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Intraoperative Hemodynamic Instability During and After Separation From Cardiopulmonary Bypass

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Abstract

Every year, more than 1 million patients worldwide undergo cardiac surgery. Because of the aging of the population, cardiac surgery will increasingly be offered to patients at a higher risk of complications. The consequence is a reduced physiological reserve and hence an increased risk of mortality. These issues will have a significant impact on future health care costs because the 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). When separation from CPB is associated with right-ventricular failure, the mortality rate will range from 44% to 86%. Therefore, the diagnosis and the preoperative prediction of difficult separation from CPB will be crucial to improve the selection and care of patients and to prevent complications for this high-risk patient population.

Keywords

cardiopulmonary bypass, hemodynamic instability, cardiac surgery

Introduction

One of the dreaded complications in cardiac surgery is difficult separation from cardiopulmonary bypass (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 ventricle (RV) failure, the mortality rate will range from 44% to 86%.[1-5] For this reason the preoperative diagnosis and the prediction 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. In the following text, we will define difficult separation from CPB and review the predictors, the significance, and the consequences of this important complication in cardiac surgery.

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. After the preoperative evaluation, the patient is brought into 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 into 3 periods: before, during, and after CPB.

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 surgeries are performed using CPB. 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 and anesthesiologist jointly decide to gradually reduce the venous return from the CPB and derive it back

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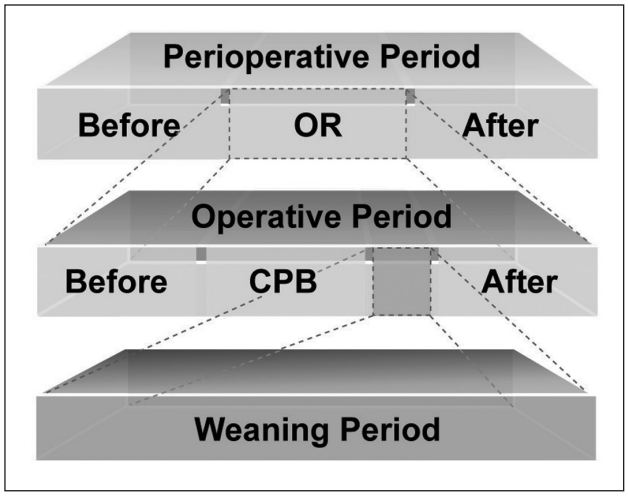

Figure 1. Time sequence of a cardiac surgical procedure: a cardiac surgical procedure can be divided into 3 periods: before, in the operating room (OR), and after the procedure. The time after the procedure includes the time spent in the intensive care unit and in the hospital. In the OR, there are 3 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. The expression *difficult separation from CPB* is related to both the weaning period and the operative period following CPB

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 manuscript, the expression *difficult separation from CPB* is related to both the weaning period and the intraoperative period following CPB.

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 intraaortic balloon pump (IABP) or a ventricular assist device will be used. There are several reasons or mechanisms to explain this failure to wean from CPB, but they are beyond the scope of this article. However, the anesthesiologist using transesophageal echocardiography (TEE) will have an important role to play if difficult weaning from CPB occurs. As TEE is now considered standard of care in cardiac surgery,[6] the role of the anesthesiologist will be to rule out any unexpected surgical complication such as a dysfunctional prosthesis. In the largest series published so far on the role of TEE in 12 566 patients undergoing cardiac surgery, Eltzschig et al[7] observed that TEE influenced cardiac surgical decisions in 9% of all cases. This has also been our experience at the Montréal Heart Institute (MHI).[8] In some of these cases, the surgeon will have to revise his or her 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. 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.[9] Several authors have studied and defined difficult separation from CPB. These definitions are summarized in Table 1.[10-28] Butterworth et al[15] 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 L/min/m^2), or both. The 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[29] defined heart failure after cardiac surgery as hypotension or low cardiac index requiring return on CPB, inotropic support, or requirement for an IABP. Muller et al[21] 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 L/min/m^2. The term *postbypass inotropic support* has been used as a synonym for difficult separation from CPB and defined as the use of dopamine, dobutamine, or epinephrine for at least 12 hours in the intensive care unit.[9,20] The use of dopamine from 0.5 to 3.0 μg/kg/min to increase urine output was not considered in the definition of inotropic support.[9] Finally, the term *low cardiac output syndrome* (LCOS) has been used in several studies[30-32] to describe the consequence of difficult separation from CPB. The term LCOS also covers the period in

