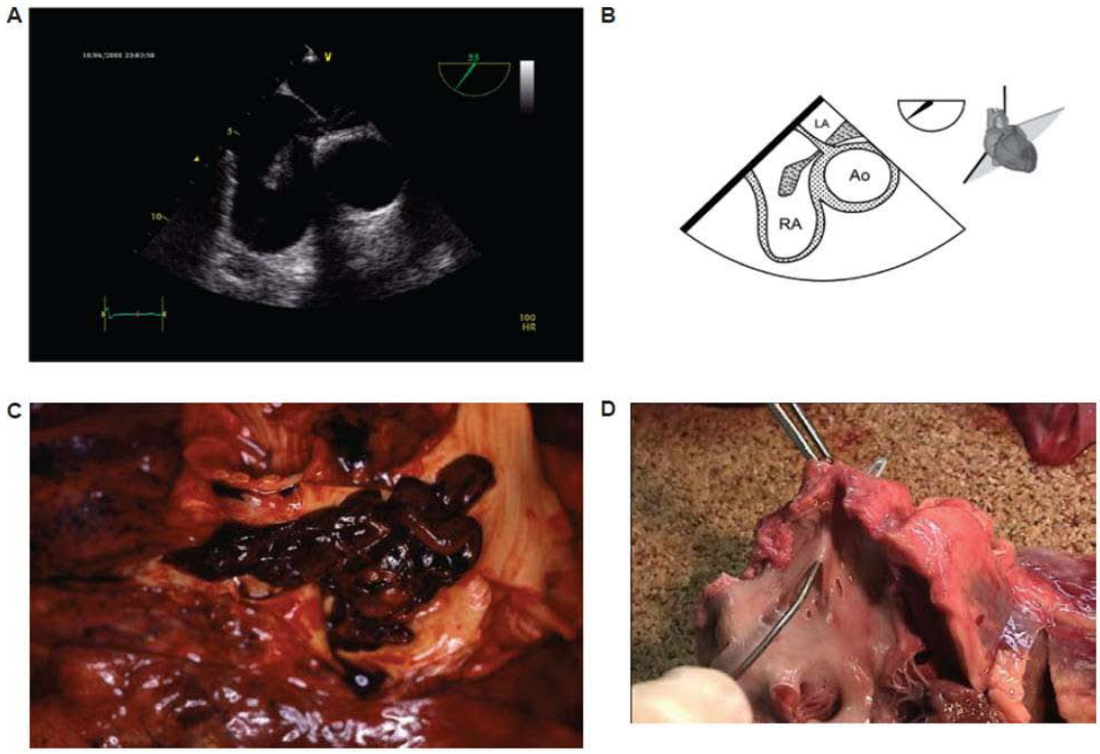


Figure 38 Paradoxical pulmonary embolism

Paradoxical pulmonary embolism in a 48-year-old man who presented with acute hypotension. (A,B) Mid-esophageal view at 55° showing a thrombus across the patent foramen ovale. (C) Intraoperative aspect of the pulmonary emboli. (D) Autopsy finding of a patent foramen ovale in a patient who died of refractory hypoxemia. (Courtesy of Dr. Michel Pellerin and Dr. Tack Ki Leung) (With permission of Denault *et al.* [12])

Hypercapnia also results in pulmonary vasoconstriction and pulmonary hypertension. The hemodynamic and echocardiographic consequences are the same as those of hypoxemia. [237;238] The effect of hypercapnia can easily be demonstrated during organ donation. In the determination of cardiac death, it is essential to demonstrate the absence of any spontaneous breathing during 10 minutes of apnea. In such a situation, the hemodynamic and echocardiographic effects of hypercapnia can be appreciated (Figure 39). Interestingly, changes in the dimension of the right atrium precede the increase in right atrial pressure (Figure 40). This is most likely secondary to the normal reduced compliance of the right atrial cavity.

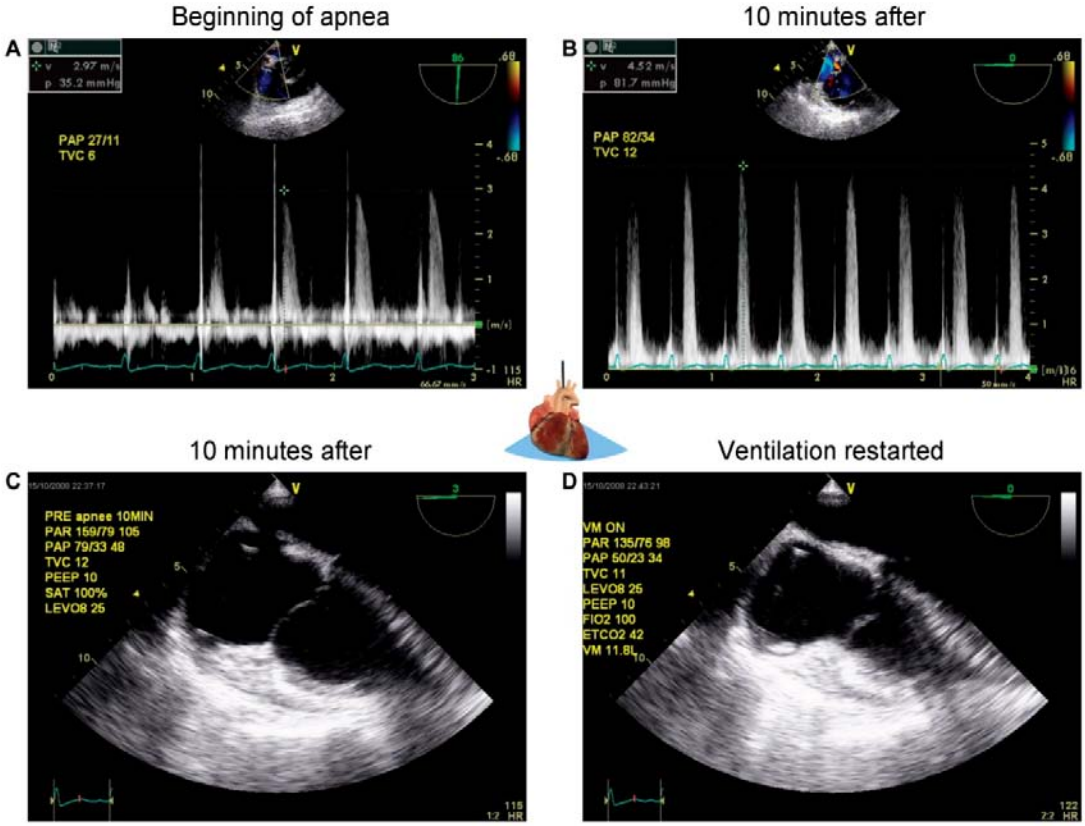


Figure 39 Hypercapnia and cardiac function

(A) Tricuspid regurgitation continuous-wave Doppler signal before the apnea testing. The peak presssure gradient is 35.2 mmHg. The pulmonary artery pressure and right atrial pressure were 27/11 and 6 mmHg. (B) After 10 minutes of apnea, the peak pressure gradient increased up to 81.7 mmHg. The pulmonary artery pressure and right atrial

pressure were 82/43 and 12 mmHg. (C) At about the same time, right ventricular and atrial dilatation were present. (D) The right-sided dilatation were reversed once mechanical ventilation was resumed.

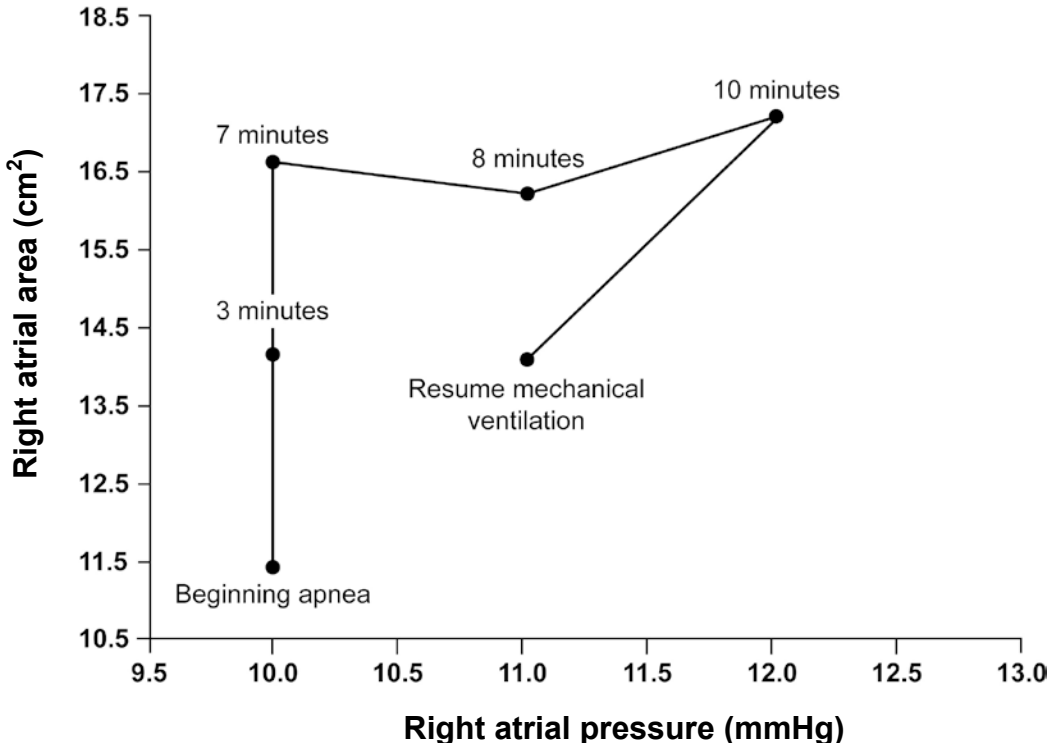


Figure 40 Hypercapnia and right atrial dimension and pressure

Relation between the right atrial area and the right atrial pressure (Pra) during apnea testing in organ donation. Initially, the right atrial area increases in size, but at 7 minutes only, the Pra starts to rise, reaching maximal value at 10 minutes. A reduction in right atrial area and Pra was observed when mechanical ventilation was resumed.

In summary, several conditions will contribute to the increase in right atrial pressure. The use of TEE is essential in the diagnosis and treatment of these various conditions. If there is no evidence of altered Pms or Pra, then the next step is to rule out any increase in resistance to venous return.

3.1.3 Increased resistance to venous return

There are two mechanisms of increased resistance to venous return: the first is the extrinsic compression of the circulatory system, or compartment syndrome, and the second is the intrinsic partial or complete occlusion of the extracardiac large vessels, or vena cava syndrome.

The resistance to venous return will be significantly impeded in situations in which pericardial, mediastinal, thoracic or abdominal pressure will increase, such as during an abdominal compartment syndrome. [148;239] In these situations, an upward shift of the pressure-volume curve will be observed. The right and left ventricular pressure will be high (from the outside compression) and volume normal or low (Figure 41).

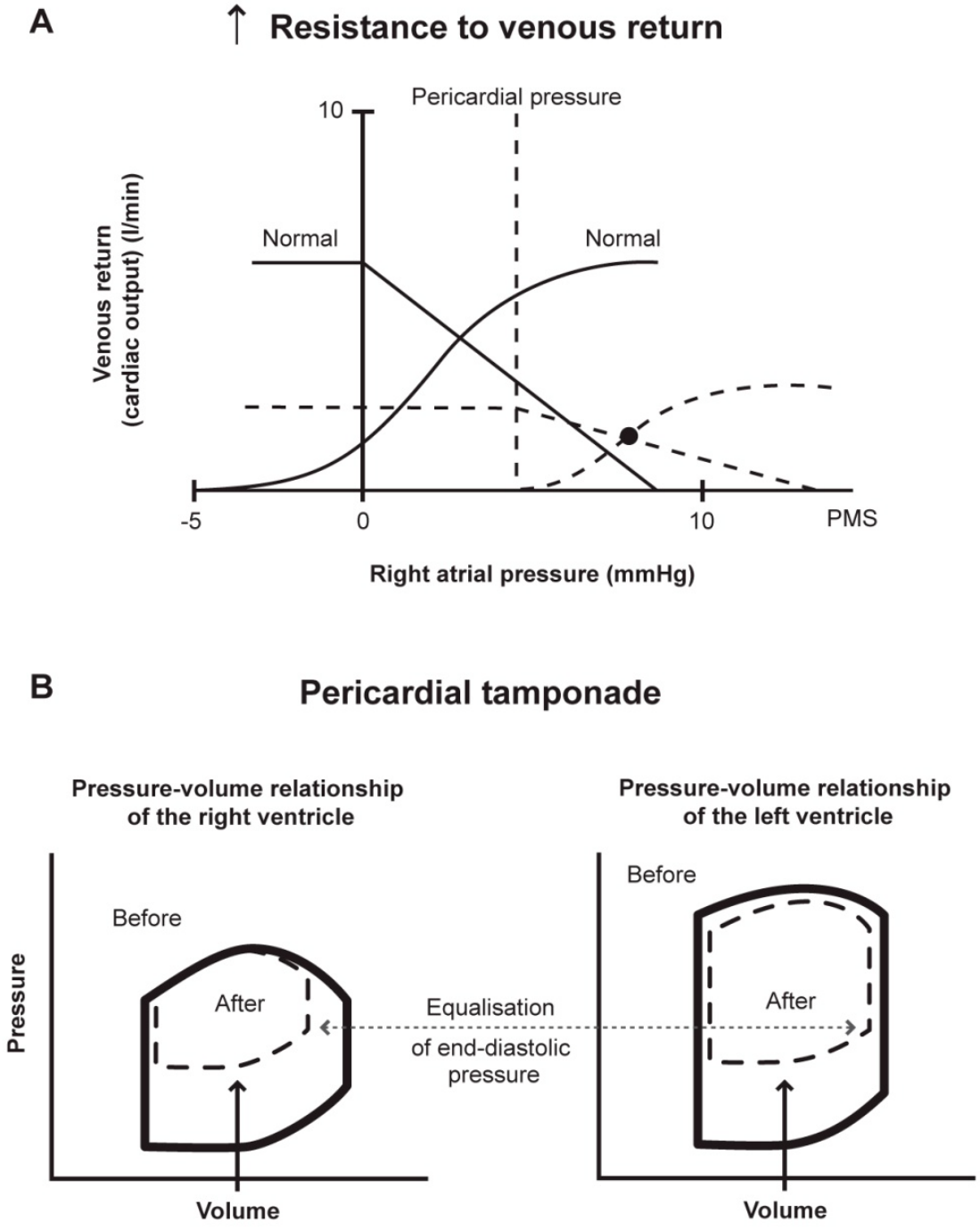


Figure 41 Mechanism of increased resistance to venous return during tamponade

In tamponade, venous return and cardiac output are reduced. Right atrial pressure is increased. This is secondary to the rise in pericardial pressure. In addition, venous return will now be limited not by subatmospheric pressure but by the pericardial pressure. As a

result, venous return is now equal to the difference between Pms and the pericardial pressure divided by the resistance to venous return. The venous return slope is reduced from an increase in the resistance to venous return. A normal compensatory increase in mean systemic pressure (Pms) will also be observed secondary to the activation of the autonomic nervous system. (B) Biventricular pressure-volume relationships in pericardial tamponade. The increase in pericardial pressure will be transmitted to both ventricles. As a consequence, an upward shift of the horizontal part of the pressure-volume relationship will be observed. This is typically associated with the equalization of end-diastolic pressures. As pericardial pressure increases and tamponade develops, biventricular volumes will be further reduced. Consequently, left ventricular pressure and systemic pressure will be reduced. (With permission of Durand *et al.* [240])

These conditions are difficult to diagnose without echocardiography and extracardiac pressure or intra-abdominal monitoring. [27] However, as the chest and pericardium are opened at the end of cardiac surgery, their contribution to hemodynamic instability is minimal and can be neglected. However, their contribution will appear as soon as the chest is closed. The causes of increased Rvr are pericardial (cardiac tamponade), mediastinal (after CPB), pleural (hemothorax and pneumothorax) and abdominal compartment syndromes.

In the classical presentation of cardiac tamponade, fluid accumulates across the pericardium. The right atrium, having the lowest pressure, will be the first cardiac chamber to collapse in diastole, followed by the right ventricle and left atrium in diastole. This can be easily diagnosed using transthoracic or transesophageal echocardiography (Figure 42).

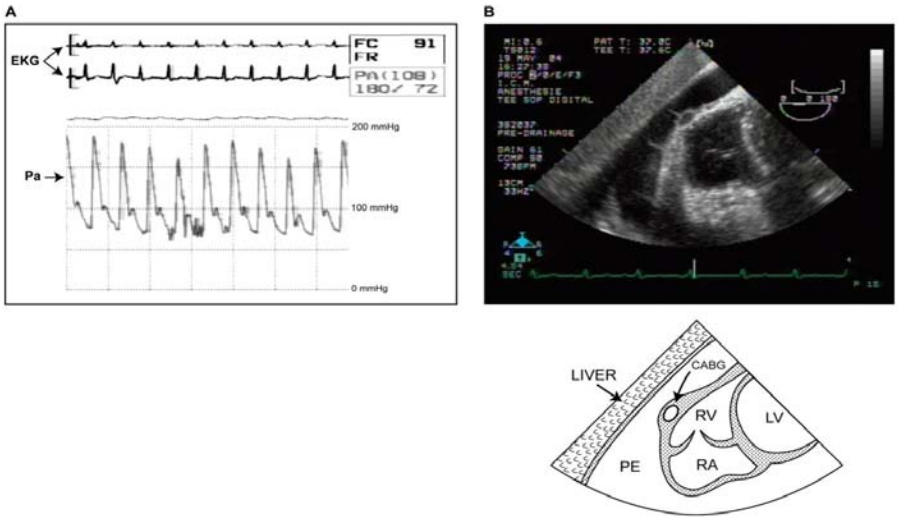


Figure 42 Classical tamponade.

Classical tamponade diagnosed using transesophageal echocardiography in a patient, developing after surgical coronary revascularization from a deep transgastric view. (A) The arterial pressure (Pa) waveform shows the typical respiratory variation of pulsus paradoxus. The patient was on significant high doses of noradrenaline. (B) The intermittent compression of the right atrium (RA) can be visualized (CABG, coronary artery bypass graft; LV, left ventricle; PE, pericardial effusion). (With permission of Durand *et al.* [240])

After cardiac surgery, however, localized tamponade can occur with the regional compression of any of the cardiac chambers. In such a situation, transesophageal echocardiography is mandatory to rule out regional tamponade (Figure 43). As tamponade progresses and shock worsens, coronary perfusion pressure is compromised, leading to additional myocardial dysfunction. [241]

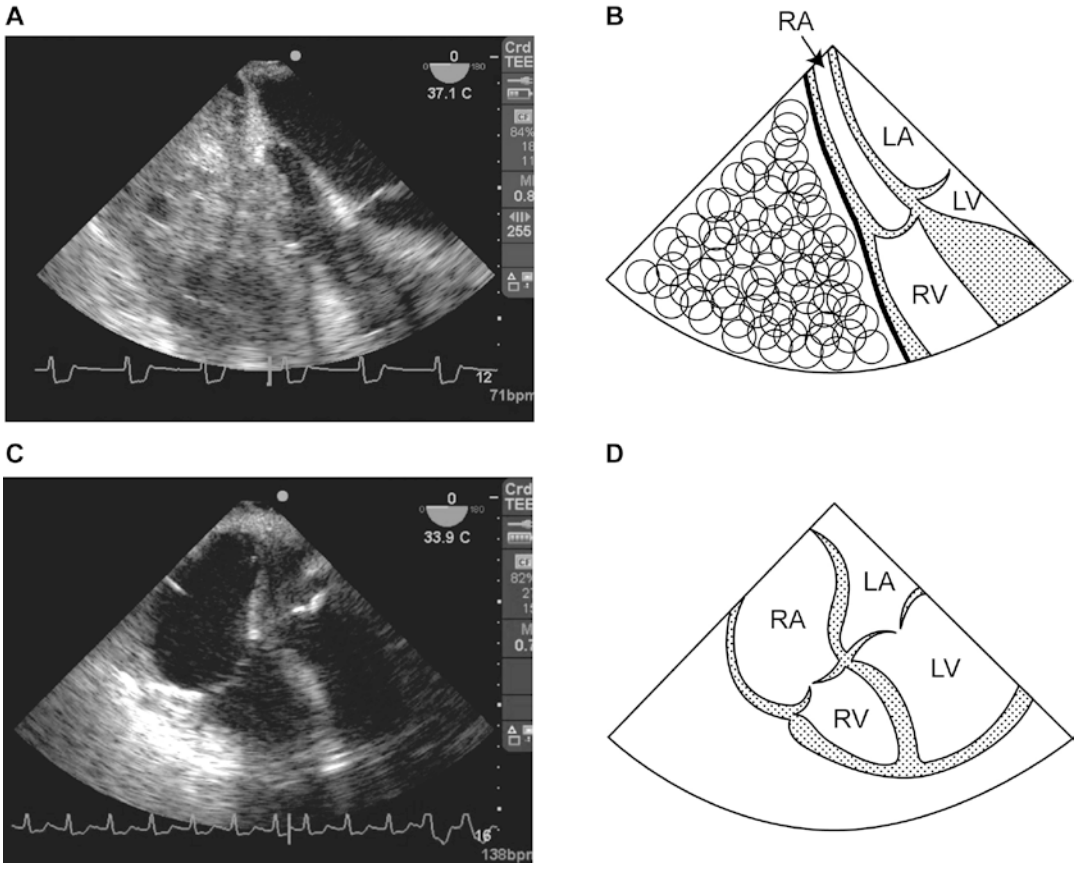


Figure 43 Regional tamponade.

Transesophageal echocardiography from a mid-esophageal view showing a large clot compressing the right atrium (RA) and right ventricle (RV) before (A,B) and after (C,D) removal . (LA: left atrium, LV: left ventricle) (With permission of Durand *et al.* [240])

The other mechanism of increased Rvr is any pleural pathology that would increase the extrinsic cardiac pressure. This can be a hemothorax or a pneumothorax. The former can be diagnosed using echocardiography (**Erreur ! Source du renvoi introuvable.**); however, the latter is more difficult to diagnose, as ultrasound does not penetrate air. Nevertheless, specific echocardiography signs of pneumothorax have been described using chest ultrasound [242] and could perhaps be used together with transthoracic echocardiography at the bedside. Just as with tamponade, the consequence of the pneumothorax is the compression of the cardiac cavity with the lowest pressure. If the

pneumothorax is anterior to the left side, the RVOT will be compressed specifically during diastole (Figure 44) We observed and reported this condition after lung transplantation. [27]

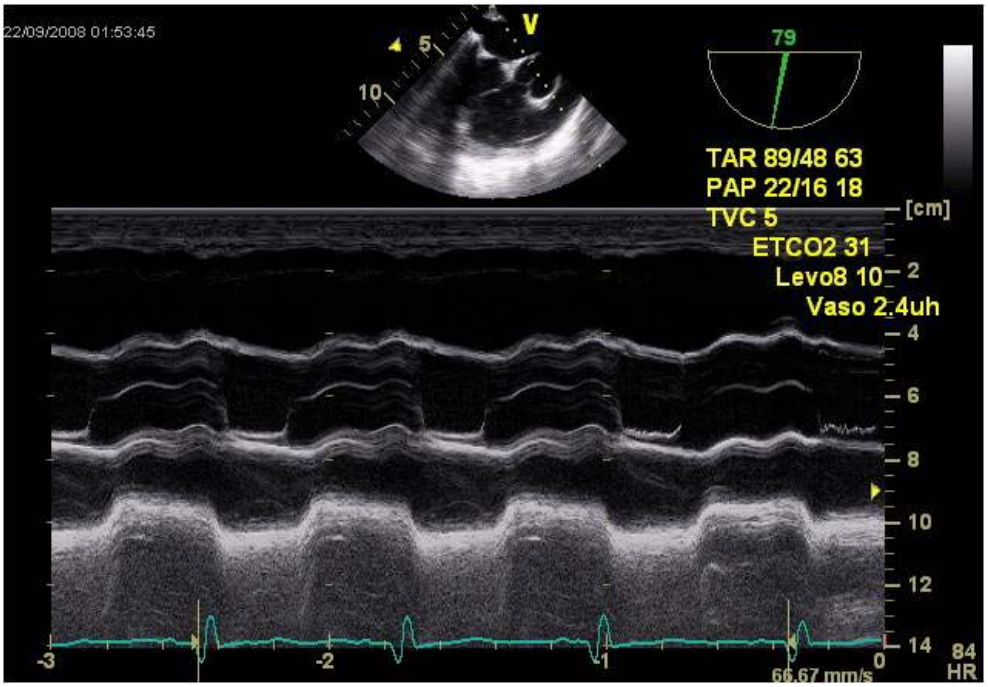


Figure 44 Hemodynamic consequence of a pneumothorax

A 19-year-old hemodynamically unstable man with chest contusion was admitted for organ donation. Using a mid-esophageal view of the right ventricular outflow tract (RVOT), a diastolic obstruction of the RVOT was observed using M-mode. The obstruction was secondary to an anterior left pneumothorax compressing the RVOT.

In complex and long procedures, it has been noted in some patients that the closure of the sternum produces hemodynamic instability that is reversible when the chest is reopened. The mechanism is secondary to extrinsic compression of the cardiac structures (Figure 45).

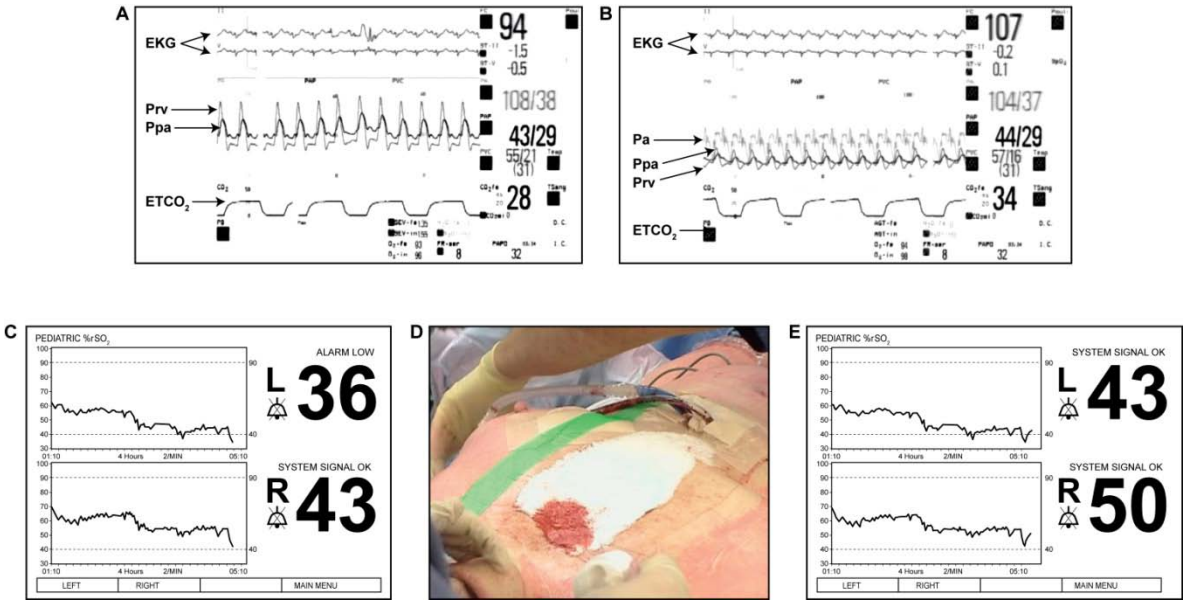


Figure 45 Mediastinal tamponade

A 62-year-old woman was admitted for urgent revascularization after failure of coronary angioplasty. She was intubated and on vasoactive agents before the surgery. (A) Her hemodynamic waveforms are shown before. As the chest was closed, she became more hemodynamically unstable with increased vasoactive requirements. This was associated with equalization of the right ventricular and diastolic pulmonary artery pressures (B). In addition, profound bilateral brain desaturation was observed using near-infrared spectroscopy (NIRS) (C). It was then decided to reopen the chest (D) and to transfer the patient to the intensive care unit with a sterile dressing on the mediastinum. The reopening of the chest was associated with an improved hemodynamic condition and improved NIRS values (E).

The last mechanism of extrinsic compression is the abdominal compartment syndrome (ACS) and, unfortunately, it is still poorly recognized and diagnosed in cardiac surgery. Abdominal compartment syndrome is defined as a sustained abdominal pressure > 20 mmHg with evidence of organ dysfunction relieved by abdominal decompression. [239] The term intra-abdominal hypertension (IAH) is used to describe abdominal pressures ranging from 12 to 20 mmHg. An increased pressure in a non-expendable compartment reduces capillary bed perfusion and promotes bacterial translocation, which is then followed by the activation of inflammatory cytokines. [136] The latter causes leakage through vascular walls and edema, which further contributes to the rise in intra-abdominal

pressure. The reduction in the abdominal perfusion pressure (APP) defined as the difference between mean arterial pressure (MAP) and intra-abdominal pressure (IAP) leads to organ ischemia. The associated rise in abdominal pressure increases the resistance to venous return (Figure 41). This will reduce venous return and lead to low cardiac output and shock. [243] Furthermore, as the IAP increases, the diaphragm is pushed cephalad which reduces thoracic or the extrapulmonary compliance. The consequences of this condition include a reduced glomerular filtration, an oligoanuric state, hepatic dysfunction and intestinal ischemia. The acute compartment syndrome has been shown to be an independent risk factor for mortality in the intensive care unit. [244] The risk factors of ACS are summarized in Table 13 and can be divided in three categories: diminished wall compliance, increased intra-abdominal content and capillary leak. [244;245]

From Table 13, it appears that several of these risk factors can be present during cardiac surgery. Clinical manifestations are non-specific and include decreased urine output, high ventilatory pressures and a tense abdomen. Monitoring the intravesical pressure is essential to establishing the diagnosis. In patients with intra-abdominal hypertension and acute compartment syndrome, the abdominal perfusion pressure should be maintained above 50-60 mmHg. [148] Treatment should be directed towards the management of the underlying cause. Specific goals should be to improve abdominal wall compliance, reduce abdominal fluid and/or air and to correct the positive fluid balance. The most definitive intervention is decompression laparotomy with temporary abdominal closure. [246] However, this approach is not without risks and is not always curative. [247] The use of diuretics, paracentesis, nasogastric tubes (Figure 46) and dialysis can be very effective.

Table 13 Abdominal compartment syndrome

1) Diminished wall compliance

Abdominal surgery
Acute respiratory distress syndrome
Major burns/trauma
Mechanical ventilation
Prone position
Obesity (body mass index > 30 kg/m²)

2) Intra-abdominal content

Liver dysfunction (ascitis)
Hemo-/pneumoperitoineum
Increasing intraluminal fluid content (Ex. contrast enema)
Ileus/gastroparesis
Acute colonic pseudo-obstruction; colonic dilatation (Ogilvie syndrome)
Tumor

3) Capillary leak/resuscitation

Massive resuscitation
Polytransfusion (> 10 blood units/24 h)
Acidosis (pH < 7.2)
Sepsis
Hypothermia (< 33^{o} C)
Hypotension
Coagulopathy
Major burns/trauma
Emergency laparotomy

(With permission of Deslauriers *et al.* [158])

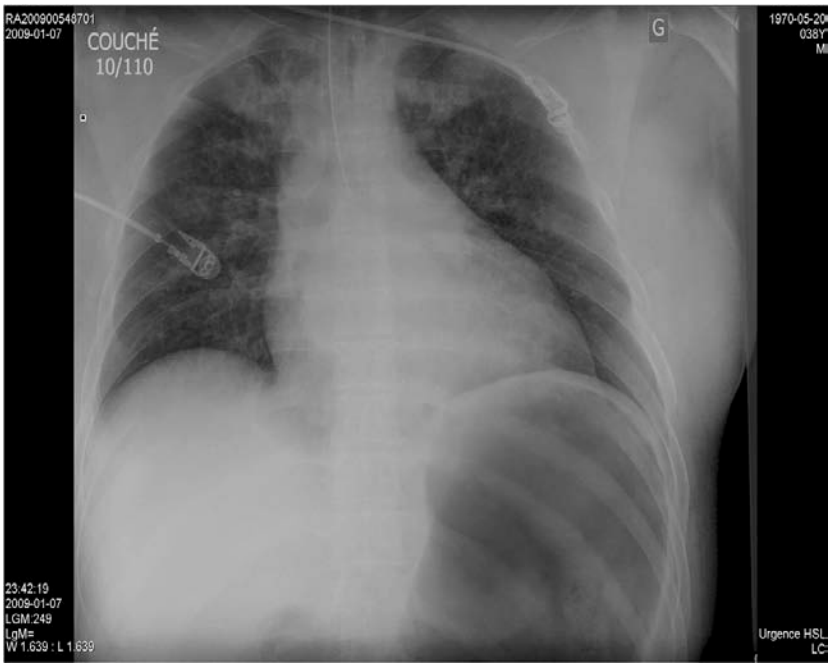


Figure 46 Acute abdominal compartment syndrome after induction of anesthesia.

A 65-year-old woman difficult to intubate and ventilate was hemodynamically unstable after the induction of general anesthesia. A chest radiograph demonstrates a distended stomach. A nasogastric tube was inserted and the vasoactive support stopped.

The second mechanism of increased resistance to venous return is the vena cava syndrome, which results in the intrinsic obstruction of the large vessels. In such a situation, a significant hemodynamic instability will be present with a normal or reduced cardiac volume similar to a reduction in Pms. This has been observed following the removal of the inferior vena cava cannula and accidental partial closure of the inferior vena cava (Figure 47). We have seen it also during a Fontan procedure during which the anastomosis to the inferior vena cava was partially obstructed (Figure 48).

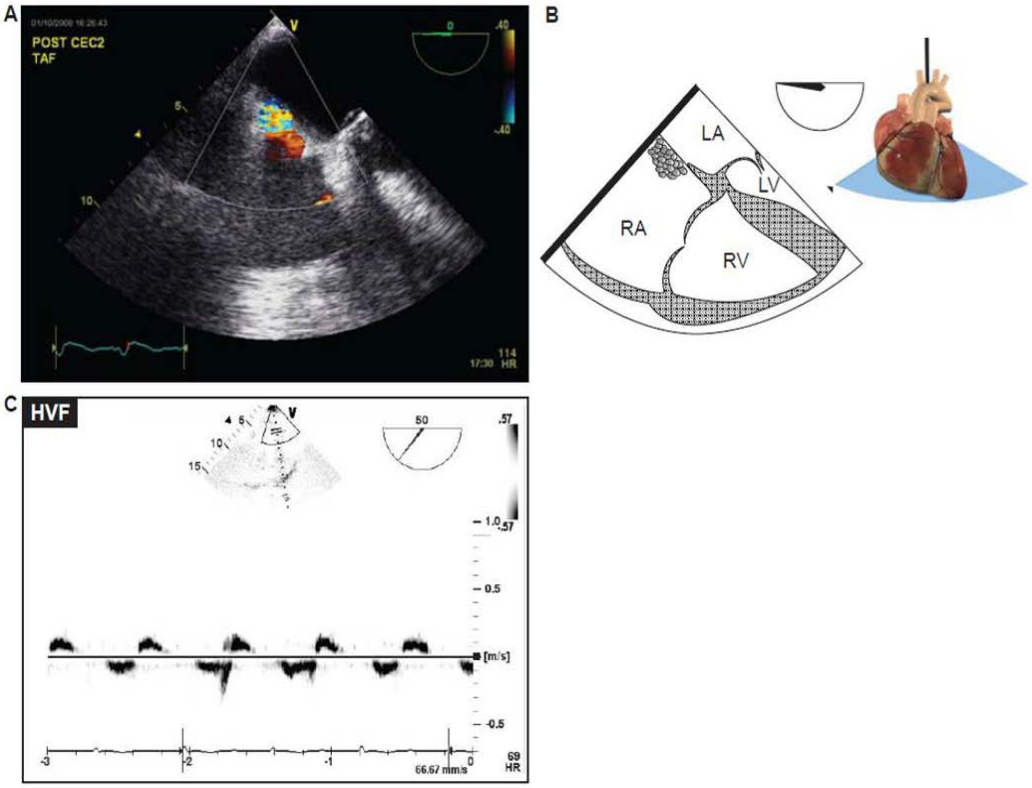


Figure 47 Partially occluded inferior vena cava (IVC)

(A,B) Mid-esophageal right ventricular view in a patient after aortic valve replacement. A turbulent flow was observed at the entrance of the IVC. It was secondary to a partial obstruction of the IVC at the site of cannulation. (C) Significantly reduced hepatic venous flow (HVF) with systolic reversal was present.

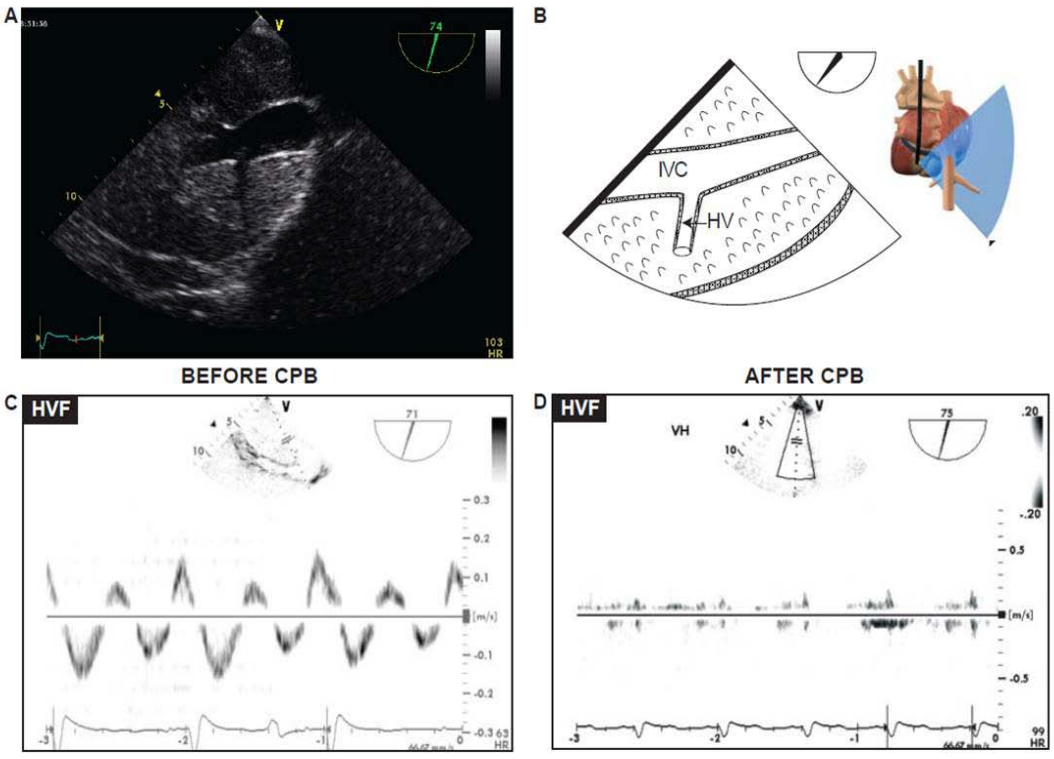


Figure 48 Inferior vena cava (IVC) occlusion during Fontan procedure

(A,B) Transgastric view showing a dilated IVC following a Fontan procedure. The occlusion was secondary to a partial occlusion at the level of the graft anastolosis to the IVC. (C,D) Hepatic venous flow (HVF) before and after cardiopulmonary bypass (CPB). The HVF is almost absent after CPB.

A misplaced intra-aortic balloon catheter in the inferior vena cava will also contribute to hemodynamic instability, particularly during diastole when it is inflated (Figure 49). All these conditions can be suspected or diagnosed with the use of TEE.

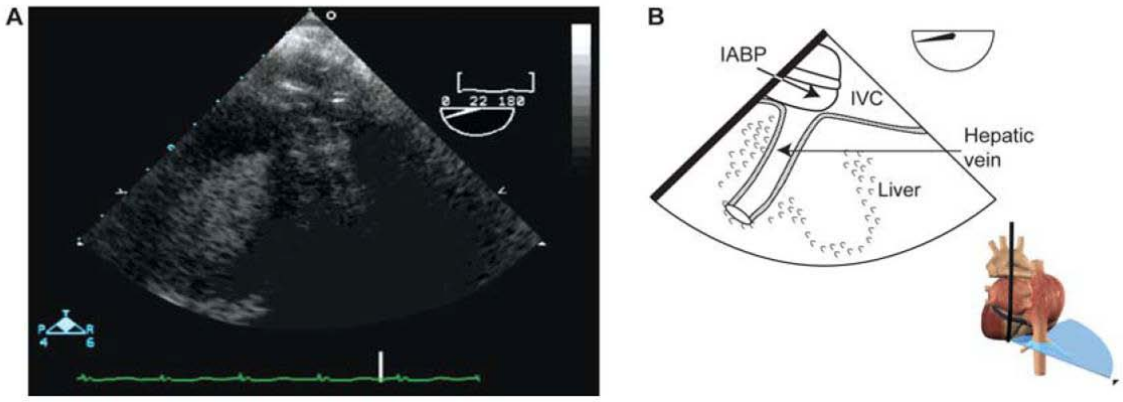


Figure 49 Intra-aortic balloon pump (IABP) catheter in the inferior vena cava (IVC).

(A,B) Emergency positioning of the IABP in the operating room after cardiopulmonary bypass. The IABP was not in the aorta but in the IVC. (With permission of Denault *et al.* [13])

The superior vena cava can also be obstructed during cardiac surgery. Typically, it is caused by a misplaced or obstructing superior vena cava venous cannula. Although this is not typically associated with hemodynamic instability, it can lead to brain hypoperfusion by reducing the cerebral perfusion pressure. Pressure monitoring of the internal jugular pressure and infrared spectroscopy are modalities useful in such diagnoses (Figure 50).

In summary, the resistance to venous return, either through the extrinsic compression of the cardiac chambers or great vessels (compartment syndrome) or through a partial or complete vascular occlusion (vena cava syndrome), is an important factor that needs to be diagnosed during cardiac surgery as a potential mechanism of hemodynamic instability and difficult separation from CPB.

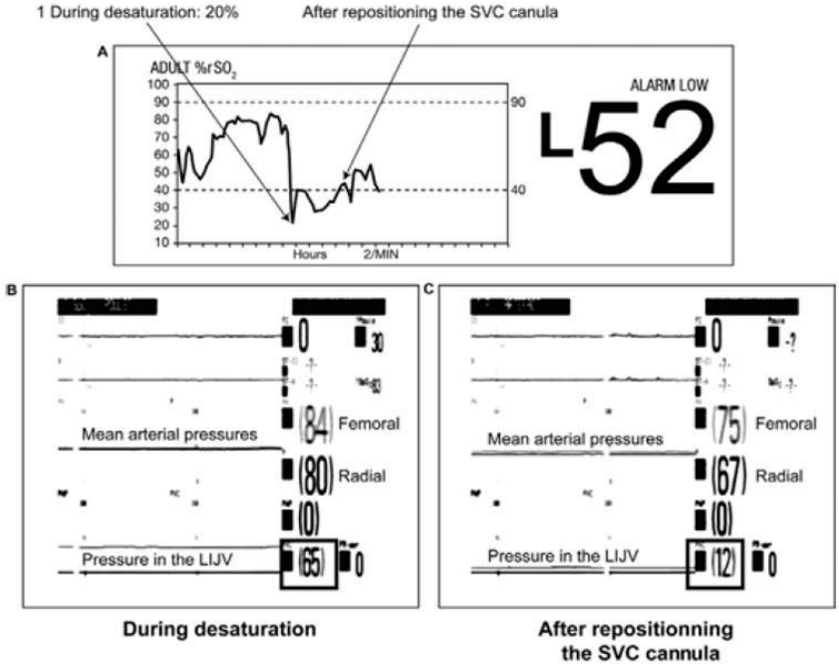


Figure 50 Brain desaturation during cardiac transplantation.

(A) A reduction down to 43% in brain saturation was observed during cardiac transplantation. (B) Despite adequate mean arterial pressure (from radial and femoral transducers) during cardiopulmonary bypass, the desaturation was associated with an increase in the left internal jugular vein (LIJV) pressure of 65 mmHg. At that point, the cardiothoracic surgeon decided to reposition the superior vena cava (SVC) cannula that was occluding cerebral venous return. The brain oximetry value increased. (C) The LIJV pressure decreased to 12 mmHg. (With permission of Denault *et al.* [130])

3.1.4 Combined mechanism

Finally, combinations of causes of difficult separation from CPB are the rule rather than the exception. [19] For instance, RV systolic failure will lead to LV diastolic dysfunction through septal interaction (Figure 27). In these conditions, the hemodynamic values will be the result of two different conditions, and only echocardiography can enable the diagnosis of these two separate entities, as previously shown. [19] Severe shock state independently of their cause, when persisting, can lead to vasodilatory shock. [137]

In our experience, the majority of these diagnoses can be made via the combination of both hemodynamic and echocardiographic modalities. These conditions require a specific treatment. [44] For instance, inotropes are indicated in the presence of left or right ventricular systolic dysfunction, but contra-indicated in the presence of outflow tract obstruction. [38] In both conditions, the hemodynamic characteristics will be the same: reduced venous return and elevated filling pressure. However, the treatment is completely the opposite: inotropic therapy is indicated with systolic dysfunction, but inotropic withdrawal is the therapy for any outflow tract obstruction.

Conditions associated with increased right atrial pressure are particularly important to differentiate using TEE. Each condition has a different therapeutic implication, as shown in Table 14. This is one of the reasons why the use of TEE is considered a type 1 indication in the presence of hemodynamic instability. [248] Echocardiography is therefore an essential tool in any research dealing with complex hemodynamic conditions. A systematic approach in the diagnosis and treatment of hemodynamic instability should be proposed in cardiac surgery. This approach should be based on the concept of venous return and uses combined and simultaneous TEE and hemodynamic monitoring to estimate biventricular pressure volume relationships.

Figure 51 summarizes the mechanisms of hemodynamic instability resulting from reduced Pms, increased Pra and Rvr. Relevant hemodynamic and echocardiographic measurements performed during cardiac surgery are summarized in Table 15.

Table 14 Mechanisms of hemodynamic instability and therapeutic implication

Etiology	**Timing**	**Possible mechanism**	**Therapeutic implication**	**Pharmacological treatment of hemodynamic instability after CPB**				
			Surgical consideration	Fluid therapy	Inotropes[1]	Vasodilators[2]	Vasopressors[3]	Other
LV systolic dysfunction	Before CPB	Coronary artery disease	Coronary revascularization					
		Natural evolution of U/L disease	No indication for revascularization					
	During CPB	Poor myocardial protection?	Retrograde cardioplegia position adequate?					
	After CPB	Air embolism	LV de-airing					
		Coronary ostium obstruction from the prosthesis	Coronary revascularization and LVAD if severe	+	++	+	+	
LV diastolic dysfunction	Before CPB	Coronary artery disease or natural evolution	Coronary revascularization					
	After CPB	Poor myocardial protection?	If associated with new systolic dysfunction, revascularization might be considered	+	-	+/-	+/-	Some benefit from beta-blockade
LV outflow tract obstruction	Before CPB	LV hypertrophy	LV outflow tract enlargement					
	After CPB	LV hypertrophy, edema and inotropes	May lead to return on CPB and MVR if associated with SAM	+	-	-	+	Some benefit from beta-blockade
Pulmonary hypertension	Before CPB	Post-capillary from increased LVEDP	Rule out absence of correctable mitral regurgitation					
	After CPB	Valve dysfunction of pulmonary reperfusion syndrome	Return of CPB if dysfunctional prosthesis	+	+	+	+	Inhaled agents may be considered
RV systolic dysfunction	Before CPB	Coronary artery disease or consequence of PHT						Preemptive inhaled agents may be considered
	After CPB	Poor myocardial protection or consequence of PH	Coronary revascularization and RVAD if severe	+	+	+	+	Inhaled agents may be considered
		Associated with septal shift		-	+	++	++	
RV diastolic dysfunction	Before CPB	Consequence of PH						

Etiology	Timing	Possible mechanism	Therapeutic implication Surgical consideration	Pharmacological treatment of hemodynamic instability after CPB Fluid therapy	Inotropes[1]	Vasodilators[2]	Vasopressors[3]	Other
	After CPB	Poor myocardial protection or consequence of PH		+/-	-	+/-	+/-	Treatment of PH may improve
RV outflow tract obstruction	Before CPB	LV septal hypertrophy						
	After CPB	LV hypertrophy, edema and inotropes		+	-	-	+	Some benefit from beta-blockade
Patient-prosthesis mismatch	Before CPB	Small aortic root	Aortic root enlargement, homograft					
	After CPB	Small prosthetic area in relation with body surface area		+	-	-	+/-	Some benefit from beta-blockade

CPB: cardiopulmonary bypass, LV: left ventricle, LVAD: left ventricular assist device, LVEDP: left ventricular end-diastolic pressure, MVR: mitral valve replacement, PH: pulmonary hypertension, RV: right ventricle, RVAD: right ventricular assist device, SAM: systolic anterior motion, U/L: underlying

1 Inotropes: adrenaline, milrinone, isoproterenol, ephedrine

2 Vasodilators: nitroglycerin, nitroprusside, milrinone

3 Vasopressors: phenylephrine, noradrenaline, vasopressin, methylene blue

Inhaled agents specific to pulmonary vessels (inhaled prostacyclin, inhaled milrinone, nitric oxide)

+ Indicated; **-** Counter-indicated; **+/-** Benefit is unclear

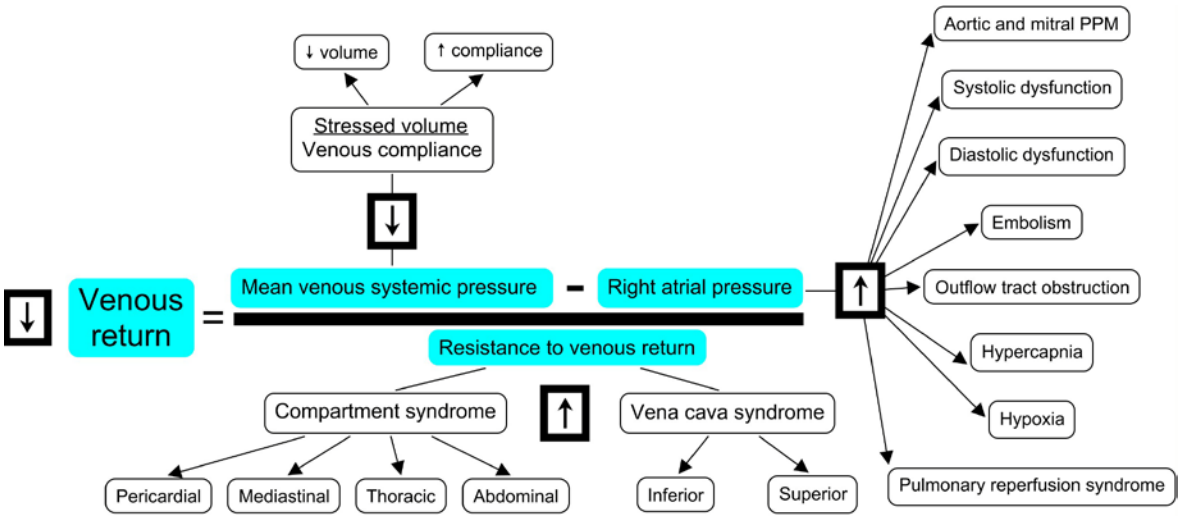


Figure 51 Mechanism of hemodynamic instability in cardiac surgery

(PPM, patient-prosthesis mismatch)

Table 15 Summary of the hemodynamic and echocardiographic measurements

Etiology	Measurement	Timing			Echocardiographic assessment
		Before CPB	During CPB	After CPB	
LV systolic dysfunction	LV hypertrophy	X			LVH based on LV mass
	LV dilatation	X		X	45 mm systole and 55 mm diastole
	LA dilatation	X		X	Maximum transverse diameter
	Regional wall motion abnormalities	X		X	1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic
	Regional wall motion score index	X		X	Total score divided by the number of segments
	Left ventricular ejection fraction	X		X	Simson's rule using a 2- and 4-chamber view
	Left ventricular fractional area change	X		X	Transgastric view in diastole and systole
	Other: air embolism, floating plaques	X		X	Continuous 2D monitoring
LV diastolic dysfunction					Classified according to an algorithm using:
	Transmitral flow	X		X	Pulsed-wave Doppler at the tip of mitral valve
	Pulmonary venous flow	X		X	Pulsed-wave Doppler 1 cm within pulmonary vein
	Mitral annular velocities	X		X	Tissue Doppler on lateral wall

Etiology	Measurement	Timing			Echocardiographic assessment
		Before CPB	During CPB	After CPB	
	Propagation velocities	X		X	Color M-Mode mid-esophageal 120º
LV outflow tract obstruction	LV outflow tract measurements	X			Measured in the ME 5 chamber
	Color Doppler in the LVOT	X		X	Color Doppler mid-esophageal 120º
	LV septal wall measurement	X			Mid-esophageal 120º
	Pressure gradient measurement across the LVOT				Mid-esophageal 120º: normally less than 4 mmHg
	Brockenborough Braunwald phenomenon	X		X	A reduced arterial pressure after a premature ventricular complex is almost pathognomonic
Pulmonary hypertension	Using the pulmonary artery catheter	X		X	Mild PHT: PAPS > 30 mmHg, MPAP > 25 mmHg and MAP/MPAP 33-50% Severe PHT: SPAP > 50 mmHg, MPAP > 30 mmHg and MAP/MPAP > 50%
RV systolic dysfunction	2D Measurement of the RA and RV	X		X	Mid-esophageal 4-chamber view
	Fractional area change	X		X	Mid-esophageal 4-chamber view
	RV myocardial performance index	X			Using CW across TV valve and deep TG view for ET

Etiology	Measurement	Timing			Echocardiographic assessment
		Before CPB	During CPB	After CPB	
	Septal shift	X		X	Eccentricity index will be used
	Tricuspid annular plane systolic excursion	X		X	Measured using anatomic M-mode
RV diastolic dysfunction					Classified according to an algorithm using:
	Transtricuspid flow	X		X	Pulsed-wave Doppler at the tip of tricuspid valve
	Hepatic venous flow	X		X	Pulsed-wave Doppler 1 cm within hepatic vein
	Tricuspid annular velocities	X		X	Tissue Doppler on inferior wall
RV outflow tract obstruction	Using the paceport of the pulmonary artery catheter	X		X	Dedicated transducer for RV measurement
	2D view of the RV inflow-outflow	X		X	Mid-esophageal 40º to 70º view
	Deep transgastric view of the RV inflow-outflow	X		X	Deep transgastric view
	Measurement of the pressure gradient across the TV	X		X	A pressure gradient superior to the systolic pulmonary artery pressure will be observed
Patient-prosthesis mismatch	Measurement of the aortic annulus	X			Mid-esophageal 120º
	Table consultation of the EOA of the inserted prosthesis	X			Table used to obtain values for each type of valve
	Pressure-gradient across the LVOT	X		X	Deep transgastric view

Etiology	Measurement	Timing			Echocardiographic assessment
		Before CPB	During CPB	After CPB	
	Measurement of the aortic valve area	X		X	Using the continuity equation
Other measurements and observations:	Confirmation of the absence of any paravalvular leaks			X	Mid-esophageal 120º
	Confirmation of the position of the retrograde cardioplegia		X		Confirm presence in the coronary sinus
	Confirmation of the position of the inferior vena cava cannula		X		Confirm presence in the inferior vena cava
	Confirmation of the position of the aortic cannula	X	X		Confirm adequate position and good flow
	Confirmation of the position of any LVAD, RVAD or IABP		X	X	Confirm adequate position and good flow
	Severity of aortic atheromatosis	X			Classified using grade 1 to 5
	Ruling out aortic dissection	X	X	X	Confirm adequate position and good flow
	Ruling out inferior vena cava obstruction			X	Low-esophageal view 0°
	Ruling out free pleural or peritoneal fluid			X	Mid-esophageal, low-esophageal and transgastric views

Legends: AVR: aortic valve replacement, 2D: two-dimensional, CPB: cardiopulmonary bypass, IABP: intra-aortic balloon pump, LV: left ventricle, LVAD: left ventricular assist device, LVEDP: left ventricular end-diastolic pressure, LVOT: left ventricular outflow tract, ME: mid-esophageal, PHT: pulmonary hypertension, RA: right atrium, RV: right ventricle, RVAD: right ventricular assist device.

3.2 Research and development since the beginning of the PhD in 2006 at the MHI

Several of the determinants of venous return were studied over the last four years. They will be discussed in this section.

3.2.1 Studies on alternative measurement of venous return and cardiac output

Venous return and cardiac output can be measured using several techniques. In the operating room, we commonly use the pulmonary artery catheter to obtain thermodilution-derived cardiac output. In addition, the use of Doppler echocardiography allows us to calculate cardiac output. [12] The limitation of these two methods is that they are invasive and provide intermittent measurements only. An alternative to this technique would be near-infrared spectroscopy (NIRS).

Near-infrared spectroscopy (NIRS) is a technique that was first developed in the 70s [249;250] and that can be used as a non-invasive and continuous monitor of the balance between cerebral oxygen delivery and consumption. [135] Several different specialties such as neurology, [251] neurosurgery, [252] traumatology, [253] vascular surgery, [254] and adult [135] and pediatric cardiac surgery [255] have been using this monitor to measure brain and tissue perfusion. [129] In fact, some randomized controlled trials have recently shown the usefulness of this monitor to predict negative outcomes in non-cardiac [133] and cardiac surgery. [134] Several factors can affect oxygen delivery to the brain such as cardiac output, hemoglobin concentration, arterial oxygen saturation and partial pressure of oxygen. However, in an awake patient, the major determinants of baseline brain oximetric signals are not clearly described. Few studies have reported the relationship between cerebral oximetry values (ScO_2) and cardiac function. [249;250] As cardiac performance is reduced, increased brain oxygen extraction and lower ScO_2 values can be observed. [249] In addition, ScO_2 has been shown to correlate with the presence of left ventricular dysfunction in patients with valvular disease during exercice testing. [250] However, ScO_2 has never been compared with both hemodynamic and echocardiographic assessments of

the cardiac function in patients undergoing cardiac surgery. Our hypothesis was that the baseline mean ScO_2 value measured before surgery is determined by cardiac function and correlates with hemodynamic and echocardiographic parameters.

In order to test our hypothesis, we performed a retrospective analysis of patients undergoing cardiac surgery with bilateral recording of their baseline cerebral brain oxygen saturation (ScO_2) using the INVOS 4100 (Somanetics, Troy, MI, USA). [47] A pulmonary artery catheter was used to obtain their hemodynamic profile. Left ventricular systolic and diastolic function were evaluated by TEE, after induction of anesthesia, using standard criteria. A model was developed to predict ScO_2. A total of 99 patients met the inclusion criteria. There were significant correlations between mean ScO_2 values and central venous pressure (CVP) ($r = -0.31$, $p = 0.0022$), pulmonary capillary wedge pressure (PCWP) ($r = -0.25$, $p = 0.0129$), mean pulmonary artery pressure (MPAP) ($r = -0.24$, $p = 0.0186$), mean arterial pressure/mean pulmonary artery pressure ratio (MAP/MPAP) ($r = 0.33$, $p = 0.0011$), LV fractional area change (< 35, 35-50, ≥ 50, $p = 0.0002$), regional wall motion score index ($r = -0.27$, $p = 0.0062$) and diastolic function ($p = 0.0060$). Mean ScO_2 presented the highest area under the receiver operating curve (ROC) (0.74; CI 0.64-0.84) to identify LV systolic dysfunction. A model predicting baseline ScO_2 was created based on LV systolic echocardiographic variables, CVP, gender, mitral valve surgery and the use of beta-blocker ($r^2 = 0.42$, $p < .001$). Baseline ScO_2 values were related to cardiac function and superior to hemodynamic parameters at predicting left ventricular dysfunction. Our observations are summarized in Figure 52.

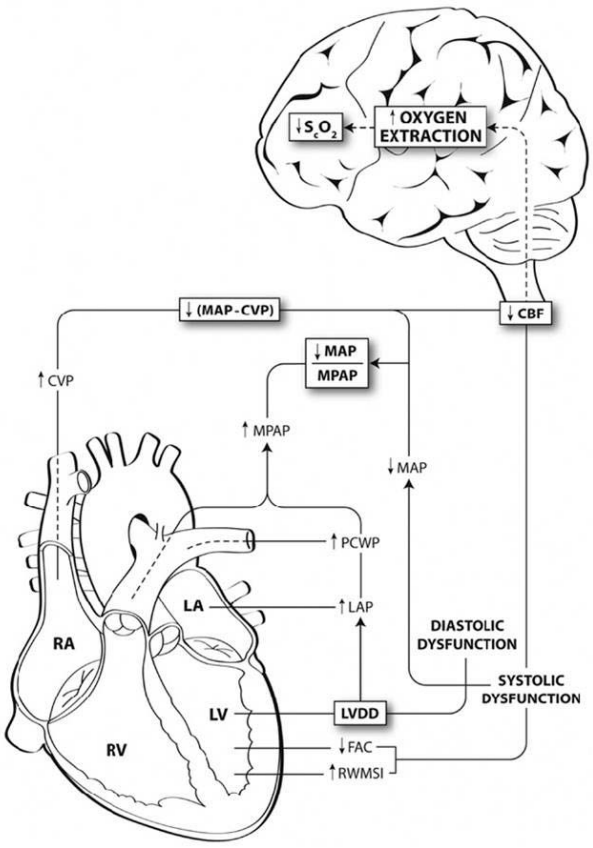


Figure 52 Brain-heart interaction

Relationship between reduced cerebral oxygen saturation (ScO_2) and cardiac systolic/diastolic function. As systolic cardiac function is reduced through a reduction in the left ventricular fractional area change (FAC) or an increase in the regional wall motion score index (RWMSI), the mean arterial pressure (MAP) will be reduced. Cardiac performance can also result from left ventricular diastolic dysfunction (LVDD), which can be present with or without systolic dysfunction. In this case, the left atrial pressure (LAP), pulmonary capillary wedge pressure (PCWP) and consequently the mean pulmonary arterial pressure (MPAP) will increase, the MAP/MPAP ratio decrease and this may lead to an increase of the central venous pressure (CVP). As the CVP is used to estimate the intra-cranial pressure, the cerebral perfusion pressure (MAP-CVP) will be reduced. The result will be a reduction in cerebral blood flow (CBF). This will lead to an increase in the oxygen extraction of the brain. This explains why a reduced cardiac function is associated with reduced ScO_2. (LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle). (With permission of Paquet *et al.* [47])

3.2.2 Studies on causes of increased Pra

Over the last 4 years we performed studies on systolic and diastolic dysfunction and documented the prevalence of RVOTO.

3.2.2.1 Left ventricular systolic and diastolic function

To support our hypothesis on the role of left ventricular systolic dysfunction as a predictor of outcome in cardiac surgery, we performed an observational study that included 3024 adult patients who underwent cardiac operations at the Montreal Heart Institute (MHI) from 1996 to 2000 (61% of the population operated in that period) and in whom left ventricular ejection fraction and other variables were measured prior to the cardiac surgery. [11] Left ventricular ejection fraction was the last measured value reported prior to surgery by left ventriculography, [256] echocardiography [257] or nuclear medicine. [258] The lowest value was selected. Surgical procedures were categorized as coronary revascularization, valvular, complex valve, re-operations and various. The complex operations were either multivalvular or valvular with or without coronary revascularization. Include also were ascending thoracic aorta operation and surgery for complications of myocardial infarction. Off-pump cardiac surgery and surgery of the descending aorta or patent ductus arteriosus were excluded. The primary outcome in this study was hospital mortality. Patients undergoing coronary revascularization were further stratified according to abnormal LV. Those left ventricular ejection fraction values were based on previous studies which identified them as cut-offs associated with increased mortality and morbidity. [8;100;259] Only variables with p values < 0.25 in univariate analysis were considered potential predictors of the primary outcome for multivariate analysis. Variable clustering was employed to further reduce the number of redundant variables before building a multivariate model. Then, stepwise multiple logistic regression analysis was undertaken to determine the independent predictors of death. P values < 0.05 were considered to be statistically significant. A total of 3024 patients were taken into account in the study. There were 99 deaths (3.3%). Of the 35 variables subjected to univariate analysis, 23 demonstrated a significant association with the occurrence of death. Stepwise

multiple logistic regressions identified eight variables to be independent predictors of death after cardiac surgery. These included age, weight, hypertension, treated diabetes, reoperation, left ventricular end-diastolic pressure, left ventricular ejection fraction and duration of CPB. Therefore, for a relative reduction of 10% of left ventricular ejection fraction, the risk of death increases by 32% (14-53%). A total 57% of deaths were attributed to hemodynamic instability. Postoperatively, 6% of those who died required vasopressors and 17% required an intra-aortic balloon pump (IABP) to be weaned, compared with 1% and 4% in the survivors group, respectively ($p < 0.0001$).

As mentioned previously, Salem *et al.* conducted an observational study to determine the relationship between preoperative left ventricular end-diastolic pressure and mortality following cardiac surgery. [11] The hypothesis was that an elevated left ventricular end-diastolic pressure, with or without preserved left ventricular systolic function, is associated with a poor outcome after cardiac surgery. As shown in Table 16, left ventricular end-diastolic pressure was found to be an independent predictor of mortality. For a relative increase in 5 mmHg of left ventricular end-diastolic pressure, the risk of mortality increases by 19% (5-35%).

Table 16 Multivariate analysis for mortality

Predictors	***P***	**Units**	**Odds ratio**	**95% CI**
Age	< 0.0001	20	4.255	2.461, 7.355
Weight, kg	0.0403	-10	1.190	1.008, 1.404
LVEDP	0.0062	5	1.195	1.052, 1.357
LVEF	0.0002	-10	1.326	1.145, 1.535
CPB length, min	< 0.0001	30	1.813	1.608, 2.044
Reoperation	< 0.0001	--	2.669	1.636, 4.354
Hypertension	0.0211	--	1.687	1.082, 2.632
Treated diabetes	0.0277	--	1.759	1.064, 2.906

CI indicates confidence interval; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass. (From Salem *et al.* [11])

Furthermore, in patients undergoing coronary revascularization ($n = 2445$), the mortality in patients with left ventricular ejection fraction < 30% was higher in those with elevated left ventricular end-diastolic pressure > 19 mmHg (12%) compared to those with left ventricular end-diastolic pressure ≤ 19 mmHg (0%) (Table 17).

Table 17 Mortality in patients undergoing coronary artery bypass grafting

	LVEDP > 19mmHg LVEF < 30%	**LVEDP > 19mmHg LVEF ≥ 30%**	**LVEDP ≤ 19mmHg LVEF < 30%**	**LVEDP ≤ 19mmHg LVEF ≥ 30%**
No	75 (88%)	1244 (97%)	30 (100%)	1033 (98%)
Yes	10 (12%)*	35 (3%)	0 (0%)	18 (2%)
Total	85	1279	30	1051

LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction * $P < 0.0001$ compared with patients with LVEDP ≤ 19 and LVEF < 30 (From Salem *et al.* [11])

A similar trend was observed in non-coronary revascularization patients ($n = 895$), but it was not statistically significant (Table 18). The definition of diastolic dysfunction can be applied to patients with or without LV systolic dysfunction who have filling abnormalities. In summary, these observations support the link between mortality and both left ventricular systolic and diastolic dysfunction.

Table 18 Mortality in patients undergoing non-coronary artery bypass grafting

	LVEDP > 19mmHg LVEF < 30%	**LVEDP > 19mmHg LVEF ≥ 30%**	**LVEDP ≤ 19mmHg LVEF < 30%**	**LVEDP ≤ 19mmHg LVEF ≥ 30%**
No	41 (89%)	292 (94%)	26 (93%)	480 (96%)
Yes	5 (11%)	19 (6%)	2 (7%)	20 (4%)
Total	46	311	28	500

LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction. (From Salem *et al.* [11])

3.2.2.2 Right ventricular systolic and diastolic function

To further assess the value of right ventricular function in relation to other validated risk factors in open valvular heart surgery, we published our experience with 50 consecutive patients undergoing valvular surgery. [46] In our study we confirmed that, in patients with a right ventricular myocardial performance index (RVMPI) above 50% ($n = 20$), the number of patients with difficult separation from CPB (16/20 (80%) *vs.* 6/30 (20%), $p < 0.0001$) and the endpoint of mortality of postoperative heart failure (14/20 (74%) *vs.* 3/30 (10%), $p < 0.0001$) were significantly higher. On a multivariate analysis, among all other demographic, hemodynamic and echocardiographic variables, the RVMPI was the only independent predictor of heart failure and mortality (OR: 25.20, 95% CI 5.24-121.15, $p < 0.0001$).

3.2.2.3 Right ventricular outflow tract obstruction

The prevalence of RVOTO was retrospectively studied in 670 consecutive patients undergoing cardiac surgery. [38] Significant RVOTO was diagnosed if the right ventricular systolic to pulmonary artery peak gradient was over 25 mmHg. The diagnosis was based on the measurement of the right ventricular and pulmonary artery systolic pressures through the paceport and distal opening of the pulmonary artery catheter. To further validate the prevalence and the importance of RVOTO, 130 patients were prospectively studied over a 12-month period. In the retrospective cohort, 6 patients (1%) undergoing various types of cardiac surgical procedures were found to have significant dynamic obstruction with a mean gradient of 31 ± 4 mmHg (26 to 35 mmHg). In the prospective study, significant dynamic obstruction was identified in 5 patients (4%) (average peak: 37 ± 15 mmHg; range: 27 to 60 mmHg). The typical transesophageal echocardiography finding was end-systolic obliteration of the RVOT (Figure 53).

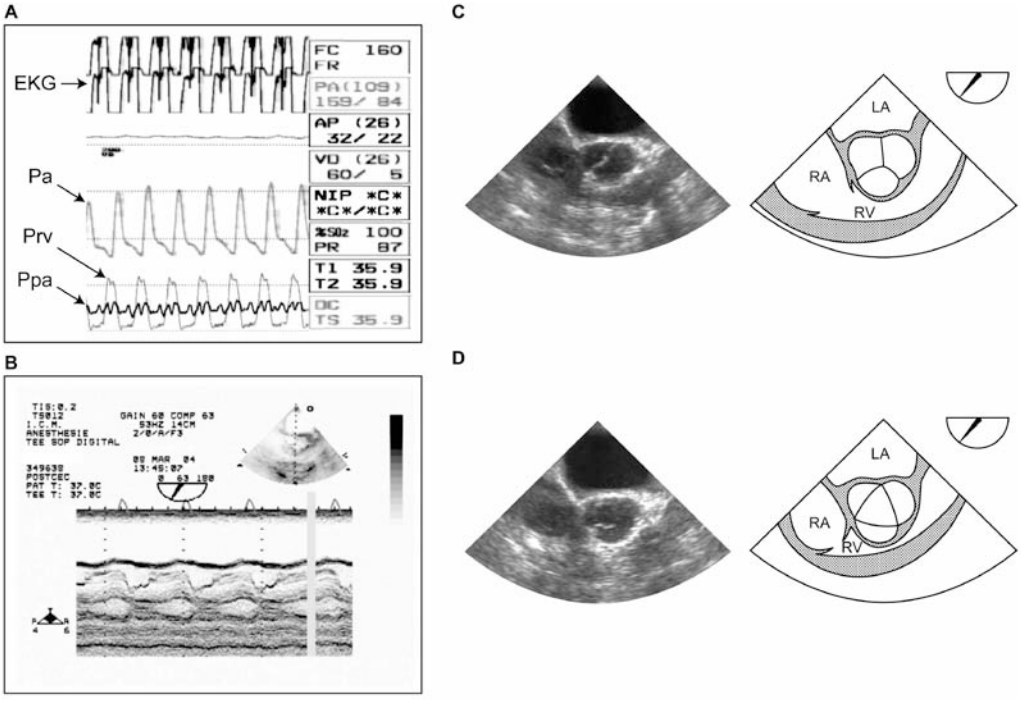


Figure 53 Dynamic right ventricular outflow tract (RVOT) obstruction

Septal myomectomy and aortic surgery in a 68-year-old man complicated by dynamic RVOT obstruction appearing during weaning from cardiopulmonary bypass. (A) The systolic gradient between the right ventricle and the pulmonary artery was 28 mmHg. (B,C,D) M-mode view from a mid-oesophageal right ventricular inflow-outflow view at 63º. Note the dynamic obstruction of the right ventricular outflow in systole in this (LA, left atrium; Pa, arterial pressure; Ppa, pulmonary artery pressure; Prv, right ventricular pressure; RA, right atrium; RV, right ventricle). (With permission of Denault *et al.* [38])

In patients with significant dynamic RVOTO, hemodynamic instability was present in 10/11 patients (91%). Therefore, RVOTO is easily diagnosed using the paceport of the pulmonary artery catheter (Figure 54) and should be considered a potential cause of hemodynamic instability, especially when TEE shows systolic right ventricular cavity obliteration.

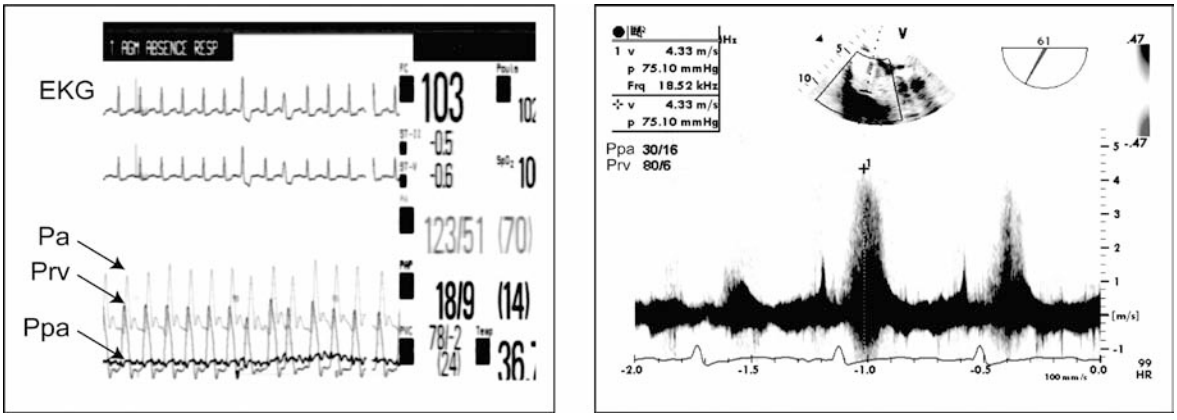


Figure 54 Hemodynamic and Doppler findings in dynamic RVOT obstruction

A 68-year-old man underwent aortic valve replacement. He became hemodynamically unstable with right ventricular dysfunction and was put back on cardiopulmonary bypass. Inotropes were initiated. On the second weaning attempt, he developed severe right ventricular outflow tract (RVOT) obstruction confirmed with the paceport of the pulmonary artery catheter and through continuous-wave Doppler interrogation of the tricuspid regurgitant flow in a mid-oesophageal ventricular inflow-outflow view at 61º. The measured pressure gradient of the tricuspid regurgitant flow was 75 mmHg (with a right ventricular systolic pressure of 80 mmHg) and the pulmonary artery pressure (Ppa) was 30/16 mmHg during the echocardiographic measurement. (EKG, electrocardiogram; Pa, arterial pressure; Prv, right ventricular pressure). (With permission of Denault *et al.* [38])

In summary, the mechanism of hemodynamic instability is complex but can be understood through a specific approach based on hemodynamic and echocardiographic variables. Therefore, such measures are essential to the evaluation of hemodynamic instability in cardiac surgery. So far, no studies have measured hemodynamic and echocardiographic variables in consecutive patients undergoing valvular surgery and determined the mechanism of difficult separation from CPB. The mechanism of difficult separation from CPB is important to understand if the next step is to prevent it.

Chapitre 4 Manuscript #2

Foreword to Manuscript #2

The second manuscript is part of a study conducted in collaboration with Dr. Yanick Beaulieu, a cardiology fellow under my supervision. It was a randomized controlled trial on the use of intravenous amiodarone in the prevention of postoperative atrial fibrillation in 120 patients undergoing valvular surgery. The postoperative part of the study will be published in *Anesthesiology* in January 2010.[56] Our objective in this study was to document, for the first time, the natural evolution of the systolic and diastolic function of both ventricles using combined hemodynamic and echocardiographic monitoring. This article also represents the first description of the acute effect of intravenous amiodarone on biventricular systolic and diastolic function. The intraoperative part of this study will also be submitted to *Anesthesiology*.

Effect of intravenous amiodarone on hemodynamic and biventricular echocardiographic changes during valvular surgery

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Short Title: Amiodarone in Cardiac Surgery

Brief Summary Statement

One hundred and twenty patients undergoing valvular surgery were randomized to receive either intravenous amiodarone for 48 hours starting intraoperatively or a placebo to prevent postoperative atrial fibrillation. The hemodynamic, biventricular echocardiographic and biochemical effects of amiodarone were compared to a placebo group.

ABSTRACT

***Background*:** Atrial fibrillation is a common complication after cardiac surgery. Postoperative atrial fibrillation is associated with increased risks of morbidity and mortality, and preventive strategies using amiodarone are commonly used during cardiac surgery. However the effect of intravenous amiodarone administered intraoperatively on hemodynamic and biventricular echocardiographic parameters assessed by transesophageal echocardiography (TEE) have not been described in patients undergoing valvular or complex surgery.

***Methods*:** Single-center double-blind, double-dummy, randomized controlled trial in patients undergoing valvular surgery. Patients received an intravenous (IV) loading dose of 300 mg of either amiodarone or placebo in the operating room, followed by a perfusion of 15 mg/kg per 24 hours for 2 days. A hemodynamic profile and biventricular comprehensive TEE exam were performed and described before, after bolus and after cardiopulmonary bypass (CPB). Postoperative complications and mortality at 6 years were also documented.

***Results*:** One hundred and twenty patients (mean age 65 ± 11 years) were randomized to receive either amiodarone or placebo. The placebo group included more patients with diabetes ($p = 0.0244$) and showed a longer duration of CPB ($p = 0.0426$), while the patients in the amiodarone group had more frequent isolated valvular procedures ($p = 0.0497$). There was no difference in the use of inotropic agents after CPB between the two groups but the amiodarone group required temporary pacing for bradyarrhythmia for up to 24 hours ($p = 0.0075$) more frequently. After the bolus, the amiodarone group showed and increase mean pulmonary artery pressure ($p = 0.0450$) with an associated reduction in S/D ratio of the hepatic venous velocity ($p = 0.0457$). A lower heart rate ($p < 0.0001$) and lower cardiac index ($p = 0.0157$) were observed after CPB in the amiodarone group with higher diastolic pulmonary venous flow velocities ($p = 0.0052$). There were no differences between groups in postoperative complications and survival at 6 years.

***Conclusion*:** In patients undergoing cardiac valvular surgery, intravenous amiodarone is well tolerated hemodynamically and not associated after CPB with significant changes in systolic and diastolic function and does not increase inotropic requirement when compared

to placebo despite a reduction in heart rate, cardiac index and increased pacemaker requirement for 24 hours.

Keywords: Cardiac surgery; Amiodarone; Transesophageal echocardiography; Cardiopulmonary bypass; Outcome.

Introduction

Atrial fibrillation is an important and frequent complication following cardiac surgery that occurs in almost one third of patients undergoing coronary artery bypass grafting [260] and in up to 44% of patients undergoing a valvular procedure. [261] Heart failure, hypotension, increased risk of stroke, the need for anticoagulation, increased length of stay in the hospital and long-term mortality are some of the various potential consequences of postoperative atrial fibrillation. [262-264] For these reasons, the prevention of atrial fibrillation has been proposed using several strategies including the use of intraoperative amiodarone. [261;265-269] In several of the amiodarone protocols, the preoperative loading regimen was administered orally days before the procedure. [261;265;267-269] The administration of amiodarone through intravenous loading could represent a more practical alternative approach in the prevention of atrial fibrillation because patients are often admitted the day before surgery. In a previous study, [56] we evaluated the safety and efficacy of intravenous amiodarone on the occurrence of perioperative atrial fibrillation. However, no studies have so far looked at the hemodynamic safety and associated biventricular echocardiographic systolic and diastolic changes induced when using intravenous amiodarone loading and infusion after anesthesia induction in patients undergoing a valvular surgical procedure. The primary aim of this study was to evaluate the hemodynamic effects, biventricular echocardiographic changes and safety of intravenous amiodarone in anesthetized patients compared to placebo.

Methods

Patient Population

This study is part of a single-center double-blind, double-dummy, randomized controlled trial to demonstrate the efficacy and safety of a 48-hour intravenous infusion of amiodarone in reducing atrial fibrillation prevalence in patients undergoing valvular surgery. [56] After approval of the research and ethic committee, patients of more than 18 years of age undergoing an isolated cardiac valvular surgery or a valvular surgery

combined with a coronary revascularization procedure were screened from November 2001 to May 2003 to be included in the study. To be eligible, they also had to be in sinus rhythm and have a left ventricular ejection fraction (LVEF) above 20% at the time of screening. Patients were excluded from the study if they met one of the following criteria: amiodarone intake in the previous 6 months, a history of anaphylactic reaction to iodine, a past history of severe reaction or toxicity to amiodarone, intake of class I or III anti-arrhythmic agents within the 48 hours before surgery, significant hypotension (systolic blood pressure <80 mmHg) necessitating sustained treatment with vasoactive agents for more than 1 hour preoperatively, urgent surgery and participation in other investigational trials.

Clinical Variables

Age, gender, body mass index (BMI) and body surface area (BSA) were determined for each patient, along with their relevant medications. Also documented were the presence of hypertension, diabetes, chronic renal failure, smoking history, recent myocardial infarction (MI, before or after 6 months), signs and symptoms of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), previous cerebrovascular disease (CVD), thyroid disorders, and LVEF measured through angiographic ventriculography or echocardiography. The different types of surgical procedures were classified as isolated valvular or valvular and coronary artery bypass grafting (CABG). The number of bypass grafts and the use of a mammary artery were noted in addition to the CPB time and aortic cross-clamping time. Length of cardiothoracic intensive care unit (CTICU) and hospital stay, postoperative complications and mortality rates were noted.

Study Protocol

Induction of anesthesia was performed using a combination of fentanyl (5–10 μg/kg) or sufentanil (0.7–1 μg/kg), midazolam (up to 0.1 mg/kg), and pancuronium (0.1 mg/kg). Isoflurane was used to control blood pressure during maintenance of anesthesia. After the induction of anesthesia, an intravenous loading dose of 300 mg of amiodarone (or placebo) was given over 10 minutes, followed by an infusion of amiodarone (15 mg/kg/24 hours,

max 1500 mg/24 hours) or placebo for 48 hours. A complete hemodynamic assessment using the pulmonary artery catheter (PAC) (7.5F 931HF75, Baxter Healthcare, Irvine, California) was performed before and after bolus infusion and after CPB. Baseline hemodynamic profiles were obtained from a radial artery catheter and a pulmonary artery catheter. TEE examination was performed at the following interval: 1) after the induction of anesthesia prior to median sternotomy and to the administration of the study drug or placebo, 2) following the bolus, and 3) after CPB during sternal closure. The following hemodynamic variables were recorded and calculated: heart rate (HR), systolic, diastolic and mean arterial pressures, systolic, diastolic and mean pulmonary artery pressures (MPAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), stroke volume (SV) and indexed systemic and pulmonary vascular resistance.

Complete laboratory data including arterial and venous blood gases were obtained just before administration of the amiodarone bolus and after weaning from CPB. The surgical valvular procedure was performed according to established guidelines. [270] Blood cardioplegia was used in all patients. Induction and maintenance of cardioplegia were cold to tepid (15-29ºC). The blood to crystalloid ratio was 4:1. The pump flow was adjusted to obtain an output of 2.2 l/min/m² of body surface area and was reduced to 0.5 l/min/m2 for aortic clamping and unclamping. SIII (Stockert, Munich, Germany) roller pumps were used in all patients. The oxygenator was Sorin Monolyth (Mirandola, Italy). Valve and complex procedures were done with temperatures of 32-34ºC. Weaning from CPB was attempted after systemic temperature (central and vesical) was > 36ºC and using a specific vasoactive treatment protocol as previously described. [52] All patients in the study had epicardial pacemaker wires (atrial and/or ventricular) placed at the end of surgery. The use of vasoactive drugs during CPB (Appendix 2) and the process of weaning from CPB (Appendix 3) were done according to a vasoactive protocol. [52] Temporary pacing was subsequently initiated if judged necessary by the anesthesiologist and the surgeon.

Echocardiographic examination

Intraoperative TEE examinations were performed by anesthesiologists with National Board Certification in perioperative echocardiography or more than 15 years of experience in TEE. The TEE examination included two-dimensional (2D) examination in the mid-esophageal and long-axis views and transgastric short-axis view at the mid-papillary level, with additional color flow imaging of the mitral, aortic and tricuspid valves in order to detect any significant valvular abnormality.

To assess left ventricular (LV) and right ventricular (RV) systolic function and dimensions, LV end-diastolic area (LVEDA), LV end-systolic area (LVESA) and LV fractional area change (LVFAC) were measured from the four-chamber and the transgastric mid-papillary view. From the mid-esophageal four-chamber view, the transverse diameter, the area and the volume of the left atrium (LA) and the right atrium (RA) were measured. From the same view, the area of the right ventricle (RV) at end-diastole (RVEDA), end-systole (RVESA), the fractional area change (RVFAC) and the tricuspid annular plane systolic excursion (TAPSE) were measured. All these measurements were obtained using published guidelines on 2D quantification [186] and right ventricular function evaluation. [48]

To assess LV and RV diastolic function, pulsed wave (PW) Doppler was used to evaluate transmitral flow (TMF) and transtricuspid inflow (TTF). Peak early (E) and late atrial (A) diastolic flow velocities were measured. Pulmonary venous flow (PVF) and hepatic venous flow (HVF) were also evaluated using PW Doppler, and peak systolic (S), diastolic (D) and atrial reversal (AR) flow velocities were measured.

Using tissue Doppler imaging (TDI), mitral annulus velocities (MAV) including the systolic (Sm) early diastolic (Em) and late atrial (Am) velocities were measured at the lateral or anterior annulus (the signal with the best definition and with the higher Em was chosen). Tricuspid annulus velocities (TAV) including the systolic (St), early (Et) and late atrial (At) velocities were also derived by TDI using a deep transgastric RV long axis view with right side rotation, as previously described. [39]

The classification of LV and RV diastolic function was based on a modification of the algorithm described by Khouri *et al.* [173] that we previously validated and used (Figure 55 and Figure 56). [12;39;43;50] All the echocardiographic data were recorded on a magnetic optical disk for off-line viewing. The measurements were done by an independent cardiologist (YS) blinded to the drug allocation, as previously described. [40] The echocardiographic images used in the classification of diastolic function were reviewed off-line by two independent observers blinded to the patient's data. Two-dimensional areas were not measured if less than 80% of the endocardial contour could be seen. [271]

In order to validate our measurements, we subjected 10 echocardiograms to 3 repeated measurements in a blinded fashion, with 3 consecutive cardiac cycles analyzed for each recording. The coefficient of variation (SD ÷ mean X 100%) between 3 consecutive cardiac cycles of the 10 echocardiograms was 2.7% ± 1.6% and 4.5% ± 1.8% for the left and right atrial areas in cardiac systole, and 3.4% ± 1.4% and 4.4% ± 1.9% for the left and right ventricular end-diastolic areas, respectively. For PW velocity and TDI velocity the coefficients of variation were 5.4% ± 2.6% and 2.6% ± 1.3%, respectively. The coefficient of variation between the 3 results based on the average of 3 cycles of these 10 echocardiograms was 1.4% ± 0.8% and 2.7% ± 1.8% for the left and right atrial areas in cardiac systole and 2.9% ± 1.1% and 2.9% ± 1.1% for the left and right ventricular end-diastolic areas, respectively. For PW velocity and TDI velocity, the coefficients of variation were 1.1% ± 0.4% and 1.0% ± 1.0% respectively. [40]

Left ventricular diastolic function was not evaluated in patients with mitral stenosis and moderate to severe mitral or aortic regurgitation. Right ventricular diastolic function was not evaluated in patients with moderate to severe tricuspid regurgitation. Patients with atrial fibrillation or a pacemaker, and contraindication to transesophageal echocardiography (TEE) were excluded from the diastolic function classification. Twenty-nine measurements for left ventricular diastolic function were excluded because the Doppler signals could not be obtained. The left ventricular diastolic function algorithm was used to evaluate 190 measurements (73, 50 and 67 patients for the three evaluation time points: before studied drug bolus, after drug bolus and after CPB, respectively). The inter-observer kappa values

were 0.82, 0.57 and 0.77 between 2 observers. Fifty measurements for right ventricular diastolic function were excluded for the reasons mentioned above. The right ventricular diastolic function algorithm was used to evaluate 178 measurements (69, 52 and 57 patients for the three evaluation time points). The inter-observer kappa values were 0.69, 0.82 and 0.91. When the three evaluation time points were pooled, the LVDD and RVDD algorithm interobserver kappa values were 0.77 and 0.82. In the evaluation of LVDD, 26/193 (13%) and 3/193 (1.6%) time points were respectively excluded by reviewers #1 and #2. In the evaluation of RVDD 23/182 (13%) and 4/182 (2%) time points were excluded by reviewer #1 and #2.

Statistical Analysis

In our previous study, [56] we estimated that 50% of patients undergoing cardiac valvular surgery would develop atrial fibrillation. In order to detect the expected reduction in AF from 50% to at least 25% in the amiodarone group, 58 patients per group would be needed to reach a power of 80% with a two-sided chi-square test at an alpha of 5%. Assuming a 3% loss, we recruited 60 patients per group. The results are presented as mean ± SD or median (minimum-maximum) according to the distribution for continuous variables and as numbers (percentage) for categorical variables. Chi-square tests were used to compare categorical variables between groups (with or without amiodarone). For continuous variables, the Student t-test or Wilcoxon test were used to compare groups. To analyze the evolution of the variables, mixed-model repeated-measures analyses of covariance controlling for the baseline value [272] were used to extract the group X time interaction and the time and group main effects. When the group X time interaction was significant, i.e. that there was a significant difference in evolution between groups, slice effect (also known as simple effect) [273] analyses were performed to evaluate differences among groups at each time level and to test the evolution of each group. The generalized estimating equation (GEE) approach was performed using the multinomial distribution to study the LV and RV diastolic function because of the distribution of patients among the diastolic scores. These analyses were performed with the mixed procedure of SAS 8.02

(SAS Institute Inc., Cary, North Carolina) to handle missing data. The Wilcoxon test was used to compare the distribution of frequencies of both left and right ventricular diastolic function patterns. A *p* value of less than .05 was considered statistically significant.

Results

Baseline pre- and intraoperative characteristics of patients are shown in Table 19. A total of 120 patients were randomized and 1 patient in the amiodarone group died intraoperatively of right ventricular failure. The mean age was 65 ± 11 years and 67 (56%) patients were men. Baseline demographic characteristics were similar among groups except for a higher proportion of patients with diabetes (23% vs. 8%; $p = 0.0244$) in the placebo group. Two-thirds of the total population (68.3%) underwent an isolated valvular surgery and one-third (31.7%) underwent combined valvular and CABG surgery. Patients in the amiodarone group underwent more isolated valvular surgeries compared to the placebo group (76.7% vs. 60%; $p = 0.0497$) There were no significant differences in the proportion of patients undergoing mitral and /or aortic valve procedures between the two groups. The total CPB time (97 ± 32 *vs*. 110 ± 37 min; $p = 0.0426$) and aortic cross-clamp time (73 ± 28 *vs*. 85 ± 30 min; $p = 0.0271$) were shorter in the amiodarone group.

The significant ($p < 0.05$) biochemical, hemodynamic, echocardiographic and Doppler variables are shown in Table 20. (Detailed tables can be found in Appendix 2 to Appendix 8). Higher levels of urea (5.7 ± 1.7 *vs*.5.4 ± 1.5 mmol/L, $p = 0.0052$), creatinine (86 ± 29 *vs*. 78 ± 27 mmol/L, $p = 0.0013$) and lower CK (436 ± 219 *vs*. 743 ± 751 ug/L, $p = 0.0117$), $PaCO_2$ (43.8 ± 4.4 *vs*. 45.7 ± 4.4 mmHg, $p = 0.0192$) and HCO_3 (25.7 ± 2.2 *vs*. 27.2 ± 2.4 mmol/L, $p = 0.0002$) were observed in the amiodarone group after CPB. After the bolus of amiodarone, an increase in MPAP from 21.8 ± 8.1 to 25.6 ± 8.6 mmHg ($p = 0.0450$) with associated reduction in HVF S/D ratio ($p = 0.0457$) in the amiodarone group. After CPB, the amiodarone group had lower heart rate ($p < 0.0001$), cardiac index ($p = 0.0157$), increased PVF D velocity ($p = 0.0052$) and reduced PVF S/D ratio ($p = 0.0112$). There were no differences in the evolution of LV and RV diastolic function

between the two groups. Figure 57 summarizes the acute effect of the bolus of amiodarone or placebo on the hemodynamic variables and biventricular function.

No difference in the number of patients receiving vasoactive support was observed during and after CPB between groups, but requirement for a pacemaker was more frequent in the amiodarone group in the first 24 hours ($p = 0.0075$) (Table 3). There were no differences in terms of duration of stay in the intensive care unit and hospital. No differences in short and long term mortality between the groups were observed.

Discussion

Our main findings are that the administration of intravenous amiodarone in anesthethized patients undergoing valvular or combined valvular and CABG surgery results in a transient increase in MPAP with an associated alteration in right ventricular diastolic parameters. In addition, amiodarone lowers heart rate and consequently cardiac index after CPB compared to a placebo. However this bradycardia was not associated with lower stroke volume in the amiodarone group. Furthermore, these differences in hemodynamic parameters between groups were not accompanied by significant differences in 2D echocardiographic parameters. The changes in HVF S/D velocities observed in the amiodarone group may be partly related to the effect of an increase in MPAP on systolic and diastolic RV function. Such increases in MPAP will lead to higher TTF and HVF atrial velocities consistent with an increase in right ventricular afterload. [207] However, atrial velocities did not differ between the two groups. We also observed higher PVF D velocities after CPB in patients receiving amiodarone. Changes in PVF diastolic velocities are associated with increased filling pressures and an alteration in both systolic and diastolic function. [274] After CPB, we observed significant increases in the filling pressure and changes in both biventricular systolic and diastolic function. However, these alterations did not differ between groups. The significance of changes in diastolic PVF velocities with amiodarone remains of unknown clinical significance.

Overall, the administration of intravenous amiodarone was well tolerated. This observation is further supported by the fact that the number of patients in the amiodarone

group necessitating inotropic agents did not differ from the placebo group. The duration of stay in the intensive care unit, the hospital stay and the mortality were also similar. The biochemical changes in the amiodarone group were minor and not clinically relevant. The lower CK could be related to the shorter CPB duration in the amiodarone group.

Effect of amiodarone on systolic biventricular cardiac function in other studies

The chronic use of amiodarone has not been associated with an alteration in left or right ventricular function in 21 patients with ventricular tachycardia. [275] However, an intravenous infusion of amiodarone has been associated with a reduction in left ventricular ejection fraction, stroke index and systolic blood pressure. [276] Therefore, in the acute state, it is possible that intravenous as opposed to oral amiodarone may be associated with a mild negative and transient inotropic effect. The changes in MPAP that we observed are consistent with these observations. The prolongation of the atrioventricular nodal conduction and refractoriness of amiodarone [277;278] could explain the observed reduction in heart rate and cardiac index without changes in stroke volume after CPB and the higher use of temporary pacing. As a negative inotropic agent, amiodarone could be detrimental after CPB. Despite these hemodynamic effects, amiodarone was well tolerated in this patient population, as suggested by the absence of difference in vasoactive requirements, as well as in systolic right and left ventricular function between the amiodarone and the placebo groups.

Effect of amiodarone on diastolic biventricular cardiac function

Our study also provides data for the evolution over time of diastolic function in patients undergoing valvular surgery. Changes in left ventricular diastolic function during cardiac surgery have been mostly described after CABG. [68;88;90;92;94-98] Variations in the parameters used in the evaluation of left ventricular diastolic function can explain some of the observed discrepancies among the different studies. Shi *et al.*, [40] using newer echocardiographic modalities and the recommended classification of the American Society

of Echocardiography [173], studied the short- and long-term evolution of biventricular diastolic performance in patients with LV diastolic dysfunction undergoing CABG. The prevalence of moderate and severe LV diastolic dysfunction increased from 2.0% preoperatively to 9.7% at 48 hours respectively. The diastolic patterns at 6 months were similar to those observed preoperatively. A similar evolution over time was found for RV diastolic function. We also observed significant abnormalities in right-sided diastolic function as reported by Shi *et al*. [40] and Couture *et al*. [43] in patients undergoing CABG. Similar changes in RV diastolic function have also been described by Diller *et al*. [92] using tricuspid annular velocities in patients undergoing CABG. These changes could be explained by many factors including inflammatory changes induced by CPB, [279] a pulmonary reperfusion syndrome, [280] ischemic cardiac arrest, poor myocardial protection or the effect of pericardectomy. [281] Despite changes over time in several of the parameters used to evaluate biventricular diastolic function, when using a comprehensive algorithm that integrates several of these parameters, we did not observe that amiodarone had any significant effect on the evolution of biventricular diastolic function in valvular surgery.

Limitations

Firstly, at baseline, there were more patients with diabetes and more complex surgeries with longer CPB duration in the placebo group. There were no clinically significant hemodynamic, echocardiographic and biochemical differences between the groups and their evolution was similar. However, it is possible that the negative inotropic effect of amiodarone was overlooked because amiodarone was administered to patients with less complex procedures and shorter CPB times. Secondly, the gold standard for evaluating diastolic dysfunction are the time constant of relaxation (Tau) and pressure-volume curves obtained by direct invasive measurements to assess chamber compliance. However, these measures are invasive and are not feasible in usual practice. We used a Doppler assessment of mitral and tricuspid inflow, as well as pulmonary and hepatic flow variables to assess diastolic function. Tissue Doppler imaging, which is a relatively

volume-insensitive modality, provided supportive information to better stratify the degree of diastolic dysfunction. [173] Changes in mitral flow velocity have been noted when changes occurred in loading conditions, differing heart rates, and the left ventricular contractile state. [282] Hemodynamic variables were relatively similar in both groups except in the amiodarone group which has a lower heart rate and cardiac index after CPB. Accordingly, we cannot totally exclude the effect of the change of cardiac output and heart rate on diastolic filling patterns in our patients nor that amiodarone may have a certain effect on diastolic function that we did not identified, even when using load-independent modalities. [173] Criteria for right ventricular diastolic dysfunction have been previously described [204] but are not yet as widely accepted as those used for LV diastolic dysfunction. So far however, no study has documented a deterioration of intraoperative biventricular diastolic function in patients undergoing valvular surgery, independently of the use of intravenous amiodarone

Conclusion

In patients undergoing cardiac valvular surgery, the intraoperative use of intravenous amiodarone compared to placebo does not alter biventricular systolic and diastolic function after CPB and is not associated with increased need for vasoactive agents despite a reduction in heart rate, cardiac index and increased pacemaker requirements for 24 hours.