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 CPB Definitions
Boldt et al[10]	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 et al[11]	1993	19	Prospective, open-labeled, phase IV study	Elective cardiac surgery patients	DPAP > 15 mm Hg or CVP > 15 mm Hg
Butterworth et al[13]	1993	39	Prospective, randomized, double-blind study	33 elective CABG patients, 6 valve surgery patients	CI < 2.2 L/min/m^2
De Hert et al[14]	1995	20	Prospective, randomized, double-blind study	Elective cardiac surgery patients. CABG only	CI < 2 L/min/m^2
Butterworth et al[15]	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 et al[16]	1998	28	Prospective study, nonrandomized and not blinded	CABG and valve surgery patients	CI < 2.2 L/min/m^2 despite NTG and inotropes infusions
Yamada et al[17]	2000	48	Prospective, randomized, double-blind study	Elective cardiac surgery patients; CABG only	CI < 2.5 L/min/m^2, SAP < 90 mm Hg
Suematsu et al[18]	2000	167	Retrospective analysis	Elective cardiac surgery patients requiring CPB	Intraoperative need for epinephrine and/or norepinephrine exceeding 0.2 μg/kg/min
Bernard et al[20]	2001	66	Prospective observational cohort study	52 elective CABGs alone, 14 combined procedures, valvular surgeries and reoperations	SAP < 80 mm Hg, DPAP > 15 mm Hg during weaning from CPB, reinstitution of CPB, or an IABP. Presence of significant vasopressor and/or inotropic support
Van der Maaten et al[19]	2001	34	Prospective, nonrandomized clinical study	Elective cardiac surgery patients. CABG only	CI < 2.4 L/min/m^2 and/or MAP < 60 mm Hg
Muller et al[21]	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 et al[22]	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 mm Hg, and/or SAP < 90 mm Hg
Wagner et al[24]	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 et al[25]	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 occurred during weaning from CPB. IABP was installed if instability persisted despite medical treatment

(continued)

Table 1. (continued)

Author and References	Year of Publication	Number of Patients	Type of Study	Population	Difficult Separation From CPB Definitions
McKinlay et al[26]	2004	1009	Retrospective analysis	Elective cardiac surgery patients. CABG and complex procedures	Inotropic support in the form of dopamine (>5 μg/kg/min) or any dose of epinephrine, norepinephrine, dobutamine, or milrinone, along with IABP versus hypotension, low cardiac output, and inability to separate from bypass
Surgenor et al[33]	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 et al[27]	2006	1498	Retrospective analysis	Elective cardiac surgery patients, all types combined (CABG, valve, complex and miscellaneous procedures)	SAP < 80 mm Hg, DPAP or wedge pressure >15 mm Hg during weaning from CPB, reinstitution of CPB or an IABP. Presence of significant vasopressor and/or inotropic support

Note: CABG = coronary artery bypass graft; CVP = central venous pressure; 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 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 mm Hg and the cardiac output at 2.2 L/min/m² for 30 minutes in the intensive care unit after correction of all 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, or ≥2 inotropes at 48 hours postoperatively.[33]

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, whereas other investigators include both periods in their definition (Table 1). In the setting of cardiac surgery, in our institution, we define difficult separation from CPB as the process that takes place between the beginning of the weaning process of CPB and continues until patients can support normal physiological functioning on their own. Each of these elements requires consideration and should be carefully analyzed.

The first element that helps define difficult separation from bypass is 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.[34,35] This is a very important point and is illustrated in Figure 2.