Table 19 Characteristics of the amiodarone versus placebo group

Characteristics	**Amiodarone (n=60)**	**Placebo (n=60)**	***P* Value**
Age, yrs	65±11	65±11	0.8599
Gender			0.5813
Men	32 (53.3)	35 (58.3)	
Women	28 (46.7)	25 (41.7)	
Body mass index	27.2±4.3	27.2±4.9	0.9381
Hypertension	29 (48.3)	28 (46.7)	0.8550
History of stroke	2 (3.3)	1 (1.7)	0.5587
Coronary artery disease	9 (15)	13 (21.7)	0.3453
Myocardial infarction			
<6 months	1 (1.7)	3 (5)	0.6186
>6 months	3 (5.0)	6 (10.0)	0.4906
Congestive heart failure	12 (20.0)	21 (35.0)	0.0658
Left ventricular ejection fraction (%)	58±9	61±12	0.1365
Smoking history	10 (16.7)	15 (25.0)	0.2611
Chronic obstructive pulmonary disease	6 (10.0)	14 (23.3)	0.0500
Diabetes mellitus	5 (8.3)	14 (23.3)	0.0244
Chronic renal failure	1 (1.7)	4 (6.7)	0.3644
Thyroid disorder	8 (13.3)	5 (8.3)	0.3782
Preoperative medication			
Beta-blockers	19 (31.7)	15 (25.0)	0.4178
Calcium antagonists	9 (15.0)	17 (28.3)	0.0763
Angiotensin converting enzyme inhibitor	17 (28.3)	21 (35.0)	0.4325
Angiotensin receptor blocker	4 (6.7)	8 (13.3)	0.2235
Diuretics	15 (25.0)	24 (40.0)	0.0794
Digitalis	1 (1.7)	1 (1.7)	1.0000

Characteristics	**Amiodarone (n=60)**	**Placebo (n=60)**	***P* Value**
Type of surgery			
Isolated valvular	46 (76.7)	36 (60.0)	0.0497
Valvular + coronary artery bypass graft	14 (23.3)	24 (40.0)	
Type of valvular surgery			
Aortic	44 (73.3)	39 (65.0)	0.3230
Mitral	16 (26.7)	23 (38.3)	0.1725
Number of bypass grafts			
1	6 (42.9)	9 (37.5)	0.4464
2	5 (35.7)	6 (25.0)	
3	3 (21.4)	8 (33.3)	
5	0	1 (4.2)	
Use of mammary artery	9 (64.3)	14 (58.3)	0.7173
Total cardiopulmonary bypass time, min	97±32	110±37	0.0426
Aortic cross-clamp time	73±28	85±30	0.0271

Data are presented as n (%) for proportions and as mean ± standard deviation for continuous variables. CPB, cardiopulmonary bypass

Table 20 Biochemical, hemodynamic and Doppler variables

Variable	Group	Baseline (Mean ± SD)	After bolus (Mean ± SD)	After CPB (Mean ± SD)	*P* value (group)	*P* value (time)	*P* value (group*time)
Urea (mmol/L)	Amiodarone	6.0 ± 1.7		5.7 ± 1.7	0.8623	< 0.001	0.0052[3]
	Placebo	6.4 ± 1.9		5.4 ± 1.5			
Creatinine (umol/L)	Amiodarone	81 ± 22		86 ± 29	0.4268	0.5917	0.0013[4]
	Placebo	84 ± 23		78 ± 27			
CK total (ug/L)	Amiodarone	70 ± 46		436 ± 219	0.0973	< 0.0001	0.0117 [5]
	Placebo	68 ± 44		743 ± 751			
HCO3 (mmol/L)	Amiodarone	26.9 ± 2.1		25.7 ± 2.2	0.0496	0.1257	0.0002[6]
	Placebo	26.7 ± 1.7		27.2 ± 2.4			
$PaCO_2$ (mmHg)	Amiodarone	37.2 ± 4.8		43.8 ± 4.4	0.3051	< 0.0001	0.0192[7]
	Placebo	36.6 ± 4.0		45.7 ± 4.4			
HR (beats per minutes)	Amiodarone	58.1 ± 9.5	63.2 ± 10.5	66.9 ± 11.9	0.0006	<.0001	<.0001[8]
	Placebo	58.1 ± 10	67.9 ± 17.1	78.7 ± 10.8			
MPAP (mmHg)	Amiodarone	21.8 ± 8.1	25.6 ± 8.6	24.1 ± 5.9	0.2531	0.0001	0.0450[9]
	Placebo	21.8 ± 7.8	22.7 ± 8.4	23.7 ± 4.9			
CI ($L/m/m^2$)	Amiodarone	2.01 ± 0.45	2.14 ± 0.61	2.48 ± 0.52	0.0193	0.0001	0.01574 [10]
	Placebo	2.03 ± 0.49	2.26 ± 0.79	2.9 ± 0.67			
PVF D wave	Amiodarone	34.1 ± 12.5	37.7 ± 15.7	61 ± 22.2	0.8846	<0.00012	0.0052[11]

[3] $P < 0.05$ baseline versus after CPB in both groups
[4] $P = 0.0071$ baseline versus after CPB in the placebo group
[5] $P = 0.0097$ after CPB in the amiodarone compared to the placebo group
[6] $P = 0.0002$ baseline versus after CPB in the amiodarone group and $p = 0.0008$ after CPB in the amiodarone compared to the placebo group
[7] $P = 0.0237$ after CPB in the amiodarone compared to the placebo group
[8] $P < 0.001$ baseline versus after bolus in the placebo group and $p < 0.001$ after CPB in the amiodarone compared to the placebo group
[9] $P = 0.0445$ after bolus in the amiodarone compared to the placebo group, $p < 0.05$ baseline versus after bolus and baseline versus after CPB in the amiodarone group
[10] $P = 0.0079$ baseline versus after bolus in the placebo group and $p < 0.001$ after CPB in the amiodarone compared to the placebo group

Variable	Group	Baseline (Mean ± SD)	After bolus (Mean ± SD)	After CPB (Mean ± SD)	*P* value (group)	*P* value (time)	*P* value (group*time)
	Placebo	39.7 ± 12.5	35.6 ± 16.8	50.3 ± 15.2			
PVF S/D ratio	Amiodarone	1.5 ± 0.6	1.3 ± 0.4	0.9 ± 0.4	0.4232	0.00033	0.0112[12]
	Placebo	1.2 ± 0.5	1.4 ± 0.5	1.0 ± 0.5			
HVF S/D ratio	Amiodarone	1.3 ± 0.8	1.1 ± 0.7	-0.3 ± 0.6	0.3795	<0.00012	0.0457[13]
	Placebo	1.4 ± 0.4	1.5 ± 0.7	-0.3 ± 0.8			

CI, cardiac index; CK, creatine kinase; D, diastolic; HR, heart rate, HVF, hepatic venous flow; L, liter; MPAP, mean pulmonary artery pressure; PVF, pulmonary venous flow; S, systolic

[11] $P = 0.0227$ after CPB in the amiodarone compared to the placebo group

[12] $P < 0.05$ baseline versus after bolus in the placebo group, baseline versus after CPB in the amiodarone group and $p = 0.0136$ baseline versus after CPB in amiodarone versus the placebo group

[13] $P = 0.0154$ after bolus in the amiodarone compared to the placebo group

Table 21 Outcome data

Characteristics	Amiodarone*	Placebo	*P* Value
Vasoactive support during and after CPB			
Noradrenaline	56 (93.3)	54 (90.0)	0.5089
Neosynephrine	53 (88.3)	53 (88.3)	1.0000
Vasopressine	13 (21.7)	10 (16.7)	0.4585
Nitroglycerine	45 (75.0)	33 (55.0)	0.0216
Adrenaline	3 (5.0)	3 (5.0)	1.0000
Milrinone	26 (43.3)	26 (43.3)	1.0000
Pacemaker requirement up to 24 hours	24 (40.7)	11 (18.3)	0.0075
CTICU duration (hours)	64±81	51±39	0.4898
Hospitalization duration (hours)	311±270	253±146	0.1996
Hospital mortality	1 (1.7)	1 (1.7)	0.9904
Number of deaths at 6 years	5(8.5)	8 (13.3)	0.4307#

CPB, cardiopulmonary bypass; CTICU, cardiothoracic intensive care unit.
Data are presented as *n* (%) for proportions and as mean ± standard deviation for continuous variables.
* One patient died intraoperatively of right ventricular failure.
# Obtained from log rank test

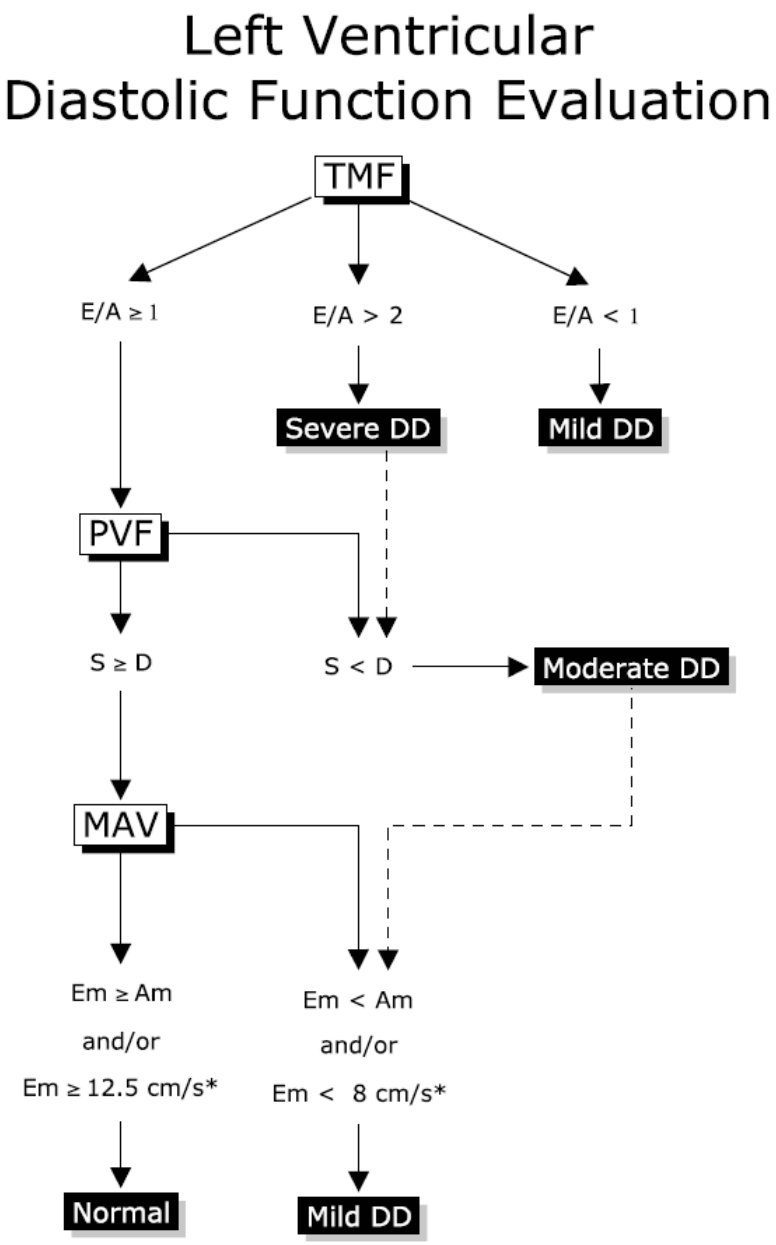

Figure 55 Left ventricular diastolic dysfunction (DD) algorithm

Left ventricular diastolic function is classified using pulsed wave Doppler of the transmitral flow (TMF), pulmonary venous flow (PVF) and tissue Doppler examination of mitral annular velocity (MAV). Patients with a pacemaker, atrial fibrillation, non-sinus rhythm, mitral stenosis, severe mitral and aortic regurgitation are excluded from analysis Left ventricular diastolic function is classified as normal (TMF E/A >1, PVF S/D >1, Em/Am >1), mild DD (E/A < 1, S/D >1, Em/Am <1), moderate DD (E/A≥ 1, S/D <1, Em/Am <1), and severe DD (E/A >2, S/D <1, Em/Am < or >1). (A, atrial component TMF; Am, atrial MAV; D, diastolic component PVF; E, early filling TMF; Em, early MAV; S, systolic component PVF.*Normal Em is within an 8–12.5 cm/sec interval) (With permission of Denault *et al.* [39]).

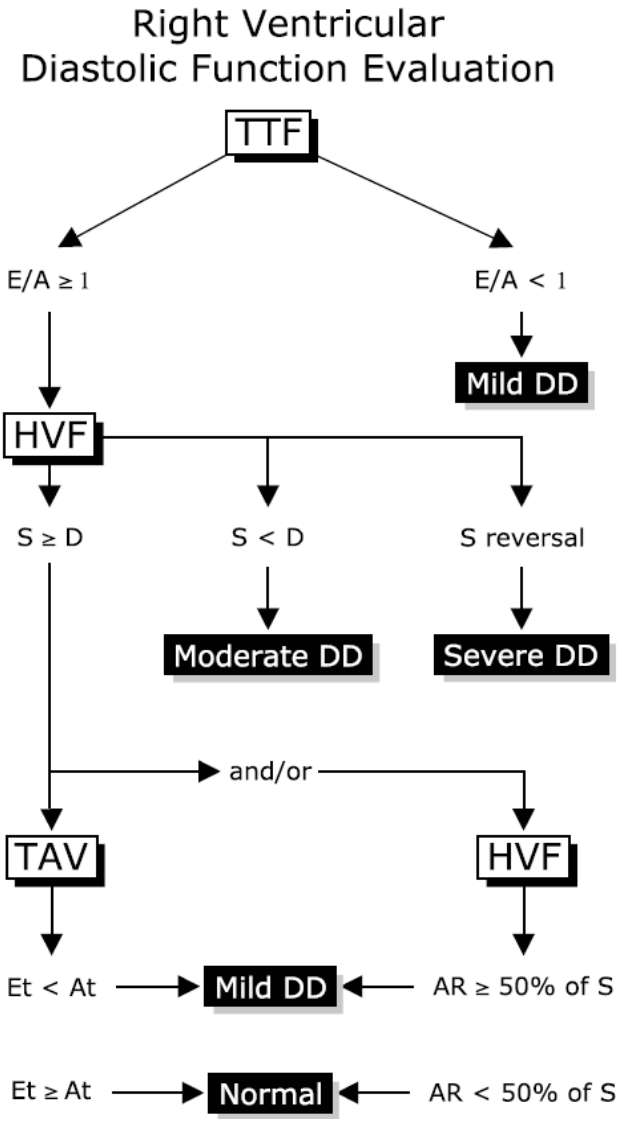

Figure 56 Right ventricular diastolic dysfunction (DD) algorithm

Diastolic function is classified by pulsed wave Doppler of the transtricuspid flow (TTF), hepatic venous flow (HVF) and tissue Doppler imaging of the tricuspid annular velocity (TAV). Patients with a pacemaker, atrial fibrillation, non-sinus rhythm, moderate to severe tricuspid regurgitation and tricuspid annuloplasty are excluded from analysis. Right ventricular diastolic function is classified as normal (TTF E/A >1, HVF S/D >1, Et/At >1), mild DD (E/A <1, or reversed AR >50% of S wave measured on HVF, or Et < At when both E/A and S/D >1), moderate DD (E/A≥ 1, S/D <1, Et/At <1), and severe DD (S wave reversal on HVF, irrespective of the E/A and S/D ratio). (A, atrial component TTF; AR, atrial reversal HVF; A_t, atrial TAV; D, diastolic HVF; E, early filling TTF; E_t, early TAV; S, systolic HVF) (Adapted from Denault *et al.* [39]).

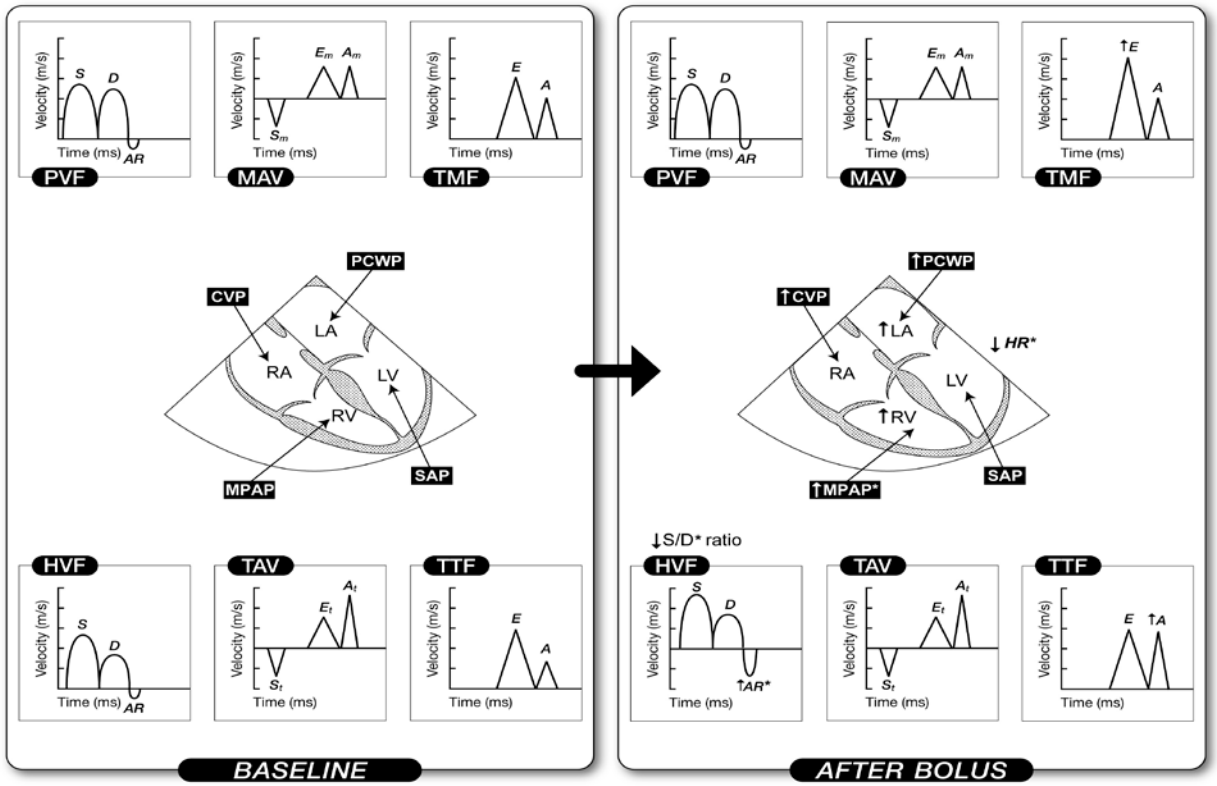

Figure 57 Hemodynamic and echocardiographic summary

Hemodynamic, biventricular echocardiographic and Doppler changes in patients undergoing valvular surgery after bolus of amiodarone or placebo (A, atrial component; Am, atrial MAV; AR, atrial reversal; A_t, atrial TAV; CVP, central venous pressure; D, diastolic; E, early filling; Em, early MAV; E_t, early TAV; HR, heart rate; HVF, hepatic venous flow; MAV, mitral annular velocity; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVF, pulmonary venous flow; S, systolic HVF, SAP, systolic artery pressure; Sm, systolic MAV; St, systolic TAV; TAV, tricuspid annular velocity; TMF, transmitral flow; TTF, transtricuspid flow; * $p < 0.05$ in the amiodarone group only)

Chapitre 5 Manuscript #3

Foreword to Manuscript #3

The third manuscript is part of a study conducted in collaboration with Dr. Yanick Beaulieu, a cardiology fellow under my supervision. It was a randomized controlled trial on the use of intravenous amiodarone in the prevention of postoperative atrial fibrillation in 120 patients undergoing valvular surgery. The postoperative part of the study will be published in *Anesthesiology* in January 2010.[56]

This paper focused on patients experiencing difficult separation from CPB. Our objective was to explore the pre- and intraoperative demographic, hemodynamic and echocardiographic characteristics and their evolution in patients requiring inotropic support after valvular surgery. This study predates our use of inhaled milrinone. Are there any factors predisposing to inotropes? What will happen six years later to patients requiring inotropes intraoperatively? These are the questions that are addressed.

This article also represents the first description of the natural evolution on biventricular systolic and diastolic function after valvular surgery. It is a similar study to the one we conducted in patients undergoing coronary revascularization, which was published in the *Canadian Journal of Anesthesia* [43] and the *Journal of Thoracic and Vascular Surgery*.[40] This study will be submitted to the *Journal of Thoracic and Cardiovascular Surgery*.

Effect of inotropic support on hemodynamic and biventricular function in patients undergoing valvular surgery.

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Short Title: Inotropic Support in Cardiac Valvular Surgery

Brief Summary Statement

The use of perioperative inotropic support was studied in one hundred and twenty patients undergoing valvular surgery as part of a randomized controlled trial on the use of intravenous amiodarone for 48 hours starting intraoperatively in the prevention of postoperative atrial fibrillation. The biochemical, hemodynamic and biventricular echocardiographic evolution was studied and the impact of inotropic support analyzed. Patients were followed-up for 6 years.

ABSTRACT

***Background*:** Inotropic agents are often needed to wean patients from cardiopulmonary bypass (CPB) in valvular or complex surgery, but their effects on systolic and diastolic function has not been well reported. The aim of this study was to evaluate the effect of inotropic support on biventricular systolic and diastolic function, as well as outcome, compared to a control group without inotropes, in patients undergoing valvular surgery. The secondary objectives were to assess factors which can predict the need for inotropic support after cardiopulmonary bypass, and also to document the change in systolic and diastolic function over time in valvular surgery.

***Methods*:** Single-center double-blind, double-dummy, randomized controlled trial in patients undergoing valvular surgery and randomized to receive intravenous amiodarone or placebo intraoperatively. Patients were divided in those requiring or not postoperative inotropic agents. Demographic and biochemical data were obtained. Hemodynamic profile and biventricular comprehensive transesophageal echocardiographic (TEE) exam were performed and described before, after bolus and after cardiopulmonary bypass (CPB). Patients were followed-up for 6 years.

Results: One hundred and twenty patients (mean age 65 ± 11 years) were randomized to receive amiodarone or placebo. There was no difference in the use of inotropic agents after CPB in patients randomized to amiodarone or placebo. There were no significant baseline biochemical or hemodynamic differences among patients receiving inotropes after CPB. The use of inotropes was associated with increased left atrial dimensions ($p = 0.0196$), increased E/e ratio ($p = 0.0104$), reduced tissue Doppler mitral systolic velocities ($p = 0.0086$), increased end-systolic right ventricular area dimension ($p = 0.0197$) with associated reduced hepatic venous flow systolic velocities ($p = 0.0093$) before CPB. Inotropic agents after CPB were associated with increased tissue Doppler mitral annular atrial velocities ($p = 0.0252$), pulmonary ($p = 0.0459$) and hepatic venous flow ($p = 0.003$) atrial reversal velocities. There were no difference in postoperative complications and in survival in both group however the number of death at 6 years was increased in patients who received intraoperative inotropes ($p = 0.0247$).

Conclusion In patients undergoing cardiac valvular surgery, significant hemodynamic and biventricular systolic and diastolic echocardiographic changes do occur after CPB. Inotropic medications were not associated with a difference in hemodynamic and echocardiographic parameters after CPB when compared to a control group. However inotropic medications were associated with increased bi-atrial activity after CPB. At 6 years, despite similar baseline demographic characteristics, an increased number of deaths was observed in patients requiring inotropic medication.

Keywords: Cardiac surgery; Amiodarone; Inotropic agents; Transesophageal echocardiography; Cardiopulmonary bypass; Outcome.

Introduction

Deterioration in systolic ventricular function following coronary revascularization has been commonly observed and was described several years ago by Breisblat *et al.* [283] A reversible ischemic injury or hibernating myocardium are thought to be potential mechanisms inducing that deterioration. [284] Changes in left ventricular diastolic function have also been described following coronary revascularization [84;86;88;95-97;285] however, changes in both left ventricular systolic and diastolic function have not been described in patients undergoing valvular surgery. Furthermore right ventricular systolic and diastolic function have been documented after coronary revascularization [40;92] but not reported in valvular surgery. In addition, inotropic support is often necessary for cardiopulmonary bypass (CPB) weaning and is likely to alter cardiac function. The impact of inotropic support on biventricular systolic and diastolic function and on postoperative outcome is not well studied in patients undergoing valvular surgery.

Accordingly, the aim of the study was to evaluate the effect of inotropic support on biventricular systolic and diastolic function, as well as outcome, compared to a control group without inotropes, in patients undergoing valvular surgery. The secondary objectives were to assess factors which can predict the need for inotropic support after CPB, and also to document the change in systolic and diastolic function over time in valvular surgery.

Methods

Patient Population

This study is part of a single-center double-blind, double-dummy, randomized controlled trial to demonstrate the efficacy and safety of a 48-hour intravenous infusion of amiodarone in reducing atrial fibrillation prevalence in patients undergoing valvular surgery. [56] After approval of the Research and Ethic Committee patients of more than 18 years of age undergoing an isolated cardiac valvular surgery or a valvular surgery combined with a coronary revascularization procedure between November 2001 and May 2003 were screened to be included in the study. To be eligible, they also had to be in sinus

rhythm and have a left ventricular ejection fraction (LVEF) above 20% at the time of screening. Patients were excluded from the study if they met one of the following criteria: amiodarone intake in the previous 6 months, a history of anaphylactic reaction to iodine, a past history of severe reaction or toxicity to amiodarone, intake of class I or III anti-arrhythmic agents within the 48 hours before surgery, significant hypotension (systolic blood pressure < 80 mmHg) necessitating sustained treatment with vasoactive agents for more than 1 hour preoperatively, urgent surgery and participation in other investigational trials.

Clinical Variables and Endpoints

Age, gender, body mass index (BMI) and body surface area (BSA) were determined for each patient, along with their relevant medications. Also documented were the presence of hypertension, diabetes, chronic renal failure, smoking history, recent myocardial infarction (MI, before or after 6 months), signs and symptoms of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), previous cerebrovascular disease (CVD), thyroid disorders, and LVEF measured through angiographic ventriculography or echocardiography. The different types of surgical procedures were classified as isolated valvular or valvular and coronary artery bypass grafting (CABG). The number of bypass grafts and the use of a mammary artery were noted in addition to the CPB time and aortic cross-clamping time. Patients were dichotomized whether they required or not inotropic agents (milrinone or epinephrine). The use of other vasopressors (noradrenaline, phenylephrine and vasopressine), length of cardiothoracic intensive care unit (CTICU) and hospital stay, postoperative complications and mortality rates were noted.

Study Protocol

Induction of anesthesia was performed using a combination of fentanyl (5–10 μg/kg) or sufentanil (0.7–1 μg/kg), midazolam (up to 0.1 mg/kg), and pancuronium (0.1 mg/kg). Isoflurane was used to control blood pressure during maintenance of anesthesia. After the

induction of anesthesia, an intravenous loading dose of 300 mg of amiodarone (or placebo) was given over 10 minutes followed by an infusion of amiodarone (15 mg/kg/24 hours, max 1500 mg/24 hours) or placebo for 48 hours. A complete hemodynamic assessment using the pulmonary artery catheter (PAC) (7.5F 931HF75, Baxter Healthcare, Irvine, California) was performed before and after bolus infusion and after CPB upon arrival in the CTICU and the following day. Baseline hemodynamic profiles were obtained from a radial artery catheter and a pulmonary artery catheter. The transesophageal echocardiography (TEE) examination was performed following induction of anesthesia prior to median sternotomy, following the bolus and after CPB during sternal closure. The following hemodynamic variables were recorded and calculated: heart rate (HR), systolic, diastolic and mean arterial pressures (MAP), systolic, diastolic and mean pulmonary artery pressures (MPAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), stroke volume (SV) and indexed systemic and pulmonary vascular resistance.

Complete laboratory data including arterial and venous blood gases were obtained just before administration of the amiodarone and after weaning from CPB. The surgical valvular procedure was performed according to established guidelines. [270] Blood cardioplegia was used in all patients. Induction and maintenance of cardioplegia were cold to tepid (15-29ºC). The blood to crystalloid ratio was 4:1. The pump flow was adjusted to obtain an output of 2.2 l/min/m^2 of body surface area and which was reduced to 0.5 l/min/m^2 for aortic clamping and unclamping. SIII (Stockert, Munich, Germany) roller pumps were used in all patients. The oxygenator was Sorin Monolyth (Mirandola, Italy). Valve and complex procedures were done with temperatures of 32-34ºC. Weaning from CPB was attempted after their systemic temperature (central and vesical) was >36ºC. All patients in the study had epicardial pacemaker wires (atrial and/or ventricular) placed at the end of surgery. The use vasoactive drugs during CPB (Appendix 2) and the process of weaning from CPB (Appendix 3) were done using established protocols as previously described. [52] Temporary pacing was subsequently initiated if judged necessary by the anesthesiologist and the surgeon.

Echocardiographic examination

Intraoperative TEE examinations were performed by anesthesiologists with National Board Certification in perioperative echocardiography with more than 15 years of experience in TEE. The TEE examination included 2D examination in the mid-esophageal and long-axis views and transgastric short-axis view at the mid-papillary level, with additional color flow imaging of the mitral, aortic and tricuspid valves in order to detect any significant valvular abnormality.

To assess left ventricular (LV) and right ventricular (RV) systolic function and dimensions, LV end-diastolic area (LVEDA), LV end-systolic area (LVESA) and LV fractional area change (LVFAC) were measured from the four-chamber and the transgastric mid-papillary view. From the mid-esophageal four-chamber view, the transverse diameter, the area and the volume of the left atrium (LA), the right atrium (RA), the area of the right ventricle (RV) at end-diastole (RVEDA), end-systole (RVESA), the fractional area change (RVFAC) and the tricuspid annular plane systolic excursion (TAPSE) were measured. All these measurements were obtained using published guidelines on two-dimensional quantification [186] and right ventricular function assessment. [48]

To assess LV and RV diastolic function, pulsed wave (PW) Doppler was used to evaluate transmitral flow (TMF) and transtricuspid inflow (TTF). Peak early (E) and peak late (A) diastolic flow velocities were measured. Pulmonary venous flow (PVF) and hepatic venous flow (HVF) were also evaluated using PW Doppler. In adition, peak systolic (S), diastolic (D) and atrial reversal (AR) flow velocities were also measured. Using tissue Doppler imaging (TDI), mitral annulus velocities (MAV) including the systolic (Sm), early diastolic (Em) and late atrial (Am) velocities were measured at the lateral or anterior annulus (the signal with the best definition and with the higher Em was chosen). Tricuspid annulus velocities (TAV) including the systolic (St), early (Et) and late atrial (At) velocities were also derived by TDI using a deep transgastric RV long axis view with right side rotation, as previously described. [39] The TMF E/e ratio was calculated.

The classification of LV (Figure 55) and RV (Figure 56) diastolic function was based on a modification of the algorithm described by Khouri *et al.*, [173] that we previously validated. [12;39;43;50] All the echocardiographic data were recorded on a magnetic optical disk for off-line viewing. The measurements were done by an independent cardiologist (YS) blinded to the drug allocation. [40] The echocardiographic images used in the classification of diastolic function were reviewed off-line by two independent observers blinded to the patient's data. Two-dimensional areas were not measured if less than 80% of the endocardial contour could be seen. [271]

In order to validate our measurements, we subjected 10 echocardiograms to 3 repeated measurements in a blinded fashion, with 3 consecutive cardiac cycles analyzed for each recording. The coefficient of variation (SD ÷ mean X 100%) between 3 consecutive cardiac cycles of the 10 echocardiograms was 2.7% ± 1.6% and 4.5% ± 1.8% for the left and right atrial areas in cardiac systole, and 3.4% ± 1.4% and 4.4% ± 1.9% for the left and right ventricular end-diastolic areas, respectively. For PW velocity and TDI velocity the coefficients of variation were 5.4% ± 2.6% and 2.6% ± 1.3%, respectively. The coefficient of variation between the 3 results based on the average of 3 cycles of these 10 echocardiograms was 1.4% ± 0.8% and 2.7% ± 1.8% for the left and right atrial areas in cardiac systole and 2.9% ± 1.1% and 2.9% ± 1.1% for the left and right ventricular end-diastolic areas, respectively. For PW velocity and TDI velocity, the coefficients of variation were 1.1% ± 0.4% and 1.0% ± 1.0% respectively. [40]

Left ventricular diastolic function was not evaluated in patients with mitral stenosis and moderate to severe mitral or aortic regurgitation. Right ventricular diastolic function was not evaluated in patients with moderate to severe tricuspid regurgitation. Patients with atrial fibrillation or a pacemaker, and contraindication to transesophageal echocardiography (TEE) were excluded from the diastolic function classification. Twenty-nine measurements for left ventricular diastolic function were excluded because the Doppler signals could not be obtained. The left ventricular diastolic function algorithm was used to evaluate 190 measurements (73, 50 and 67 patients for the three evaluation time points: before studied drug bolus, after drug bolus and after CPB, respectively). The inter-observer kappa values

were 0.82, 0.57 and 0.77 between 2 observers. Fifty measurements for right ventricular diastolic function were excluded for the reasons mentioned above. The right ventricular diastolic function algorithm was used to evaluate 178 measurements (69, 52 and 57 patients for the three evaluation time points). The inter-observer kappa values were 0.69, 0.82 and 0.91. When the three evaluation time points were pooled, the LVDD and RVDD algorithm interobserver kappa values were 0.77 and 0.82. In the evaluation of LVDD, 26/193 (13%) and 3/193 (1.6%) time points were respectively excluded by reviewers #1 and #2. In the evaluation of RVDD 23/182 (13%) and 4/182 (2%) time points were excluded by reviewer #1 and #2.

Upon arrival in the CTICU, a Holter monitor (Marquette Electronics Series 8500, Boston, Massachusetts) was installed on each patient. Three-lead continuous Holter monitoring was performed for the first 4 postoperative days. The recorded data were stored for 24 hours and reviewed by an independent electrophysiologist on a daily basis. Three-lead continuous telemetric monitoring (Fukuda DF 3310 and LW 3100, Fukuda, Japan) was concomitantly performed from the time of admission to the CTICU until hospital discharge. Daily 12-lead electrocardiogram recordings were also performed on all patients. Postoperative AF was treated by the CTICU and surgical teams at their discretion, in accordance with the American College of Cardiology and American Heart Association (ACC/AHA) guidelines. [286] Atrial fibrillation was defined as an uncoordinated atrial activation with consequent deterioration of atrial mechanical function. [286]

Statistical Analysis

Based on our previous study, [56] we estimated that 50% of patients undergoing cardiac valvular surgery would develop AF. In order to detect the expected reduction in AF from 50% to at least 25% in the amiodarone group, 58 patients per group would be needed to reach a power of 80% with a two-sided chi-square test at an alpha of 5%. Assuming a 3% loss, we recruited 60 patients per group.

Categorical variables are described as frequencies and percentages; the chi-square test was used to assess group differences. Continuous variables are expressed as the mean value ± SD; their differences were tested by the unpaired t-test due to the normality assumption. Repeated measures ANOVA models were used to study the hemodynamic, echocardiographic, arterial blood gases and biochemistry parameters across time and between groups. Models included time, group and group X time interaction as independent variables. If the interaction term was significant at the 0.05 level, then comparisons between groups at each time point and between time points within each group were done. The generalized estimating equation (GEE) model was performed to study left and right ventricular diastolic function using the multinomial distribution due to the nature of the diastolic scores (normal, mild, moderate, severe).

Multivariate logistic regression was used to identify the independent predictors of the use of inotropes. Three separate regression models were performed for this outcome using the following potential predictor variables: (1) Preoperative baseline & surgical characteristics (listed in Table 22 with the exception of the use of mammary graft) and the use of amiodarone; (2) Baseline arterial blood gases and biochemistry parameters and the use of amiodarone; (3) Baseline hemodynamic and echocardiographic variables and the use of amiodarone. The models were constructed with the use of backward stepwise variable selection, and a probability value of 0.05 was used as the criterion for variable selection. The c index and the Hosmer-Lemeshow test are also reported for the appropriateness of the model. To evaluate the long-term effect of inotropes treatment on mortality, a log-rank test was performed. Statistical analyses were performed using SAS version 8.02 (SAS Institute Inc., Cary, North Carolina). A p value ≤ 0.05 was considered significant.

Results

A total of 120 patients were randomized and 1 patient in the amiodarone group died intraoperatively (right ventricular failure). The mean age was 65 ± 11 years and 67 (56%) patients were men. Two-thirds of the total population (68.3%) underwent an isolated

valvular surgery and one-third (31.7%) underwent combined valvular and CABG surgery. There were 56 patients (46.6%) requiring inotropic support after CPB. A total of 52 required milrinone, 4 epinephrine and 2 both agents. Baseline demographic characteristics were similar among patients with or without inotropes (Table 22).

Table 23 summarizes the significant findings (Detailed tables can be found in Appendix 9 to Appendix 13). The evolution in terms of laboratory and hemodynamic variables was similar between groups. Before CPB, patients requiring postoperative inotropes developed increased left atrial size ($p = 0.0196$) and volume ($p = 0.0247$), increased baseline E/e ratio ($p = 0.0104$), reduced systolic MAV ($p = 0.0086$), increased RVESA ($p = 0.0197$) and reduced systolic HVF velocities ($p = 0.0093$). After CPB, the atrial MAV ($p = 0.0252$), the atrial reversal of the PVF velocities ($p = 0.0459$) and of the HVF velocities ($p = 0.003$) increased in the group requiring inotropes. Ventricular diastolic function evaluation of the left and right ventricle changed after CPB with a shift from the normal and mild to moderate and severe diastolic dysfunction, but there were no differences between the groups. Figure 58 summarizes the biventricular hemodynamic, two-dimensional and Doppler changes before and after CPB.

The use of amiodarone was not associated with increased inotropic requirement during and after CPB. Adrenaline was required in 3 patients and milrinone in 26 patients in both the amiodarone and the placebo group. There were no differences in postoperative complications between the groups (Table 24), except for an increase in the use of noradrenaline ($p = 0.0152$) and higher mortality at 6 years in patients requiring inotropic agents ($p = 0.0247$) (Figure 59). No baseline preoperative factors were found to be independently associated with a higher risk of requiring inotropes after valvular surgery.

Discussion

In this study evaluating a population undergoing valvular or complex surgery, we found that the administration of inotropic agents after CPB was not associated with differences in biventricular systolic or diastolic function when compared to a group without inotropic support. However, we also observed that the administration of inotropic agents was associated with an increased left and right atrial activity. Increased left atrial activity has been described with ketamine through activation of the sympathetic nervous system. [287] Increased right atrial function has been also described in an animal model of milrinone-induced toxicity. [288] In addition, Couture *et al.* [43] made similar observations on increased bi-atrial activity in a randomized controlled trial using milrinone. This increased atrial activity could explain why the administration of milrinone can be associated with an increased risk of atrial fibrillation. [289;290] However such a postoperative association was not observed in this study.

We also document that, even if patients requiring inotropes were similar at baseline, patients likely to require inotropes showed significant alterations in echocardiographic indices of biventricular function before CPB. We observed reduction in left ventricular systolic function, elevation of left ventricular filling pressure indices (E/e ratio), [291;292] and enlargement of the left atrium before CPB in patients requiring inotropes after CPB. In addition, evidence of altered right ventricular function and dilatation was also present before CPB. These changes in biventricular function may represent the early manifestation of reduced cardiovascular reserve to sternotomy, pericariectomy, and CPB. Some authors have observed reduced intramyocardial pH and increased myocardial lactate production before CPB in patients requiring inotropic agents postoperatively. [109;110] Despite no difference in the duration of CPB, altered biventricular function could have predisposed patients to the use of inotropic medication. In patients undergoing valvular disease, Haddad *et al.* [46] observed that echocardiographic intraoperative indices of right ventricular dysfunction obtained before CPB were significant predictors of vasoactive requirement after CPB. However, none of the baseline hemodynamic and echocardiographic variables were independent predictors of post-CPB inotropic requirements.

As secondary findings, we also showed that patients undergoing valvular surgery will have significant hemodynamic, two-dimensional and Doppler changes during cardiac surgery, whether or not they received inotropic agents after CPB. Overall, systemic arterial, pulmonary and right atrial pressures will increase with right-sided atrial dilatation and right ventricular systolic dilatation after CPB. These changes in right ventricular dimensions will be associated with a reciprocal reduction in the left atrial diameter and left ventricular end-diastolic dimension. We also observed a reduction in left ventricular systolic function after CPB in both groups. While the RVFAC did not change, the decrease in TAPSE suggests that right ventricular systolic function also decreased after CPB.

After valvular surgery, significant changes in biventricular diastolic function will also occur. The increase in right atrial filling pressure and volume is associated with a deterioration of right ventricular diastolic function and right ventricular dilatation. This could contribute to the reduced left-sided dimension. These changes are similar to some extent to those our group described in patients undergoing CABG [40;43] however the alterations in biventricular diastolic function are more pronounced particularly on the right-sided cavities.

Studies on diastolic function in cardiac surgery

Changes in left ventricular diastolic function during cardiac surgery have been mostly described after CABG [68;88;90;92;94-98] but not in valvular surgery using both hemodynamic and biventricular echocardiographic parameters. The selection and the variations in the parameters used in the evaluation of left ventricular diastolic function can explain some of the observed discrepancies among the results. In a study involving 49 CABG patients, using TMF, PVF and TDI modalities and velocity of propagation with transthoracic echocardiography, Shi *et al*. [40] observed a deterioration of left ventricular diastolic function at 48 hours with a normalization of the parameters at 6 months and a return at their values before CABG. In a similar study but using invasive hemodynamic monitoring and TEE, Couture *et al*. [50] demonstrated that induction of anesthesia will alter diastolic function. In addition, he also demonstrated that the changes observed at 48 hours

by Shi *et al.* were already present after CPB. [43] Our observations were similar, however baseline left ventricular dimensions were larger in our population than those reported by Royse *et al*. [293] and those of Couture *et al.* [43] The larger LVEDA observed in our study could be secondary to the fact that we studied patients with valvular disease and with longer CPB duration compared to CABG patients.

We also observed significant changes in right-sided diastolic function, as reported by Shi *et al.* [40] and Couture *et al.* [43] in patients undergoing CABG. Similar changes have also been described by Diller *et al.* [92] using TDI of the tricuspid annulus in patients undergoing CABG. These changes could be explained by many factors including inflammatory changes induced by CPB, [279] a pulmonary reperfusion syndrome, [280] poor myocardial protection or the effect of pericardictomy. [281]

In this trial, 46.7% of patients received inotropes. In our practice using vasoactive agents, inotropic agents are considered a second and third line treatment (see Appendix 3). This use of inotrope is within reported range of 32% to 52% during the weaning from CPB. [64;69] However, the persisting use of inotropes after CPB is associated with an increased risk of postoperative morbidity and mortality. [10;75;77;106] We observed an association between long-term survival and the use of inotropic agents. This association has been reported in the use of oral [294] and intravenous milrinone for patients with ischemic cardiomyopathy. [295] Our study is not powered enough to demonstrate that inotropic agents are independent predictors of postoperative mortality.

Limitations

The gold standards for evaluating diastolic dysfunction are the time constant of relaxation (Tau) and pressure-volume curves obtained by direct invasive measurements to assess chamber compliance. However, these measures are invasive and are not feasible in everyday practice. We used a Doppler assessment of mitral and tricuspid inflow, as well as pulmonary and hepatic flow variables to assess diastolic function. Tissue Doppler imaging which is a relatively volume-insensitive modality, provided supportive information to better

stratify the degree of diastolic dysfunction. [173] Changes in mitral flow velocity have been noted with changes in loading conditions, differing heart rates, and the left ventricular contractile state. [282] However, in this study the hemodynamic variables were similar in both groups. Criteria for right ventricular diastolic dysfunction have been previously described [204] but are not yet as widely accepted as those used for left ventricular diastolic dysfunction. So far however, no study has evaluated and reported the changes after CPB in biventricular systolic and diastolic function in patients undergoing valvular surgery. Several factors can influence the use of inotropic agents and one of them being the anaesthesiologist. [64] A vasoactive agent protocol was used to reduce this potential confounding factor, however, we cannot completely exclude this factor as a trigger for the use of inotropic agent. Finally, the use of amiodarone as a negative inotropic agent may have influenced the results. However, amiodarone was not associated with an increase in inotropic agents through logistic regression analysis.

Conclusion

In patients undergoing cardiac valvular surgery, significant hemodynamic and biventricular systolic and diastolic echocardiographic changes do occur after CPB. Inotropic medications were not associated with differences in hemodynamic and echocardiographic parameters when compared to a control group, except for increased bi-atrial activity after CPB. However at 6 years, despite similar baseline demographic, hemodynamic and echocardiographic characteristics, an increased number of deaths was observed in patients requiring inotropic agents after valvular surgery.

Table 22 Characteristics of patients with and without inotropes

Characteristics	**Inotropes (n = 56)**	**No inotropes (n = 64)**	***P* Value**
Age, yrs	64.8 ± 9.9	65.4 ± 12.3	0.7664
Gender			0.1159
Men	27 (48.2)	40 (62.5)	
Women	29 (51.8)	24 (37.5)	
Body mass index	27.4 ± 5.2	27.0 ± 3.9	0.6601
Hypertension	29 (51.8)	28 (43.7)	0.3792
History of stroke	2 (3.6)	1 (1.6)	0.4819
Coronary artery disease	8 (14.3)	14 (21.9)	0.2838
Myocardial infarction			
<6 months	2 (3.6)	2 (3.1)	0.8919
>6 months	4 (7.1)	5 (7.8)	0.8895
Congestive heart failure	13 (23.2)	20 (31.2)	0.3254
Left ventricular ejection fraction (%)	58.7 ± 10.3	60.3 ± 10.9	0.4465
Smoking history	11 (19.6)	14 (21.9)	0.7639
Chronic obstructive pulmonary disease	7 (12.5)	13 (20.3)	0.2519
Diabetes mellitus	7 (12.5)	12 (18.8)	0.3494
Chronic renal failure	2 (3.6)	3 (4.7)	0.7602
Thyroid disorder	6 (10.7)	7 (10.9)	0.9687
Preoperative medication			
Beta-blockers	20 (35.7)	14 (21.9)	0.0933
Calcium antagonists	11 (19.6)	15 (23.4)	0.6147
Angiotensin converting enzyme inhibitor	17 (30.4)	21 (32.8)	0.7730
Angiotensin receptor blocker			
Diuretics	4 (7.1)	8 (12.5)	0.3291
Digitalis	15 (26.8)	24 (37.5)	0.2112
	1 (1.8)	1 (1.6)	0.9241
Type of surgery			
Isolated valvular	37 (66.1)	45 (70.3)	0.6183
Valvular + coronary artery bypass graft	19 (33.9)	19 (29.7)	

Characteristics	**Inotropes (n = 56)**	**No inotropes (n = 64)**	***P* Value**
Type of valvular surgery			
Aortic	38 (67.8)	45 (70.3)	0.7714
Mitral	20 (35.7)	19 (29.7)	0.4819
Number of bypass grafts			0.2449
1	8 (42.1)	7 (36.8)	
2	3 (15.8)	8 (42.1)	
3	7 (36.8)	4 (21.1)	
5	1 (5.3)	0	
Use of mammary artery	14 (73.7)	9 (47.4)	0.0970
Total CPB time (min)	107 ± 43	101 ± 26	0.3152
Aortic cross-clamp (min)	81 ± 34	77 ± 25	0.4984
Vasoactive support during and after CPB			
Noradrenaline			
Neosynephrine	55 (98.2)	55 (85.9)	0.0152
Vasopressine	50 (89.3)	56 (87.5)	0.7611
Nitroglycerine	10 (17.9)	13 (20.6)	0.7017
	39 (69.6)	39 (60.9)	0.3185

Data are presented as *n* (%) for proportions and as mean ± standard deviation for continuous variables. CPB, cardiopulmonary bypass

Table 23 Biochemical, hemodynamic and Doppler variables

Variable	Group	Baseline (Mean ± SD)	After bolus (Mean ± SD)	After CPB (Mean ± SD)	*P* value (group)	*P* value (time)	*P* value (group*time)
LA area (cm^2)	Inotropes	20.2 ± 7.1	22.4 ± 7.5	19.1 ± 4.1	0.0983	0.0243	0.0196[14]
	No inotropes	18.6 ± 5.3	18.0 ± 4.8	18.4 ± 3.8			
LA volume (ml)	Inotropes	67.2 ± 34.6	80.0 ± 40.5	57.9 ± 19.3	0.1035	0.0410	0.02470[15]
	No inotropes	58.6 ± 25.9	55.6 ± 22.2	56.3 ± 18.4			
RVESA (cm^2)	Inotropes	7.3 ± 2.4	8.0 ± 2.5	7.4 ± 2.1	0.3383	0.0265	0.0197[16]
	No inotropes	6.7 ± 1.9	7.4 ± 2.0	7.9 ± 2.4			
E/e ratio	Inotropes	13.9 ± 11.9	13.6 ± 3.7	16.6 ±6.8	0.0104	0.0587	0.5347
	No inotropes	10.4 ± 2.6	11.7 ± 3.3	12.5 ± 4.3			
MAV a wave	Inotropes	8.8 ± 2.5	7.6 ± 1.8	9.1 ± 4.3	0.434	0.8709	0.0252[17]
	No inotropes	8.2 ± 2.6	8.7 ± 3.1	7.2 ± 2.6			
MAV s wave	Inotropes	8.4 ± 2	7.6 ± 1.2	9.8 ± 3.2	0.9906	0.2593	0.0086[18]
	No inotropes	8 ± 1.8	9.1 ± 2.9	8.2 ± 2			
PVF AR wave	Inotropes	19.9 ± 6.7	18.3 ± 5.3	32.9 ± 15.7	0.5166	0.0004	0.0459[19]
	No inotropes	20.7 ± 7.8	23.2 ± 10.4	25.2 ± 11.8			
TTF A velocity	Inotropes	29.8 ± 11.4	47 ± 18.2	38.1 ± 21.6	0.4135	<.0001	0.0034[20]
	No inotropes	31.7 ± 13.2	37.8 ± 11.4	38.1 ± 16.2			
HVF S wave	Inotropes	21.5 ± 12.4	18.6 ± 7.6	-14.4 ± 23.9	0.3965	<.0001	0.0093[21]
	No inotropes	16.2 ± 10.1	22.4 ± 16.7	-7.3 ± 20.4			

[14] $P = 0.0135$ after bolus in the inotropes versus no inotropes group.
[15] $P = 0.0117$ after bolus in the inotropes versus no inotropes group.
[16] $P < 0.05$ baseline versus after CPB in the no inotropes group and $p = 0.0596$ after bolus in the inotrope versus no inotropes group
[17] $P = 0.0373$ after CPB in the inotropes versus no inotropes group.
[18] $P = 0.0351$ after bolus in the inotropes versus no inotropes group.
[19] $P < 0.05$ baseline and after bolus versus after CPB in the inotropes group and $p = 0.0510$ after CPB in the inotropes versus no inotropes group
[20] $P = 0.0001$ baseline versus after bolus in the inotropes group and $p = 0.0273$ after bolus in the inotropes versus no inotropes group
[21] $P = 0.0654$ baseline in the inotropes versus no inotropes group

Variable	Group	Baseline (Mean ± SD)	After bolus (Mean ± SD)	After CPB (Mean ± SD)	*P* value (group)	*P* value (time)	*P* value (group*time)
HVF AR wave	Inotropes	13.8 ± 9.9	13.5 ± 7.7	29.8 ± 17.6	0.0904	0.0004	0.003[22]
	No inotropes	10.9 ± 4.8	17.9 ± 9.2	15.3 ± 5.1			

CI, cardiac index; CK, creatine kinase; D, diastolic; HR, heart rate, HVF, hepatic venous flow; L, liter; MPAP, mean pulmonary artery pressure; PVF, pulmonary venous flow; S, systolic; TTF, transtricuspid flow

[22] $P = 0.0102$ after CPB in the inotropes versus no inotropes group and $p < 0.05$ baseline versus after CPB in the inotrope group and baseline versus after bolus in the non-inotropes group

Table 24 Outcome data

Characteristics	**Inotropic support**	**No inotropic support***	***P* Value**
Atrial fibrillation	26 (46%)	33 (52%)	0.5746
CTICU duration (hours)	43 (27.5-69.5)[1]	39.5 (24.5-68.5)[1]	0.1795
Hospitalization duration (hours)	216 (144-288)[1]	168 (144-240)[1]	0.2805
Rhythm on discharge			0.1879
Sinus	49 (89%)	60 (95%)	
Atrial fibrillation	0 (0%)	1 (2%)	
Other	3 (5%)	0 (0%)	
Pacemaker	3 (5%)	2 (3%)	
Non-sustained ventricular tachycardia	6 (11%)	7 (11%)	0.9687
Acute respiratory distress syndrome	0	0	
Myocardial infarction	1 (2%)	0 (0%)	0.2830
Stroke	1 (2%)	2 (3%)	0.6392
Acute renal failure	2 (4%)	2 (3%)	0.8919
Rehospitalization for atrial fibrillation	1 (2%)	5 (8%)	0.1375
Hospital mortality	2 (4%)	1 (2%)	0.4819
Number of death at 6 years	10 (18%)	3 (5%)	0.0247

CTICU, cardiothoracic intensive care unit. Data are presented as n (%) for proportions and as mean ± standard deviation for continuous variables. * One patient died intraoperatively of right ventricular failure.

[1] The median (lower adn upper quartile) are presented.

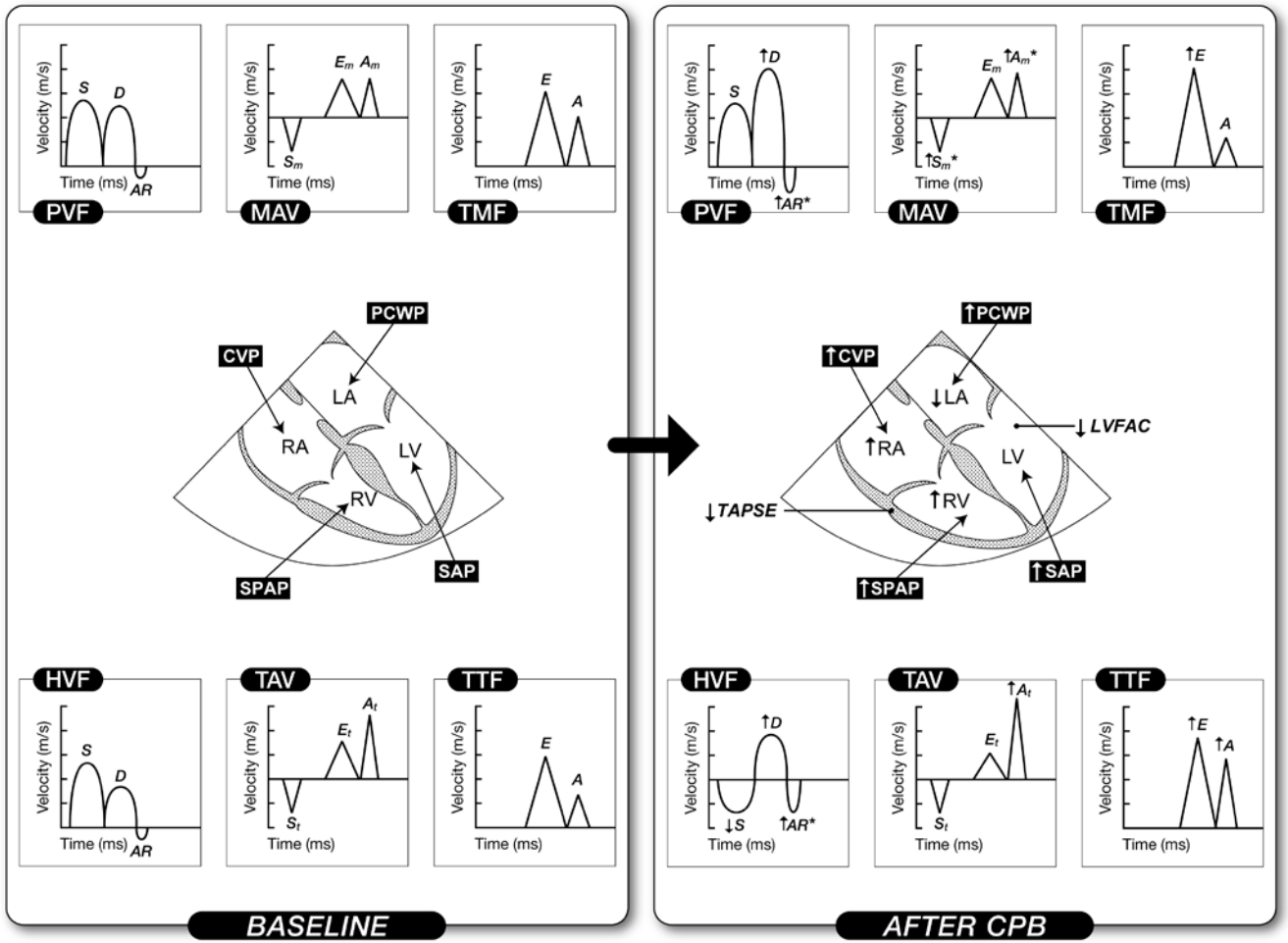

Figure 58 Hemodynamic and echocardiographic summary

Hemodynamic, biventricular echocardiographic and Doppler changes in patients undergoing valvular surgery after cardiopulmonary bypass (CPB). (A, atrial component; Am, atrial MAV; AR, atrial reversal; A_t, atrial TAV; CVP, central venous pressure; D, diastolic; E, early filling; Em, early MAV; E_t, early TAV; HR, heart rate; HVF, hepatic venous flow; MAV, mitral annular velocity; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVF, pulmonary venous flow; S, systolic HVF, SAP, systolic artery pressure; Sm, systolic MAV; St, systolic TAV; TAV, tricuspid annular velocity; TMF, transmitral flow; TTF, transtricuspid flow; * $p < 0.05$ in the inotropic group only)

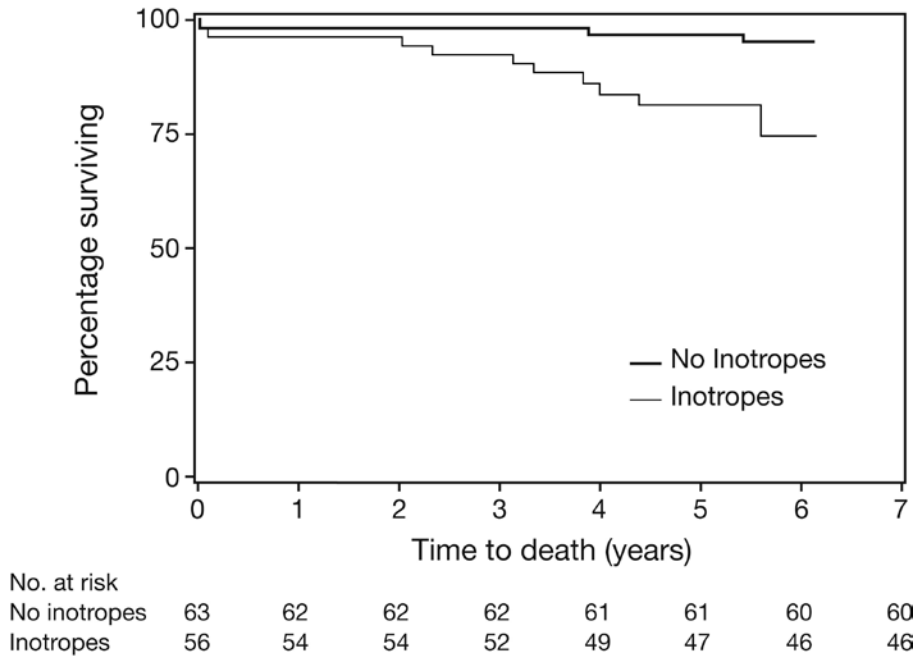

Figure 59 Probability of survival at 6 years.

Mortality was increased in patients exposed to inotropes after cardiopulmonary bypass ($p = 0.0247$).

Chapter 6 Inhaled milrinone

As we have previously seen, difficult separation from CPB is a major cause of morbidity and mortality. The mechanism of difficult separation from CPB is complex but can be approached based on three variables, Pms, Pra and Rvr. Pulmonary hypertension and right ventricular dysfunction were identified as significant predictors of difficult separation from CPB. [46] Finally, on the basis of our preliminary data, right ventricular dilatation and dysfunction are commonly observed after CPB and their severity is associated with inotropic requirement, increased morbidity and mortality. [46] Therefore, pulmonary hypertension and its consequences on right ventricular dysfunction could appear as a potential target for intervention.

6.1. Definition of pulmonary hypertension

There are several hemodynamic parameters that are used to define pulmonary hypertension (Table 25). [296] Several of these definitions have been used in various studies. In cardiac surgery, we obtain information on pulmonary hypertension before the procedure and usually from an awake patient. This preoperative information is either acquired through preoperative catheterization or, more frequently, estimated via transthoracic echocardiography by using Bernoulli's equation. In the presence of tricuspid regurgitation, as shown in

Figure 60, [12] the simplified Bernoulli's equation will give an estimation of the pressure gradient across the tricuspid valve. This pressure gradient is equal to the difference between the systolic pressure of the right ventricle and the right atrium. Therefore, knowledge (or estimation) of the right atrial pressure allows the estimation of the right ventricular systolic pressure. In the absence of RVOTO or pulmonic valve stenosis, this value will be an estimation of the systolic pulmonary artery pressure.

Table 25 Definitions of pulmonary hypertension used in clinical research

Hemodynamic parameter	**Normal value**	**Abnormal value**
Systolic pulmonary artery pressure (SPAP)	15-30 mmHg	> 30 or ≥ 40 mmHg
Mean pulmonary artery pressure (MPAP)	9-16 mmHg	Moderate: > 18 mmHg Significant: > 25 mmHg Exercise-induced: > 30 mmHg
Pulmonary vascular resistance (PVR) = (MPAP – PCWP) X 80/CO	60-120 dyn·s·cm^{-5}	Moderate > 125 dyn s cm^{-5} Severe >200-300 dyn s cm^{-5}
Indexed pulmonary vascular resistance (PVRI) = (MPAP – PCWP) X 80/CI	250-340 dyn·s·cm^{-5}·m^{-2}	> 340 dyn·s·cm^{-5}·m^{-2}
Pulmonary to systemic vascular resistance index (PVRI/SVRI) X 100%	≤ 10%	> 10%
Transpulmonary gradient (MPAP – PCWP)	≤ 14 mmHg	> 14 mmHg
Mean pulmonary to systemic pressure ratio (MPAP/MAP) X 100%	< 25%	Moderate: 33-50% Severe: > 50%
Mean systemic to pulmonary pressure ratio (MAP/MPAP) X 100%	≥ 4	< 4 [10]

CO: cardiac output; CI: cardiac index; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; PVRI, indexed pulmonary vascular resistance; SPAP, systolic pulmonary artery pressure; SVRI, indexed systemic vascular resistance. (Adapted from Gomez [296])

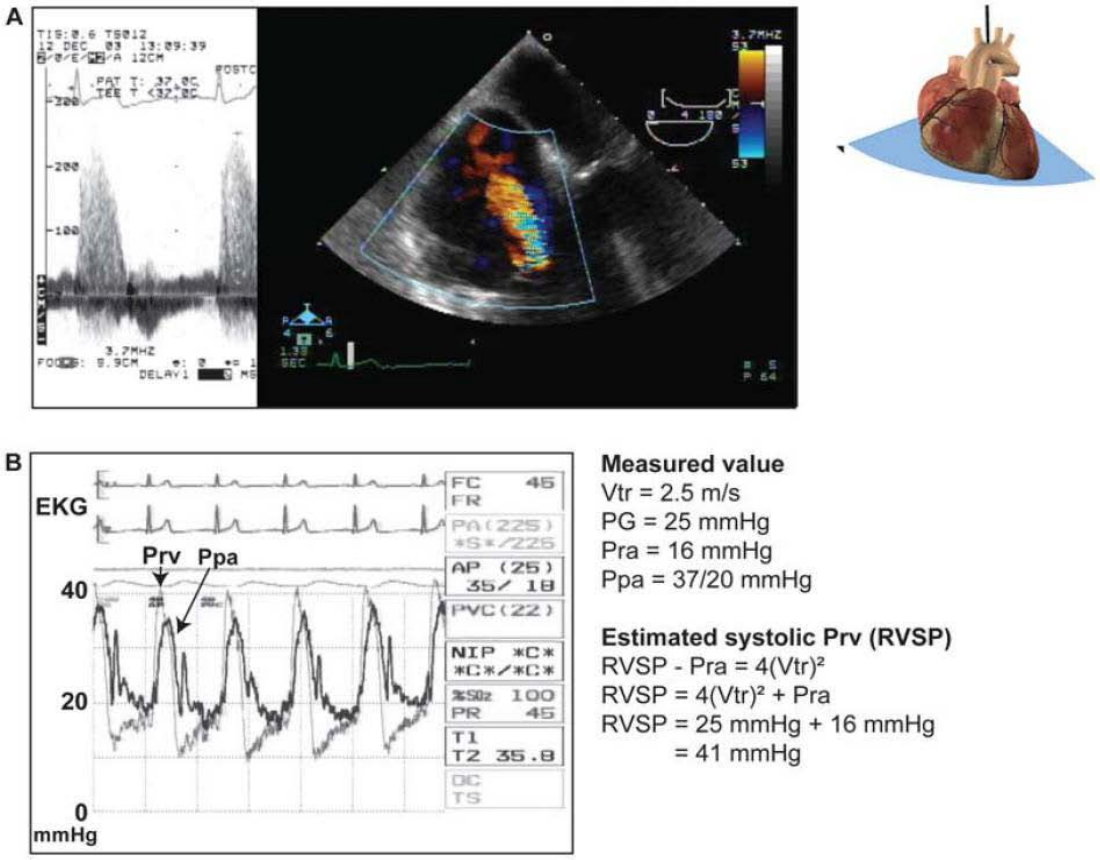

Figure 60 Doppler estimation of the severity of pulmonary hypertension

(A) Estimation of right ventricular systolic pressure (systolic Prv or RVSP) using the pressure gradient (PG) obtained from tricuspid regurgitation (TR) and right atrial pressure (Pra or RAP). (B) Note that the RVSP is higher than the systolic pulmonary artery pressure (Ppa) due to a small gradient across the pulmonic valve (EKG, electrocardiogram; V, velocity). (With permission of Denault *et al.* [12])

Following the induction of general anesthesia, a reduction of both the systemic and the pulmonary artery pressures will be observed. Consequently, absolute values of systolic pulmonary artery pressure used in defining pulmonary hypertension will tend to underestimate its severity. In 2006, we addressed this issue and published a study involving 1557 patients undergoing cardiac surgery. [10] We first demonstrated that the induction of general anesthesia in 32 patients was associated with a significant reduction in mean

arterial pressure (MAP) and mean pulmonary artery pressure (MPAP), but the MAP/MPAP ratio did not change (Figure 61). Therefore, this ratio (normal value > 4) seems to be a very robust estimator of the severity of pulmonary hypertension.

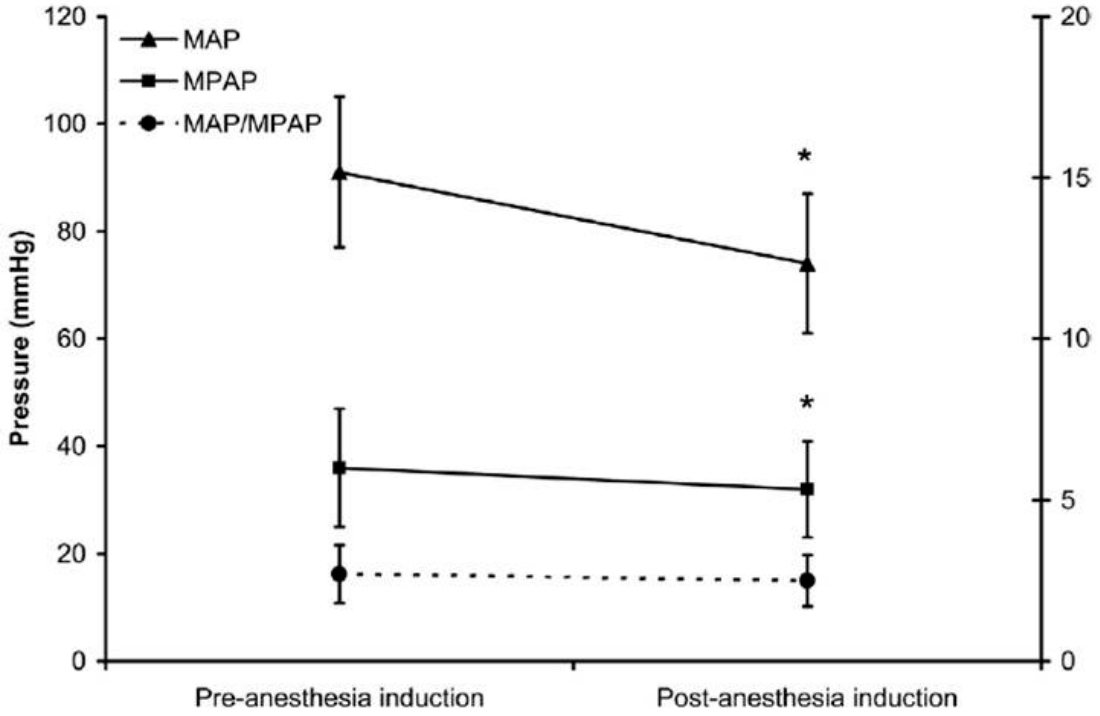

Figure 61 The MAP/MPAP ratio

Change in mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and the MAP/MPAP ratio after the induction of anesthesia in 32 patients with preoperative pulmonary hypertension. No significant change in the MAP/MPAP ratio was observed. (MAP: mean arterial pressure, MPAP: mean pulmonary artery pressure) (With permission of Robitaille *et al.* [10])

To demonstrate the utility of the MAP/MPAP ratio, we compared it to the other hemodynamic parameters (Table 25) in 1439 patients undergoing cardiac surgery after the induction of general anesthesia but before CPB. We observed that the MAP/MPAP ratio behaved similarly to the other hemodynamic parameters (Figure 62), and had the highest receiver operating curve value to predict hemodynamic complications after cardiac surgery.

The hemodynamic complications were defined as postoperative death or requirement for an intra-aortic balloon pump, cardiac arrest and vasoactive support for more than 24 hours.

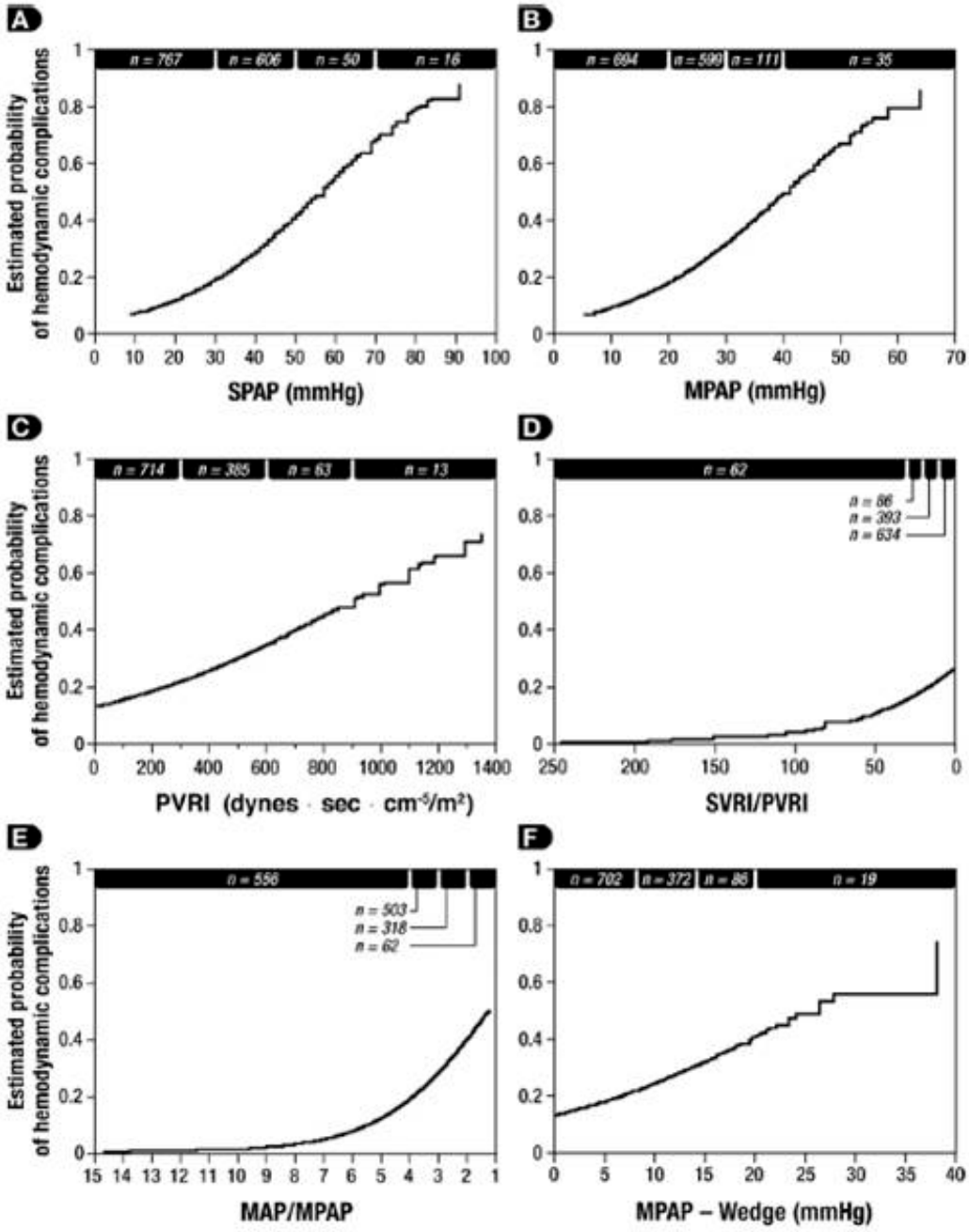

Figure 62 Pulmonary hypertension and outcome

Relationship between the estimated probability of hemodynamic complications and variables used in the evaluation of pulmonary hypertension: (A) systolic pulmonary artery pressure (SPAP), (B) mean pulmonary artery pressure (MPAP), (C) indexed pulmonary vascular resistance (PVRI), (D) the ratio of indexed systemic vascular resistance (SVRI) to PVRI, (E) the mean arterial pressure MAP/MPAP ratio, and (F) the transpulmonary gradient defined as MPAP minus wedge or pulmonary capillary wedge pressure (PCWP). For easier comparison, the scale of the *x* axis of the SVRI/PVRI and the MAP/MPAP are inverted. (*n* = number of patients). (With permission of Robitaille *et al.* [10])

Finally, using TEE, we can confirm that the presence of an abnormal MAP/MPAP ratio is almost invariably associated with abnormal systolic or diastolic cardiac function (Figure 63). [10] This concept of using the relative instead of absolute value of pulmonary hypertension indices is currently used in congenital cardiology. [225-227]

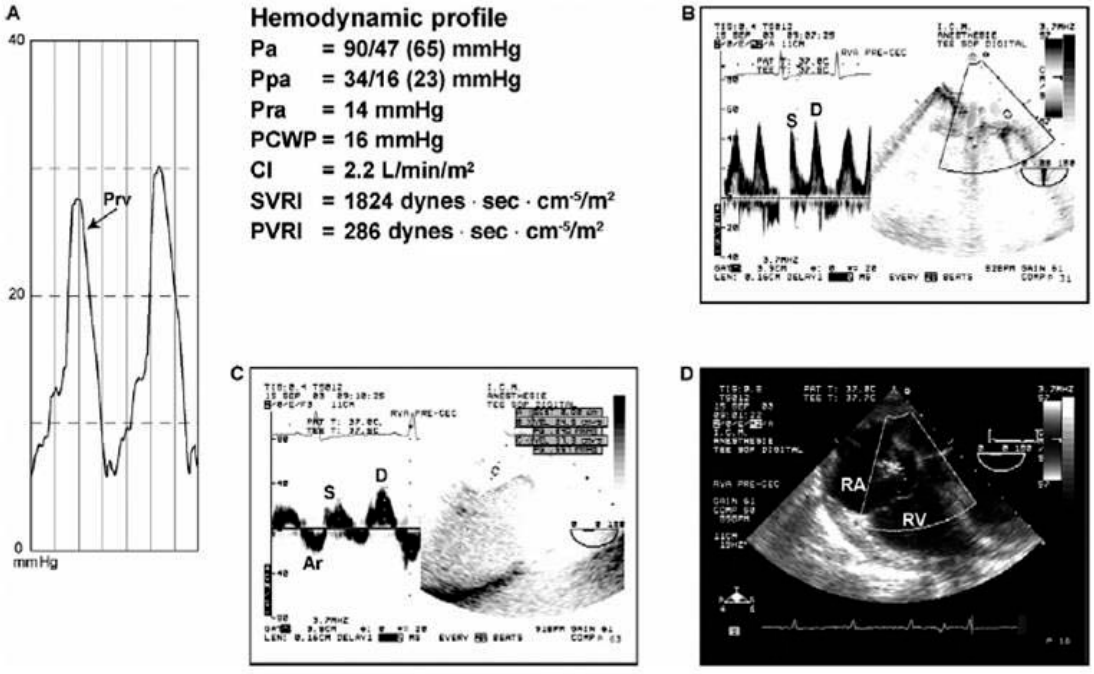

Figure 63 Doppler and hemodynamic signs of right ventricular dysfunction

Hemodynamic and transesophageal echocardiographic evaluation of a 46-year-old woman scheduled for aortic valve surgery. Despite a normal pulmonary artery pressure of 34/16 mmHg and indexed pulmonary vascular resistance (PVRI) at 286 $dyn \cdot s \cdot cm^{-5} \cdot m^{-2}$, this patient had an abnormal right ventricular diastolic filling pressure waveform characterized by a rapid upstroke (A) and reduced systolic (S) to diastolic (D) pulmonary (B) and hepatic

(C) venous flow, consistent with left and right ventricular diastolic dysfunction. In addition, a dilated right atrium and ventricle were present without significant tricuspid regurgitation in a mid-esophageal right ventricular view (D). The mean arterial pressure (MAP) divided by the mean pulmonary artery pressure (MPAP) ratio was 65/23 or 2.8. (CI: cardiac index, Pa: arterial pressure, PCWP: pulmonary capillary wedge pressure, Ppa: pulmonary arterial pressure, Pra: right atrial pressure, Prv: right ventricular pressure, RA: right atrium, RV: right ventricle, SVRI: systemic vascular resistance index) (With permission of Robitaille *et al.* [10])

Finally, pulmonary hypertension is typically classified as capillary, pre-capillary or postcapillary, depending on the site where the cause of pulmonary hypertension is present. In cardiac surgery, it is typically postcapillary because the cause of pulmonary hypertension is of cardiac origin and, consequently, localized after the pulmonary capillary. This is confirmed using pulmonary artery catheterization during which the diastolic pulmonary artery pressure is equal to the pulmonary capillary wedge pressure (PCWP). In a situation where the diastolic pulmonary artery pressure (DPAP) is significantly higher than the PCWP in the absence of tachycardia, a capillary or pre-capillary cause could be sought. [296]

In summary, pulmonary hypertension in cardiac surgery should be carefully defined. It is generally postcapillary pulmonary hypertension. In awake patients, the absolute values have been used and correlated with outcome. However, in patients under general anesthesia, a relative value such as MAP/MPAP seems to be more appropriate as long as the measurement of the MAP is accurate (see section 1.4.1).

6.2. Pulmonary hypertension in cardiac surgery: mechanism and etiology

The mechanism of pulmonary hypertension in cardiac surgery is complex and can result from several mechanisms acting alone or in combination to each other. These mechanisms can be present before the operation, secondary for instance to valvular heart disease. The cause of pulmonary hypertension can appear after CPB from mechanical failure or from a pulmonary reperfusion syndrome. Finally, pulmonary hypertension can be

present or persist postoperatively secondary for instance to a mitral or aortic patient-prosthesis mismatch, as discussed previously. Figure 64 focuses on the most important mechanism of pulmonary hypertension in cardiac surgery [31] based on current literature, our research findings and our experience of this population.

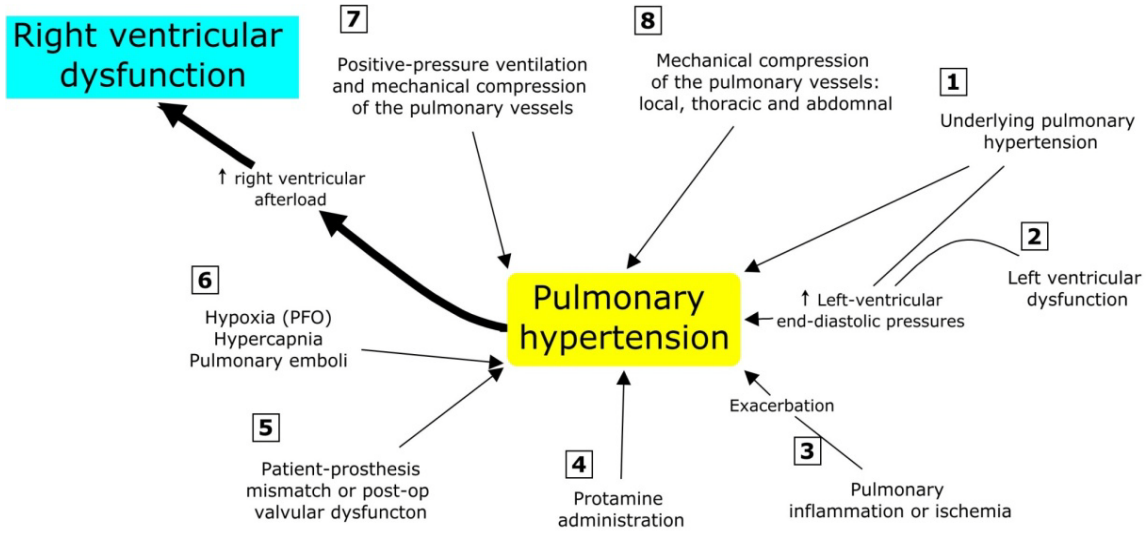

Figure 64 Mechanisms that could induce pulmonary hypertension in cardiac surgery

(PFO: patent foramen ovale)

6.2.1 Factors involved in pulmonary hypertension in cardiac surgery

The most important causes of pulmonary hypertension in cardiac surgery are illustrated in Figure 64. Some of these factors have been reviewed and explained previously.

1) Pre-existing substrates for pulmonary hypertension such as left ventricular dysfunction. Left ventricular dysfunction is indeed a common cause of pulmonary hypertension in cardiac surgery. As demonstrated in Figure 64, the severity of pulmonary hypertension before CPB is related to postoperative outcome.

2) Postoperative myocardial failure secondary to post-cardiotomy syndrome, postoperative myocardial infarction or aortic and mitral prosthetic valvular dysfunction. Myocardial stunning can result from suboptimal myocardial protection during aortic cross-clamp. Incomplete revascularization can lead to elevated left ventricular end-diastolic pressure and, consequently, to post-capillary pulmonary hypertension.

3) Pulmonary inflammatory or ischemic mechanisms. The extent of the systemic inflammatory response, the pulmonary reperfusion syndrome and the need for blood transfusions may all exacerbate pulmonary hypertension (Figure 65). [5;297] The mechanism of pulmonary damage during extracorporeal circulation is thought to be triggered by 1) release of cytokines [298] through endotoxin production, 2) complement activation and 3) ischemia-reperfusion injury. [279;299] This leads to the production of free radicals, endothelin and arachidonic acid degradation products, with both nitric oxide (NO) and prostacyclin inhibition. [279] The systemic inflammatory response to cardiac surgery was reviewed by Laffey et al.[300]

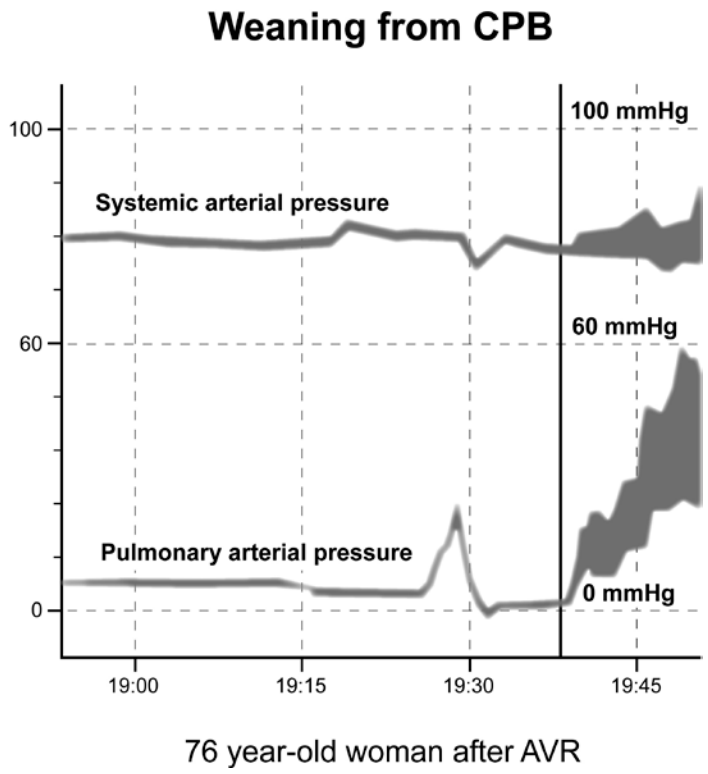

Figure 65 Pulmonary reperfusion syndrome after cardiopulmonary bypass

Unexpected pulmonary hypertension upon weaning from cardiopulmonary bypass (CPB) in a 76-year-old woman after aortic valve replacement (AVR). The CPB duration was 71 minutes. A significant increase in pulmonary arterial pressure in relation to the systemic arterial pressure was observed as the patient was weaned from CPB. No mechanical causes were found.

4) The administration of protamine can induce catastrophic pulmonary vasoconstriction in up to 1.8% of patients. [164] Protamine can also activate complement and, when given at the end of CPB, can induce pulmonary hypertension associated with adverse hemodynamic responses ranging from minor perturbations to cardiovascular collapse. Three types of response have been described: systemic hypotension, anaphylactoid reaction and catastrophic pulmonary hypertension. [163] The mechanism of pulmonary hypertension with protamine is thought to occur through an imbalance of vasoconstrictors and vasodilators, which leads to a reduction in the release of NO from the pulmonary vasculature. [163]

5) Patient-prosthesis mismatches have also been recently described as a cause of postoperative pulmonary hypertension. Aortic patient-prosthesis mismatch may cause left diastolic heart failure through a reduction in coronary reserve [126] and an increased ventricular loading, which could also contribute to postoperative pulmonary hypertension. Mitral patient-prosthesis mismatch is another recently described cause of residual postoperative pulmonary hypertension. [128] Magne *et al.* [128] studied 929 patients who underwent mitral valve replacement (MVR) and followed them up for 15 years. Mitral valve patient-prosthesis mismatch was defined as not clinically significant if > 1.2 cm^2/m^2, as moderate if > 0.9 and ≤ 1.2 cm^2/m^2, and as severe if ≤ 0.9 cm^2/m^2. The prevalence of moderate mitral patient-prosthesis mismatch was 69% and that of severe patient-prosthesis mismatch was 9%. Severe patient-prosthesis mismatch was found to be associated with residual pulmonary hypertension and a 3-fold increase in postoperative mortality after adjustment for other risk factors. This new and relevant information is currently absent from the majority of the studies dealing with predictors of survival in mitral valvular surgery.

6) Hypoxemia, hypercarbia and pulmonary embolism are other causes of pulmonary hypertension (see section 3.1.2). They can appear before, during or after CPB. For instance, pulmonary hypertension can cause RV dysfunction, which will lead to an increase in right atrial pressure. This can lead to the opening of a patent foramen ovale (PFO)(Figure 37), which is present in 20-30% of the general population. [301] The increase in right atrial pressure can cause opening of a patent foramen ovale leading to a right-to-left shunt. This shunt would increase the severity of hypoxemia and lead to an exacerbation of pulmonary hypertension. Pulmonary vessels constrict with hypoxemia (Euler-Liljestrand reflex) and relax in the presence of hyperoxia. [302] Hypercarbia can occur particularly if acute lung injury occurs during or after the procedure. The increase in PCO_2 will increase pulmonary hypertension through vasoconstriction (Figure 39). Finally, although pulmonary embolisms are rare in the immediate postoperative period, they can occur particularly in patients with predisposing factors (Figure 32).

7) Suboptimal lung volume settings may also contribute to pulmonary hypertension. Physiologically, the lung volume has a differential effect on intra- and extra-alveolar vessels, which accounts for the unique U-shaped relationship between lung volume and pulmonary vascular resistance. Pulmonary vascular resistance is minimal at functional residual capacity and increased at large and small lung volumes (Figure 66). Clinically, this may be observed as hyperinflation of the lungs greatly increases pulmonary vascular resistance. [302] Application of high levels of positive end-expiratory pressure (PEEP) may narrow the capillaries in the well-ventilated lung areas and divert flow to less well-ventilated or non-ventilated areas, potentially leading to hypoxemia. An increase in cardiac output distends open vessels and may recruit previously closed vessels, decreasing pulmonary vascular resistance. Regional blood flow to lung is also influenced by gravity; pulmonary blood flow is greater in the dependant areas of the lung. In addition, increases in intrathoracic pressure are transmitted to the surrounding heart and contribute to elevate pulmonary artery pressure.

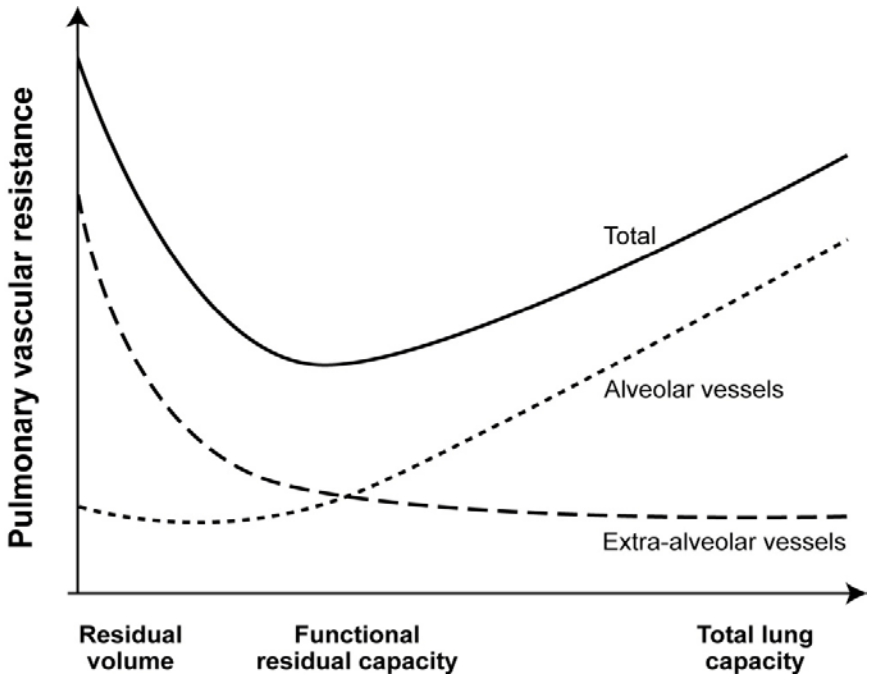

Figure 66 Effect of lung volume on pulmonary vascular resistance

The pulmonary vascular resistance (PVR) is minimal at functional residual capacity (FRC). The PVR increases with increases in total lung capacity (TLC). It also increases with small lung volumes at residual volume. The differential effect on intra- and extra-alveolar vessels accounts for the U-shaped relationship of PVR and lung volume. (Adapted from Fisher *et al.* [302]

8) Mechanical compression of pulmonary vessels can also be caused by hematomas, hemothoraces, tension pneumothoraces and abdominal compartment syndrome. [148;239] This mechanism has been previously discussed (see section 3.1.3). Suboptimal pulmonary anastomosis in heart transplantation may also occur postoperatively and cause increased right ventricular afterload and right ventricular failure.

In some of these situations, the treatment of the underlying cause such as the correction of hypoxemia will result in a reduction in the severity of pulmonary hypertension. However, in recent years, the understanding of basic pathways involved in the pathophysiology of pulmonary hypertension has also rapidly evolved. This understanding provides the basis for much of the pharmacotherapy used in the treatment or prevention of pulmonary hypertension. The most common pathways include the nitric oxide, prostacyclin, endothelin-1 and serotonin pathways. [303] Nitric oxide and prostacyclin are endogenous vasodilators produced in the pulmonary vascular endothelium. Endothelin-1 is an endogenous vasoconstrictor peptide secreted by the vascular endothelium and plays a role in pulmonary vasoconstriction and vascular smooth muscle proliferation. [304] The neurotransmitter serotonin and the serotonin receptor transporter have also been implicated in the regulation of pulmonary vascular tone. An imbalance in these pathways may lead to vasoconstriction and vascular remodelling, potentially leading to progressive pulmonary vascular disease. [305]

6.3 Importance and impact of pulmonary hypertension in cardiac surgery

Preoperative pulmonary hypertension has been consistently shown to be an important risk factor for increased morbidity and mortality. [8;100;115-117] However, the

presence of pulmonary hypertension has not always been not routinely reported to the cardiac surgical and anesthesia team. This may account for the fact that only a small proportion of preoperative risk stratification models in cardiac surgery include pulmonary hypertension. [141] Interestingly, the EuroSCORE model, which had the highest discriminatory capacity, is one of the few models in which pulmonary hypertension is included. In a study that included 4351 patients undergoing coronary revascularization in Sweden, the EuroSCORE model had the best sensitivity (0.86) and specificity (0.75) with the highest receiver operating characteristics (ROC) to predict the 30-day and one-year mortalities, respectively. There are however several limitations in the few studies in which pulmonary hypertension was used in the stratification process. First, the selected thresholds differ. A mean pulmonary artery pressure of 30 mmHg and systolic pulmonary artery pressure of 60 mmHg are used in the Parsonnet score [100] and the EuroSCORE, [101] respectively. Then, absolute values are used in these studies, except for the Tuman score, where pulmonary hypertension is defined as MPAP≥ 25% of mean values. [115] Finally, the impact of pulmonary hypertension on right ventricular function has not been addressed in large studies.

It is suspected that the presence of pulmonary hypertension before the operation or appearing during or after the intervention will have an impact on survival, mostly through its effect on right ventricular function. The most dreadful consequence of pulmonary hypertension is the increase in right ventricular afterload and right ventricular dysfunction; this issue will be addressed here.

6.4 Right ventricular dysfunction

There is growing evidence that morbidity and mortality associated with pulmonary hypertension are related to the degree of right ventricular adaptation to disease rather than to the absolute values of pulmonary arterial pressure. [46;189-191;306] This hypothesis would be consistent with studies in pulmonary hypertension where markers of right ventricular function have been shown to be the most important prognostic factors. [189;192] Unfortunately, to date, parameters of right ventricular function have not

been included in large-scale risk stratification models, and therefore their incremental values to the Parsonnet score or the EuroSCORE have not been well established. [100;103;200;201] A recent panel from the National Institutes of Health (NIH) has stressed the importance of research in the understanding of right ventricular failure. [191]

Right ventricular dysfunction in mitral or mitro-aortic surgery has also been strongly associated with worsening outcome. In a retrospective study of patients undergoing mitral and mitral-aortic valvular surgery, Pinzani *et al.* [193] demonstrated that preoperative right ventricular failure was associated with an increase in perioperative mortality. In this same study, postoperative right ventricular failure was the most important independent predictor of late survival at 75 months. In a small prospective study of 14 patients with severe non-ischemic mitral regurgitation and high-risk descriptors (left ventricular ejection (LVEF) ≤ 45% or right ventricular ejection fraction (RVEF) ≤ 20%), Wencker *et al.* [203] found that preoperative RVEF ≤ 20% predicted postoperative death.

Pulmonary hypertension may also be associated with refractory postoperative right ventricular failure, which portends a very poor prognosis. In unstable cardiac surgery patients, post-CPB severe right ventricular failure has been associated with a mortality rate ranging from 44% to 86% [4] (seeTable 12). The next question deals with how to prevent or treat pulmonary hypertension and its consequence, right ventricular failure.

6.5 Treatment and prevention of pulmonary hypertension in cardiac surgery

The choice of the appropriate therapy should be based on the best available evidence. A MEDLINE search was performed using the key words ‘randomized controlled trial’ (RCT), ‘humans’, ‘adults’, ‘English’ and ‘pulmonary hypertension’. Articles related to cardiac surgery were then selected and classified according to the levels of evidence proposed by Sackett [307] for evidence-based medical practice. Using this strategy, a total of 11 articles were retrieved. In addition, the Consort statement group has developed

guidelines to assess the quality of randomized controlled clinical trials, [308] which we used. These studies are summarized in Table 26 and will be discussed in the following section.

Table 26 RCT in adult cardiac surgery and pulmonary hypertension

Author	Year	Agents used	Design	*N*	Inclusion criteria	Primary endpoint	Level of evidence
Hachenberg *et al.* [309]	1997	Enoximone *vs.* dobutamine + NTG	RCT Unicenter	20	PH in MVR before and after surgery	Hemodynamic	A1b
Schmid *et al.* [310]	1999	iNO *vs.* NTG *vs.* PGE_1	Crossover Unicenter	14	PH after surgery	Hemodynamic	B
Solina *et al.* [311]	2000	iNO *vs.* milrinone	RCT Unicenter	45	PH after surgery	Hemodynamic	A1b
Solina *et al.* [312]	2001	iNO *vs.* milrinone	RCT Unicenter	62	PH after surgery	Hemodynamic	B
Feneck *et al.* [313]	2001	Milrinone *vs.* dobutamine	RCT Multicenter	120	CO < 2 L/min/m² and PCWP > 10 mmHg after cardiac surgery	Hemodynamic	A1b
Hache *et al.* [26]	2003	$iPGI_2$ *vs.* placebo	RCT Unicenter	20	PH before CPB	Hemodynamic	A1b
Fattouch *et al.* [314]	2005	$iPGI_2$ *vs.* iNO *vs.* intravenous vasodilators	RCT Unicenter	58	MVR + PH in the intensive care unit	Hemodynamic	A1b
Stafford *et al.* [315]	2005	Heparinase *vs.* protamine	Non-inferiority clinical trial design Multicenter	167	CABG on + off pump after CPB	Bleeding	A1b
Ocal *et al.* [164]	2005	$iPGI_2$ *vs.* NTG	RCT Multicenter	68	CABG with protamine reaction after CPB	Hemodynamic	A1b

Fattouch *et al.* [316]	2006	$iPGI_2$ *vs.* iNO *vs.* intravenous vasodilators	RCT Unicenter	58	MVR + PH before the end of CPB	Hemodynamic	A1b
Rex *et al.* [317]	2007	$iPGI_2$ *vs.* NTG	RCT Unicenter	20	MV repair + PH before surgery	Hemodynamic	A1b

CABG: coronary artery bypass graft, CO: cardiac output, CPB: cardiopulmonary bypass, iNO: inhaled nitric oxide, $iPGI_2$: inhaled prostacyclin, MV, mitral valve; MVR: mitral valve replacement, NO: nitric oxide, NTG: nitroglycerin, OR: operating room, PCWP: pulmonary capillary wedge pressure, PGE_1: prostaglandin E_1, PGI_2: prostacyclin, PH: pulmonary hypertension, RCT: randomized controlled trial.