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[34,36] in the literature, the mechanisms responsible for this gradient remain poorly understood,[37] and its presence is not routinely recognized. The pressure gradient is normally <20 mm Hg between the aortic root and radial artery, being higher in the distal arteries.[38] In our clinical experience involving a large series of patients undergoing cardiac

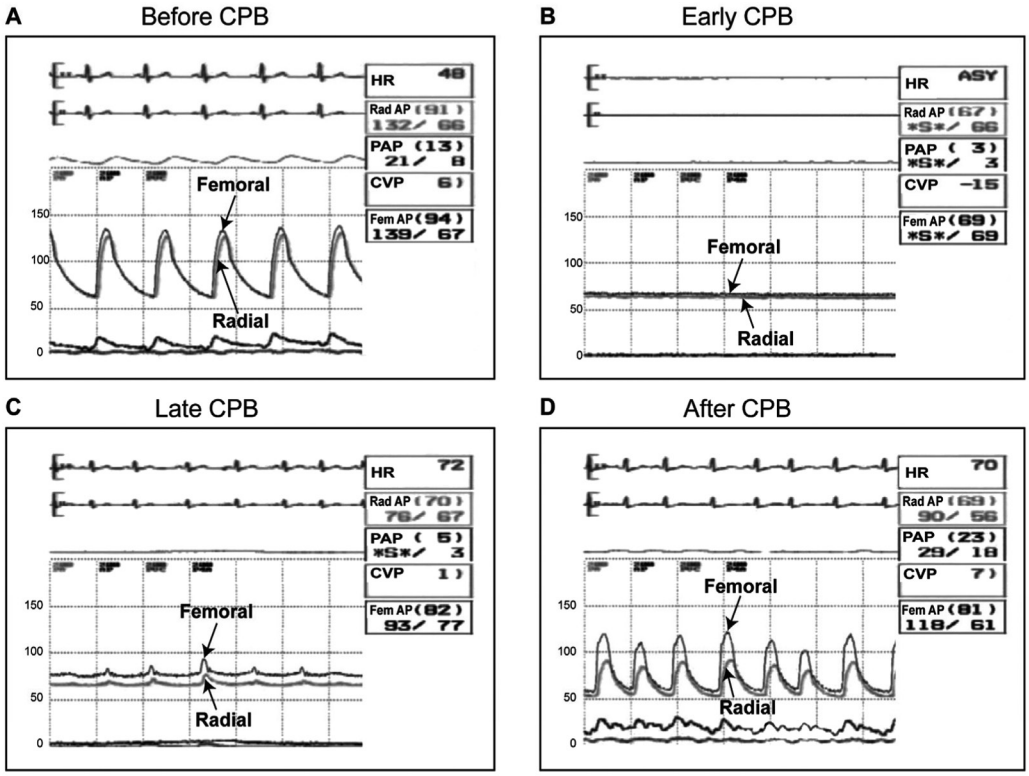

Figure 2. Radial to femoral artery pressure gradient during cardiac surgery: A. Before cardiopulmonary bypass (CPB) a normal gradient between the radial (Rad) and femoral (Fem) artery was observed. B. During the early part of CPB, no abnormality in gradient was observed. C. The gradient appears during the later part of CPB. D. After CPB, the systolic and mean femoral artery pressures were 118 mm Hg and 81 mm Hg, respectively. The systolic and mean radial artery pressures were 90 mm Hg and 69 mm Hg, respectively (with permission of Denault et al[35])
Note: HR = heart rate; AP = arterial pressure; PAP = pulmonary artery pressure; CVP = central venous pressure.

surgery, radial artery/aortic root systolic pressure gradients >25 mm Hg (the radial being lower than the aortic) occur in approximately 30% to 50% of cardiac procedures. Maximum gradients are usually observed just after separation from CPB. In some patients, these gradients resolve toward the end of the procedure, but there is limited predictability regarding their dynamic variations. In the operating room using TEE and the intensive care unit using either TEE or transthoracic echocardiography can also be used to detect an abnormal arterial gradient when clinically significant mitral regurgitation is present.[35] Early recognition of an abnormally wide aortic–radial-arterial pressure gradient is one of the first and most important steps in recognizing true 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 mm Hg[11] or 20 mm Hg.[22] 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.[40-48] If ventricular compliance is reduced after cardiac surgery, ventricular filling pressures will increase to maintain an appropriate preload and cardiac output. This observation explains why Reichert et al[49] defined post–cardiac surgery hypovolemia as a pulmonary capillary wedge pressure value less than the preoperative wedge pressure +10 mm Hg. 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 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 LV[19,44,46,48,50-54] as opposed to biventricular systolic and diastolic evaluation.[55,56] This limitation could result in a misinterpretation of the actual change in cardiac function. Thus, the appreciation of cardiac filling pressure in relation to fluid responsiveness is not an easy measurement to make and there is ongoing research to better define this situation.