6.4.1 Treatment of pulmonary hypertension

Both pharmacological and non-pharmacological treatment of pulmonary hypertension have been reported.

6.4.1.1 Pharmacological treatment

The agents studied to vasodilate the pulmonary vasculature were: inhaled prostacyclin, epoprostenol or iloprost (PGI_2), inhaled nitric oxide (iNO) and intravenous vasodilators such as prostaglandin E_1 (PGE_1), nitroglycerin (NTG), nitroprusside (NTP), milrinone, enoximone and dobutamine. A total of 11 trials have been reported (Table 26).

Hachenberger *et al.* [309] explored the role of enoximone compared to NTG and dobutamine, given after induction of anesthesia and then restarted before the end of CPB. Only enoximone was associated with a decrease in mean pulmonary artery pressure and pulmonary vascular resistance.

Schmid *et al.* [310] compared three approaches (iNO *vs.* PGE_1 *vs.* NTG) in a crossover study. These drugs were used to treat pulmonary hypertension after cardiac surgery in 14 patients. Only stable patients were included in the study, limiting the application of the results. Inhaled nitric oxide decreased pulmonary vascular resistance without reducing systemic vascular resistance, did not change coronary perfusion pressure of the right coronary pressure, and increased oxygen transport.

Solina *et al.* explored the dose-responsiveness of inhaled nitric oxide given upon termination of CPB at 10, 20, 30 and 40 ppm compared to intravenous milrinone. [312] Nitric oxide was associated with a reduction in pulmonary vascular resistance with a maximum dose of 10 ppm. No significant difference in the reduction of pulmonary vascular resistance or inotropic requirement was observed compared to milrinone. The same authors compared inhaled nitric oxide 20 ppm and 40 ppm to milrinone in patients with pulmonary vascular resistance above 125 $dyn \cdot s \cdot cm^{-5}$ after cardiac surgery. [311] The drugs were initiated after CPB and for 24 hours in the intensive care unit. Higher systemic arterial pressures were observed in the 20 ppm group and higher RV ejection fraction were obtained in the 40 ppm NO group. The milrinone group required significantly more

phenylephrine and tended to have higher heart rates than either of the nitric oxide groups in the intensive care unit.

Feneck *et al.* compared milrinone to dobutamine in 120 patients with cardiac outputs below 2 L/min/m² with pulmonary capillary wedge pressure > 10 mmHg. [313] In a subset of patients with pulmonary hypertension defined as (pulmonary vascular resistance > 200 dyn·s·cm^{-5}, mean pulmonary artery pressure > 25 mmHg), milrinone had a similar effect to dobutamine on the reduction of pulmonary vascular resistance and increase in cardiac index. The pulmonary capillary wedge pressure and systemic vascular resistance were reduced more significantly by milrinone.

Hache *et al.* [26] studied the hemodynamic and biventricular echocardiographic of inhaled PGI_2 in 20 patients with pulmonary hypertension before CPB. Inhaled epoprostenol significantly reduced indexed right ventricular stroke work from 10.7 ± 4.57 g/m/m² to 7.8 ± 3.94 g/m/m² (P=0 .003) and systolic pulmonary artery pressure from 48.4 ± 18 mm Hg to 38.9 ± 11.9 mm Hg (P=0.002). The effect was correlated with the severity of pulmonary hypertension (r = 0.76, P =0.01) and was no longer apparent after 25 minutes.

In 2006 Fattouch *et al.* studied patients with pulmonary hypertension (n = 58) undergoing mitral valve replacement (MVR) for mitral stenosis. [316] Inhaled PGI_2 ($iPGI_2$) and iNO were compared to conventional intravenous vasodilators. The inhaled drugs were given just before the end of CPB. Inhaled medications were associated with significant reductions in pulmonary hypertension indices as well as with an increase in cardiac output and in RV ejection fraction compared to the conventional treatment. In addition, in both inhaled groups, separation from CPB was easier, the amount of vasoactive drugs administered was smaller and the duration of stay in the intensive care unit (ICU) and hospital was shorter. The same group also compared the same three strategies in the treatment of PH after MVR upon arrival in the ICU. [316] Inhalation of PGI_2 was associated with a reduction in pulmonary vascular resistance and an increase in stroke volume. Inhaled NO reduced pulmonary vascular resistance but did not increase stroke

volume, and nitroprusside was associated with a reduction in systemic arterial pressure and systemic vascular resistance.

Finally Rex *et al.* [317] compared inhaled iloprost in 30 patients with pulmonary hypertension undergoing mitral valve repair. Inhaled iloprost improved right ventricular ejection fraction, stroke volume index and reduced the transpulmonary gradient. All patients receiving iloprost were weaned compared to 3 patients in the control group requiring return on CPB and rescue medication.

Although these studies included only a small number of patients and had various timings of administration, it appears that the use of inhaled agents could be superior to that of intravenous drugs. Inhaled PGI_2 seems as effective as nitric oxide and would represent an advantage in terms of simplicity of use and cost. If nitric oxide is to be used, 40 ppm has more effect on right ventricular function. Milrinone efficacy is inferior to inhaled agents and limited by systemic hypotension, which would reduce coronary perfusion. Larger studies in high-risk patients with pulmonary hypertension in which specific pulmonary vasodilators would be compared to conventional treatment should be performed.

6.4.1.2 Non-pharmacological approaches

The non-pharmacological approach to the treatment of pulmonary hypertension is directed to the cause or the consequence of pulmonary hypertension, as illustrated in Figure 64. In the presence of pulmonary hypertension secondary to left ventricular failure, intra-aortic balloon counterpulsation may facilitate recovery of left ventricular dysfunction. If prosthetic valve dysfunction is present after CPB, re-initiation of CPB and correction of the problem will be the treatment of choice. The correction of hypoxemia, hypercapnia and surgical thrombo-embolectomy (when surgically indicated) can help reduce pulmonary vascular resistance. In patients with elevated intrathoracic pressures or compartment syndrome from accumulated air or blood, chest drainage should correct that component of elevated pulmonary artery pressure. However, in some patients undergoing long procedures and long CPB duration, chest closure can be associated with hemodynamic instability (Figure 45). This “thoracic compartment” syndrome can be caused by reduced right

ventricular filling through increased resistance to venous return, right ventricular compression and increased pulmonary vascular resistances. In these situations, the chest can be temporarily left open to reduce the surrounding pressures. The use of a pulmonary artery balloon pump, right ventricular assist device (RVAD) or cavopulmonary diversion have been described as potential treatments for severe RV dysfunction. [5] The abdominal compartment syndrome (see Section 3.1.3) has recently been described as a cause of increased intrathoracic pressure; however, its diagnosis and treatment approach are beyond the scope of this review. [148] Lastly, increased right ventricular afterload may be due to mechanical complications at the site of anastomosis such as the main or secondary pulmonary arteries (in heart or lung transplantation or congenital cardiac surgery), [12] or more rarely stenosis of pulmonary veins (in lung and heart transplantation) [318] or after left atrial venting through a pulmonary vein (Figure 67). [12]

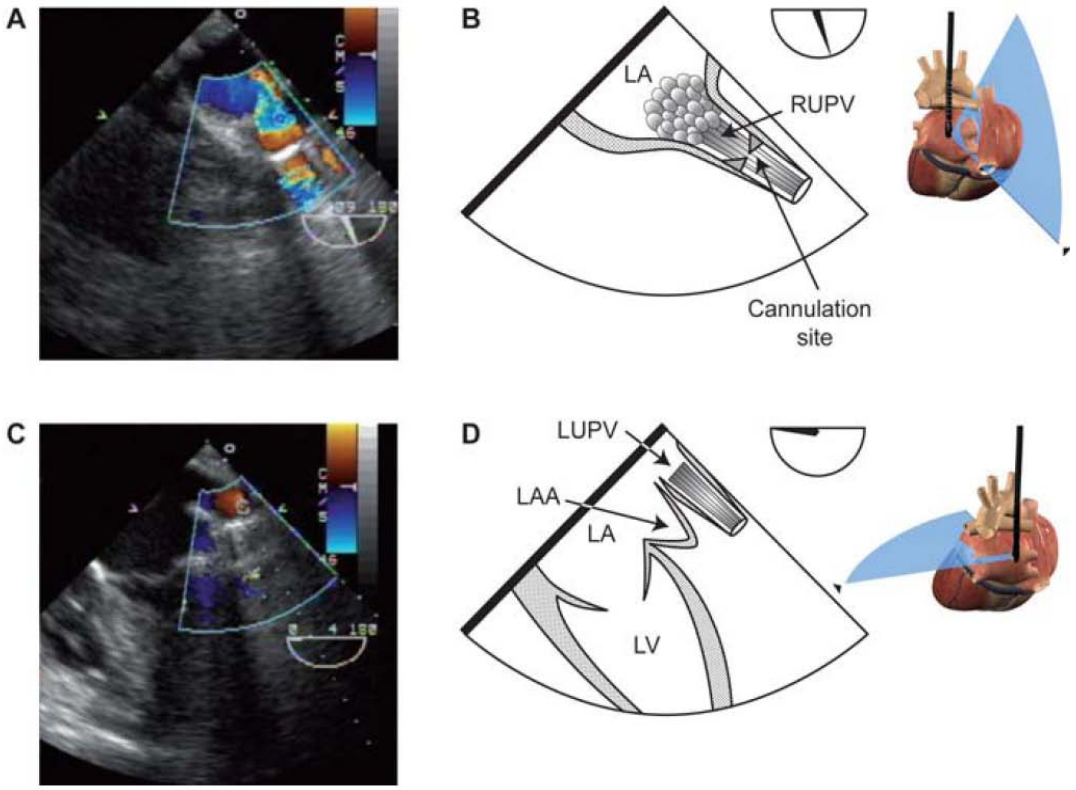

Figure 67 Vent complication

(A,B) Color Doppler evaluation shows right upper pulmonary vein (RUPV) stenosis after removal of the left atrial vent in a patient who underwent a repeated aortic valve procedure. A peak systolic velocity of 120 cm/sec is recorded with flow acceleration and aliasing in the RUPV in this modified bicaval view. (C,D) In contrast, a velocity of 80 cm/sec with no aliasing is found in the left upper pulmonary vein (LUPV) in this mid-esophageal four-chamber view (LA, left atrium; LAA, left atrial appendage; LV, left ventricle). (With permission of Denault *et al.* [12])

6.4.2 Treatment of right ventricular failure

The most severe consequence of pulmonary hypertension is right ventricular failure. The treatment strategy used at the Montreal Heart Institute for the treatment of right ventricular failure is summarized in Figure 68.

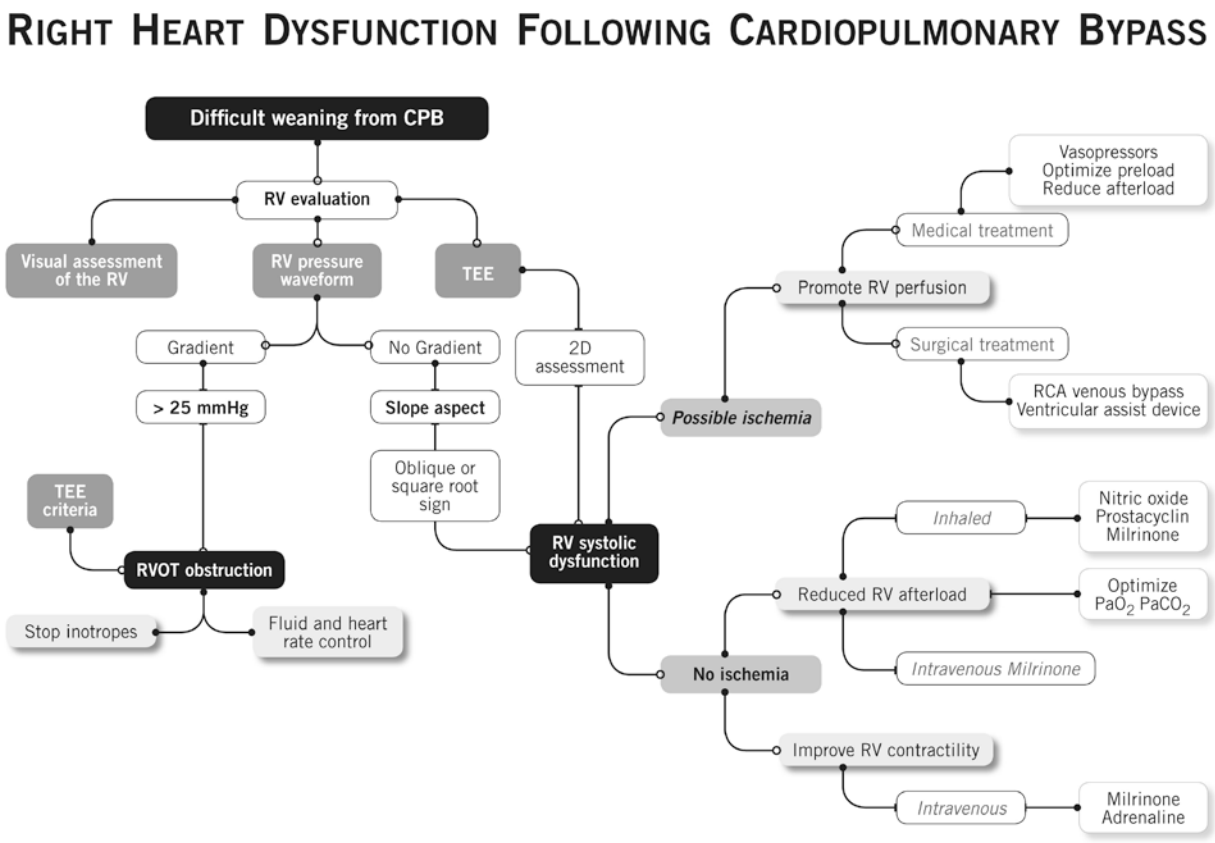

Figure 68 Proposed approach in the treatment of right ventricular dysfunction

(RCA, right coronary artery; RV, right ventricular; RVOT, right ventricular outflow tract; TEE, transesophageal echocardiography) (Presented by Dr. Y. Lamarche at the 2006 CCS meeting in Vancouver).

Right ventricular function is evaluated visually, using the RV pressure waveform (Figure 69) and transesophageal echocardiography (TEE). A failing RV is suggested by abnormal right ventricular pressure waveform (Figure 70) decreased cardiac output, increased central venous pressure, dilated right atrium and right ventricle and decreased systolic function. In the presence of a failing right ventricle, RVOTO and severe tricuspid regurgitation should be ruled out. Once RVOTO is ruled out, the etiology of right ventricular systolic dysfunction is divided in two categories. If ischemia is suspected to contribute to right ventricular failure, then both the medical and the surgical treatment are oriented toward the promotion of right ventricular perfusion. If a non-ischemic etiology is suspected, the medical and surgical treatment will be oriented toward an increase in contractility (inotropes) and a reduction in right ventricular afterload through optimization of oxygenation, pH and $PaCO_2$, iNO, $iPGI_2$, inhaled and intravenous milrinone (Figure 71).

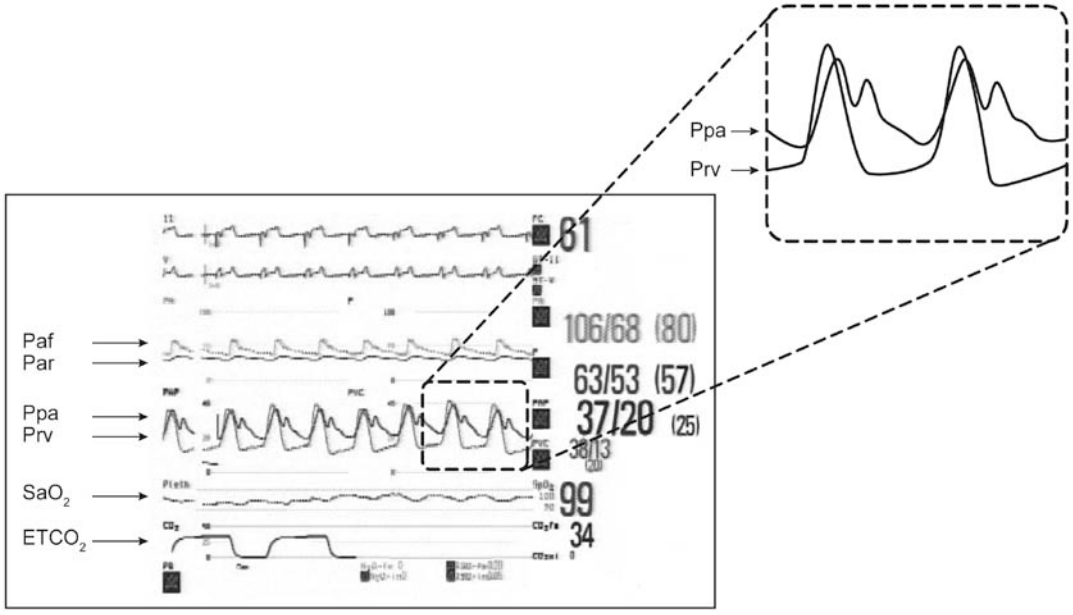

Figure 69 Right ventricular pressure waveform

Baseline hemodynamic waveforms in a patient before cardiac surgery. Note the relatively horizontal right ventricular pressure waveform. ($ETCO_2$, end-tidal carbon dioxide; Paf, femoral arterial pressure; Par, radial arterial pressure; Ppa, pulmonary artery pressure; Prv, right ventricular pressure; SaO_2, oxygen saturation)

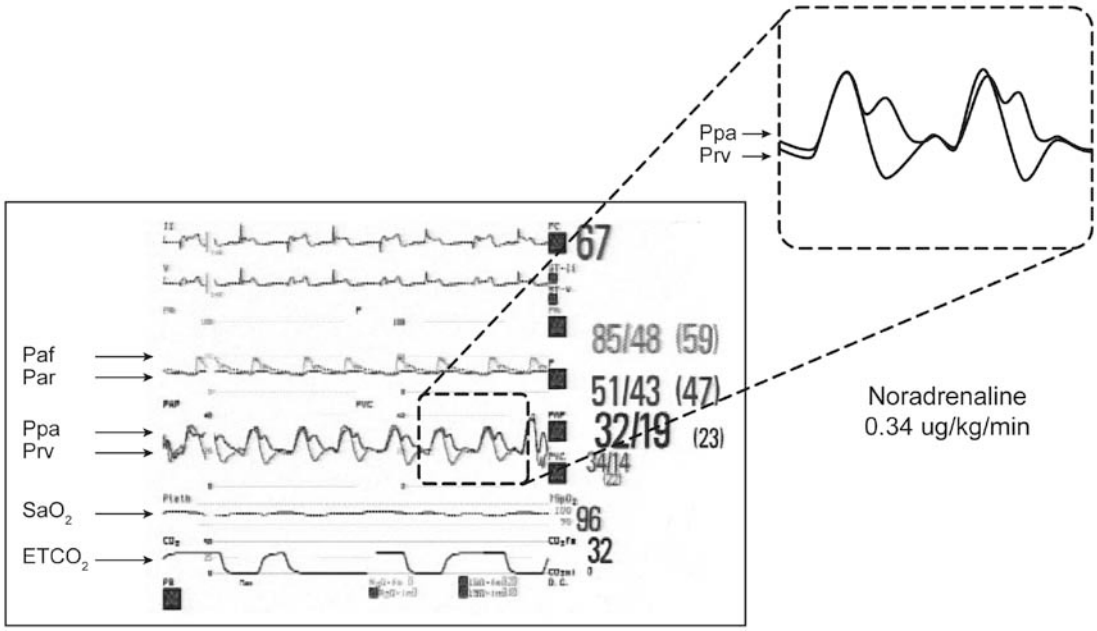

Figure 70 Right ventricular pressure waveform with hemodynamic instability

Same patient during hemodynamic instability secondary to right ventricular failure requiring noradrenaline. Note the change in the diastolic slope of the right ventricular pressure waveform. ($ETCO_2$, end-tidal carbon dioxide; Paf, femoral arterial pressure; Par, radial arterial pressure; Ppa, pulmonary artery pressure; Prv, right ventricular pressure; SaO_2, oxygen saturation)

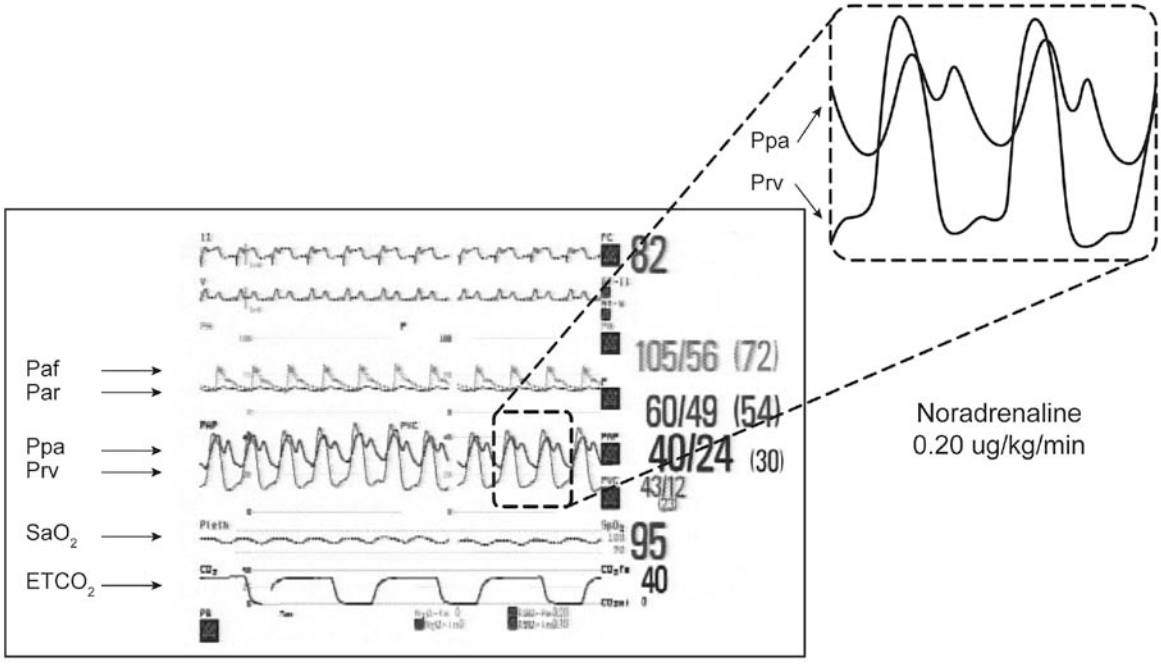

Figure 71 Right ventricular pressure waveform after inhaled milrinone

Same patient following the administration of inhaled milrinone. Note the change in the diastolic slope of the right ventricular pressure waveform back to a more horizontal aspect. A mild gradient between the systolic right ventricular pressure (Prv) and pulmonary artery pressure (Ppa) appeared. ($ETCO_2$, end-tidal carbon dioxide; Paf, femoral arterial pressure; Par, radial arterial pressure; SaO_2, oxygen saturation)

6.4.3 Milrinone

Milrinone is a cyclic AMP-specific phosphodiesterase inhibitor that can exert both positive inotropic effects and vasodilation independently of $ß_1$-adrenergic receptor stimulation in the cardiovascular system. [41;319] Studies ($n = 36$) evaluating the use of intravenous milrinone in adult cardiac surgical patients have been performed on a small number of patients undergoing coronary revascularization (Table 27). [41]

Table 27 Clinical studies on the use of milrinone in cardiac surgery

Author	Reference	*N*	Population	Dosage	Timing	Result
De Hert *et al.* 1995	[63]	20	Coronary revascularization	Milrinone 20 μg/kg Milrinone 40 μg /kg (*n* = 10 per group)	After CPB	Similar CI between group The 40 μg /kg group had higher vasoactive requirement
Kikura *et al.* 1995	[320]	27	Cardiac surgical patients	Milrinone 50-75 μg /kg/min + perfusion 0.5-0.75 μg/kg/min (*n* = 17) Placebo (*n* = 10)	During CPB	No change in platelet number or function
Doolan *et al.* 1997	[321]	30	LVEF ≤ 35% PCWP ≥ 20 mmHg pre-bypass	Milrinone bolus 50 μg /kg + perfusion 0.5 μg /kg/min Placebo (*n* = 15 per group)	15 minutes before en CPB	All patients with milrinone weaned from byp *vs*. 5/15 placebo
Kikura *et al.* 1997	[322]	37	Post-CPB patients on catecholamines	Placebo (*n* = 10) Milrione bolus 50 μg /kg (*n* = 8) Bolus 50 μg /kg and perfusion of 0.5 μg /kg/min (*n* = 10) Bolus 75 μg /kg and perfusion 0.75 μg /kg/min (*n* = 9)	After CPB	Higher CI and velocity of shortening measured by TEE in all 3 milrinone groups
Rathmell *et al.* 1998	[323]	44	Elective cardiac surgery	Amrinone 0.75 mg/kg Milrinone 25 μg/kg (n = 22 per group)	After CPB	Amrinone and milrinone produced similar hemodynamic effects
Lobato *et al.* 1998	[324]	21	Coronary revascularization	Milrinone bolus 50 μg/kg (*n* = 11) Placebo (*n* = 10)	After CPB	Milrinone increase CI, no change in PAP. Less dobutamine required
Mollhoff *et al.* 19989	[325]	22	Coronary revascularization	Milrinone 30 μg/kg with 0.5 μg/kg/min perfusion Placebo (*n* = 11 per group)	Before CPB	Milrinone did not prevent GI acidosis but reduced IL-6
McNicol *et al.* 1999	[326]	24	Coronary revascularization	Milrinone during CPB Dopamine during CPB Placebo (*n* = 8 per group)	During CPB	Neither drug prevented splanchnic and systemic endotoxin levels
Hamada *et al.* 1999	[327]	30	Open heart surgery	Milrinone 50 μg/kg after declamping Amrinone 1 mg/kg Placebo (*n* = 10 per group)	During CPB after declamping	Milrinone and amrinone increase cardiac index and reduce SVR. No change in PAP
Hayashida *et al.* 1999	[328]	24	Coronary	Milrinone 0.5 μg/kg/min	After induction of	LIMA blood flow greater with milrinone

Author	Reference	*N*	Population	Dosage	Timing	Result
			revascularization	Placebo (*n* = 12 per group)	anesthesia X 24 hours	
Hayashida *et al.* 1999	[329]	24	Coronary revascularization	Milrinone 0.5 μg/kg/min Placebo (*n* = 12 per group)	After induction of anesthesia X 24 hours	Milrinone increase c-AMP and reduces IL-1b and IL-6 after CPB
Yamada *et al.* 2000	[66]	48	Patients with a low pre-CPB CI < 2.5 L/min/m^2) and in patients with a high pre-CPB CI (> or = 2.5 L/min/m^2)	(1) low pre-CPB CI/placebo, (2) low pre-CPB CI/milrinone, (3) high pre-CPB CI/placebo (4) high pre-CPB CI/milrinone Dose: milrinone 20 μg/kg and perfusion 0.2 μg/kg/min (*n* = 12 per group)	15 minutes before end of CPB	Infusion of epinephrine in 5 of the 12 patients for hemodynamic support in placebo *vs*. norepinephrine in 6 of 12 patients in the low pre-CPB CI groups receiving milrinone
13-Lobato *et al.* 2000	[330]	20	Coronary revascularization	Milrinone 50 μg/kg Epinephrine 0.03 μg/kg/min (*n* = 10 per group)	After separation from CPB	LIMA blood flow greater with milrinone
Lobato *et al.* 2000	[331]	20	Coronary revascularization	Milrinone 50 μg/kg Epinephrine 0.03 μg/kg/min (*n* = 10 per group)	After separation from CPB	Milrinone maintained left ventricular compliance (measured as LVEDA)
Solina *et al.* 2000	[311]	45	Pulmonary hypertension	Group 1 milrinone Group 2 20 ppm NO Group 3 40 ppm NO (*n* = 15 per group)	After separation from CPB	Group 3 (40 ppm) higher RVEF compared to group 1 and 2. The milrinone group required significantly more phenylephrine in the intensive care unit
Sha *et al.* 2001	[332]	46	Valvular cardiac surgery	Amrinone (*n* = 17) Milrinone (*n* = 15) Olprinone (*n* = 14)	15 minutes before end of CPB	No difference in the dosage of catecholamines used
Yamaura *et al.* 2001	[333]	20	Hypothermic CPB	Milrinone 0.25 μg/kg/min from CPB to 1 hour in the ICU Placebo (*n* = 10 per group)	Beginning of CPB until 1 hour in the ICU	Milrinone prevents gastric intramucosal acidosis and elevation in IL-6
Iwagaki *et al.* 2001	[334]	24	Coronary revascularization	Milrinone 50 μg/kg Placebo prior to separation from CPB (*n* = 12 per group)	Before separation from CPB	Milrinone increased cardiac index but reduced mean arterial pressure and SVR

Author	Reference	*N*	Population	Dosage	Timing	Result
Janelle *et al.* 2001	[335]	20	Coronary revascularization	Milrinone 50 µg/kg Placebo (*n* = 10 per group)	10 minutes before aortic cross-clamping	Milrinone patients had increased myocardial c-AMP
Shibata *et al.* 2001	[336]	20	Coronary revascularization	Milrinone 5 µg/kg/min Placebo (*n* = 10 per group)	Infusion in the ICU (no bolus)	Cardiac index and HR increase in the milrinone group
Zabeeda *et al.* 2001	[337]	50	Coronary revascularization: LIMA and radial artery flow	Group 1: nitroglycerin (*n* = 10) Group 2: nitroprusside (*n* = 10) Group 3: dobutamine (*n* = 10) Group 4: milrinone (*n* = 10) Group 5: placebo (*n* = 10)	Before CPB	Nitroglycerin use is the only predictor of increased flow in the LIMA and radial artery
Solina *et al.* 2001	[312]	62	Cardiac surgery patients with pulmonary hypertension	Group 1 NO 10 ppm (*n* = 11) Group 2 NO 20 ppm (*n* = 12) Group 3 NO 30 ppm (*n* = 12) Group 4 NO 40 ppm (*n* = 12) Group 5 milrinone bolus 50 µg/kg (*n* = 15)	After CPB	No difference in inotropic use in all groups. NO 10 ppm is adequate
Feneck *et al.* 2001	[313]	120	Low CO after cardiac surgery	Milrinone 50 µg/kg and perfusion of 0.5 µg/kg/min Dobutamine: 10 to 20 µg/kg/min (*n* = 60 per group)	Within 2 hours after CPB	Dobutamine elicits greater increases in CI. Milrinone evoked greater decreases in mean PCWP. Milrinone and dobutamine: both appropriate and comparable.
Lobato *et al.* 2001	[338]	30	Coronary revascularization after CPB	Nitroglycerin 2 µg /kg/min Milrinone 50 µg/kg/min Nitroglycerin and milrinone (*n* = 10 per group)	After CPB	Greater increase in internal mammary flow with milrinone
Mollhoff *et al.* 2002	[339]	30	Patients with LVEF < 40%	Nifedipine 0.2 µg /kg/min Milrinone 0.375 µg /kg/min (*n* = 15 per group)	Before CPB	Myocardial ischemia in 33% with milrinone compared to 86.6% with nifedipine
Kikura *et al.* 2002	[340]	45	Patients undergoing coronary bypass after CPB	Milrinone 50 µg /kg and 0.5 µg /kg/min Amrinone 1.5 mg/kg and 10 µg /kg/min	At release of aortic cross-clamping	Milrinone and amrinone increased SV and TO2 and reduced dopamine requirement

Author	Reference	*N*	Population	Dosage	Timing	Result
				Placebo (*n* = 15 per group)		
Kikura *et al.* 2003	[341]	45	Patients undergoing coronary bypass after CPB	Milrinone 50 µg /kg and 0.5 µg /kg/min Amrinone 1.5 mg/kg and 10 µg /kg/min Placebo (*n* = 15 per group)	At release of aortic cross-clamping	No deterioration in platelet function and in hemostasis with milrinone and amrinone
Kim *et al.* 2003	[342]	30	Off-pump bypass surgery patients with atenolol	Milrinone 50 µg /kg and perfusion of 0.83 µg/kg/min X 1 hour then 0.40 Placebo (*n* = 15 per group)	Before off-pump bypass of the obtuse marginal (OM) artery	During OM, milrinone increased CI but with more phenylephrine
Hoffman *et al.* 2003	[343]	238	Congenital heart surgery neonates and young children	Low dose: 0.25 µg /kg and 0.25 µg /kg/min (*n* = 79) High dose: 0.75 µg /kg and 0.75 ug/kg/min (*n* = 73) Placebo (*n* = 75)	Intensive care unit: 35 hours infusion	Reduced incidence of low CO state with high dose *vs*. low dose *vs*. placebo (11.7% *vs*. 17.5% *vs*. 25.9%). 2 unrelated deaths with milrinone
Kwak *et al.* 2004	[344]	82	Off-pump bypass surgery patients	Milrinone 0.5 µg /min/kg Placebo (*n* = 41 per group)	After internal mammary harvest	Milrinone prevents the reduction in cardiac index
Kwak *et al.* 2004	[345]	52	Off-pump bypass surgery patients	Milrinone (*n* = 33) 0.5 µg /min/kg Placebo (*n* = 29)	After internal mammary harvest	Milrinone associated with smaller reduction in CO and MVO2 during off-pump bypass
Maslow *et al.* 2004	[346]	34	Patients after aortic valve replacement	Epinephrine 30 ng/kg/min (*n* = 11) Milrinone 30 µg /kg and 0.3 µg /kg/min (*n* = 11) Placebo (*n* = 12)	After removal of aortic cross-clamping	Milrinone and epinephrine increased LVEF, RVEF and CO. No change in diastolic function.
Khazin *et al.* 2004	[347]	90	Congenital heart surgery children with pulmonary hypertension	1-NO 2-Milrinone infusion 3-NO and milrinone (*n* = 30 per group)	After CPB:	NO and milrinone produce a more pronounced reduction in MPAP than milrinone alone

Author	Reference	*N*	Population	Dosage	Timing	Result
Omae *et al.* 2004	[348]	140	Off-pump bypass surgery patients with mitral regurgitation 1+ to 2+	Without MR (*n* = 57) With MR (*n* = 41) With MR + milrinone (*n* = 42)	After induction of anesthesia	No increase in MR and MPAP in the milrinone group during left coronary artery anastomosis
Lobato *et al.* 2005	[349]	36	Coronary artery bypass patients	Epinephrine 0.03 µg /kg/min (*n* = 12) Milrinone 50 µg /kg and 0.5 µg/kg/min (*n* = 13) Placebo (*n* = 11)	During separation from CPB	No change in diastolic function with either epinephrine or milrinone No change in MPAP with milrinone
Shi *et al.* 2006	[40]	50	Coronary artery bypass patients with LV diastolic dysfunction	Milrinone 50 µg /kg and 0.5 µg /kg/min perfusion Placebo (*n* = 25 per group)	Before CPB until skin closure	Milrinone increased CI, HR but no change in LV and RV diastolic function post-CPB, at 48 hours and at 6 months. More phenylephrine in the milrinone group.

AMP, adenosine monophosphate; CI, cardiac index; CO, cardiac output; CPB, cardiopulmonary bypass; ICU, intensive care unit; IL, interleukin; LIMA, left internal mammary artery; LV, left ventricular; LVEDA, left ventricular end-diastolic area; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; MR, mitral regurgitation; MVO_2, mixed venous oxygen; NO, nitric oxide; OM, obtuse marginal; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RV, right ventricular; RVEF, right ventricular ejection fraction; SV, stroke volume; TEE, transesophageal echocardiography; TO_2, oxygen transport

Although intravenous milrinone has been shown to increase cardiac index [322;324;334;336;342;343;346] and to facilitate separation from CPB, [321] the major problem encountered with intravenous milrinone is the high incidence of systemic hypotension resulting in an increased need for vasoactive drugs [66;311;324;342] from either vasodilation or from left and right ventricular dynamic outflow tract obstruction. [38] Two randomized controlled trials on the use of milrinone in a non-cardiac surgical setting, the PROMISE trial in 1991 (on the use of oral milrinone) [294] ($n = 1088$) and the OPTIME-CHF trial in 2002 (on a 48-hour intravenous milrinone perfusion) [289] ($n = 949$) showed no advantage in terms of hospitalization duration. However, patients receiving oral or intravenous milrinone had more adverse events and increased mortality in the PROMISE trial. Even if these large studies were performed in a non-cardiac surgical setting, they could suggest that the indiscriminate use of milrinone in cardiac surgery could be detrimental. Therefore, it appears relevant to explore alternative strategies that would reduce the severity of pulmonary hypertension without systemic hypotension. So far, only two reports outside of the MHI, with a small number of patients, have addressed the role of inhaled milrinone in cardiac surgery in humans. [350-353] These studies have shown that inhaled milrinone reduces pulmonary artery pressure without causing systemic hypotension.

6.4.4 Inhaled milrinone

The use of the inhaled route for milrinone has been recently described in animal [354-357] and human studies. [53;350-353] As an alternative to inhaled nitric oxide and inhaled prostacyclin, inhaled milrinone is also less expensive and does not require a complex set-up and monitoring of toxic metabolites. Furthermore, inhaled milrinone is readily available in operating rooms and needs no special preparation, as opposed to inhaled prostacyclin. In addition, inhaled milrinone before CPB has been shown to be superior to an intravenous administration in reducing the pulmonary reperfusion syndrome, [354] preventing pulmonary arterial endothelial dysfunction [356;357] and improving oxygenation in a porcine model. [354] Only four observational studies addressing the role of inhaled milrinone in cardiac surgery have been published so far. [53;350;351;353] The effect of inhaled milrinone was first described by Haraldsson *et*

al. [350] in an open-label trial of 20 cardiac surgical patients in the intensive care unit. The first part of the trial included 9 patients and showed a dose-response effect of incremental concentrations of inhaled milrinone with decreases in MPAP, PVR and PVR/SVR. No patient presented systemic hypotension. The hemodynamic parameters of patients treated with inhaled milrinone returned to baseline within 20 minutes of the end of the inhalation period, similar to our observation. In the second study, [351] inhaled milrinone was given to 18 heart transplant candidates in the intensive care unit. The MPAP, transpulmonary gradient and PVR decreased only in patients with PH, defined as MPAP above 30 mmHg. Improvement in CO was observed, but there was no systemic hypotension. The dosage was 2 mg based on intravenous milrinone loading doses used in heart transplantation, which was almost half of the dose used in our protocol. In these studies, there was no control group, and the intraoperative usage and the timing of inhaled milrinone in relation to CPB were not recorded. We have previously described the administration of inhaled milrinone before CPB in 40 high-risk patients with a Parsonnet score of 30.4 ± 14.2. [53] Compared to the administration of inhaled milrinone after CPB, pre-CPB inhaled milrinone was associated with a reduction of difficult separation from CPB (18% *vs*. 82%) defined as the use of more than two inotropes, need for introduction of an intra-aortic balloon pump or reinitiation of CPB. In the current study, the same ratio was observed; 4 patients in the control group compared to 1 in the inhaled milrinone group would have qualified for this definition. Significantly lower SPAP and unchanged LV function were also observed after CPB in the group who received inhaled milrinone pre-CPB, as observed in the current study, but RV function was not analyzed. Finally a recent study compared the use of intravenous versus inhaled milrinone in 48 patients with pulmonary hypertension after mitral valve surgery. [353] With milrinone administration, mean pulmonary artery pressure and pulmonary vascular resistance decreased in both groups. However, the mean arterial pressure and systemic vascular resistance in the inhaled group were significantly higher than in the intravenous group. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction in the inhaled milrinone group.

6.5. Prevention of pulmonary hypertension

There are three elements in the prevention of pulmonary hypertension: pharmacological treatment, non-pharmacological approaches and prevention of pulmonary hypertension induced by protamine.

6.5.1 Pharmacological approach

The prevention of pulmonary hypertension and its consequences is a promising strategy to prevent right ventricular failure. However, very few studies have addressed this issue. One of the potential targets could be the prevention of the pulmonary reperfusion syndrome. In that regard, our group has demonstrated in animal models that $iPGI_2$ [358] and inhaled milrinone [354] prevent pulmonary arterial endothelial dysfunction induced by CPB; similarly, ventilation during CPB could also reduce pulmonary arterial endothelial dysfunction. [359] Hache *et al.* [26] conducted a pilot RCT in patients with preoperative pulmonary hypertension and demonstrated that $iPGI_2$ given before CPB was superior to placebo in reducing post-bypass pulmonary hypertension. Furthermore, in patients who received $iPGI_2$, the amount of vasoactive support was reduced.

6.5.2 Protamine

The administration of protamine may be associated with severe pulmonary hypertension followed by right ventricular failure. This condition requires immediate treatment. In a study of coronary revascularization patients ($n = 3800$), Ocal *et al.* [164] compared two therapeutic approaches in the treatment of the protamine reaction observed in 68 patients (1.8%). One group received $iPGI_2$ and the other intravenous nitroglycerin (NTG) in addition to standard vasoactive agents. The $iPGI_2$ group showed improved hemodynamics and only 14 patients (39%) had to return on CPB compared to all 30 patients (100%) in the NTG group. A tendency for shorter length of stay in the intensive care unit and reduced mortality was observed in the $iPGI_2$ group, but the numbers were too small to be statistically significant. To avoid protamine reaction, heparinase, a heparin degrading enzyme, was compared in a multicentered randomized controlled trial that

included 167 patients. [315] However, the results of the trial were negative and heparinase was not associated with any reduction in the intervention to treat pulmonary hypertension or any reduction in bleeding.

6.5.3 Non-pharmacological approach

The selection of the appropriate type and size of aortic prosthetic valve is key . If the effective orifice area (EOA) of the aortic valve is too small compared to body size, creating a so-called patient-prosthesis mismatch (PPM), both the intraoperative and long-term mortality are increased. [118-125] Hence, anticipatory strategies aimed at preventing PPM, such as the implantation of a better performing prosthesis (e.g. new generation bileaflet mechanical valve, new generation supra-annular stented bioprosthetic valve) or the enlargement of the aortic root to accommodate a larger prosthesis, could contribute to the reduction of pulmonary hypertension after cardiac surgery and facilitate the separation from CPB. However, this issue remains controversial. [360] On the other hand, some of the alternative options that can be used to prevent PPM are complex and may increase the risk of difficult separation from CPB by prolonging the duration of the surgical procedure, and thus CPB time. As a consequence, in some cases, the drawbacks of using alternative procedures may overcome the benefits of avoiding PPM. It is therefore essential to establish accurate criteria to better assess the risk-benefit ratio with respect to the prevention of PPM. In order to avoid mitral valve PPM, one option is to repair rather than replace the mitral valve. However, mitral valve repair is not possible or feasible in a sizeable proportion of patients. In those patients in whom mitral valve replacement is needed, the surgeon has less option than for AVR, since it is not possible to enlarge the annulus. Hence, one option, which should be considered, is to select the prosthesis with the larger EOA. [128] Mitral valve PPM has also been hypothesized as a potential cause of postoperative pulmonary hypertension. [128] The prevention and impact of mitral valve PPM on surgical management remain unclear.

6.6 Research and development since the beginning of the PhD in 2006 at the MHI

Since 2006, we have been interested in determining the importance of pulmonary hypertension and right ventricular dysfunction in cardiac surgery. In addition to our retrospective analysis, pharmacological studies and randomized controlled trials exploring various strategies were performed.

6.6.1 Importance of pulmonary hypertension and right ventricular dysfunction

As shown in Figure 62, pulmonary hypertension measured before CPB and defined as the mean arterial to mean pulmonary artery ratio was found to be only independent hemodynamic predictor of a composite endpoint of postoperative hemodynamic complications defined as death, resuscitated cardiac arrest, new requirement for intra-aortic balloon pump and vasoactive support for 24 hours postoperatively in 1439 cardiac surgical patients. [10] The odds ratio was 1.3 (CI 1.1-1.5) In this study, the mean preoperative systolic pulmonary artery pressure was 31 ± 10 mmHg. Elevated systolic pulmonary artery pressure defined as > 30 mmHg was present in combined coronary revascularization and valve surgery ($n = 126$, 36 ± 13 mmHg), followed by mitral valve replacement ($n = 80$, 40 ± 14 mmHg), multiple valves surgeries ($n = 60$, 36 ± 16 mmHg) and heart transplantation ($n = 6$, 36 ± 14 mmHg). Only 16 patients experienced a more severe pulmonary hypertension, using a MAP/MPAP ratio < 2, and all experienced difficult separation from CPB, 3 of whom died (18.7% mortality) and half required vasoactive support for more than 24 hours after the procedure.

In a subsequent study, we observed however, that alteration of right ventricular function before CPB was even a stronger predictor of circulatory failure after CPB than pulmonary hypertension.[46] To further assess the value of right ventricular function in relation to pulmonary hypertension or other validated risk factors in valvular heart surgery,

we published our initial experience with 50 consecutive patients undergoing cardiac valvular surgery with pulmonary hypertension. A total of 17 patients (34%) developed circulatory failure defined as hypotension (systolic arterial pressure < 90 mm Hg) or low cardiac output (cardiac index < 2.0 L/min/m²) with evidence of end-organ dysfunction or hypoperfusion, such as lactic acidosis or acute renal failure defined as an increase of creatinine of at least 25% or urinary output less than 0.5 mL/kg/h for several hours. In this subgroup of patients, preoperative right ventricular dysfunction, measured by an abnormal myocardial performance index (RVMPI) (≥ 50%) or a decreased right ventricular fractional area change (RVFAC), was strongly associated with postoperative circulatory failure. The OR were 25.2 (95% CI 5.24-121.15) for RVMPI and 0.001 (95% CI of 0.001-0.727) for every 1% increase in RVFAC. These OR have been so far the highest observed in any study dealing with predictors of postoperative cardiac shock state.

6.6.2 Intravenous therapy

Several vasodilators can be used in the treatment and prevention of pulmonary hypertension. Two randomized controlled trial using nitroglycerine and milrinone will be described.

6.6.2.1 Intravenous nitroglycerin

The use of intravenous milrinone as a prevention tool against pulmonary hypertension has been the topic of Dr. Dominique Piquette for her thesis. [52] To determine whether or not intravenous nitroglycerin (IV NTG) can prevent a decrease in near-infrared spectroscopy (NIRS) values during CPB, she conducted a randomized, double-blind study in a tertiary academic center including 30 patients with a Parsonnet score ≥ 15 and scheduled for a high-risk cardiac surgery. The patients were randomized to receive either IV NTG (initial dose of 0.05 µg/kg/min, followed by 0.1 µg/kg/min) or placebo after induction of anesthesia and until the end of the CPB. The primary outcome was a decrease of 10% in NIRS values during CPB. Despite the absence of between-group differences in the mean cerebral oxygen saturation during CPB, there was a significant decrease in NIRS

values during the CPB in the placebo group, whereas mean NIRS values were maintained in the IV NTG group (-16.7% *vs*. 2.3% in the NTG group, $p = 0.019$). Major hemodynamic variables were similar at corresponding time periods in both groups, while patients in the IV NTG group had higher CK-MB values and experienced greater blood loss during the first 24 hrs postoperatively. The conclusion of this study was that IV NTG administration before and during CPB may prevent a decrease in NIRS values associated with CPB in high-risk cardiac surgery. However, further studies are warranted to determine the efficacy and risks associated with IV NTG infusion for this indication during CPB in high-risk patients. This study was useful in demonstrating the natural hemodynamic evolution in this population (Table 28). This study demonstrates that, in high-risk patients, there is an increase in right atrial pressure and systolic pulmonary artery pressure after CPB compared to the pre-CPB values.