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.[57] At the MHI, significant vasopressive and/or inotropic support is defined by one of the following: norepinephrine > 0.06 μg/kg/min; epinephrine > 0.06 μg//kg/min, dobutamine > 2 μg/kg/min or the use of milrinone.[58] Returning on CPB can be secondary to hemodynamic or mechanical complications and is a severity criterion. The use of an IABP and a ventricular assist device to wean from CPB implies a severe mechanical problem most likely related to the patient's underlying condition. Finally, to standardize the vasoactive management during CPB and the weaning process, we developed algorithms to be applied in studies dealing with separation from CPB.[58-60]

At our institution, we classify difficult separation from CPB into 3 categories. Easy separation is defined as the use of one vasoactive drug, difficult when both a vasopressor and an inotrope are required, and very difficult when, despite pharmacological support, return on CPB is necessary or mechanical devices such as an IABP are used. To explore the relationship between difficult separation from CPB, mortality, and morbidity, we analyzed 6120 consecutive patients from 1995 to 1999 operated at the MHI. 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 neurological 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 2 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 having had easy, difficult, and very difficult separation from CPB. Their mortality rates were 0.7%, 4.5%, and 22.4% ($P < .001$), respectively. In patients with difficult and very difficult separation from CPB, 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 ($P < .0001$).

In summary, the definition used to describe difficult separation from CPB varies significantly among investigators. Clearly 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 because each patient can serve as his or her 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 because it appears that different grades of severity in separation from CPB can be present. A more severe form of difficult separation from CPB would be the one associated with the requirement for mechanical devices and the worst one would be intraoperative death.

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,[61] the Parsonnet score,[62] the EuroSCORE,[63] the Cardiac Anesthesia Risk Evaluation (CARE) score,[64] and the Society of Thoracic Surgeons score.[65] 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.

Demographic and Surgical Variables

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

Coronary revascularization. In patients undergoing coronary revascularization, Surgenor et al[29] 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,[9] previous myocardial infarction, and chronic pulmonary obstructive disease.[21] Rao et al[30] 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 ratios in parentheses) LV ejection fraction (LVEF) < 20% (5.7), repeat operation (4.4), emergency operation (3.7), female gender (2.5), diabetes (1.6), age >70 years (1.5), left main coronary artery stenosis (1.4), recent myocardial infarction (1.4), and triple-vessel disease (1.3).

Valvular surgery. With the exception of aortic valve replacement (AVR), 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[26] identified coronary revascularization in association with mitral valve repair or replacement as an independent risk factor for postoperative inotropic support. Maganti et al[32] retrospectively analyzed the risk of LCOS from a database of 2255 patients operated for isolated AVR 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 ratios in parentheses): renal failure (5.0), earlier year of operation (4.4), LVEF < 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.[15] In a study involving AVR in combination with revascularization, Ahmed et al[66] identified preoperative renal disease, elevated LV end-diastolic pressure (LVEDP; ≥20 mm Hg), reduced LVEF (≤40%), and low cardiac index (≤2.5 L/m/m^2) as predictors of postoperative inotropic requirements.

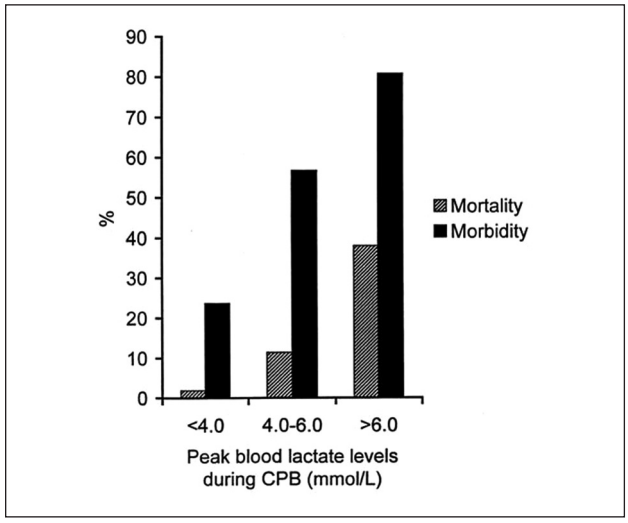

Figure 3. Mortality and morbidity in relation with lactate level during cardiopulmonary bypass (CPB): positive correlation in 1376 cardiac surgical patients between peak blood lactate levels during CPB and the rate of postoperative morbidity and mortality ($P < .001$; with permission of Demers et al[71])

Duration and utilization of CPB. Both the duration of CPB and cross-clamping are surgical variables that predict hemodynamic complications in several studies.[9,20-22,25-27,67,68] We have also documented that hemodynamic complications were observed in 53% of patients undergoing coronary revascularization in whom CPB was used, as opposed to 14% of patients undergoing surgery with off-pump bypass.[27] The use of CPB was indeed an independent predictor of hemodynamic complications ($P < .0001$), and this was also observed by other authors.[9,25,69] As suggested by Butterworth et al,[15] 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.[25,33]

Biochemical Variables

Among the biochemical variables, our group observed that an elevated venoarterial PCO_2 gradient before the cardiac surgical procedure was an independent variable associated with an increased risk of difficult separation from CPB.[67] Elevated venoarterial PCO_2 gradient is a marker of

ischemia,[70] 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).[71]

These 2 studies, conducted at the MHI, tend to support the theory 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[31] 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 LVEF were the only 2 predictors of this metabolic abnormality after CPB. The rise in creatinine kinase was not a predictor of LCOS. Other authors have also confirmed that reduced myocardial pH[72] (Figure 4) or increased myocardial lactate measured during CPB[73] 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 article by Turer et al[74] 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 LV dysfunction have limited myocardial metabolic reserve and flexibility after global ischemia/reperfusion stress.

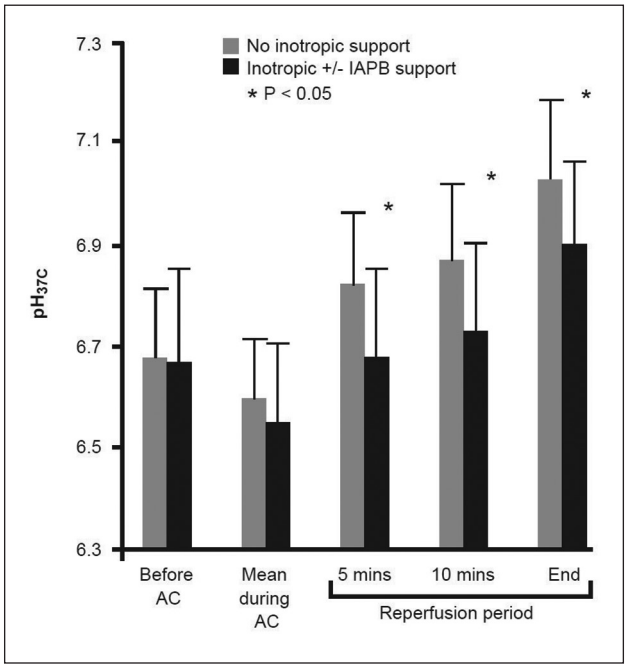

Figure 4. Intramyocardial acidosis and inotropic requirement: comparison of myocardial tissue pH_{37C} between patients who needed inotropic support versus those who did not at 5 time points during surgery: Before aortic occlusion (AC), mean during AC, at 5 minutes of reperfusion, at 10 minutes of reperfusion, and at the end of reperfusion (adapted from Kumbhani et al[72])
Note: IABP = intra-aortic balloon pump.