Table 28 Hemodynamic values during surgery

Hemodynamic variables		T0	T1	T2	*P* value (group)	*P* value (time)	*P* value (group*time)
Systolic BP (mmHg)	Control	109 ± 16	101 ± 15	109 ± 20	0.41	0.053	0.95
	NTG	105 ± 21	95 ± 17	106 ± 15			
Heart rate (beats/min)	Control	53 ± 11	59 ± 11	70 ± 11	0.08	< 0.0001*	0.83
	NTG	55 ± 9	61 ± 15	78 ± 15			
RAP (mmHg)	Control	10 ± 3	10 ± 5	12 ± 5	0.03	0.01*	0.42
	NTG	13 ± 5	12 ± 6	17 ± 3			
Systolic PAP (mmHg)	Control	32 ± 6	32 ± 7	37 ± 8	0.004	0.0006*	0.16
	NTG	44 ± 18	37 ± 10	48 ± 10			
PCWP (mmHg)	Control	15 ± 4	15 ± 4	20 ± 4	0.35	0.06	0.77
	NTG	18 ± 7	15 ± 9	22 ± 3			
Indexed cardiac output (l/min/m^2)	Control	2.0 ± 0.3	1.9 ± 0.4	2.2 ± 0.4	0.70	0.0003*	0.43
	NTG	1.9 ± 0.4	1.9 ± 0.4	2.4 ± 0.8			

BP, blood pressure; NTG, nitroglycerin; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; T0, baseline value before nitroglycerin infusion; T1, beginning of cardiopulmonary bypass; T2, end of cardiopulmonary bypass times.* T0 and T1 are statistically different from T2. (With permission of Piquette *et al.* [52])

6.6.2.2 Intravenous milrinone

Our group recently published the results of the first randomized controlled trial of intravenous milrinone in patients with diastolic dysfunction undergoing coronary artery revascularization. [43] To evaluate the effect of milrinone on diastolic function, 50 patients undergoing coronary revascularization were randomized to receive a bolus and infusion of milrinone or placebo before CPB and until skin closure. Hemodynamic and transesophageal echocardiographic measurements of systolic and diastolic function were obtained. Pulsed wave Doppler measurements of the early (E wave) and atrial components (A wave) of the transmitral (TMF) and transtricuspid (TTF) flow, and systolic (S wave), diastolic (D wave) and atrial components (Ar) of the pulmonary (PVF) and hepatic venous blood flow (HVF) velocities were performed. Early and atrial components of the mitral (Em and Am waves) and tricuspid annulus velocities (Et and At waves) were assessed by tissue Doppler imaging (TDI). Assessment of diastolic dysfunction was graded from normal to severe using a scale score. The results were the following: cardiac index (CI) (2.8 ± 0.6 *vs*. 2.1 ± 0.5 L/min/m^2) ($P < 0.0001$) and heart rate (67 ± 8 *vs*. 60 ± 12 bpm) ($P < 0.05$) were higher in the milrinone group compared to placebo. There were no changes in left and right ventricular diastolic dysfunction scores between study groups. Higher PVF S wave, HVF S wave, TTF A wave and At measured by tissue Doppler imaging in the milrinone group compared with placebo suggested an improvement in ventricular systolic and atrial contraction. Thus, milrinone administered before CPB was not associated with improved biventricular diastolic function in patients undergoing coronary revascularization. Intravenous milrinone did not facilitate separation from CPB but was associated with more vasoactive drug requirement. This study was also useful in demonstrating the natural hemodynamic evolution in a lower risk population in terms of right ventricular echocardiographic changes after CPB (Table 29).

Table 29 Right ventricular echocardiographic data

Variable	Time	Milrinone (mean ± sd)	Placebo (mean ± sd)	Group x time interaction *P* value	Group *P* value*
Right ventricle					
RVFAC	Pre-bolus	0.42 ± 0.15	0.43 ± 0.12		
	Post-bolus	0.49 ± 0.13	0.45 ± 0.11	0.2102	0.1298
	Post-CPB	0.53 ± 0.11	0.45 ± 0.12		
RVD (cm)	Pre-bolus	3.50 ± 0.59	3.73 ± 0.72		
	Post-bolus	3.54 ± 0.66	3.82 ± 0.55	0.1842	0.0825
	Post-CPB	3.68 ± 0.43	3.83 ± 0.52		
RAD (cm)	Pre-bolus	4.64 ± 0.83	4.79 ± 0.82		
	Post-bolus	4.45 ± 0.77	5.01 ± 1.01	0.0860	0.0086
	Post-CPB	4.30 ± 0.59	5.17 ± 0.87		
TTF E wave (cm/sec)	Pre-bolus	35.88 ± 6.44	35.76 ± 12.31		
	Post-bolus	43.34 ± 12.78	35.61 ± 9.36	0.2590	0.2077
	Post-CPB	37.41 ± 8.68	35.64 ± 8.89		
TTF A wave (cm/sec)	Pre-bolus	28.34 ± 9.89	31.09 ± 14.33		0.6444
	Post-bolus	38.56 ±12.24	30.98 ± 10.02	0.0184	0.0314
	Post-CPB	42.24 ± 16.33	32.64 ± 9.17		0.0358
TTF E/A	Pre-bolus	1.42 ± 0.60	1.21 ± 0.30		
	Post-bolus	1.17 ± 0.29	1.19 ± 0.32	0.0629	0.7570
	Post-CPB	0.92 ± 0.37	1.22 ± 0.57		
HVF S wave (cm/s)	Pre-bolus	21.86 ± 7.98	22.64 ± 9.21		0.8432
	Post-bolus	33.75 ± 16.29	20.06 ± 7.89	0.0061	0.0026
	Post-CPB	19.40 ± 23.00	14.53 ± 17.68		0.6101
HVF D wave (cm/s)	Pre-bolus	13.55 ± 5.74	16.68 ± 7.78		
	Post-bolus	20.01 ± 10.62	19.19 ± 10.80	0.2946	0.8615
	Post-CPB	25.14 ± 9.38	22.51 ± 12.42		

CPB, cardiopulmonary bypass; HVF, hepatic venous flow; RVD, right ventricular dimension; RVFAC, right ventricular fractional area change; TTF, trans-tricuspid flow.

*overall group *p* value in case of a non-significant group x time interaction; group *p* value at given time point in case of a significant group x time interaction (With permission of Couture *et al.* [43])

In summary, both studies using intravenous agents were not successful in facilitating weaning from CPB. However, they confirmed the natural evolution of cardiac function in two different populations. In the nitroglycerin study, worsening of pulmonary hypertension was observed in both groups, and in the intravenous milrinone study, a deterioration in biventricular diastolic function was also observed.

6.6.3 Inhalation therapy: inhaled milrinone

In the following sections we will describe our initial work using inhaled milrinone through pharmacokinetic and pharmacodynamic studies, animal experiments and preliminary clinical observation in humans.

6.6.3.1 Pharmacokinetic and pharmacodynamic studies

In order to examine the pharmacokinetics of inhaled milrinone, Nguyen *et al.* developed an analytical assay and validated it for the quantification of milrinone concentrations in patients undergoing cardiac surgery. [361] A solid-phase extraction was optimized to isolate milrinone from a plasma matrix followed by high performance liquid chromatography (HPLC) using UV detection. Plasma samples (1 mL) were extracted using a C18 solid-phase cartridge. Milrinone was separated on a strong cation exchange analytical column maintained at 23.4°C. The mobile phase consisted of a gradient (10:90 to 45:55), 0.05 M phosphate buffer (pH 3):acetonitrile. Calibration curves were linear in the concentration range of 1.25–320 ng/mL. Mean drug recovery and accuracy were respectively $\geq$ 96% and $\geq$ 92%. Intra- and inter-day precisions (% coefficient of variation) were $\leq$ 6.7% and $\leq$ 7.9%, respectively. This method proved to be reliable, specific and accurate. Using different types of column for extraction and separation of milrinone proved to be a necessary step in order to achieve the sensitivity and specificity required when

milrinone is given by inhalation. The blood concentration of inhaled milrinone in a typical patient is shown in Figure 72.

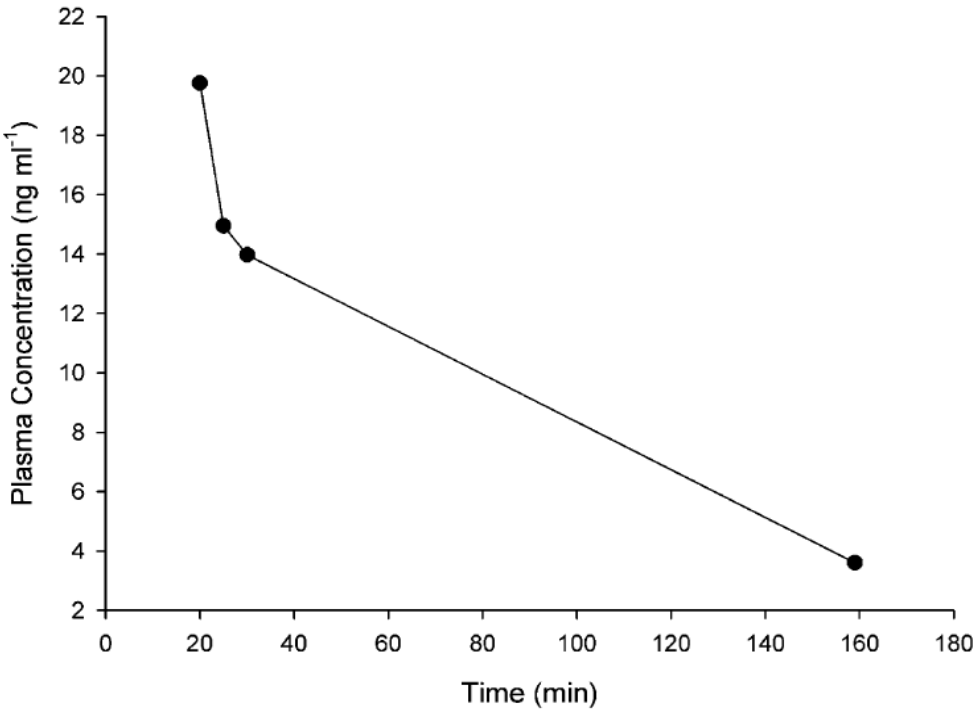

Figure 72 Milrinone plasma concentration–time profile

Plasma concentration of milrinone in a cardiac patient after inhalation of a 5 mg dose over 15 min. No blood samples were drawn during cardiopulmonary bypass (44–159 min). (With permission of Nguyen *et al.* [361])

6.6.3.2 Milrinone plasma concentration and the type of nebulizer

The first pilot study on the systemic exposure of inhaled milrinone administered before CPB in cardiac patients with pulmonary hypertension was performed by Nguyen *et al.* (presented at the 2008 Canadian Anesthesiology Society meeting in Halifax). Preliminary results were obtained in 12 patients randomized to receive milrinone either by a simple jet nebulizer or an ultrasonic nebulizer. At the end of a 15 min period of inhalation, plasma levels of milrinone were below 80 ng/mL. Figure 73 illustrates a

maximal milrinone concentration observed at the first sampling time followed by decreasing concentrations until weaning from CPB in both groups. For a same sampling time, plasma levels were almost twice lower after simple jet compared to ultrasonic inhalation.

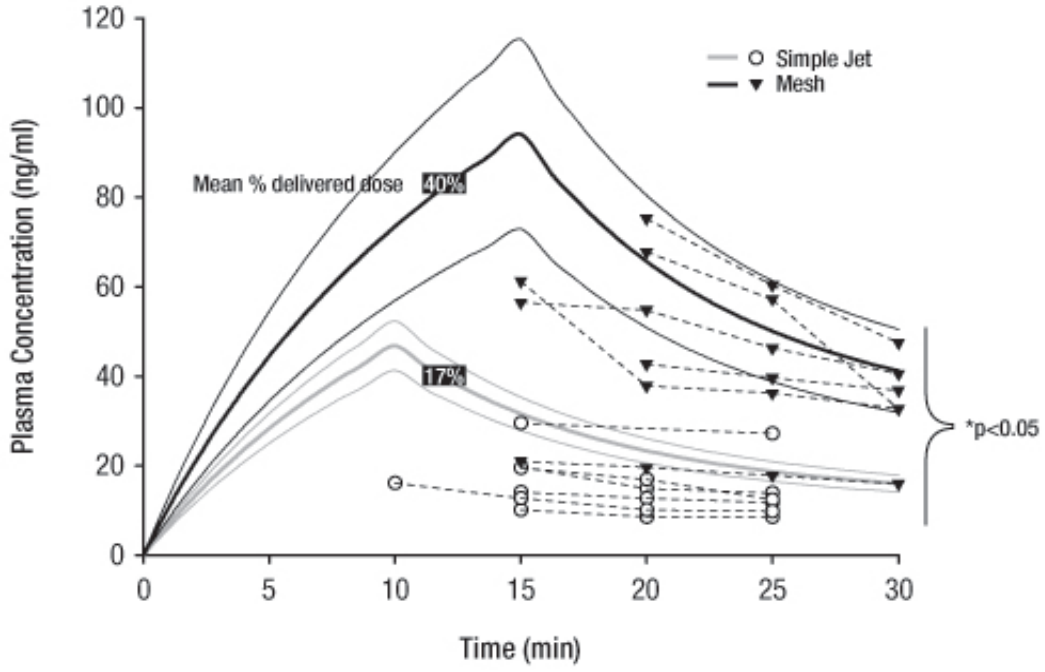

Figure 73 Milrinone plasma concentration during inhalation

Milrinone plasma concentration-time profile in 12 cardiac patients after inhalation of a 5 mg dose over 10 min (simple jet) or 15 min (mesh). Simulations were based on a two-compartment model using pharmacokinetic parameters reported after IV administration of milrinone with zero-order input, k_{01} = 0.33 ng/min (simple jet) or 0.50 ng/min (mesh), and were corrected for mean % of delivered dose including lower and upper bounds. (Courtesy of Nguyen *et al.*(submitted for publication))

Simulations based on pharmacokinetic parameters observed in cardiac patients after intravenous injection of milrinone [362] have been carried out and these levels corresponded to a bioavailability of 15 and 40%, respectively. Because in most patients the first sample was drawn 5 min after stopping inhalation, peak concentrations may have been underestimated. However, these concentrations remain significantly lower than those

measured after the intravenous administration of milrinone. In view of the reported low incidence of systemic hypotension associated with a 15 min inhalation, this technique may result in a better delivery to the lungs without necessarily increasing systemic availability. Indeed, pulmonary deposition of inhaled vasodilators (e.g. prostacyclin) has been shown to vary depending on the nebulizer's charge of droplets by less than 5 μm. [363] In addition, after dosing milrinone concentrations in the patient samples, we noticed that those who had received milrinone by ultrasonic nebulizer showed higher plasma levels than those who received milrinone by conventional nebulizer (Figure 73). Concentrations in both groups were below 100 ng/mL. Finally in order to determine a dose response after exploratory analyses, the maximum relative change in the MAP/MPAP ratios (Emax) was chosen as the pharmacodynamic marker. Milrinone plasma concentrations measured or interpolated) at the corresponding time were obtained for each patient. These times were 24.4 ± 6.2 min for the simple jet nebulizer and 20.7 ± 4.5 for the mesh nebulizer (p=0.276). A sigmoid Emax model was directly applied to describe the effect-plasma concentration relationship and yielded a correlation coefficient (r=0.6499; p=0.112) (Figure 74).

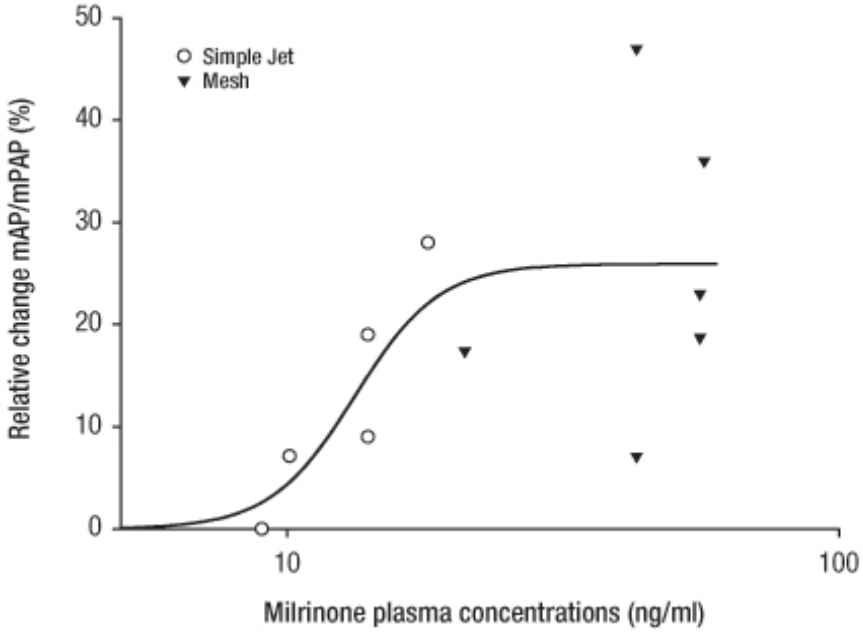

Figure 74 Pharmacokinetic/pharmacodynamic analysis of inhaled milrinone

Exploratory pharmacokinetic and pharmacodynamic analysis of inhaled milrinone in 11 patients with pulmonary hypertension before cardiopulmonary bypass. Courtesy of Nguyen *et al.*(submitted for publication)

6.6.3.3 Animal studies

Inhaled milrinone in an animal model: A porcine model of CPB has shown a reduction in pulmonary artery pressure without systemic hypotension in pigs submitted to inhaled milrinone before CPB. [354] In addition, prevention of the pulmonary reperfusion syndrome was observed.

6.6.3.4 Human studies

Preliminary experience in the use of inhaled milrinone involving 70 high-risk patients (Parsonnet score of 27 ± 14) was published by Lamarche *et al.* [53] Compared with a control group with similar baseline characteristics, we observed that the administration of inhaled milrinone prior to CPB ($n = 30$) was associated with no systemic hypotension, lower systolic pulmonary artery pressure and a lesser rate of difficult separation from CPB (9 *vs.* 1; $P = 0.021$). Further prospective and randomized studies will be required to determine the efficacy of this approach.

In summary, pulmonary hypertension is a very important variable in cardiac surgery due to its effect on right ventricular function, outcome and survival. Future studies on the impact, prevention and treatment of pulmonary hypertension on right ventricular function will provide definitive strategies to improve the care of cardiac surgical patients.

Chapitre 7 Manuscript #4

Foreword to Manuscript #4

This last study is the first randomized controlled trial to be conducted on the use of inhaled milrinone before CPB. It follows the description of the use of inhaled milrinone in animal models exposed to CPB [354], the publication of the preliminary experience on humans [53] and the validation of the pharmacokinetic measurements. [361] It also describes for the first time the evolution of biventricular function in patients with preoperative pulmonary hypertension and the effect of inhaled milrinone. This article will be submitted to the *European Journal of Cardiothoracic Surgery*.

Randomized Controlled Trial of Inhaled Milrinone in High-Risk Cardiac Surgical Patients

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Short title: Inhaled Milrinone in Cardiac Surgery

Brief Summary Statement

Inhaled milrinone administered through a randomized controlled trial in high-risk patients before valvular surgery is not associated with systemic hypotension, but with a reduction in pulmonary vascular resistance and prevention of the increase in right-sided ventricular dimensions.

ABSTRACT

Background: Pulmonary hypertension is a major cause of mortality and morbidity in patients undergoing valvular and complex heart surgery. Inhaled milrinone has been used for the treatment of pulmonary hypertension, but its safety and effects compared with a placebo on hemodynamics and ventricular function have not been studied in patients undergoing high-risk valvular surgery.

Methods: Twenty-one high-risk cardiac surgical patients with preoperative pulmonary hypertension were randomized in a double-blind study to receive inhaled milrinone or placebo. The inhalation occurred after the induction of anesthesia and before the surgical incision and cardiopulmonary bypass. The effects on ventricular function were evaluated by means of pulmonary artery catheterization and transesophageal echocardiography. The primary outcome variable was the systemic mean arterial pressure.

Results: There were 8 men and 13 women (mean age 71 ± 6 years) with a mean Parsonnet score of 32 ± 9 who underwent a total of 17 complex procedures and 6 reoperations. There were no significant changes in mean arterial pressure throughout the study. A reduction in pulmonary vascular resistance ($p = 0.0458$) was observed in the inhaled milrinone group, but the change in mean pulmonary artery pressure was not significant ($p = 0.1655$). Right ventricular end-diastolic area ($p = 0.0363$) and right atrial transverse diameter ($p < 0.0001$) increased in the control group, but not with inhaled milrinone. No significant side effects occurred in the inhaled milrinone group.

Conclusion: In this high-risk cardiac surgery cohort, the use of inhaled milrinone was not associated with systemic hypotension but with a reduced pulmonary vascular resistance and prevention of the increase in right-sided cavity dimensions.

Keywords: Cardiac surgery; Milrinone; Transesophageal echocardiography; Cardiopulmonary bypass; Outcome; Pulmonary hypertension.

Introduction

Pulmonary hypertension is a major cause of mortality and morbidity in patients undergoing cardiac surgery. [100] Several conditions increase the risk of developing perioperative pulmonary hypertension, including pre-existing pulmonary hypertension, mitral stenosis or regurgitation, left ventricular (LV) dysfunction pulmonary disease and cardiopulmonary bypass (CPB). [364] Studies have suggested that milrinone may be beneficial in the treatment of pulmonary hypertension in cardiac surgery. [311;313] However, intravenous milrinone can be associated with systemic hypotension, [43] increased vasoactive drug requirements, [365] morbidity [289] and mortality in ischemic cardiomyopathy. [295]

The use of the inhaled route for milrinone has been recently described in animal [354-357] and human studies. [53;350-353] As an alternative to inhaled nitric oxide and inhaled prostacyclin, inhaled milrinone (iMil) is also less expensive and does not require a complex set-up and monitoring of toxic metabolites. Furthermore, iMil is readily available in operating rooms and needs no special preparation, as opposed to inhaled prostacyclin. In addition, iMil before CPB has been shown to be superior to an intravenous administration in reducing the pulmonary reperfusion syndrome, [354] preventing pulmonary arterial endothelial dysfunction [356;357] and improving oxygenation in a porcine model. [354] Only two open-label studies described the use of iMil after cardiac surgery and in heart transplant candidates undergoing catheterization, [350;351] with no significant side effects.

However, in these studies, the timing of administration was constant, the effect on ventricular function using combined hemodynamic and echocardiographic monitoring not evaluated and the investigators were not blind to the effect of iMil. The primary hypothesis of our study was that the administration of milrinone through nebulization before CPB would not be associated with significant systemic hypotension. Our secondary hypothesis was that iMil administered before CPB is better than placebo in improving pulmonary hemodynamics and both LV and right ventricular (RV) function.

Methods

Study Population

After approval by our local research and ethics committees and with permission from Health Canada, informed consent was obtained from 22 patients with pulmonary hypertension undergoing cardiac surgery with CPB. Patients were considered to have pulmonary hypertension if the systolic pulmonary artery pressure (SPAP) was greater than 30 mmHg or the mean pulmonary artery pressure (MPAP) above 25 mmHg, as measured during the preoperative period or estimated by using Doppler echocardiography. This was confirmed after insertion of a pulmonary artery catheter and before induction of general anesthesia. Patients with severe LV dysfunction (LV ejection fraction of less than 30%) were excluded. Other exclusion criteria were the presence of contraindications to transesophageal echocardiography (TEE), including esophageal disease or unstable cervical spine.

Treatment Protocol

Patients were premedicated with 1 to 2 mg of lorazepam administered orally 1 hour before the operation, as well as 0.1 mg/kg of morphine administered intramuscularly before being taken to the operating room. Additional midazolam was administered (0.01-0.05 mg/kg intravenously) in the operating room as needed for patient comfort. Usual monitoring was installed, including a 5-lead electrocardiogram, pulse oximeter, peripheral venous line, radial arterial line, a 15-cm 3-lumen catheter (CS-12703, Arrow International Inc., Reading, CA), and thermodilution pulmonary artery catheter (Swan-Ganz catheter 7.5F; Baxter Healthcare Corporation, Irvine, CA). Anesthesia was induced with 0.04 mg/kg midazolam and 1 μg/kg sufentanil, and muscle relaxation was achieved with 0.1 mg/kg pancuronium. After tracheal intubation, anesthesia was maintained with 1 μg/kg/hr sufentanil and 0.04 mg/kg/hr midazolam. No anesthetic gases were used for the induction. Minute ventilation was adjusted to maintain end-tidal carbon dioxide between 30 and 40 mmHg with an infrared carbon dioxide analyzer. Transesophageal echocardiography (Vivid 7 imaging system, GE Healthcare, Amersham, Sweden) was performed after induction of

general anesthesia. Intravenous fluids (0.9% normal saline) were administered according to estimated insensible losses of 7 ml/kg/hr during the surgery and titrated according to blood pressure and central venous pressure (CVP). A decrease in mean arterial pressure (MAP) below 60 mmHg was treated by fluids administration in the presence of a low CVP or by the use of vasopressors according to a predetermined protocol (Appendix 3). [52] In case of low cardiac output CO with reduced contractility documented using TEE, the anesthesiologist could use intravenous milrinone at his discretion. Postoperative management in case of pulmonary hypertension included intravenous nitroglycerin and milrinone and, in more severe cases, inhaled nitric oxide or inhaled prostacyclin. During CPB, blood cardioplegia was used in all patients. Induction and maintenance of cardioplegia were cold to tepid (15 to 29º Celsius). The blood to crystalloid ratio was 4:1. The pump flow was adjusted to obtain an output of 2.2 L/min/m^2 of body surface area. The pump flow was reduced to 0.5 L/min for aortic clamping and unclamping. The pumps used for all patients were SIII (Stockert, Munchen, Germany) roller pumps and the oxygenators were Sorin Monolyth (Mirandola, MO, Italy). For coronary artery bypass procedures, temperature was allowed to drift to 34ºC. Valve and complex procedures were done with temperatures of 32-34ºC. Selective antegrade and retrograde cerebral perfusion were used on a case by case basis. Weaning from CPB was attempted after systemic temperature (central and vesical) was > 36ºC using a predetermined protocol (Appendix 3). [52]

Drug Administration Protocol

Randomization was done according to a list of computerized random numbers generated by the Montreal Heart Institute Coordinating Center and assignment to study treatment was directly transmitted to the pharmacist the day before the surgery. The investigator had no access to the randomization list. The study drug was prepared by the pharmacist and delivered to the operating room wrapped up in an opaque paper to maintain blinding. Patients were equally divided into 2 groups to receive either iMil or placebo in a double-blind randomized manner. Inhaled milrinone (Primacor, Sanofi-Synthelabo Canada Inc., Markham, ON, Canada) or the placebo (0.9% saline) were administered through the

endotracheal tube after the induction of anesthesia once baseline hemodynamic profiles and TEE exam were completed. [53] Five milligrams (1 mg/mL) were administered, resulting in a dose ranging from 50-80 μg/kg, over 5 minutes. The study drug and the placebo were administered through a jet nebulizer (Ref 8901; Salter Labs, Arvin, CA) attached to the inspiratory limb of the ventilator near the endotracheal tube with a bypass flow of oxygen at 10 L/min, as previously described. [53]

Data Collection

At the time of randomization, demographic, diagnostic (New York Heart Association (NYHA) class, Parsonnet score, comorbidities, LV ejection fraction) and therapeutic (medication, type of surgery, reoperations) information was obtained for every patient. Complex surgery was defined as a combination of valve or aortic surgery and coronary procedure or reoperative surgery. Hemodynamic values were indexed for patient body surface area and obtained in the awake state before induction of anesthesia to confirm the presence of pulmonary hypertension, after induction of anesthesia (baseline or T1), at the end of nebulization (T2), 20 minutes after the end of nebulization before CPB (T3) and after CPB during chest closure (T4). The measured hemodynamic parameters included heart rate (HR), systemic arterial pressure (SAP), MAP, CVP, pulmonary capillary wedge pressure (PCWP), SPAP, MPAP and diastolic pulmonary artery pressure (DPAP). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) was calculated using the standard formula. Cardiac output was assessed by using the thermodilution technique with 3 injections of room temperature dextrose 5% (10 mL) at end-expiration. All TEE were performed by 2 anesthesiologists with more than 15 years of experience and with National Board Certification. All TEE exams were reviewed offline by a cardiologist expert in echocardiography who was blinded to the allocation group. The exam was obtained after induction (T1), at the end of nebulization (T2), before CPB (T3) and after CPB (T4). The TEE examination included a mid-esophageal, 4-chamber view, a short-axis transgastric view at the mid-papillary level, and color flow Doppler imaging of all the valves to detect any unsuspected significant valvular disease. All 2-dimensional images in which the LV

and RV endocardial border could not be traced adequately by using Schnittger criteria [271] were excluded. The RV function was evaluated using the 4-chamber view according to published guidelines. [186] The following measures were also obtained from the 4-chamber view: the maximal transverse dimensions of the right atrium (RADt) and left atrium (LADt), the right ventricular end-diastolic area (RVEDA), right ventricular end-systolic area (RVESA), the RV fractional area change (RVFAC) in % calculated as (RVEDA-RVESA)/RVEDA and the tricuspid systolic annular plane excursion (TAPSE). The LV function was evaluated using the 4-chamber view and the transgastric short-axis view. LV end-diastolic area (LVEDA), LV end-systolic area (LVESA) and the LV fractional area change (LVFAC) in % calculated as (LVEDA - LVESA)/LVEDA were obtained from both views. Measures were averaged over three consecutive cycles and standardized to end-expiration. The inter-observer variability for area measurements was 2.9 ± 2.0% (absolute difference) with an intra-class correlation coefficient of 0.95.

Outcome Measures

The primary outcome measure was the change in MAP. Secondary outcomes were the changes in MPAP, PVR and PVR/SVR reduction, RV and LV areas. We were also interested in exploring the impact of iMil on weaning from CPB support, vasopressors use > 24 hours, postoperative atrial fibrillation, intensive care unit and hospital stays and mortality. Difficult separation from bypass was defined as SAP < 80 mmHg, confirmed by central measurement (femoral or aortic); DPAP or PCWP > 15 mmHg during progressive weaning from CPB; and the use of inotropic or vasopressive support (norepinephrine > 4 µg/min, epinephrine > 2 µg/min, dobutamine > 2 µg/kg/min) for at least 1 hour, intra-aortic balloon pump requirement or reinitiation of CPB. [19;53]

Statistical Analysis

Patient characteristics were expressed as mean ± standard error (SE) or simple frequencies and percentages. Comparisons of continuous variables between groups were performed with the Student *t*-test for normally distributed variables (original or after

appropriate transformations) or with the Wilcoxon test for non-normally distributed variables. Due to very low power, categorical variables were not compared between or within groups. One-way analysis of variance (ANOVA) on repeated measurements were used to study variations over time within each groups. Two-way analysis of co-variance (ANCOVA) adjusted for baseline values (T1) were used to compare groups at T2, T3 and T4. Sample size was calculated for a power of 80% and a 1-sided α error value of 0.05. Assuming a MAP of 75 mmHg in the placebo group, a common standard deviation of 13 mmHg, 11 patients per group would be sufficient to detect a 15 mmHg reduction in MAP in the iMil group. Statistical analyses were done with the computer software SAS version 9.1 (SAS Institute Inc., Cary, NC). A P value < 0.05 was considered statistically significant.

Results

A total of 22 patients were recruited. One patient was excluded because the pulmonary artery catheter did not confirm the presence of pulmonary hypertension; therefore, a total of 10 controls and 11 iMil were studied. Patients' characteristics for each group are listed in Table 30. For all patients, the mean age was 71 ± 6 years and there were 8 men and 13 women with a mean Parsonnet score of 32 ± 9. A total of 17 complex procedures and 6 reoperations were performed. Among the complex procedures there were 4 multiple valve procedures: 11 were complex surgeries, one was mitral valve replacements (MVR) with atrial septal defect (ASD) closure and the other mitral valve repair with ASD closure and myomectomy. The ASD were secondary to iatrogenic septal perforation from preoperative right-sided catheterization. The pre-induction hemodynamic variables (not shown) were similar between the groups for the HR, SAP, MAP, CVP, PCWP and CO. Before the induction of anesthesia, the SPAP (66 ± 20 *vs*. 46 ± 13 mmHg, $p = 0.0121$) and MPAP (45.5 ± 12 *vs*. 33 ± 8 mmHg, $p = 0.0047$) were higher in the iMil group compared to the control group.

Within Groups Comparison

Hemodynamic Measurements

Hemodynamic evolutions are shown in

Table 31 for the control and iMil separately. There were no changes over time for MAP in the iMil group ($p = 0.3781$) and in the control group ($p = 0.9478$). In patients receiving iMil, there were changes over time for HR ($p = 0.0174$) and SVR ($p = 0.0465$). Multiple comparisons (details at the bottom of

Table 31 showed HR increases at T3 and T4 and SVR decreases at T3 and T4 as compared to T1 and/or T2 in the iMil group. Changes over time were observed for SPAP in the control group ($p = 0.0147$) and there was a significant decrease at T3. Changes over time were observed for PVR in both groups (iMil: $p = 0.0458$; control: $p = 0.0376$); there was a decrease at T4 *vs*. T2 in the iMil group and increase at T2 and T3 *vs*. T1 in the control group. Finally, changes over time were observed in the control group for CVP ($p = 0.0157$) and for CO ($p < 0.0001$) and according to multiple comparisons, increases were observed at T4 *vs*. T2 for both variables (Figure 75).

Echocardiographic Measurements

Sequential echocardiographic changes are shown in

Table 32 for the control and iMil groups separately. A total of 66 (83%) 4-chamber views for RV area were analyzed; 58 (73%) 4-chamber views and 49 (61%) transgastric views were used for LV area measurements. No changes over time were observed in the iMil group. However, changes over time were observed in the control group for RVEDA ($p = 0.0363$), RADt ($p < 0.0001$) and TAPSE ($p = 0.0167$). Multiple comparisons showed that increases were observed at T3 and T4 *vs*. T1 and T2 for RVEDA, that an increase was observed at T4 *vs*. T1 and T3 for RADt and that decreases for TAPSE were observed at T2 and T4 *vs*. T1 (Figure 75).

Between Groups Comparison

Between group comparisons are depicted in Table 33 where only variables with significant differences are presented.

Hemodynamic Measurements

Groups were similar at T2 for all variables. However at T3, the means of the iMil group were higher for PCWP ($p = 0.0182$) and DPAP ($p = 0.0479$) and lower for PVR/SVR ($p = 0.0043$) as compared to the placebo group, but all of these differences vanished at T4. The only significant result at T4 was for CO, which had a lower mean in the iMil group ($p = 0.0445$).

Echocardiographic Measurements

As depicted in Table 33, the RVEDA and RVESA were different between groups. While the RVEDA mean was lower in the iMil group at T4 ($p = 0.0023$), the RVESA mean was higher in the iMil group at T2 ($p = 0.0361$). Also at T2, the means of the iMil group were higher for RADt ($p = 0.0367$) and lower for RVFAC ($p = 0.0366$). Finally, the only significant result at T3 was for LVESA with a higher mean in the iMil group ($p = 0.0106$).

The outcome and safety data are presented in Table 34. Because of the small number of patients, no statistical analysis was performed. The iMil group required less intravenous milrinone (18% *vs*. 40%), no adrenaline after CPB and no intra-aortic balloon pump. One death occurred in the iMil group and two in the control group. The need for vasopressors for more than 24 hours, the prevalence of atrial fibrillation, the ICU and hospital stay durations were similar. An example of the effect of milrinone on two patients is illustrated in Figure 76. The biventricular hemodynamic and echocardiographic observations are summarized in Figure 77.

Discussion

This is the first randomized controlled double-blind trial on the use and safety of iMil in cardiac surgery in which both simultaneous hemodynamic and echocardiographic measurements were obtained. The administration of iMil in this high-risk population was not associated with any significant systemic hypotension compared to the control group. Furthermore, compared with a control group, we observed in the iMil group a modest reduction in the hemodynamic severity of pulmonary hypertension with unaltered ventricular dimensions consistent with a reduction or prevention of the increase in RV afterload. These hemodynamic effects of iMil are consistent with previous observations in animal [354;355] and human studies. [53;350;351]

In our patients, before induction and at baseline, the iMil group had much more severe pulmonary hypertension with associated increased right-sided dimensions. Despite this unfavorable condition, no significant systemic hypotension was observed; only 2 patients (18%) required inotropes, and none returned on CPB or needed IABP to be weaned from CPB. Furthermore, reduction in right-sided chambers with reciprocal increase in LV dimensions appeared in the iMil group when compared to the control group. These changes could be explained by a reduction in RV afterload by iMil, leading to an increase in pulmonary flow. This would explain the maintenance of LV filling pressure (higher PCWP and DPAP) at 20 minutes after nebulization.

Milrinone is a cyclic AMP-specific phosphodiestersase inhibitor that can exert both positive inotropic effects and vasodilation independently of $ß_1$-adrenergic receptor stimulation in the cardiovascular system. [41;319] Previous studies evaluating the use of intravenous milrinone in cardiac surgical patients were underpowered and performed on a small number of patients undergoing coronary revascularization. [348] Although milrinone has been shown to increase CO [322;324;334] and to facilitate separation from CPB, [321] the major problem encountered with intravenous milrinone is the high incidence of systemic hypotension resulting in an increased need for vasoactive drugs. [66;311;324;342] The hypotension resulting from intravenous milrinone is either caused by vasodilation or through dynamic left or right ventricular outflow tract obstruction. [38] Two randomized

controlled trials on the use of milrinone in a non-cardiac surgical setting showed no advantage in terms of hospitalization duration. [289;294] Furthermore, patients receiving milrinone had more adverse events and higher mortality in the PROMISE trial. [294] So far, randomized controlled trials in cardiac surgery have not been designed, or sufficiently powered, to correlate mortality with intravenous milrinone, but the same issue could be encountered. Therefore, it appears relevant to explore alternative strategies such as iMil, which could reduce the severity of pulmonary hypertension without causing systemic hypotension. However, the first step was to document the absence of significant systemic hypotension in patients receiving iMil.

Only four observational studies addressing the role of iMil in cardiac surgery have been published so far. [53;350;351;353] The effect of iMil was first described by Haraldsson *et al.* [350] in an open-label trial of 20 cardiac surgical patients in the intensive care unit. The first part of the trial included 9 patients and showed a dose-response effect of incremental concentrations of iMil with decreases in MPAP, PVR and PVR/SVR. No patient presented systemic hypotension. The hemodynamic parameters of patients treated with iMil returned to baseline within 20 minutes of the end of the inhalation period, similar to our observation. In the second study, [351] iMil was given to 18 heart transplant candidates in the intensive care unit. The MPAP, transpulmonary gradient and PVR decreased only in patients with pulmonary hypertension, defined as MPAP above 30 mmHg. Improvement in CO was observed, but there was no systemic hypotension. The dosage was 2 mg based on intravenous milrinone loading doses used in heart transplantation, which was almost half of the dose used in our protocol. In these studies, there was no control group, and the intraoperative usage and the timing of iMil in relation to CPB were not recorded. We have previously described the administration of iMil before CPB in 40 high-risk patients with a Parsonnet score of 30.4 ± 14.2. [53] Compared to the administration of iMil after CPB, pre-CPB iMil was associated with a reduction of difficult separation from CPB (18% *vs*. 82%) defined as the use of more than two inotropes, need for introduction of an intra-aortic balloon pump or reinitiation of CPB. Finally a recent study compared the use of intravenous versus inhaled milrinone in 48 patients with

pulmonary hypertension after mitral valve surgery. [353] With milrinone administration, mean pulmonary artery pressure and pulmonary vascular resistance decreased in both groups. However, the mean arterial pressure and systemic vascular resistance in the inhaled group were significantly higher than in the intravenous group. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction in the inhaled milrinone group.

In the current study, the same ratio was observed; 4 patients in the control group compared to 1 in the iMil group would have qualified for this definition. Significantly lower SPAP and unchanged LV function were also observed after CPB in the group who received iMil pre-CPB, as observed in the current study, but RV function was not analyzed. Finally a recent study compared the use of intravenous versus inhaled milrinone in 48 patients with pulmonary hypertension after mitral valve surgery. [353] With milrinone administration, mean pulmonary artery pressure and pulmonary vascular resistance decreased in both groups. However, the mean arterial pressure and systemic vascular resistance in the inhaled group were significantly higher than in the intravenous group. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction in the inhaled milrinone group.

Administration of iMil before CPB could be advantageous for several reasons. First, iMil could protect the pulmonary vasculature during weaning from CPB when ischemia-reperfusion injury occurs through a more uniform distribution and penetration in mechanically ventilated lungs free of significant post-CPB atelectasis. [354] This may explain why patients receiving iMil before CPB were found to have lower or similar MPAP after separation from CPB. [53] These findings were not observed when intravenous milrinone [354] was administered or when the administration of the drug occurred after CPB. [53] Secondly, the administration of iMil before CPB could prevent the reperfusion syndrome. [297]

Limitations

There are several study limitations that need to be addressed. There is a small number of patients. It was important for us to determine the safety of iMil given intraoperatively in patients under general anesthesia because it had not been studied in this context previously. Before the induction and at baseline before drug administration, the iMil patients had more severe pulmonary hypertension. Therefore, after presenting the observed values and performing the same analysis as originally published by Haraldsson and Sablotzki, [350;351] we compared both groups using two-way ANCOVA with adjusted values. Despite the small number of patients, we observed differences in PVR/SVR and RV dimensions between the groups consistent with a RV afterload effect of iMil. The absolute effect of iMil on the severity of pulmonary hypertension was modest but similar to that described in previous observational studies. [350;351] The number of patients was too small to explore other significant outcomes such as length of intensive care unit stay, hospitalization duration and mortality. However, this study was the necessary step to confirm our animal and preliminary human observations and the safety of this new strategy. Finally, systemic exposition to milrinone was not documented in these patients. We have previously reported that milrinone concentration obtained in cardiac patients having the same characteristics are below 30 ng/mL when milrinone is given by inhalation. [361] Milrinone levels below 100 ng/mL are not likely to induce significant systemic hypotension in cardiac patients. [366]

Conclusion

In summary, the administration of iMil before initiation of CPB is not associated with any significant systemic hypotension. In patients receiving iMil, we observed a mild reduction in the severity of pulmonary hypertension with improved right-sided cavity dimensions compared to the control group. Further studies with larger numbers of patients are required to document the potential benefit of this approach in the care of cardiac surgical patients with pulmonary hypertension.

Table 30 Baseline Characteristics of the Study Population

Characteristics	**Control (*n* = 10)**	**Inhaled Milrinone (*n* = 11)**
Age (yrs)	71 ± 1	70 ± 3
Sex		
Male	3 (30%)	5 (45%)
BMI (kg/m^2)	27 ± 2	26 ± 1
NYHA class		
1	0	0
2	2 (20%)	0
3	8 (80%)	10 (91%)
4	0	1 (9%)
Parsonnet score	32 ± 3	32 ± 3
Current smoking	2 (20%)	0
Type of surgery		
Isolated valve	4 (40%)	0
Multiple valves	0	4 (36%)
Complex	5 (50%)	6 (54%)
Other	1 (10%)	1 (9%)
Reoperation**s**	2 (20%)	4 (36%)
Cardiac disease		
Prior myocardial infarction	1 (10%)	2 (18%)
Congestive heart failure	8 (80%)	9 (82%)
Comorbidities		
Hypertension	7 (70%)	7 (64%)
Diabetes mellitus	4 (40%)	5 (45%)
Peripheral vascular disease	5 (50%)	0
Renal failure	3 (30%)	3 (27%)
COPD	3 (30%)	2 (18%)
Coronary artery disease	6 (60%)	4 (36%)

Characteristics	**Control (*n* = 10)**	**Inhaled Milrinone (*n* = 11)**
Drug therapy at admission		
Coumadin	4 (40%)	5 (45%)
Heparin	2 (20%)	1 (9%)
Nitrates	0	1 (9%)
Calcium-channel antagonists	2 (20%)	2 (18%)
Beta-blockers	7 (70%)	5 (45%)
ACE inhibitors	4 (40%)	4 (36%)
Digoxin	3 (30%)	2 (18%)
Diuretics	6 (60%)	3 (27%)
Salicylates	3 (30%)	4 (36%)
Statins	7 (70%)	4 (36%)
Left ventricular ejection fraction (%)	55 (50-60)*	58 (40-65)*
Duration of surgery (min)		
CPB	119 ± 13	123 ± 7
Aorta clamping	88 ± 10	97 ± 9

ASD, atrial septal defect; AVR, aortic valve replacement; ACE, angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; COPD, chronic obstructive pulmonary disease; MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; TV, tricuspid valve. *1st and 3rd interquartile range.

Table 31 Hemodynamic variables: one-way repeated ANOVA

Variables*	**Group**	**T1 (Baseline)**	**T2 (End Nebulization)**	**T3 (20 minutes)**	**T4 (After CPB)**	***P* value**
HR (beats/min)	Control	70.2 ± 4.4	67.5 ± 4.0	64.6 ± 3.1	77.3 ± 3.6	0.1035
	Inhaled Milrinone	63.9 ± 3.6	59.3 ± 3.6	65.6 ± 4.3	72.1 ± 2.4	0.0174[1]
SAP (mmHg)	Control	109.1 ± 7.5	109.8 ± 5.7	106.2 ± 2.2	111.3 ± 4.8	0.8375
	Inhaled Milrinone	114.3 ± 3.7	105.5 ± 9.0	106.2 ± 5.8	105.4 ± 5.6	0.2976
MAP (mmHg)	Control	73.4 ± 4.1	74.2 ± 3.4	71.9 ± 3.4	71.9 ± 2.8	0.9478
	Inhaled Milrinone	78.7 ± 4.3	75.2 ± 3.9	71.6 ± 4.0	72.4 ± 3.9	0.3781
CVP (mm Hg)	Control	10.1 ± 0.7	11.0 ± 1.2	10.9 ± 1.2	14.2 ± 2.0	0.0157[2]
	Inhaled Milrinone	12.7 ± 1.4	11.3 ± 1.6	13.0 ± 1.6	14.7 ± 1.6	0.2757
PCWP (mmHg)	Control	21.9 ± 1.6	20.3 ± 1.3	15.8 ± 1.7	21.5 ± 2.0	0.0632
	Inhaled Milrinone	24.2 ± 3.0	24.1 ± 2.1	23.5 ± 2.2	24.1 ± 2.8	0.8942
SPAP (mmHg)	Control	37.2 ± 3.6	39.4 ± 2.9	36.5 ± 3.0	39.3 ± 4.9	0.0147[3]
	Inhaled Milrinone	54.6 ± 7.0	49.6 ± 4.8	50.2 ± 7.8	47.0 ± 4.2	0.1338
DPAP (mmHg)	Control	20.7 ± 1.8	21.7 ± 1.6	19.5 ± 1.3	22.0 ± 2.5	0.0207[4]
	Inhaled Milrinone	26.2 ± 1.9	24.9 ± 1.7	26.0 ± 2.4	28.6 ± 4.7	0.5694
MPAP (mmHg)	Control	27.7 ± 2.5	29.3 ± 2.1	27.8 ± 2.3	29.1 ± 3.4	0.3788
	Inhaled Milrinone	38.1 ± 3.9	34.7 ± 3.0	36.1 ± 4.5	33.9 ± 2.3	0.1655

Variables*	Group	T1 (Baseline)	T2 (End Nebulization)	T3 (20 minutes)	T4 (After CPB)	*P* value
CO (L/min)	Control	3.1 ± 0.3	3.3 ± 0.3	3.0 ± 0.3	4.6 ± 0.3	<0.0001[5]
	Inhaled Milrinone	3.5 ± 0.3	3.5 ± 0.3	3.7 ± 0.3	3.8 ± 0.1	0.1150
SVR (dynes.sec.cm^{-5})	Control	1737.7 ± 170.9	1733.1 ± 181.3	1836.3 ± 249.6	1064.1 ± 80.0	0.0542
	Inhaled Milrinone	1647.5 ± 176.5	1541.4 ± 181.7	1347.8 ± 134.7	1106.4 ± 80.8	0.0465[6]
PVR (dynes.sec.cm^{-5})	Control	149.4 ± 26.7	216.9 ± 30.7	295.3 ± 41.7	134.0 ± 35.4	0.0376[7]
	Inhaled Milrinone	326.0 ± 35.0	265.1 ± 30.6	253.6 ± 45.5	164.8 ± 25.9	0.0458[8]
PVR/SVR (%)	Control	9.1 ± 1.3	12.9 ± 2.8	16.7 ± 2.2	11.6 ± 2.7	0.1292
	Inhaled Milrinone	20.7 ± 1.6	18.9 ± 3.1	20.9 ± 4.2	15.4 ± 2.4	0.2585

*Variables expressed as adjusted mean ± standard error. T1: baseline after induction of anesthesia, T2: at the end of nebulization, T3: 20 minutes after nebulization before cardiopulmonary bypass (CPB), T4: during chest closure after CPB.

ANOVA, analysis of variance; HR, Heart rate; SAP, systemdic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SPAP, systolic pulmonary arterial pressure; PAP, diastolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

[1]HR increase in the milrinone group in T4 compared to T1 and T2 and in T3 compared withT2

[2]CVP in the control group became higher at T4 compared to T2

[3]SPAP in the control group lower at T3 compared to T2; [4]DPAP in the control group lower at T3 compared to T2

[5]CO in the control group lower at T3 compared to T2 and higher at T4 compared with T1,T2,T3

[6]SVR decrease in the milrinone group at T3 compared to T1 and T4 compared to T1 and T2

[7]PVR in the control group increase at T2 and T3 compared with T1 and decrease at T4 compared with T3

[8]PVR in the milrinone group became lower at T4 compared to T2

Table 32 Echocardiographic variables: one-way repeated ANOVA

Variables*	**Group**	**T1 (Baseline)**	**T2 (End Nebulization)**	**T3 (20 minutes)**	**T4 (After CPB)**	***P* value**
RVEDA (cm^2)	Control	14.1 ± 1.1	12.7 ± 1.5	17.2 ± 1.6	16.2 ± 1.1	0.0363[1]
	Inhaled Milrinone	18.3 ± 1.2	17.7± 1.3	16.2 ± 1.4	16.1 ± 1.3	0.1937
LVEDA_4ch (cm^2)	Control	30.0 ± 2.9	28.1 ± 3.0	31.6 ± 3.6	32.5 ± 3.1	0.3910
	Inhaled Milrinone	32.6 ± 2.3	32.1 ± 2.6	27.6 ± 3.2	29.0 ± 2.5	0.3218
RVESA (cm^2)	Control	7.8 ± 0.9	6.8 ± 0.9	8.5 ± 1.0	9.5 ± 0.9	0.1720
	Inhaled Milrinone	10.2 ± 1.1	10.7 ± 1.2	8.5 ± 1.3	9.3 ± 1.2	0.2365
LVESA_4ch (cm^2)	Control	19.0 ± 1.8	17.1 ± 1.9	20.0 ± 2.4	20.3 ± 2.0	0.3383
	Inhaled Milrinone	20.5 ± 2.0	20.1 ± 2.3	17.6 ± 2.9	18.5 ± 2.2	0.7381
RADt (cm)	Control	4.0 ± 0.2	4.2 ± 0.3	3.9 ± 0.2	4.4 ± 0.2	< 0.0001[2]
	Inhaled Milrinone	4.1 ± 0.3	4.4 ± 0.3	3.5 ± 0.4	4.1 ± 0.2	0.3569
LADt (cm)	Control	4.9 ± 0.3	4.8 ± 0.3	4.6 ± 0.3	4.9 ± 0.3	0.4471
	Inhaled Milrinone	5.2 ± 0.5	4.8 ± 0.5	5.0 ± 0.6	5.3 ± 0.5	0.6304
LVEDA_sax (cm^2)	Control	20.6 ± 2.3	18.5 ± 2.6	17.7 ± 2.7	18.4 ± 2.4	0.3790
	Inhaled Milrinone	23.8 ± 3.2	23.6 ± 3.2	22.6 ± 3.2	21.8 ± 3.0	0.6409
LVESA_sax (cm^2)	Control	11.8 ± 2.0	10.7 ± 2.1	10.6 ± 2.2	12.1 ± 2.0	0.5851
	Inhaled Milrinone	13.6 ± 2.8	13.0 ± 2.8	13.1 ± 2.8	13.6 ± 2.8	0.8630

Variables*	Group	T1 (Baseline)	T2 (End Nebulization)	T3 (20 minutes)	T4 (After CPB)	*P* value
Calculated values						
RVFAC (%)	Control	45.6 ± 2.4	49.5 ± 3.1	50.8 ± 3.6	41.2 ± 4.0	0.2408
	Inhaled milrinone	45.7 ± 3.1	40.3 ± 3.3	48.2 ± 3.9	43.5 ± 3.3	0.1742
LVFAC_4ch (%)	Control	36.8 ± 2.5	37.4 ± 2.6	35.8 ± 3.7	36.4 ± 2.8	0.9873
	Inhaled Milrinone	39.1 ± 3.1	37.4 ± 3.6	37.0 ± 4.7	36.9 ± 3.4	0.9379
TAPSE (cm^2)	Control	2.0 ± 0.2	1.4 ± 0.2	1.9 ± 0.3	1.4 ± 0.2	0.0167[3]
	Inhaled Milrinone	1.8 ± 0.2	1.6 ± 0.2	1.7 ± 0.3	1.5 ± 0.2	0.6951
LVFAC_sax (%)	Control	44.5 ± 4.7	45.8 ± 5.6	40.2 ± 6.0	38.4 ± 5.0	0.4371
	Inhaled Milrinone	45.4 ± 5.6	46.5 ± 5.6	46.5 ± 5.6	42.0 ± 4.9	0.6369

*Variables expressed as adjusted mean ± standard error. T1: after induction of anesthesia, T2: at the end of nebulization, T3: 20 minutes after nebulization before cardiopulmonary bypass (CPB), T4: during chest closure after CPB. ANOVA, analysis of variance; RVEDA, right ventricular end-diastolic area; LVEDA_4ch, left ventricular end-diastolic area obtained from a 4-chamber view; RVESA, right ventricular end-systolic area; LVESA_4ch, left ventricular end-systolic area obtained from a 4-chamber view; RADt, right atrial transverse diameter; LADt, left atrial transverse diameter; LVEDA_sax, left ventricular end-diastolic area obtained from short-axis view; LVESA_sax, left ventricular end-systolic area obtained from a short axis view; RVFAC, right ventricular fractional area change; LVFAC_4ch, left ventricular fractional area change obtained from a 4-chamber view; TAPSE, tricuspid annular systolic plane excursion.

[1]RVEDA in the control group increases at T3 ($p = 0.0199$) and T4 ($p = 0.0355$) compared to T1 and RVEDA became larger at T3 ($p = 0.0145$) and T4 ($p = 0.0257$) compared to T2

[2]RADt in the control group increases at T4 compared to T1 ($p = 0.0362$) and T3 ($p = 0.0016$)

[3]TAPSE in the control group was reduced at T2 compared to T1 ($p = 0.0072$) and T4 compared to T1 ($p = 0.0139$).

Table 33 One-way ANCOVA adjusted for T1 at separate time interval

Variables*	Group	T2 (End Nebulization)	*P* value	T3 (20 minutes)	*P* value	T4 (After CPB)	*P* value
Hemodynamic							
PCWP (mmHg)	Control	20.5 ± 1.5	0.2539	16.6 ± 1.8	0.0182	22.3 ± 1.7	0.6198
	Inhaled milrinone	22.8 ± 1.3		22.7 ± 1.3		23.5 ± 1.6	
DPAP	Control	24 ± 1.0	0.4636	21 ± 0.9	0.0479[1]	26.7 ± 3.0	0.8447
	Inhaled milrinone	23.0 ± 0.97		23 ± 1.3		25.8 ± 3.0	
CO (L/min)	Control	3.5 ± 0.1	0.3198	3.1 ± 0.2	0.1992	4.6 ± 0.2	0.0445
	Inhaled milrinone	3.3 ± 0.1		3.5 ± 0.2		3.9 ± 0.2	
PVR/SVR (%)	Control	21 ± 4.4	0.3543	13.8 ± 5.2	0.0043[2]	8.3 ± 4.1	0.1953
	Inhaled milrinone	14.4 ± 3.7		8.3 ± 3.5		17.3 ± 3.7	
Echocardio-graphic							
RVEDA 4ch (cm^2)	Control	14.0 ± 1.2	0.4759	19.1 ± 1.1	0.061	17.3 ± 0.7	0.0023
	Inhaled milrinone	15.4 ± 1.3		14.9 ± 1.5		12.7 ± 0.9	
RVESA 4ch (cm^2)	Control	6.7 ± 0.8	0.0361	9.6 ± 0.9	0.2917	9.8 ± 0.8	0.0535
	Inhaled milrinone	10.1 ± 1.1		7.9 ± 1.2		7.3 ± 0.9	
RADt (cm)	Control	4.2 ± 0.2	0.0367[3]	4.1 ± 0.1	0.0905	4.3 ± 0.2	0.2129
	Inhaled milrinone	4.4 ± 0.2		3.5 ± 0.2		3.8 ± 0.3	
LVESA_sax (cm^2)	Control	14 ± 0.7	0.5223	11.9 ± 0.29	0.0106[5]	13.3 ± 1.2	0.6105

Variables*	Group	T2 (End Nebulization)	*P* value	T3 (20 minutes)	*P* value	T4 (After CPB)	*P* value
	Inhaled milrinone	15 ± 1.2		14.1 ± 0.4		12.1 ± 1.9	
RVFAC (%)	Control	50.7 ± 3.1	0.0366[4]	49.5 ± 4	0.9662	41.7 ± 3.9	0.5458
	Inhaled milrinone	39 ± 2.9		49.2 ± 5.6		45.5 ± 4.7	

*Variables expressed as adjusted mean ± standard error. Only significant variables are presented. T1: baseline after induction of anesthesia, T2: at the end of nebulization, T3: 20 minutes after nebulization before cardiopulmonary bypass (CPB), T4: during chest closure after CPB. ANCOVA, analysis of covariance; PCWP, pulmonary capillary wedge pressure; DPAP, diastolic pulmonary arterial pressure; CO, cardiac output; PVR/SVR, pulmonary to systemic vascular resistance ratio; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RADt, right atrial transverse diameter; LVESA_sax, left ventricular short axis view from a mid-papillary transgastric view; RVFAC, right ventricular fractional area.

[1] DPAP had a tendency to be higher at T3 ($p = 0.0639$) in the upper quartile group of the inhaled milrinone group

[2] PVR/SVR ratio was higher in the control group in the lower quartile ($p = 0.0043$);

[3] RADt: Control group was smaller at T2 in the lower quartile ($p = 0.0437$)

[4] RVFAC was higher in the control group in the lower ($p = 0.0056$) and middle quartile ($p = 0.0182$)

[5] LVESA_sax was lower in the control group for the middle ($p = 0.0373$) and higher quartile ($p = 0.0130$)

Table 34 Outcome data

	Control (n = 10)	**Inhaled Milrinone** (n = 11)
Difficult separation from CPB	7 (70%)	7 (64%)
Intravenous milrinone post-CPB	4 (40%)	2 (18%)
Intravenous adrenaline post-CPB	1 (10%)	0
Intra-aortic balloon pump requirement	1 (10%)	0
Vasopressors use > 24 hours	4 (40%)	5 (45%)
Atrial fibrillation	5 (50%)	6 (55%)
Death	2 (20%)	1 (9%)
ICU stay (hours)	45 (27-96)	72 (45-120)
Hospital stay (days)	6 (5-13)	13 (6-23)

Variables expressed as number (%) or as mean with 1st and 3rd interquartile range.
CPB, cardiopulmonary bypass; ICU, intensive care unit.

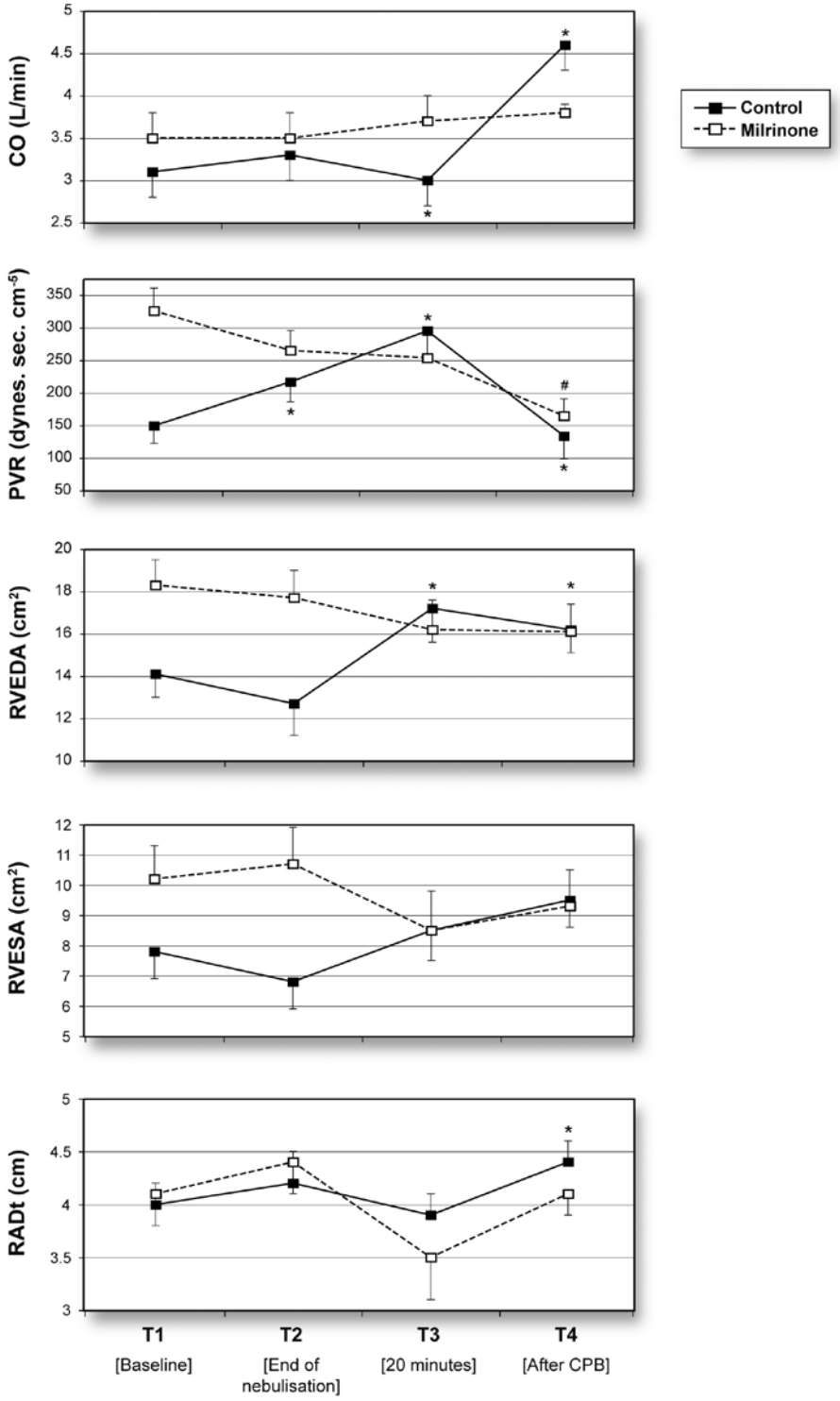


Figure 75 Hemodynamic and echocardiographic changes

Graphical display of changes in cardiac output (CO), pulmonary vascular resistance (PVR), right ventricular end-diastolic area (RVEDA), right ventricular end-systolic area (RVESA) and the right atrial transverse diameter (RADt). (* = $p < 0.05$ for the control group and # for the iMil group, see text for details).

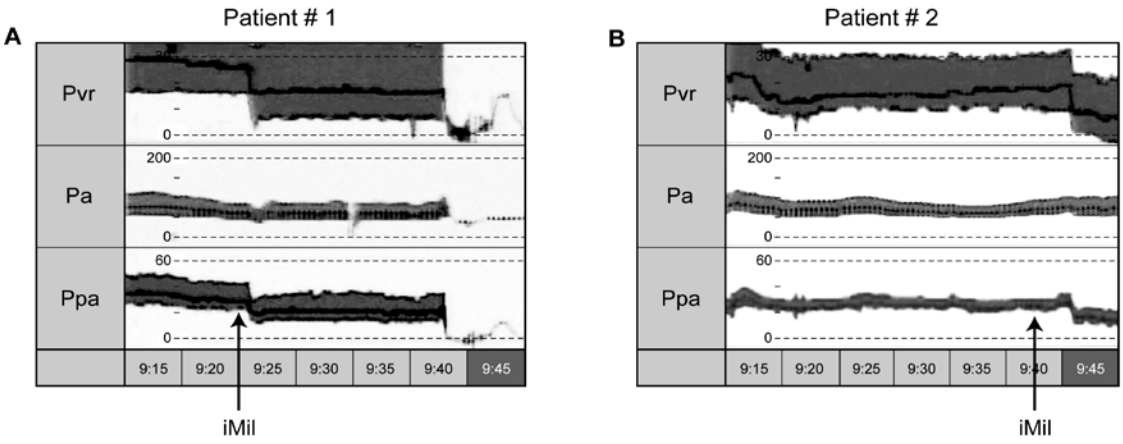


Figure 76 Inhaled milrinone in two patients

Hemodynamic evolution of the right ventricular pressure (Prv), systemic arterial pressure (Pa) and pulmonary artery pressure (Pap) in two patients after receiving inhaled milrinone (iMil) (arrow) before cardiopulmonary bypass. A reduction of the diastolic Prv and Pap without any significant changes in systemic arterial pressure (Pa) is observed.

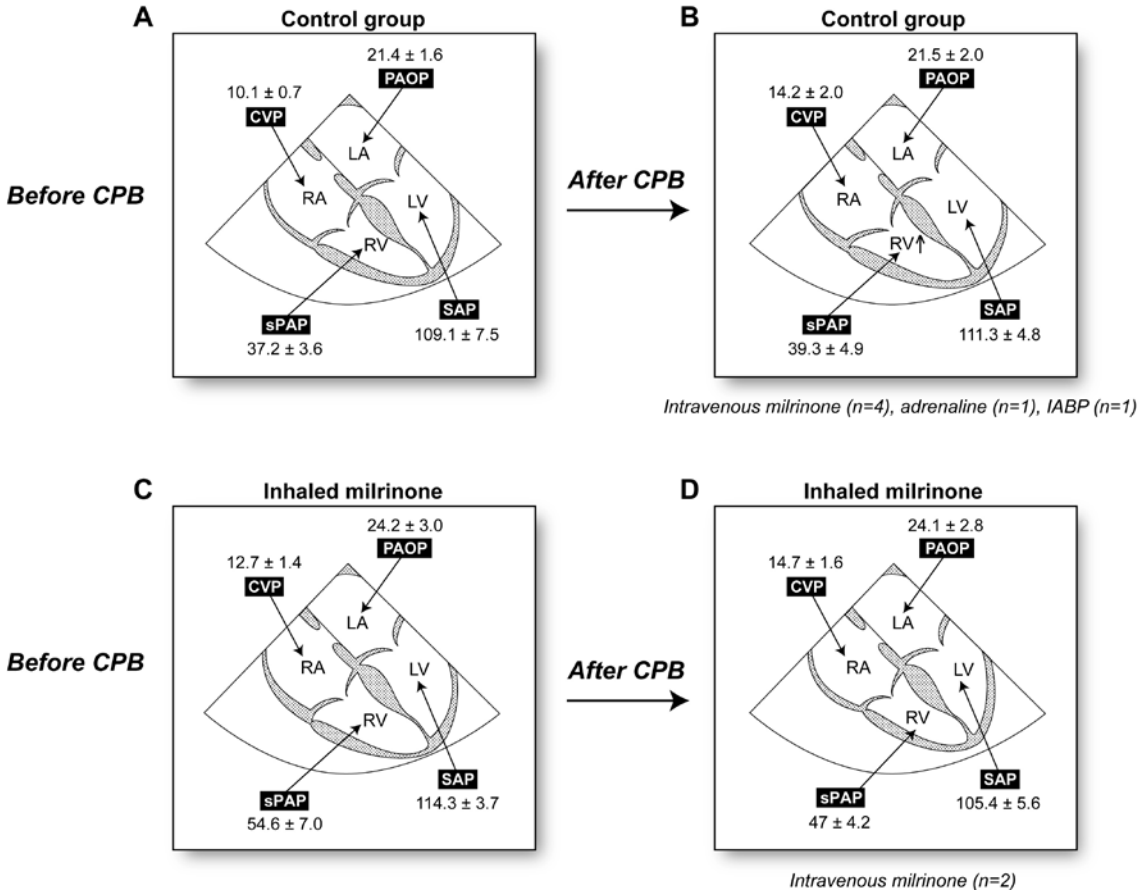


Figure 77 Hemodynamic and echocardiographic summary

Echocardiographic and hemodynamic comparison of the control (A,B) and inhaled milrinone (C,D) groups at baseline before and after cardiopulmonary bypass (CPB). (CVP, central venous pressure; IABP, intra-aortic balloon pump; LA, left atrium; LV, left ventricle; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle; SAP, systemic arterial pressure; SPAP, systolic pulmonary artery pressure).

Chapitre 8: Discussion

Hemodynamic instability present from the beginning of the weaning from CPB to the end of surgical procedure is our definition of difficult separation from CPB. It is a serious complication in cardiac surgery. In this thesis, we tried to demonstrate that 1) difficult separation from CPB is independently associated with an increased risk of morbidity and mortality, 2) the mechanism of difficult separation from CPB can be understood through a systematic approach based on the venous return concept, 3) inhaled milrinone is a preventive and therapeutic approach in the patient at risk for difficult weaning from CPB after cardiac surgery.

8.1 Summary and originality of the thesis

In Chapter 1, we explored the various definitions and proposed one based on several important elements. The first element that needs to be taken into account is the accurate measurement of arterial blood pressure. [80] In hemodynamically unstable patients, arterial pressure is more accurately measured with central aortic or femoral pressure. The second element is an elevated filling pressure which is the most common finding associated with difficult separation from CPB. In an open chest condition, that value obtained from a central venous catheter is reliable. However, in closed chest conditions, it will be influenced by the surrounding pressures. Finally, the third element that needs to be considered when defining difficult separation from CPB will be the pharmacological or mechanical support. The amount of support will be proportional to the degree of difficulty. Some patients will require only pharmacological support but others will need a surgical intervention as well, such as returning on CPB or mechanical devices. There is also in the literature overlapping in terms of the timing of difficult separation from CPB. Some consider it intraoperatively, others postoperatively and finally in some investigators both period are included in the definition. We defined difficult separation

from CPB as the period as starting from the beginning of the weaning process to the end of the operation.

Several factors have been identified to predict difficult separation from CPB and were discussed in Chapter 1.2. When difficult separation from CPB occurs, there is an association with increased risk of post-operative hemodynamic complications [10]. Furthermore, this association between difficult separation from CPB, morbidity and mortality was observed in 6120 patients from the database of the MHI from 1995 to 1999 (Table 6).

In Manuscript #1, we were able to confirm our observations from the MHI in a multicentered study performed between 2002 and 2007. The results of a study that included 2331 high-risk cardiac surgical patients conducted in 19 centers across Canada are reported. In this study, we observed an association between the amount of pharmacological and mechanical support during separation from CPB, life-threatening or serious adverse clinical events, length of ICU and hospital stay, and mortality. A total of 108 patients died and of those, 77.8% experienced difficulty in the process of separation from CPB. Furthermore, patients failing to be weaned on the first attempt and requiring an additional surgical intervention or mechanical devices experienced an increased mortality, independently of their underlying condition. Both difficult and very difficult separations from CPB were also related. In patients with very difficult separation from CPB, 84.4% of patients also presented pharmacological criteria for difficult separation from CPB. In addition, we observed that predictors of difficult and very difficult separation from CPB were not the same. These variables were also different to those predicting mortality (Figure 11). This could explain why preoperative risk factors alone do not completely predict mortality and morbidity. [141] As the patient is admitted to the ICU, the inclusion of intraoperative factors would allow to reset risk stratification in terms of predicting morbidity and mortality. Furthermore as the process of weaning from CPB can influence postoperative outcome, the potential identification and correction of factors associated with difficult separation from CPB could represent a new field of research. Consequently, prevention of

difficult separation from CPB could be seen as a strategy to maintain tissue perfusion. This can only be done if the mechanism leading to hypoperfusion is clearly understood.

In order to understand the mechanism of difficult separation from CPB, we proposed in Chapter 2 a systematic approach based on the combination of the venous return concept as described by Guyton [54] and biventricular pressure-volume relationships. We describe this approach in Chapter 3 and we also use it in Manuscript #1 to explain the various risk factors identified with difficult separation from CPB and mortality. Basically, difficult separation from CPB will occur when the three determinants of venous return are altered (Table 11) In some patients, similarly to septic shock, [367] several factors can be present simultaneously. Mean systemic pressure is the first of these factors. It will be reduced with the loss of stress volume or an increase in venous compliance. The diagnosis can be made using echocardiography. When a reduction in mean systemic pressure is observed, respiratory variations of the inferior vena cava will be seen in spontaneously breathing patients [368;369] or the superior vena cava in patients under positive-pressure ventilation. [370] In such conditions, volume repletion with or without blood products and agents that would reduce venous compliance such as noradrenaline or vasopressine should be considered. The second mechanism is the increase in right atrial pressure. In such a situation, careful identification of the etiology is of paramount importance because the treatment of one cause of elevated right atrial pressure can be contra-indicated in another one. Echocardiography plays an important role in this situation. For instance, inotropes would be appropriate in left ventricular systolic dysfunction but contra-indicated in left ventricular outflow tract obstruction. [211] Both conditions could be associated with elevated right atrial pressure and reduced cardiac output. Finally, the third mechanism is resistance to venous return. It can be secondary to extrinsic obstruction of the inferior or superior vena cavae or to an intrinsic reduction in diameter. Resistance to venous return can be diagnosed or suspected using echography and abdominal pressure measurement, particularly in closed chest conditions. [158] The risk factors of abdominal compartment syndrome were summarized in Table 13 and can be divided in three categories: diminished wall compliance, increased intra-abdominal content and capillary leak. [244;245] From

Table 13, it appears that several of these risk factors can be present during cardiac surgery. Increased resistance to venous return secondary to obstruction of the inferior vena cava has been observed in cardiac surgery (Figure 47-49) but abdominal compartment syndrome is poorly documented in cardiac surgery. It could occur as the chest is closed and would lead to hemodynamic instability, as shown in Figure 45. Clinical manifestations are non-specific and include decreased urine output, high ventilatory pressures, tense abdomen and reduced brain saturation (Figure 45). Monitoring the intravesical pressure is essential to establishing the diagnosis. [158] In patients with intra-abdominal hypertension and acute compartment syndrome, the abdominal perfusion pressure should be maintained above 50-60 mmHg. [148] Treatment should be directed towards the management of the underlying cause but it is necessary first to make the diagnosis.

In order to describe the mechanism of hemodynamic instability, it is first important to understand the natural evolution of biventricular cardiac function after cardiac surgery. These hemodynamic and echocardiographic changes after coronary revascularization (Figure 10) have been described by Shi *et al.* [40;43] However these changes in the pressure-volume relationship have not been described after valvular surgery. This was the goal of Manuscript #2. The most significant changes that can be observed after cardiac surgery are both a deterioration in biventricular diastolic function and a reduction in right ventricular systolic function. These changes are more pronounced after valvular surgery. This is illustrated in Figure 57.

Furthermore the intraoperative use of amiodarone, a negative inotropic agent, was not associated with any increase in inotropic requirement. [56] This strongly supports the hypothesis that the mechanism of hemodynamic instability after cardiac surgery cannot be explained only by a post-CPB reduction in systolic function. This finding could also imply that the routine use of inotropes after cardiac surgery might even be detrimental. Indeed, as shown in Manuscript #3, despite identical preoperative demographic, hemodynamic and echocardiographic characteristics, patients undergoing valvular surgery and exposed to inotropic agents after CPB showed an increased mortality up to 6 years after surgery (Figure 59). In contrast, such an increase in mortality was not observed in patients exposed

to amiodarone for the same follow-up period. [56] Consequently, in Manuscript #3, which describes a study performed in a single center, the link or association between the use of inotropic agents and mortality can be further supported.

Is the link between difficult separation from CPB and postoperative outcome an association or one of causality? Using Hill's criteria for causality [371] evidences, that difficult separation from CPB is responsible for the postoperative outcome, can be found. Indeed, predictors of outcome in septic shock and the mechanism of hemodynamic instability are, to some extent, similar to what we can observe in difficult separation from CPB. [372] Several mechanisms of hemodynamic instability and risk factors are present in septic shock. These include vasodilation, [137] myocardial depression, [373] abdominal hypertension, [374] predisposing factors such as age, [375] and worse outcome if inotropic agents are used. [99] A potential common denominator between both conditions is most likely to be tissue hypoperfusion. Such condition has been found to be a predictor of outcome in septic shock patients. [129;376-378] In addition, strategies based on maintaining optimal oxygen transport have been shown to be efficacious both in septic shock, [379] in non-cardiac surgery [380;381] and also in cardiac surgery. [382].

However the association between inotropes and mortality may not necessarily imply causality because other factors unmeasured or unknown could explain this link. In that regard a recent paper by Turer *et al.* [111] explored the new field of metabolomics in cardiac surgery. The measurements of several metabolites produced from ischemia/reperfusion during retrograde cardioplegia were analyzed. An association between the duration of inotropic support and myocardial lactate was observed (Figure 78). This study suggests that patients with left ventricular dysfunction have limited myocardial metabolic reserve and flexibility after global ischemia/reperfusion stress. These findings are consistent with other authors who also confirmed that a reduced myocardial pH [109] (Figure 4) or increased myocardial lactate measured during CPB [110] (Figure 3) are predictors of increased postoperative inotropic support and mortality. This abnormal lactate release could imply delayed recovery of normal aerobic myocardial metabolism. As the myocardial metabolism is altered, myocardial function will be abnormal. Therefore the risk

of difficult separation from CPB is likely again to correlate with indices of global or regional myocardial tissue hypoperfusion that could have occurred even before CPB. Consequently, strategies enhancing the patient's metabolic myocardial function in prevention of difficult separation from CPB could be also be considered. [383-385].

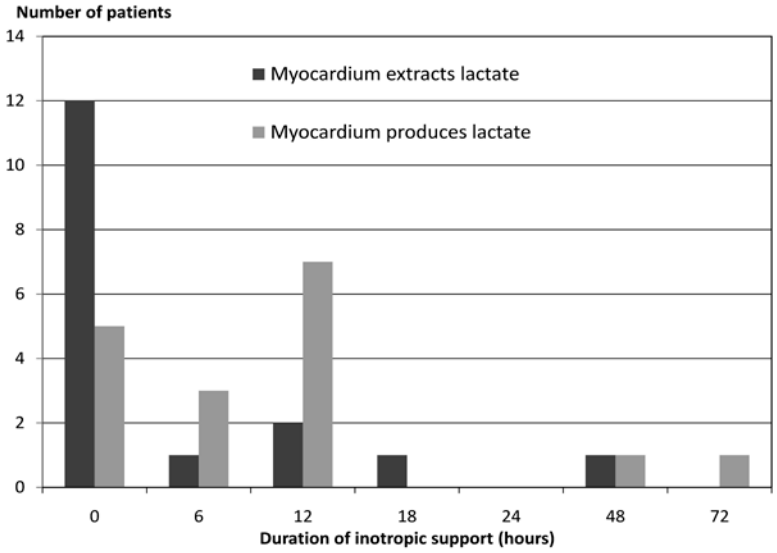


Figure 78 Inotropic support and lactate.

Duration of inotropic support after surgery in patients whose myocardium continued to extract lactate (black) and in those where the myocardium was a net producer of lactate (grey), suggesting predominantly anaerobic metabolism. The median durations of inotrope infusions (0 *vs*. 9 hours) were significantly different ($P < 0.02$). (Adapted from Turer *et al.* [111])

In that regard, difficult separation from CPB could also be seen as a surrogate endpoint. Four criteria have been proposed to define a surrogate endpoint. [386] First, reliability must be present. Our definition of difficult separation from CPB is straightforward and reproducible. Second, as mentioned by Ventetuelo *et al*. [386], "a surrogate is ideally integral to the causal pathway of the disease, and the intervention being tested should act on the disease pathway that is represented by the surrogate". This calls

back the issue of causality, as previously discussed. Third, there is epidemiologic evidence that the surrogate endpoint is linked to survival. The first and the third manuscripts were consistent with this definition. Finally, the surrogate marker will change proportionally to the probability of reaching the clinical endpoints through therapy. This requires randomized controlled trials of sufficient power and duration. Our fourth Manuscript is, to some extent, in support of this criterion, but not powered enough nor with a long enough follow-up period.

However, in my opinion, it is unlikely that a strategy based on the modulation of a single factor will be the solution to a problem as complex as difficult separation from CPB. If difficult separation from CPB is secondary to left ventricular outflow tract obstruction, then the benefit of improving systolic myocardial function would not be as useful as if left ventricular impairment was the main etiology.

Among factors predisposing to difficult separation from CPB, pulmonary hypertension has been known for several years and is discussed in Chapter 6. [8;100;115-117] In a study of 1439 patients we observed a logarithmic relationship between the severity of pulmonary hypertension and postoperative hemodynamic complications (Figure 62). This relationship has also been observed also by several investigators and is a component of several preoperative risk stratification models. [100;101] Several mechanisms can explain the presence of pre and postoperative pulmonary hypertension (Figure 64). They include pre and postoperative conditions such as left ventricular dysfunction, patient-prosthesis mismatch, reperfusion injury, protamine reaction, hypoxia, hypercarbia, pulmonary embolism and positive-pressure ventilation. Morbidity and mortality associated with pulmonary hypertension have also been more related to the degree of right ventricular adaptation to disease than to the absolute values of pulmonary arterial pressure. [46;189-191;306] This hypothesis would be consistent with studies in pulmonary hypertension where markers of right ventricular function have been shown to be the most important prognostic factors. [189;192]

In order to prevent the increase in pulmonary hypertension after cardiac surgery and its consequence on right ventricular function, several investigations exploring the use of inhaled milrinone were designed. Milrinone is a cyclic AMP-specific phosphodiesterase inhibitor that can exert both positive inotropic effects and vasodilation independently of $ß_1$-adrenergic receptor stimulation in the cardiovascular system. [41;319] Previous studies evaluating the use of intravenous milrinone in cardiac surgical patients were underpowered and performed on a small number of patients undergoing coronary revascularization. [348] Although milrinone has been shown to increase cardiac output [322;324;334] and to facilitate separation from CPB, [321] the major problem encountered with intravenous milrinone is the high incidence of systemic hypotension resulting in an increased need for vasoactive drugs. [66;311;324;342] The hypotension resulting from intravenous milrinone is either caused by vasodilation or through dynamic left or right ventricular outflow tract obstruction. [38]

Only four observational studies addressing the role of inhaled milrinone in cardiac surgery have been published so far. [53;350;351;353] The effect of inhaled milrinone was first described by Haraldsson *et al.* [350] in an open-label trial of 20 cardiac surgical patients in the intensive care unit. The first part of the trial included 9 patients and showed a dose-response effect of incremental concentrations of inhaled milrinone with decreases in MPAP, PVR and PVR/SVR. No patient presented systemic hypotension. The hemodynamic parameters of patients treated with inhaled milrinone returned to baseline within 20 minutes after the end of the inhalation period, similar to our observation. In the second study, [351] inhaled milrinone was given to 18 heart transplant candidates in the intensive care unit. The MPAP, transpulmonary gradient and PVR decreased only in patients with pulmonary hypertension, defined as MPAP > 30 mmHg. Improvement in CO was observed, but there was no systemic hypotension. The administration of inhaled milrinone before CPB in high-risk patients with a Parsonnet score of 30.4 ± 14.2 was described. [53] Compared to the administration of inhaled milrinone after CPB, pre-CPB administration was associated with a reduction of difficult separation from CPB (18% *vs*. 82%) defined as the use of more than two inotropes, the need for introduction of an intra-

aortic balloon pump or reinitiation of CPB. Finally a recent study compared the use of intravenous versus inhaled milrinone in 48 patients with pulmonary hypertension after mitral valve surgery. [353] The mean pulmonary artery pressure and pulmonary vascular resistance decreased in both groups. However, the mean arterial pressure and systemic vascular resistance in the inhaled group were significantly higher than in the intravenous group. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction. The main finding of these four studies is that a reduction in indices of pulmonary hypertension is observed without any systemic hypotension with inhaled milrinone. None of them however were both randomized and performed during cardiac surgery.

The last manuscript in Chapter 7 represents the first randomized controlled trial of inhaled milrinone in cardiac surgery administered before CPB. The objective of the study was to determine the safety of this strategy. As other investigators, we did not observe any hypotension in patients exposed to inhaled milrinone compared to placebo. As secondary outcomes, we noted that patients exposed to inhaled milrinone before CPB showed a reduced need for vasoactive agents in the same ratio as was described in the retrospective study of Lamarche *et al.* [53] Furthermore, patients exposed to inhaled milrinone had no significant changes in biventricular systolic function and compliance compared to the control group even if more severe pulmonary hypertension was present in the treatment group. The biventricular changes normally observed after CPB and described in Manuscript #3 were present in the control group but absent from the inhaled milrinone group. These findings do support the hypothesis that, as demonstrated in an animal model [354], inhaled milrinone may prevent pulmonary reperfusion syndrome. By preventing reperfusion injury, no significant increase in pulmonary artery pressures would be observed. This would facilitate right ventricular function and consequently separation from CPB. Thus inhaled milrinone could reduce right ventricular afterload and be considered as a pharmacologic “intra-aortic balloon pump” for the right ventricle.

8.2 Limitations and future projects

There are several limitations to each of these studies. In the first manuscript, for instance, the role of a difficult separation from CPB in predicting mortality is unknown at the time the patient is seen before a cardiac surgical operation. This predictor will only be made apparent later in the operating room. For this reason, preoperative risk stratification models are still useful. Knowing the difficulty in separation from CPB is an advantage in the postoperative period only. For the critical care physician, resources allocation and outcome will be influenced by how well separation from CPB went. In our first manuscript, the precise mechanism leading to this condition was not identified for each patient due to the scope of the original study. Intraoperative echocardiography was used in 2075 (89.1%) patients, but the exam was not standardized and the final report not collected. Other variables are also associated with difficult separation from CPB such as pulmonary artery pressure, [10;100;101;115] left ventricular end-diastolic pressure, [11] diastolic function parameters, [155] right ventricular function indices, [46;112] and myocardial pH and lactate [76;109;110]; these were not routinely used and, consequently, unavailable for analysis. For all these reasons, further studies using a systematic approach for the diagnosis of conditions resulting in difficult separation from CPB are warranted and will offer more insight into the mechanism of this critical condition.

In our second study, randomization allocated more patients with diabetes and more complex surgeries with longer CPB duration in the placebo group, but there were no clinically significant hemodynamic, echocardiographic and biochemical differences between the groups and their evolution was similar. It is nevertheless possible that the negative inotropic effect of amiodarone was overlooked because amiodarone was administered to patients with less complex procedures and shorter CPB times. Secondly, the gold standards for evaluating diastolic dysfunction are the time constant of relaxation (Tau) and pressure-volume curves obtained by direct invasive measurements to assess chamber compliance. However, these measures are invasive and are not feasible in everyday practice. Instead, we used a Doppler assessment of mitral and tricuspid inflow, as

well as pulmonary and hepatic flow variables to assess diastolic function. Tissue Doppler imaging, which is a relatively volume-insensitive modality, provided supportive information that allowed us to better stratify the degree of diastolic dysfunction. [173] Changes in mitral flow velocity have been noted when changes occurred in loading conditions, heart rates, and the left ventricular contractile state. [282] Hemodynamic variables were relatively similar in both groups except for a lower heart rate and cardiac index after CPB in the amiodarone group. Accordingly, we could not totally exclude the effect of the change of cardiac output and heart rate on diastolic filling patterns in our patients; neither were we able to totally exclude the possibility that amiodarone may have a certain effect on diastolic function that we did not identify, even when using load-independent modalities. [173] Criteria for right ventricular diastolic dysfunction have been previously described [204] but are not yet as widely accepted as those used for LV diastolic dysfunction. So far however, no study has documented a deterioration of intraoperative biventricular diastolic function in patients undergoing valvular surgery, independently of the use of intravenous amiodarone.

In the third manuscript, we observed an association between the use of inotropes and mortality. The number of deaths was however too small to perform logistic regression and thus determine the strength or weakness of the association. Several factors can influence the use of inotropic agents and one of them is the anesthesiologist. [64] A vasoactive agent protocol was used to reduce this potentially confounding factor; nevertheless, we cannot completely exclude it as a trigger for the use of inotropic agent.

Finally, in our last study, the most important limitation was the small number of patients. We are currently performing a national multicentered randomized controlled trial using the same protocol (clinicaltrials.gov NCT00819377). So far 37 patients have been recruited. Despite these promising results, the use of inhaled milrinone will only tackle one of the three variables that determine venous return, i.e. right atrial pressure. Inhaled milrinone would be useless in case of massive hemorrhage (reduction in mean systemic pressure) or if there was a partial occlusion of the inferior vena cava (increased resistance to venous return) (Figure 47). However in such a critical situation, the ability to maintain a

normal venous return by having a reduced or normal atrial pressure and pulmonary vascular resistance could facilitate the maintenance of an adequate systemic perfusion.

For this reason, a global strategy based on the accurate hemodynamic and echocardiographic determination of the mechanism of hemodynamic instability with appreciation of the normal pressure-volume changes expected after cardiac surgery is the first step in managing patients with difficult separation from CPB. Preventive strategies such as inhaled milrinone are appealing because of their simplicity, reduced cost compared to inhaled nitric oxide, and widespread application. Their benefit has yet to be confirmed but only within protocols that incorporate an understanding and recognition of the mechanism of hemodynamic instability. Such intraoperative protocols cannot be operational without the use of TEE.

Further studies will have to explore further the mechanism of hemodynamic instability in cardiac surgery using new technologies such as strain imaging and three-dimensional echocardiography. The monitoring of the autonomic nervous system will also provide more insight into the mechanism of difficult separation from CPB. Such monitoring can be performed at the bedside and will be presented by Dr. Alain Deschamps during the Canadian Anesthesia meeting in 2010. [387;388] The inflammatory reaction induced by CPB and monitored using tissue ultrasonography is currently analyzed by collaborators from Dr. Guy Cloutier's laboratory. Red-cell aggregation, as a surrogate for inflammation, can be monitored continuously and non-invasively. [389;390] Combination therapy using inhaled prostacyclin and other agents in animal models and eventually in human experiments is currently under study by Maxime Laflamme in Dr. Louis Perrault's laboratory. The pharmacokinetic and pharmacodynamic characterization of inhaled agents is under investigation in collaboration with France Varin, PhD and Ann Nguyen. We might consider exploring new strategies, for instance the administration of a second dose prior to weaning from CPB. Finally, the ultimate goal of cardiac surgery is to maintain cardiac function and consequently tissue and brain perfusion. A protocol on the use of brain oximetry as an endpoint of resuscitation is currently under investigation. [130] In that regard, with the collaboration of the École Polytechnique, as well as the Neurology,

Medicine and Anesthesiology departments of the University of Montreal, a portable wireless near-infrared non-invasive spectroscopy system combined with electroencephalography for bedside monitoring of stroke and cardiac patients is under development. (CIHR CIF grant #99516) This monitor will be tested in the operating room.

Conclusion

In summary, we observed in this thesis that the process of separation from CPB after a cardiac surgical procedure is a very critical moment of the cardiac surgery. When the process is difficult, it will significantly alter postoperative outcome and result in increased morbidity and mortality. There are several risk factors for difficult separation from CPB but difficult separation from CPB will by itself increase mortality, independently of all other risk factors. Consequently, a clear understanding of the mechanism of difficult separation from CPB is the first step if any strategies are to be used to reduce this fearful complication. The mechanism is best understood using the concept of venous return described by Guyton. [54] It allows us to clearly identify one of the three mechanisms that could lead to reduced cardiac output or venous return. In addition, as venous return is one of the oxygen transport determinants, arterial oxygen content is the fourth variable that needs to be taken into account.

The word “monitor” originates from the Latin “monere”, meaning warning. A monitor that can give us a clear reading of the balance between oxygen transport and consumption seems to be the ideal warning device in cardiac surgery. Another useful thing to do is monitor the adequacy of treatment. Such a monitoring system, now available, should inform us on tissue perfusion or microcirculation. The latter has been shown to be more sensitive in detecting the adequacy of the imbalance between oxygen transport and delivery compared to global hemodynamic and oxygen transport variables. [129] However, when this signal indicates an imbalance, every effort should be directed toward identifying the mechanism. This is where echocardiography plays an essential role. The treatment should be directed toward the corrections of the three determinants of venous return and arterial oxygen content.

We observed significant changes in biventricular cardiac function after CPB in patients undergoing cardiac surgery. These changes were mostly evident on the right

ventricle. As right ventricular dysfunction is associated with such a poor outcome, the prevention of right ventricular dysfunction through modulation of afterload could represent a potential strategy in preventing difficult separation from CPB. Our preliminary observations using inhaled milrinone are promising. In patients exposed to inhaled milrinone before CPB, we observed that the natural right ventricular dilatation was prevented possibly through a reduction in right ventricular afterload or the prevention of the reperfusion syndrome, as demonstrated in several animal models. Inhaled agents could therefore represent a pharmacological "intra-aortic balloon pump" (IABP) of the right ventricle. As we know, IABPs do not change the underlying process for which they were inserted. However, they may increase cardiac reserve and buy some time until the primary cause of failure is removed or has dissipated.

It is important however to keep in mind that inhaled agents such as milrinone will only modulate one of the determinants of venous return, namely the right atrial pressure. If for instance severe vasodilatory shock, acute hemorrhage or iatrogenic occlusion of the inferior vena cava is the etiology of difficult separation form CPB, the impact of preemptive inhaled agents will be significantly reduced.

In summary, the process of weaning CPB is critical in cardiac surgery and when present, it will alter the outcome. A systematic approach to difficult separation from CPB should be considered. Clear understanding of the determinants of venous return is essential. This can be only gained by using combined hemodynamic, echocardiography and oxygen supply-demand monitoring. This approach should be part of modern care in every operating room and intensive care unit dealing with cardiac surgical patients. Finally, the alteration of some of the determinants of venous return such as right atrial pressure through a pharmacological strategy such as inhaled milrinone that does not, at the same time, reduce mean systemic pressure, could represent an effective way of reducing the prevalence of difficult separation from CPB. Should such a strategy be demonstrated effective in improving outcome after cardiac surgery through adequately powered randomized controlled trials, then difficult separation from CPB could definitively be considered a surrogate endpoint in cardiac surgery.

Appendices

Appendix 1 Definitions of variables in the BART study

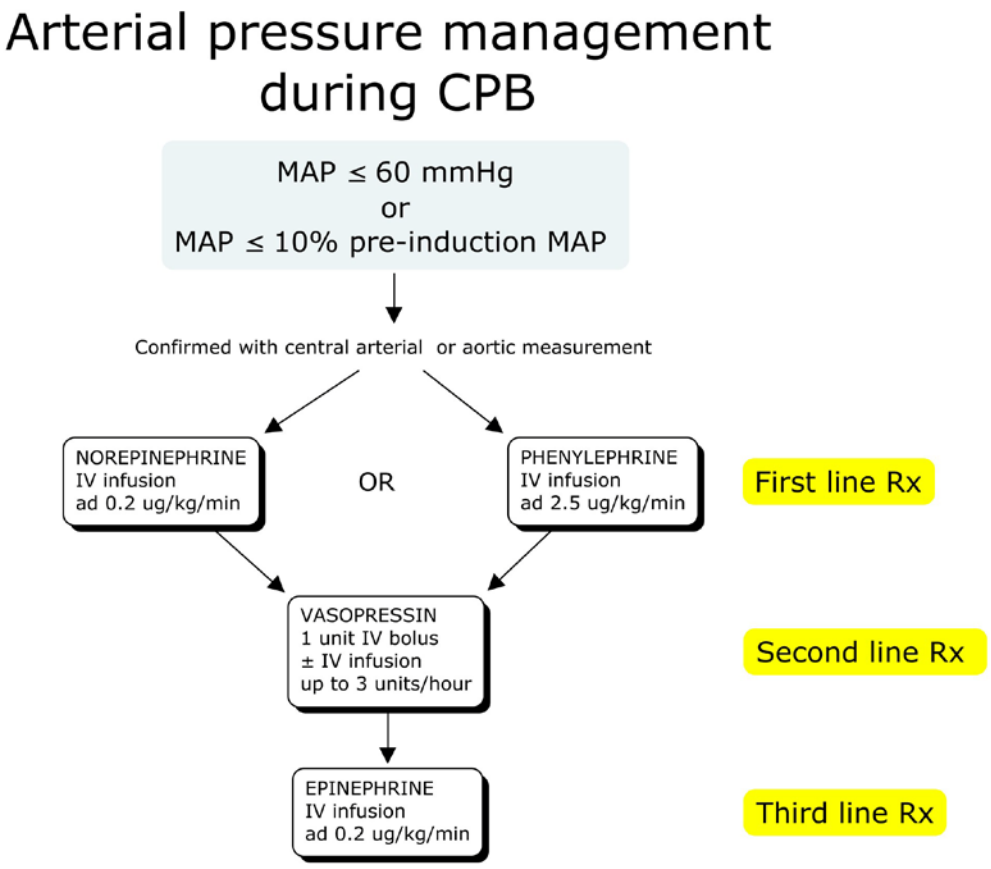
Demographic factors	
Body mass index (kg/cm²)	Weight/height
Body surface area	$[(\text{Height X weight})/3600]^{1/2}$
Cardiovascular risk factors	
Hypertension	Documented history of treated or untreated hypertension
Dyslipidemia	Elevated triglycerides, cholesterol or lipids
Severe obesity	Body mass index > 30 kg/cm²
Smoking	Actively smoking or stop within 6 weeks
History of smoking	Stop smoking > 6 weeks
Ischemic heart disease risk factors	
Angina	Angina < 6 weeks before surgery. Patients with crescendo angina or main left artery stenosis who were in the hospital waiting for surgery were included in this category
Myocardial infarction	History of documented myocardial infarction
Poor left ventricular function	Left ventricular ejection fraction < 30%. Left ventricular ejection fraction was the last measured value reported prior to surgery by left ventriculography, echocardiography or nuclear medicine. The lowest value was selected.
History of congestive heart failure	Congestive heart failure was reported when present or previously-documented episode(s) of pulmonary congestion with or without clinical or radiological signs
Coexisting illness	
Disabling stroke	Permanent neurological deficit
Previous thromboembolism	Previous deep venous thrombosis, or pulmonary embolism
Severe lung disease	Obstructive, asthmatic or restrictive lung disease associated with disability
Chronic renal dysfunction	Dialysis requirement
Diabetes mellitus	Diabetes with drug or insulin requirement

Intraoperative variables	
American Society of Anesthesiologist Class	The risk score of the American Society of Anesthesiologists ranges from 1 (healthy and low risk) to 5 (moribund and high risk).
Complex	Cardiac surgery involving repair or replacement of 2 or more valves without CABG
Combined + CABG	Valvular, aortic or complex surgery associated with coronary revascularization
Postoperative outcome	
Death	Death at 30 days.
Stroke	Focal neurologic deficit lasting more than 24 hours
Myocardial infarction	Presence of an increase of CK-MB of more than 100 units, new Q waves in two contiguous electrocardiogram leads or confirmed graft occlusion within the first 30 days after surgery
Cardiogenic shock	Need for vasopressors and inotropic agents, an intra-aortic balloon pump, or a ventricular-assist device for more than 48 hours. Patients with a ventricular-assist device during surgery were excluded from that category
Respiratory failure	Duration of intubation for more than 48 hours or reintubation for a pulmonary cause
Renal complications	One dialysis treatment, a doubling of the baseline serum creatinine level, or a serum creatinine level of more than 150 μmol per liter (1.7 mg per deciliter)
Massive bleeding	Composite outcome of bleeding from chest tubes that exceeded 1.5 liters during any 8-hour period or massive transfusion, which was defined as the administration of more than 10 units of red cells within 24 hours after surgery, death from hemorrhage, re-operation for bleeding all within 30 days

CABG, coronary artery bypass graft, BART, Blood Conservation Using Antifibrinolytics in a Randomized Trial.

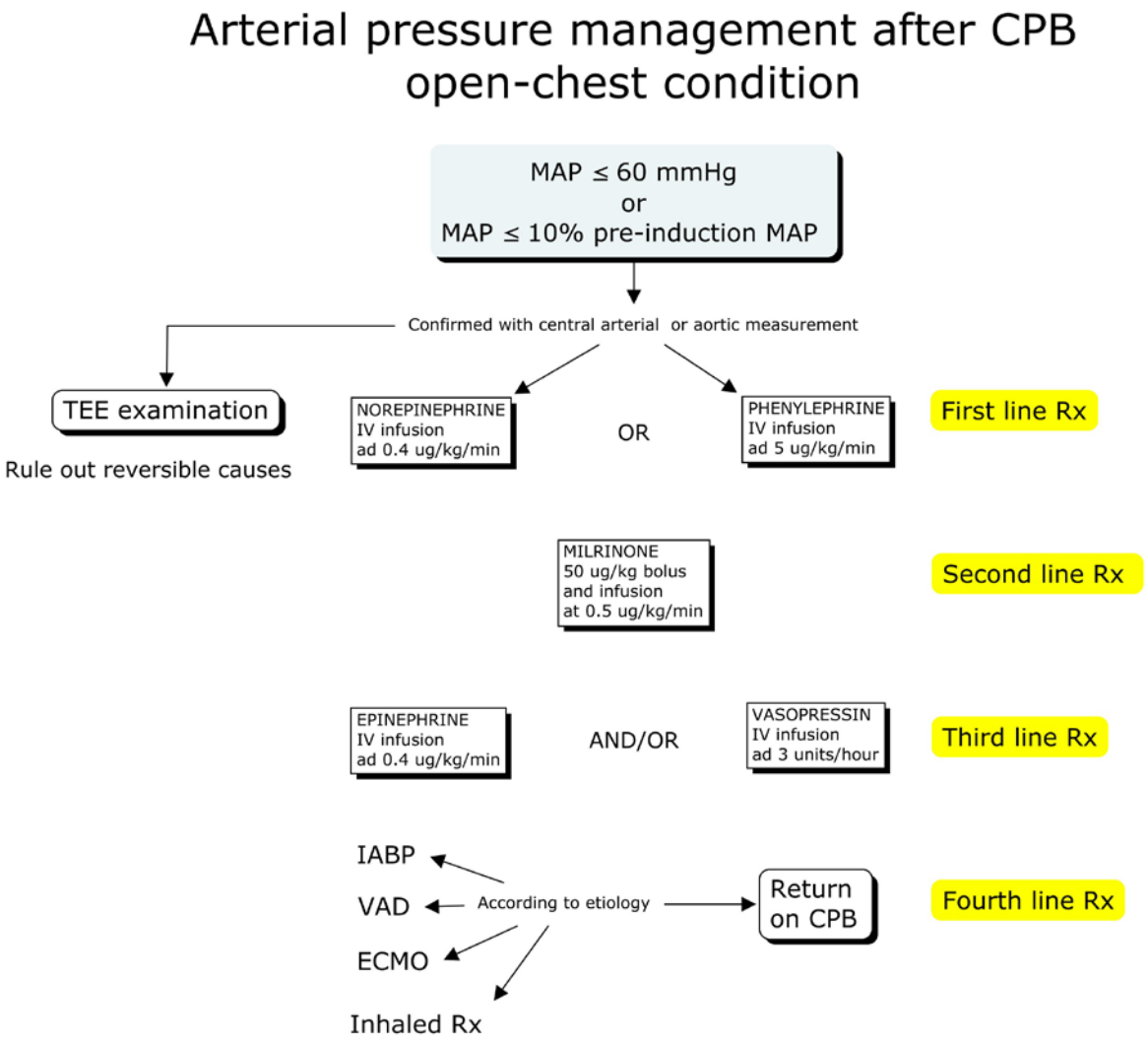
Appendix 2 Protocol for vasoactive management during CPB

(CPB, cardiopulmonary bypass; IV, intravenous; MAP, mean arterial pressure)



Appendix 3 Protocol for vasoactive management during weaning from CPB

(CPB, cardiopulmonary bypass; ECMO, extra-corporeal membrane oxygenator; IABP, intra-aortic balloon pump; IV, intravenous; MAP, mean arterial pressure; Rx, therapy; TEE, transesophageal echocardiography; VAD, ventricular assist device)



Appendix 4 Arterial blood gases and biochemistry variables

	Group	Baseline	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
Hemoglobin (g/L)	Amiodarone	123 ± 14	95 ±10	0.5790	< .001	0.7594
	Placebo	124 ±13	96 ±12			
Na (mmol/L)	Amiodarone	141 ±3	139 ±3	0.1271	< .001	0.3909
	Placebo	142 ±3	140 ±3			
K (mmol/L)	Amiodarone	4.1 ±0.3	4.5 ±0.4	0.3095	< .001	0.1898
	Placebo	4.1 ±0.3	4.4 ±0.4			
Urea (mmol/L	Amiodarone	6.0 ±1.7	5.7 ±1.7	0.8623	< .001	0.0052[23]
	Placebo	6.4 ±1.9	5.4 ±1.5			
Creatinine (umol/L)	Amiodarone	81 ±22	86 ±29	0.4268	0.5917	0.0013[24]
	Placebo	84 ±23	78 ±27			
Mg (mmol/L)	Amiodarone	0.8 ±0.09	0.95 ±0.15	0.8443	< .001	0.9497
	Placebo	0.8 ±0.08	0.95 ±0.17			
CK total (ug/L)	Amiodarone	70 ±46	436 ±219	0.0973	< .0001	0.0117[23,25]
	Placebo	68 ±44	743 ±751			
CK-MB (ug/L)	Amiodarone	1.9 ±1.0	23 ±12	0.4894	< .0001	0.2769
	Placebo	1.9 ±1	32 ±50			
pH (arterial)	Amiodarone	7.47 ±0.04	7.37 ±0.05	0.3981	< .0001	0.7110
	Placebo	7.47 ±0.04	7.38 ±0.04			
PaO_2 /FiO_2 (mmHg)	Amiodarone	424 ±88	284 ±123	0.6540	< .0001	0.5599
	Placebo	438 ±90	283 ±111			
$PaCO_2$ (mmHg)	Amiodarone	37.2 ±4.8	43.8 ±4.4	0.3051	< .0001	0.0192[23,26]
	Placebo	36.6 ±4.0	45.7 ±4.4			

[23] $P < 0.05$ baseline versus after CPB in both groups
[24] $P = 0.0071$ baseline versus after CPB in the placebo group
[25] $P = 0.0097$ after CPB in the amiodarone compared to the placebo group
[26] $P = 0.0237$ after CPB in the amiodarone compared to the placebo group

	Group	Baseline	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
HCO3 (mmol/L)	Amiodarone	26.9 ±2.1	25.7 ±2.2	0.0496	0.1257	0.0002[27]
	Placebo	26.7 ±1.7	27.2 ±2.4			
pH (venous)	Amiodarone	7.43 ±0.04	7.34 ±0.04	0.4544	< .0001	0.4989
	Placebo	7.43 ±0.04	7.35 ±0.03			
PvO_2 (mmHg)	Amiodarone	44.6 ±5.4	37.8 ±4.5	0.3219	< .0001	0.1010
	Placebo	44.3 ±6.0	39.6 ±4.1			
$PvCO_2$ (mmHg)	Amiodarone	43.5 ±4.8	49.3 ±3.9	0.3641	< .0001	0.3393
	Placebo	43.6 ±4.4	50.4 ±4.9			
HCO_3 (venous) (mmol/L)	Amiodarone	28.8 ±1.9	27.0 ±2.1	0.1381	< .0001	0.0707
	Placebo	28.9 ±1.8	28.0 ±2.6			

[27] *P* = 0.0002 baseline versus after CPB in the amiodarone group and p = 0.0008 after CPB in the amiodarone compared to the placebo group

Appendix 5 Hemodynamic variables

Variable	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
SAP (mmHg)	Amiodarone	109.1 ±16.2	105.8 ±18.9	120.9 ±14.4	0.8710	< .0001[28,29]	0.4104
	Placebo	107.6 ±17.9	103.4 ±18.4	123.8 ±15.4			
DAP (mmHg)	Amiodarone	55.1 ±7.8	57 ±9.6	55.6 ±7.4	0.8712	0.0903	0.2414
	Placebo	55.5 ±9.4	56.3 ±11.4	57.5 ±8.6			
MAP (mmHg)	Amiodarone	73.1 ±9.3	73.3 ±11.7	77.4 ±8.7	0.9792	< .0001[28,29]	0.2492
	Placebo	72.2 ±10.4	72 ±12.6	79.6 ±8.7			
HR (beats per minutes)	Amiodarone	58.1 ±9.5	63.2 ±10.5	66.9 ±11.9	0.0006	< .0001	< .0001[1,30,31]
	Placebo	58.1 ±10	67.9 ±17.1	78.7 ±10.8			
SPAP (mmHg)	Amiodarone	31.9 ±13.4	37.8 ±13.3	36.8 ±8.8	0.2215	< .0001[28,5]	0.0652
	Placebo	31.5 ±11.2	33.2 ±12.9	35.9 ±8.1			
DPAP (mmHg)	Amiodarone	16.8 ±6.1	19.6 ±6.6	17.8 ±5.1	0.3354	0.0028[32]	0.0859
	Placebo	16.8 ±6.7	17.5 ±6.5	17.6 ±3.9			
MPAP (mmHg)	Amiodarone	21.8 ±8.1	25.6 ±8.6	24.1 ±5.9	0.2531	0.0001	0.0450[33,34]
	Placebo	21.8 ±7.8	22.7 ±8.4	23.7 ±4.9			

[28] $P < 0.05$ baseline versus after CPB in both groups
[29] $P < 0.05$ after bolus versus after CPB in both groups
[30] $P < 0.001$ after CPB in the amiodarone versus placebo group
[31] $P < 0.001$ baseline versus after bolus in the placebo group
[32] $P < 0.05$ baseline versus after bolus in both groups
[33] $P < 0.05$ baseline versus after bolus and baseline versus after CPB in the amiodarone group
[34] $P = 0.0445$ after bolus in the amiodarone compared to the placebo group

Variable	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
CVP (mmHg)	Amiodarone	11 ±3.5	12.8 ±5.1	14.3 ±3.7	0.0700	< .0001[28,29,32]	0.0697
	Placebo	10.9 ±3.7	11.2 ±3.9	12.8 ±3.6			
PCWP (mmHg)	Amiodarone	13.9 ±5.2	16.8 ±5.9	15.7 ±4.6	0.3342	< .0001[28,5]	0.6520
	Placebo	13.6 ±4.7	15.6 ±6.1	15.1 ±3.4			
SV (ml)	Amiodarone	62.4 ±15.2	60.2 ±16.7	67.4 ±16.3	0.6666	0.0022[28,29]	0.8829
	Placebo	64.3 ±19.1	61.4 ±18.4	68 ±20.4			
CI ($L/m/m^2$)	Amiodarone	2.01 ±0.45	2.14 ±0.61	2.48 ±0.52	0.0193	< .0001[28,29]	0.0157[30,8]
	Placebo	2.03 ±0.49	2.26 ±0.79	2.9 ±0.67			
SVRI ($dynes,sec,cm^{-5}/m^2$)	Amiodarone	2584 ±670	2425 ±801	2101.2 ±455.9	0.2760	< .0001[28,29]	0.6054
	Placebo	2534 ±649	2379.9 ±870	1925.1 ±420.1			
PVRI ($dynes,sec,cm^{-5}/m^2$)	Amiodarone	324 ±203	350 ±235	282.7 ±103.8	0.1947	0.2275	0.1715
	Placebo	337 ±217	294 ±260	246.8 ±86.8			

CI, cardiac index; CVP, central venous pressure; CPB, cardiopulmonary bypass; DAP, diastolic arterial pressure; DPAP, diastolic pulmonary artery pressure; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, indexed pulmonary vascular resistance; SAP, systolic arterial pressure; SPAP, systolic pulmonary artery pressure; SV, stroke volume; SVRI, indexed systemic vascular resistance.

[8] $P = 0.0079$ baseline versus after bolus in the placebo group

Appendix 6 Two-dimensional echocardiographic variables

Variables	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
LADt (cm)	Amiodarone	4.2 ± 0.78	4.6 ± 0.9	4.1 ± 0.7	0.7945	0.0136 [35,36]	0.8321
	Placebo	4.3 ± 0.8	4.5 ± 0.5	4.2 ± 0.6			
LA area (cm^2)	Amiodarone	18.5 ± 5.7	20.6 ± 8.2	17.7 ± 3.5	0.2358	0.3043	0.8573
	Placebo	20.6 ± 6.8	19.8 ± 4.2	19.8 ± 4.1			
LA volume (ml)	Amiodarone	59.2 ± 29.3	70.9 ± 44.1	52.4 ± 16.2	0.3811	0.2975	0.8080
	Placebo	67.5 ± 31.9	64.1 ± 18.7	62.1 ± 20			
LVEDA_4ch (cm^2)	Amiodarone	18.7 ± 5.3	20.0 ± 7.3	17.9 ± 4.1	0.0733	0.0002 [36,37]	0.4548
	Placebo	22.3 ± 6.6	21.1 ± 6.6	19.4 ± 5.2			
LVESA_4ch (cm^2)	Amiodarone	9.1 ± 3.8	9.9 ± 5.9	9 ± 3.8	0.2130	0.1058	0.7849
	Placebo	10.6 ± 4.6	10.3 ± 4.9	10.4 ± 4.7			
LVFAC_4ch (%)	Amiodarone	39.1 ± 9.1	38.7 ± 8.1	35.1 ± 7.2	0.3701	0.0006 [36,37]	0.3852
	Placebo	41.8 ± 8.8	40.5 ± 6.8	33.8 ± 8.1			
LVEDA_sax (cm^2)	Amiodarone	29.8 ± 7.3	31.2 ± 8.0	29.6 ± 5.9	0.2839	0.6423	0.5196
	Placebo	31.9 ± 7.9	32.2 ± 8.5	31.5 ± 8.3			
LVESA_sax (cm^2)	Amiodarone	18.4 ± 6.3	19.4 ± 6.5	19.3 ± 4.7	0.6495	0.0701	0.2628
	Placebo	18.9 ± 6.9	19.1 ± 5.7	21.1 ± 7			
LVFAC_sax (%)	Amiodarone	51.8 ± 9.6	52.5 ± 11.4	49.9 ± 12.5	0.9397	0.0049 [36,37]	0.5000
	Placebo	53.5 ± 9.6	52.6 ± 9.8	48.3 ± 11.9			
RADt (cm)	Amiodarone	4.0 ± 0.6	4.1 ± 0.6	4.1 ± 0.6	0.2719	0.0687	0.5656
	Placebo	3.9 ± 0.5	4.0 ± 0.7	4.1 ± 0.6			
RA area (cm^2)	Amiodarone	15.7 ± 3.5	15.4 ± 3.0	17.1 ± 4.2	0.8956	0.0033 [36,37]	0.5673
	Placebo	15.6 ± 3.7	15.4 ± 4.4	17.8 ± 4.8			
RA volume (ml)	Amiodarone	43.7 ± 16.6	45.2 ± 13.6	50.3 ± 18.6	0.6651	0.0037 [37]	0.0510
	Placebo	42.8 ± 15.4	42.8 ± 18.9	53.7 ± 26.1			

[35] $P < 0.05$ baseline versus after bolus in both groups
[36] $P < 0.05$ after bolus versus after CPB in both groups
[37] $P < 0.05$ baseline versus after CPB in both groups

Variables	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
RV Diameter	Amiodarone	3.2 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	0.8119	0.2139	0.6561
	Placebo	3.3 ± 0.5	3.2 ± 0.7	3.4 ± 0.6			
RVEDA (cm^2)	Amiodarone	13.7 ± 2.8	14.2 ± 3.9	14.1 ± 3.6	0.2104	0.1514	0.9429
	Placebo	14.4 ± 4.3	15.5 ± 4.2	15.4 ± 3.7			
RVESA (cm^2)	Amiodarone	6.9 ± 1.8	7.6 ± 2.5	7.4 ± 2.3	0.4708	0.0022 [35,36]	0.9902
	Placebo	7.1 ± 2.4	7.8 ± 2	8 ± 2.2			
RVFAC (%)	Amiodarone	49.5 ± 8.9	46.2 ± 10.1	47.0 ± 11	0.4949	0.0555	0.9737
	Placebo	50.6 ± 8	48.7 ± 7.2	47.6 ± 8.9			
TAPSE (cm^2)	Amiodarone	25.5 ± 7.3	22.2 ± 6.9	18.8 ± 5.1	0.7816	< .0001 [36,37]	0.8442
	Placebo	25.4 ± 7.6	23.7 ± 7.4	18.8 ± 7.6			

CPB, cardiopulmonary bypass; LA, left atrium; LADt, left atrial transverse diameter; LVEDA, left ventricular end-diastolic area; LVESA, left ventricular end-systolic area; LVFAC, left ventricular fractional area change; RA, right atrium; RADt, right atrial transverse diameter; RV, right ventricle, RVEDA, right ventricular end-diastolic area, RVESA, right ventricular end-diastolic area, RVFAC, right ventricular fractional area change, TAPSE, tricuspid annular plane systolic excursion

Appendix 7 Doppler echocardiographic variables

Variables	Group	Baseline (Mean ± SD)	After bolus (Mean ± SD)	After CPB (Mean ± SD)	*P* value (group)	*P* value (time)	*P* value (group*time)
Mitral Doppler E (cm/s)	Amiodarone	80.0 ± 36.4	88.6 ± 23.1	106.9 ± 33.4	0.2613	<0.0001[38,3 9,40]	0.6826
	Placebo	79.2 ± 24.7	78 ± 17.6	98.5 ± 23.6			
Mitral Doppler A (cm/s)	Amiodarone	72.3 ± 30	73.8 ± 22.3	66.9 ± 27.5	0.0883	0.8450	0.6390
	Placebo	62.5 ± 22.1	62.8 ± 22.6	62.8 ± 18.8			
Mitral Doppler E/A (cm/s)	Amiodarone	1.2 ± 0.7	1.2 ± 0.3	1.7 ± 0.7	0.1640	0.0124[38,39]	0.0512
	Placebo	1.4 ± 0.7	1.4 ± 0.8	1.6 ± 0.6			
MAV e wave (cm/sec)	Amiodarone	6.9 ± 2.6	7.1 ± 1.7	7.4 ± 1.8	0.5873	0.2250	0.2429
	Placebo	7.8 ± 3.5	7 ± 2.3	7.4 ± 2.0			
MAV a wave	Amiodarone	8.7 ± 2.3	8.1 ± 2.7	8.4 ± 3.8	0.5068	0.8530	0.7383
	Placebo	8.1 ± 2.7	8.4 ± 2.8	7.6 ± 3.3			
MAV e/a wave	Amiodarone	0.8 ± 0.3	0.9 ± 0.3	1.1 ± 0.6	0.3773	0.1735	0.1500
	Placebo	1.1 ± 0.6	0.9 ± 0.4	1.2 ± 0.7			
MAV s wave	Amiodarone	7.9 ± 1.8	8.2 ± 2.9	9.4 ± 3	0.9250	0.0716	0.3480
	Placebo	8.4 ± 2.0	8.7 ± 1.7	8.3 ± 2.2			
E/e ratio	Amiodarone	12.8 ± 10.7	12.6 ± 3.7	15.1 ± 6.9	0.2049	0.0032[39]	0.5783
	Placebo	11.1 ± 4.1	12.4 ± 3.6	13.4 ± 4.3			
PVF S wave	Amiodarone	48.1 ± 21.3	44.5 ± 14.3	57.2 ± 29	0.2714	0.1113	0.3164
	Placebo	43.3 ± 15.2	45.3 ± 16.1	47.8 ± 21.8			
PVF AR wave	Amiodarone	21.1 ± 7.7	22.3 ± 8.7	29 ± 13.7	0.3957	0.0020 [39,40]	0.9299
	Placebo	19.4 ± 6.8	19.5 ± 8.8	27.1 ± 14.2			
PVF D wave	Amiodarone	34.1 ± 12.5	37.7 ± 15.7	61 ± 22.2	0.8846	<0.0001[39,4]	0.0052[41]

[38] $P < 0.05$ baseline versus after bolus in both groups
[39] $P < 0.05$ baseline versus after CPB in both groups
[40] $P < 0.05$ after bolus versus after CPB in both groups
[41] $P = 0.0227$ after CPB in the amiodarone versus placebo group

Variables	Group	Baseline (Mean ± SD)	After bolus (Mean ± SD)	After CPB (Mean ± SD)	*P* value (group)	*P* value (time)	*P* value (group*time)
						0	
	Placebo	39.7 ± 12.5	35.6 ± 16.8	50.3 ± 15.2			
PVF S/D ratio	Amiodarone	1.5 ± 0.6	1.3 ± 0.4	0.9 ± 0.4	0.4232	0.0003[40,5]	0.0112[6]
	Placebo	1.2 ± 0.5	1.4 ± 0.5	1 ± 0.5			
Tricuspid Doppler E (cm/s)	Amiodarone	38.7 ± 11.5	38.5 ± 8.8	47.6 ± 14.2	0.8896	0.0002 [39,40]	0.4455
	Placebo	37.9 ± 10.8	36.8 ± 11.5	53.1 ± 15.8			
Tricuspid Doppler A (cm/s)	Amiodarone	32.3 ± 14.4	44.3 ± 15.7	35.4 ± 18.1	0.6986	0.0013 [38]	0.4440
	Placebo	29.4 ± 10	39.3 ± 15.1	40.5 ± 19.2			
Tricuspid Doppler E/A (cm/s)	Amiodarone	1.3 ± 0.3	0.9 ± 0.2	1.5 ± 0.6	0.8412	<0.0001[38,4 0]	0.3903
	Placebo	1.4 ± 0.6	1 ± 0.3	1.4 ± 0.6			
TAV e wave (cm/sec)	Amiodarone	7.3 ± 2.0	7.1 ± 2	6.9 ± 1.7	0.5660	0.8245	0.2296
	Placebo	7.3 ± 2.6	6.7 ± 1.4	7.7 ± 2.3			
TAV a wave	Amiodarone	11.2 ± 2.7	10.2 ± 3.1	7.8 ± 2.8	0.7881	0.0005 [39,40]	0.5594
	Placebo	10.9 ± 3.3	10.5 ± 2.5	8.8 ± 2.5			
TAV e/a wave	Amiodarone	0.7 ± 0.2	0.8 ± 0.4	1 ± 0.5	0.9933	0.0428 [39,40]	0.6237
	Placebo	0.8 ± 0.8	0.7 ± 0.2	0.9 ± 0.3			
TAV s wave	Amiodarone	8.5 ± 2.3	8.4 ± 2.5	6.7 ± 2.0	0.2006	0.1226	0.2915
	Placebo	8.5 ± 2.1	8.8 ± 3.1	8.2 ± 2.2			
HVF S wave	Amiodarone	19.2 ± 14.7	17.4 ± 15.2	-9.3 ± 21.2	0.8338	<0.0001[39,4 0]	0.1139
	Placebo	17.8 ± 6.3	24.6 ± 11.7	-11.4 ± 23.3			
HVF D wave	Amiodarone	14.8 ± 8.5	17.8 ± 9.6	34.1 ± 15.8	0.2233	<0.0001 [39,40]	0.3519
	Placebo	13.4 ± 5.9	17.8 ± 8.5	28.8 ± 8.5			
HVF AR wave	Amiodarone	12.2 ± 5.7	15.5 ± 8.8	22.3 ± 14.5	0.8067	0.0002 [38,39]	0.5387
	Placebo	12.2 ± 9.4	17.3 ± 9.1	19.9 ± 13.1			

[5] $P < 0.05$ baseline versus after bolus in the placebo group and baseline versus after CPB in the amiodarone group

[6] $P = 0.0136$ baseline compared to after CPB in amiodarone versus placebo

Variables	Group	Baseline (Mean ± SD)	After bolus (Mean ± SD)	After CPB (Mean ± SD)	*P* value (group)	*P* value (time)	*P* value (group*time)
HVF S/D ratio	Amiodarone	1.3 ± 0.8	1.1 ± 0.7	-0.3 ± 0.6	0.3795	<0.0001[39,40]	0.0457[7]
	Placebo	1.4 ± 0.4	1.5 ± 0.7	-0.3 ± 0.8			

AR: atrial reversal; CPB, cardiopulmonary bypass; E: early velocity; A: atrial filling; DT: deceleration time; HVF: hepatic venous flow; MAV: mitral annular velocity, PVF: pulmonary venous flow, SD, standard deviation; TAV: tricuspid annular velocity

[7] *P* = 0.0154 after bolus in the amiodarone compared to the placebo group

Appendix 8 Diastolic function evaluation

Variables	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group*time)
LV diastolic filling abnormality					0.3564*	0.0098[42],[43]	0.0703
Normal	Amiodarone	7 (18%)	8 (30%)	3 (9%)			
	Placebo	2 (6%)	5 (22%)	6 (18%)			
Mild	Amiodarone	24 (62%)	12 (44%)	12 (35%)			
	Placebo	17 (50%)	12 (52%)	11 (33%)			
Moderate	Amiodarone	6 (15%)	7 (26%)	15 (44%)			
	Placebo	10 (29%)	5 (22%)	13 (40%)			
Severe	Amiodarone	2 (5%)	0 (0%)	4 (12%)			
	Placebo	5 (15%)	1 (4%)	3 (9%)			
RV diastolic filling abnormality					0.2332	< .0001[42,43,44]	0.8065
Normal	Amiodarone	3 (8%)	1 (4%)	1 (3%)			
	Placebo	6 (19%)	2 (8%)	1 (4%)			
Mild	Amiodarone	28 (76%)	18 (67%)	1 (3%)			
	Placebo	22 (69%)	16 (64%)	1 (4%)			
Moderate	Amiodarone	3 (8%)	5 (18%)	8 (27%)			
	Placebo	4 (12%)	7 (28%)	8 (29%)			
Severe	Amiodarone	3 (8%)	3 (11%)	20 (67%)			
	Placebo	0 (0%)	0 (0%)	17 (63%)			

CPB, cardiopulmonary bypass; LV, left ventricular; RV, right ventricular

*Generalized estimating equation (GEE) model including group as independent variable was performed at each time point because patients were not evenly distributed among the five-scale score and the model including time, group and groupX time did not converge.

[42] $P < 0.05$ baseline versus after bolus

[43] $P < 0.05$ after bolus versus after CPB

[44] $P < 0.05$ baseline versus after CPB

Appendix 9 Arterial blood gases and biochemistry variables

Variables	Group	Baseline	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
Hemoglobin (g/L)	Inotropes	123 ± 13	95 ± 10	0.6892	< .0001	0.9791
	No inotropes	124 ± 14	96 ± 11			
Na (mmol/L)	Inotropes	141 ± 2	139 ± 3	0.5840	< .0001	0.4216
	No inotropes	141 ± 3	139 ± 3			
K (mmol/L)	Inotropes	4.2 ± 0.3	4.5 ± 0.4	0.3406	< .0001	0.2778
	No inotropes	4.1 ± 0.3	4.5 ± 0.4			
Urea (mmol/L	Inotropes	6.2 ± 1.5	5.6 ± 1.3	0.8087	< .0001	0.3562
	No inotropes	6.2 ± 2.0	5.5 ± 1.8			
Creatinine (umol/L)	Inotropes	80.1 ± 19.9	81.4 ± 27.3	0.4331	0.5825	0.1464
	No inotropes	84.5 ± 25.2	82.8 ± 28.4			
Mg (mmol/L)	Inotropes	0.80 ± 0.08	0.93 ± 0.16	0.1896	< .0001	0.4159
	No inotropes	0.81 ± 0.09	0.97 ± 0.16			
CK total (ug/L)	Inotropes	71.5 ± 52.5	628.5 ± 710.7	0.5573	< .0001	0.5987
	No inotropes	67.5 ± 37.1	562.9 ± 443.7			
CK-MB (ug/L)	Inotropes	1.9 ± 1.1	31.4 ± 51.1	0.2624	< .0001	0.2611
	No inotropes	1.9 ± 0.9	23.9 ± 12.8			
pH (arterial)	Inotropes	7.47 ± 0.04	7.38 ± 0.03	0.6544	< .0001	0.2220
	No inotropes	7.47 ± 0.04	7.37 ± 0.05			
PaO_2 /FiO_2 (mmHg)	Inotropes	411.4 ± 93.5	289.5 ± 126.4	0.3984	< .0001	0.0594
	No inotropes	447.4 ± 82.0	277.3 ± 108.0			
$PaCO_2$ (mmHg)	Inotropes	36.9 ± 4.9	43.9 ± 4.4	0.2331	< .0001	0.1223
	No inotropes	36.8 ± 4.1	45.5 ± 4.5			
HCO3 (mmol/L)	Inotropes	26.6 ± 2.1	26.4 ± 2.5	0.5322	0.1625	0.8421
	No inotropes	26.9 ± 1.7	26.5 ± 2.4			

Variables	Group	Baseline	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
pH (venous)	Inotropes	7.42 ± 0.04	7.35 ± 0.03	0.6245	< .0001	0.2862
	No inotropes	7.43 ± 0.04	7.34 ± 0.04			
PvO_2 (mmHg)	Inotropes	43.50 ± 4.56	37.79 ± 4.09	0.0116	< .0001	0.9668
	No inotropes	45.25 ± 6.43	39.50 ± 4.42			
$PvCO_2$ (mmHg)	Inotropes	43.57 ± 4.31	49.52 ± 4.69	0.6740	< .0001	0.5601
	No inotropes	43.52 ± 4.88	50.09 ± 4.30			
HCO_3 (venous) (mmol/L)	Inotropes	28.63 ± 1.77	27.43 ± 2.28	0.3865	< .0001	0.6117
	No inotropes	29.05 ± 1.93	27.53 ± 2.56			

Appendix 10 Hemodynamic variables

Variable	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
SAP (mmHg)	Inotropes	106.2 ± 15.7	103.5 ± 16.7	121.3 ± 14.9	0.1599	< .0001[45,46]	0.8672
	No inotropes	110.2 ± 18.1	105.6 ± 20.2	123.3 ± 14.9			
DAP (mmHg)	Inotropes	54.3 ± 8	57.4 ± 10.4	56.3 ± 7.5	0.9684	0.0782	0.432
	No inotropes	55.3 ± 9.1	56.1 ± 10.7	56.8 ± 8.645			
MAP (mmHg)	Inotropes	71.6 ± 8.8	72.8 ± 11.6	78 ± 8.8	0.4769	< .0001[45,46]	0.703
	No inotropes	73.6 ± 10.6	72.6 ± 12.6	78.9 ± 8.7			
HR (beats per minutes)	Inotropes	58.4 ± 9	65.7 ± 14.5	72.9 ± 12.6	0.8931	< .0001[45,46,47]	0.9816
	No inotropes	57.9 ± 10.4	65.5 ± 14.3	72.8 ± 13.1			
SPAP (mmHg)	Inotropes	33.3 ± 15.7	38.9 ± 15.2	37 ± 8.8	0.0615	<. 0001[45,46,47]	0.1442
	No inotropes	30.4 ± 8.3	32.6 ± 10.6	35.8 ± 8.2			
DPAP (mmHg)	Inotropes	17.4 ± 7.8	20.1 ± 7.5	17.9 ± 4.9	0.0987	0.0029[47]	0.1244
	No inotropes	16.3 ± 4.8	17.2 ± 5.5	17.6 ± 4.2			
MPAP (mmHg)	Inotropes	22.7 ± 10.1	26.4 ± 9.8	24.2 ± 5.6	0.0704	0.0002[45,47]	0.1179
	No inotropes	21 ± 5.4	22.4 ± 7	23.7 ± 5.3			
CVP (mmHg)	Inotropes	11 ± 3.7	12.2 ± 4.8	13.6 ± 3.9	0.7157	< .0001[45,46,47]	0.8189

[45] $P < 0.05$ baseline versus after CPB

[46] $P < 0.05$ after bolus versus after CPB

[47] $P < 0.05$ baseline versus after bolus

Variable	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
	No inotropes	10.9 ± 3.5	11.8 ± 4.5	13.5 ± 3.6			
PCWP (mmHg)	Inotropes	13.9 ± 5.5	17.1 ± 6.4	15.7 ± 4.3	0.2791	< .0001[46,47]	0.3183
	No inotropes	13.6 ± 4.4	15.4 ± 5.5	15.2 ± 3.9			
SV (ml)	Inotropes	61.7 ± 15	60.1 ± 17.9	66.8 ± 18.9	0.4635	0.0024[45,46]	0.7236
	No inotropes	64.8 ± 18.9	61.4 ± 17.4	68.5 ± 18.1			
CI ($L/m/m^2$)	Inotropes	2 ± 0.4	2.2 ± 0.7	2.7 ± 0.7	0.8752	< .0001[45,46,47]	0.8981
	No inotropes	2 ± 0.5	2.2 ± 0.7	2.7 ± 0.645			
SVRI ($dynes,sec,cm^{-5}/m^2$)	Inotropes	2521 ± 553	2439 ± 915	2010 ± 454	0.9284	< .000145[45]	0.7388
	No inotropes	2592 ± 738	2371 ± 761	2016 ± 440			
PVRI ($dynes,sec,cm^{-5}/m^2$)	Inotropes	358 ± 235	368 ± 238	268 ± 86	0.1187	0.0019[45,46]	0.2905
	No inotropes	307 ± 183	284 ± 251	262 ± 106			

CI, cardiac index; CVP, central venous pressure; CPB, cardiopulmonary bypass; DAP, diastolic arterial pressure; DPAP, dia stolic pulmonary artery pressure; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, indexed pulmonary vascular resistance; SAP, systolic arterial pressure; SPAP, systolic pulmonary artery pressure; SV, stroke volume; SVRI, indexed systemic vascular resistance.

Appendix 11 Two-dimensional echocardiographic variables

Variable	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
LADt (cm)	Inotropes	4.3 ± 0.8	4.8 ± 0.9	4.2 ± 0.9	0.3046	0.0006[48,49]	0.0833
	No inotropes	4.2 ± 0.7	4.4 ± 0.5	4.1 ± 0.5			
LA area (cm^2)	Inotropes	20.2 ± 7.1	22.4 ± 7.5	19.1 ± 4.1	0.0983	0.0243[50]	0.0196[,51]
	No inotropes	18.6 ± 5.3	18.0 ± 4.8	18.4 ± 3.8			
LA volume (ml)	Inotropes	67.2 ± 34.6	80.0 ± 40.5	57.9 ± 19.3	0.1035	0.0410	0.0247[,52]
	No inotropes	58.6 ± 25.9	55.6 ± 22.2	56.3 ± 18.4			
LVEDA_4ch (cm^2)	Inotropes	20.5 ± 5.9	21.1 ± 7.4	18.7 ± 3.8	0.8564	0.0003[49,53]	0.8335
	No inotropes	20.3 ± 6.4	20.2 ± 6.7	18.5 ± 5.4			
LVESA_4ch (cm^2)	Inotropes	9.7 ± 4.1	9.9 ± 5.2	9.3 ± 3.3	0.7292	0.0760	0.5879
	No inotropes	9.9 ± 4.3	10.3 ± 5.6	10.0 ± 5.0			
LVFAC_4ch (%)	Inotropes	41.1 ± 7.6	39.9 ± 7.9	35.9 ± 6.6	0.1738	0.0013[49,53]	0.8206
	No inotropes	39.8 ± 9.9	39.3 ± 7.2	33.2 ± 8.3			
LVEDA_sax (cm^2)	Inotropes	31.7 ± 6.4	31.9 ± 8.1	30.5 ± 5.3	0.8790	0.7867	0.2383
	No inotropes	30.1 ± 8.4	31.4 ± 8.4	30.5 ± 8.5			
LVESA_sax (cm^2)	Inotropes	18.8 ± 5.2	19.4 ± 6.5	19.6 ± 4.3	0.7658	0.0957	0.1956
	No inotropes	18.5 ± 7.3	19.1 ± 5.7	20.7 ± 7.1			
LVFAC_sax (%)	Inotropes	53.5 ± 8.9	54.4 ± 10.0	50.9 ± 10.1	0.2298	0.0058[49,53]	0.6633
	No inotropes	52.0 ± 10.1	51.1 ± 10.8	47.6 ± 13.7			

[48] P <0.05 baseline versus after bolus in both groups
[49] P < 0.05 after bolus versus after CPB in both groups
[50] P < 0.05 baseline versus after bolus in the inotropes group
[51] P = 0.0135 after bolus in the inotropes versus no inotropes group.
[52] P = 0.0117 after bolus in the inotropes versus no inotropes group.
[53] P < 0.05 baseline versus after CPB in both groups

Variable	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
RADt (cm)	Inotropes	3.9 ± 0.5	4.0 ± 0.7	4.0 ± 0.7	0.3409	0.1738	0.4578
	No inotropes	4.0 ± 0.5	4.2 ± 0.5	4.3 ± 0.5			
RA area (cm^2)	Inotropes	15.8 ± 4.2	14.5 ± 3.7	16.5 ± 4.8	0.6457	0.0049[49,53]	0.5822
	No inotropes	15.6 ± 3.1	16.8 ± 3.7	18.0 ± 4.2			
RA volume (ml)	Inotropes	44.2 ± 18.2	39.3 ± 15.1	47.2 ± 20.9	0.4803	0.0268[49]	0.3501
	No inotropes	42.5 ± 14.1	51.2 ± 16.9	55.3 ± 22.9			
RV Diameter	Inotropes	3.3 ± 0.5	3.2 ± 0.5	3.4 ± 0.5	0.9016	0.3020	0.2890
	No inotropes	3.2 ± 0.5	3.3 ± 0.7	3.3 ± 0.6			
RVEDA (cm^2)	Inotropes	14.4 ± 3.8	14.8 ± 3.3	14.3 ± 3.5	0.7268	0.1646	0.2699
	No inotropes	13.7 ± 3.5	14.8 ± 4.7	14.9 ± 3.9			
RVESA (cm^2)	Inotropes	7.3 ± 2.4	8.0 ± 2.5	7.4 ± 2.1	0.3383	0.0265[50,54]	0.0197[,55]
	No inotropes	6.7 ± 1.9	7.4 ± 2.0	7.9 ± 2.4			
RVFAC (%)	Inotropes	49.2 ± 9.4	45.5 ± 10.0	47.9 ± 9.7	0.3611	0.1405	0.1724
	No inotropes	50.7 ± 7.8	49.1 ± 7.6	46.7 ± 10.5			
TAPSE (cm^2)	Inotropes	25.2 ± 6.4	23.1 ± 7.7	19.8 ± 7.3	0.7944	< .0001[48,49,53]	0.4321
	No inotropes	25.7 ± 8.2	22.5 ± 6.6	17.9 ± 5.2			

CPB, cardiopulmonary bypass; LA, left atrium; LAA, feft atrial area; LADt, left atrial transverse diameter; LVEDA, left ventricular end-diastolic area; LVESA, left ventricular end-systolic area; LVFAC, left ventricular fractional area change; RA, right atrium; RAA, right atrial aappendage; RADt, right atrial transverse diameter; RV, right ventricle, RVEDA, right ventricular end-diastolic area, RVESA, right ventricular end-diastolic area, RVFAC, right ventricular fractional area change, TAPSE, tricuspid annular plane systolic excursion.

[54] $P < 0.05$ baseline versus after CPB in the no inotropes group
[55] $P = 0.0596$ after bolus in the inotrope versus no inotropes group

Appendix 12 Doppler echocardiographic variables

Variables	Group	Baseline	Afterbolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
Mitral Doppler E (cm/s)						< .0001[56, 57]	
	Inotropes	90.8 ± 39.7	93.9 ± 19.8	111 ± 30.8	0.0028		0.8033
	No inotropes	71.5 ± 20.2	75.5 ± 18.9	96.3 ± 26.7			
Mitral Doppler A (cm/s)	Inotropes	74.6 ± 31.4	71.2 ± 25.7	76.1 ± 21.8	0.0076	0.3766	0.4747
	No inotropes	62.7 ± 22.1	66.6 ± 20.9	53.6 ± 19.4			
Mitral Doppler E/A (cm/s)	Inotropes	1.3 ± 0.7	1.5 ± 0.7	1.6 ± 0.7	0.6883	0.0048[56,58]	0.2728
	No inotropes	1.3 ± 0.7	1.2 ± 0.4	1.8 ± 0.7			
MAV e wave (cm/sec)	Inotropes	7.5 ± 3.7	7 ± 1.6	7.2 ± 1.8	0.978	0.2231	0.4579
	No inotropes	7.2 ± 2.6	7.1 ± 2.3	7.5 ± 2			
MAV a wave	Inotropes	8.8 ± 2.5	7.6 ± 1.8	9.1 ± 4.3	0.434	0.8709	0.0252[59]
	No inotropes	8.2 ± 2.6	8.7 ± 3.1	7.2 ± 2.6			
MAV e/a wave	Inotropes	0.94 ± 0.61	1.01 ± 0.43	1.04 ± 0.62	0.8168	0.2325	0.0789

[56] $P < 0.05$ baseline versus after CPB in both groups
[57] $P < 0.05$ after bolus versus after CPB in both groups
[58] $P < 0.05$ baseline versus after bolus in both groups
[59] $P = 0.0373$ after CPB in the inotropes versus no inotropes group.

Variables	Group	Baseline	Afterbolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
	No inotropes	0.95 ± 0.39	0.87 ± 0.29	1.2 ± 0.61			
MAV s wave	Inotropes	8.4 ± 2	7.6 ± 1.2	9.8 ± 3.2	0.9906	0.2593	0.0086[60]
	No inotropes	8 ± 1.8	9.1 ± 2.9	8.2 ± 2			
E/e ratio	Inotropes	13.9 ± 11.9	13.6 ± 3.7	16.6 ±6.8	0.0104	0.0587	0.5347
	No inotropes	10.4 ± 2.6	11.7 ± 3.3	12.5 ± 4.3			
PVF S wave	Inotropes	46.4 ± 23	42.8 ± 13.4	57.3 ± 34	0.5504	0.0538	0.247
	No inotropes	45.5 ± 15.4	46.4 ± 16.1	48.9 ± 18			
PVF AR wave	Inotropes	19.9 ± 6.7	18.3 ± 5.3	32.9 ± 15.7	0.5166	0.0004[61]	0.0459[62]
	No inotropes	20.7 ± 7.8	23.2 ± 10.4	25.2 ± 11.8			
PVF D wave						< .0001[56,57]	
	Inotropes	37.1 ± 12.8	38.4 ± 17.2	60.3 ± 20	0.1095		0.3141
	No inotropes	36.4 ± 12.9	35.5 ± 15.5	52.2 ± 18.7			
PVF S/D ratio	Inotropes	1.37 ± 0.66	1.29 ± 0.51	0.98 ± 0.52	0.5688	0.0005[63]	0.5907
	No inotropes	1.36 ± 0.55	1.41 ± 0.45	1.03 ± 0.44			

[60] $P = 0.0351$ after bolus in the inotropes versus no inotropes group.
[61] $P < 0.05$ baseline and after bolus versus after CPB in the inotropes group
[62] $P = 0.0510$ after CPB in the inotropes versus no inotropes group
[63] $P = 0.0004$ baseline versus after CPB and P = 0.0003 after bolus versus after CPB

Variables	Group	Baseline	Afterbolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
Tricuspid Doppler E (cm/s)						< .0001[56,5]	
	Inotropes	40.4 ± 12.9	40.7 ± 11.5	55.4 ± 13.8	0.0188	[7]	0.3733
	No inotropes	36.5 ± 9	35.2 ± 8.2	45.8 ± 15.2			
Tricuspid Doppler A (cm/s)	Inotropes	29.8 ± 11.4	47 ± 18.2	38.1 ± 21.6	0.4135	< .0001[64]	0.0034[65]
	No inotropes	31.7 ± 13.2	37.8 ± 11.4	38.1 ± 16.2			
Tricuspid Doppler E/A (cm/s)						< .0001[57,5]	
	Inotropes	1.48 ± 0.6	0.92 ± 0.24	1.66 ± 0.57	0.1006	[8]	0.1001
	No inotropes	1.25 ± 0.36	0.99 ± 0.3	1.35 ± 0.58			
TAV e wave (cm/sec)	Inotropes	7.5 ± 2.7	6.3 ± 1.7	6.6 ± 2.4	0.1916	0.6139	0.2062
	No inotropes	7.2 ± 2	7.4 ± 1.8	7.7 ± 1.6			
TAV a wave	Inotropes	11 ± 3	10.7 ± 3	9 ± 2.6	0.3541	0.0007[56,57]	0.5037
	No inotropes	11 ± 3	10.1 ± 2.7	7.8 ± 2.7			
TAV e/a wave	Inotropes	0.83 ± 0.86	0.61 ± 0.17	0.77 ± 0.3	0.1976	0.0306[57]	0.151
	No inotropes	0.66 ± 0.23	0.81 ± 0.41	1.11 ± 0.45			
TAV s wave	Inotropes	8.2 ± 1.7	8.3 ± 3	7.3 ± 2.7	0.4917	0.1067	0.9421

[64] $P = 0.0001$ baseline versus after bolus in the inotropes group
[65] $P = 0.0273$ after bolus in the inotropes versus no inotropes group

Variables	Group	Baseline	Afterbolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group * time)
	No inotropes	8.6 ± 2.5	8.8 ± 2.6	7.4 ± 1.9			
HVF S wave	Inotropes	21.5 ± 12.4	18.6 ± 7.6	-14.4 ± 23.9	0.3965	<.0001[56,57]	0.0093[66]
	No inotropes	16.2 ± 10.1	22.4 ± 16.7	-7.3 ± 20.4			
HVF D wave						< .0001[56,5	
	Inotropes	15.2 ± 8.7	16.5 ± 10.1	31.6 ± 12.7	0.8754	7,3]	0.3452
	No inotropes	13.3 ± 6.1	18.7 ± 8.3	31.5 ± 13.3			
HVF AR wave	Inotropes	13.8 ± 9.9	13.5 ± 7.7	29.8 ± 17.6	0.0904	0.0004[57,67]	0.003[68]
	No inotropes	10.9 ± 4.8	17.9 ± 9.2	15.3 ± 5.1			
HVF S/D ratio						< .0001[56,5	
	Inotropes	1.44 ± 0.38	1.23 ± 0.46	-0.37 ± 0.73	0.946	7]	0.2721
	No inotropes	1.29 ± 0.75	1.28 ± 0.85	-0.22 ± 0.64			

E: early velocity, A: atrial filling; AR: atrial reversal; CPB, cardiopulmonary bypass; DT: deceleration time, HVF: hepatic venous flow; MAV: mitral annular velocity, PVF: pulmonary venous flow, TAV: tricuspid annular velocity

[66] $P = 0.0654$ baseline in the inotropes versus no inotropes group

[67] $P < 0.05$ baseline versus after CPB in the inotrope group and baseline versus after bolus in the non-inotropes group.

[68] $P = 0.0102$ after CPB in the inotropes versus no inotropes group

[3] $P = 0.0654$ baseline in the inotropes versus no inotropes group

Appendix 13 Diastolic function evaluation

Variable	Group	Baseline	After bolus	After CPB	*P* value (group)	*P* value (time)	*P* value (group*time)
LV diastolic filling abnormality							
Normal	Inotropes	5 (16%)	6 (28%)	3 (10%)	0.9045*	0.0120[69]	0.6665
	No inotropes	4 (9%)	7 (24%)	6 (16%)			
Mild	Inotropes	17 (55%)	8 (38%)	10 (35%)			
	No inotropes	24 (57%)	16 (55%)	13 (34%)			
Moderate	Inotropes	6 (19%)	6 (29%)	14 (48%)			
	No inotropes	10 (24%)	6 (21%)	14 (37%)			
Severe	Inotropes	3 (10%)	1 (5%)	2 (7%)			
	No inotropes	4 (10%)	0 (0%)	5 (13%)			
RV diastolic filling abnormality					0.5703	< .0001[42,70]	0.2623
Normal	Inotropes	6 (21%)	1 (4%)	1 (4%)			
	No inotropes	3 (8%)	2 (7%)	1 (3%)			
Mild	Inotropes	20 (69%)	14 (64%)	1 (4%)			
	No inotropes	30 (75%)	20 (67%)	1 (3%)			
Moderate	Inotropes	3 (10%)	7 (32%)	6 (24%)			
	No inotropes	4 (10%)	5 (17%)	10 (31%)			
Severe	Inotropes	0 (0%)	0 (0%)	17 (68%)			
	No inotropes	3 (7%)	3 (10%)	20 (63%)			

CPB, cardiopulmonary bypass; LV, left ventricular; RV, right ventricular

*Generalized estimating equation (GEE) model including group as independent variable was performed at each time point because patients were not evenly distributed among the five-scale score and the model including time, group and groupX time did not converge.

[69] $P < 0.05$ after bolus versus after CPB

[70] $P < 0.05$ baseline versus after CPB

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