Hemodynamic and Echocardiographic Variables

Among the hemodynamic data predicting post-CPB inotropic support and mortality after cardiac surgery, LV systolic dysfunction is frequently found to be the most important and frequently reported variable.[9,15,21,22,26,30,32,33,66,68,72] LV dysfunction is either defined by a history of congestive heart failure, by a cardiac variable such as reduced 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.[9,15,21,27,33] LV dysfunction will be associated with echocardiographic evidence of abnormal regional or global wall motion and can also be associated with an elevated LVEDP. This parameter has also been reported as an independent predictor of inotropic requirement[9,66] and mortality.[75]

RV systolic and diastolic dysfunction may also be a predictor of mortality and morbidity. Maslow et al[76] studied patients with reduced LV systolic function (LVEF ≤ 25%) before coronary revascularization. Those without RV 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 RV dysfunction experienced more frequent difficult separation from CPB and a mortality rate of 100% within 18 months. This study supports the hypothesis that preoperative RV systolic dysfunction is a predictor of difficult weaning from CPB and mortality before cardiac surgery. However, RV diastolic dysfunction may also be an important criterion to be evaluated. In a pilot study of 121 patients undergoing cardiac surgery, Carricart et al[77] observed that preoperative abnormal hepatic venous flow, as a marker of RV diastolic dysfunction,[78,79] 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

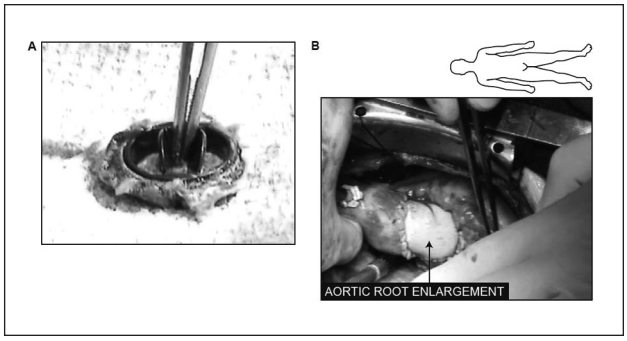

Figure 5. Patient–prosthesis mismatch: A. A 71-year-old man with a body surface area of 1.89 m² was reoperated for symptoms of severe aortic valve stenosis (severe dyspnea, NYHA class IV, and pulmonary hypertension of 60/15 mm Hg). He had had aortic valve replacement (AVR) 4 years ago with a Carbomedics #19 mechanical bileaflet prosthesis (effective orifice area = 1.06 cm²). The preoperative mean gradient was 41 mm Hg. 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[92])

abnormal RV 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.[61,62,80-82] However, few studies have reported an association between pulmonary hypertension and difficult weaning from CPB.[27,77,83]

Patient–Prosthesis Mismatch (PPM)

Aortic PPM is the result of a prosthesis that is too small for the patient's body surface area.[84-91] 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 there occurs a so-called PPM, which increases intraoperative and long-term mortality (Figure 5).[84-91]

From various studies, PPM can be found in 19% to 70% of patients undergoing AVR.[85-88] In a study including 1266 patients who underwent AVR at the Quebec Heart and Lung Institute, the prevalence of moderate PPM defined as an index EOA (iEOA) ≤ 0.85 cm^2/m^2 was 38% and that of severe PPM (iEOA ≤ 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 LV afterload with associated reduced coronary flow reserve[93] 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[94] 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[95] and defined as an iEOA ≤ 1.2 cm^2/m^2. In a study that 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, RV 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.

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).

Coronary embolization from air or residual debris that can occur after CPB (Figure 7) could also be associated with difficult weaning from CPB. Additionally, technical problems such as a residual paravalvular leak or dysfunctional prosthesis (Figure 8) could also contribute to difficult weaning from CPB. All these conditions can be diagnosed and prevented with TEE. Finally, the reperfusion syndrome could also be associated with unexpected pulmonary hypertension on weaning from CPB.

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 LV and RV 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

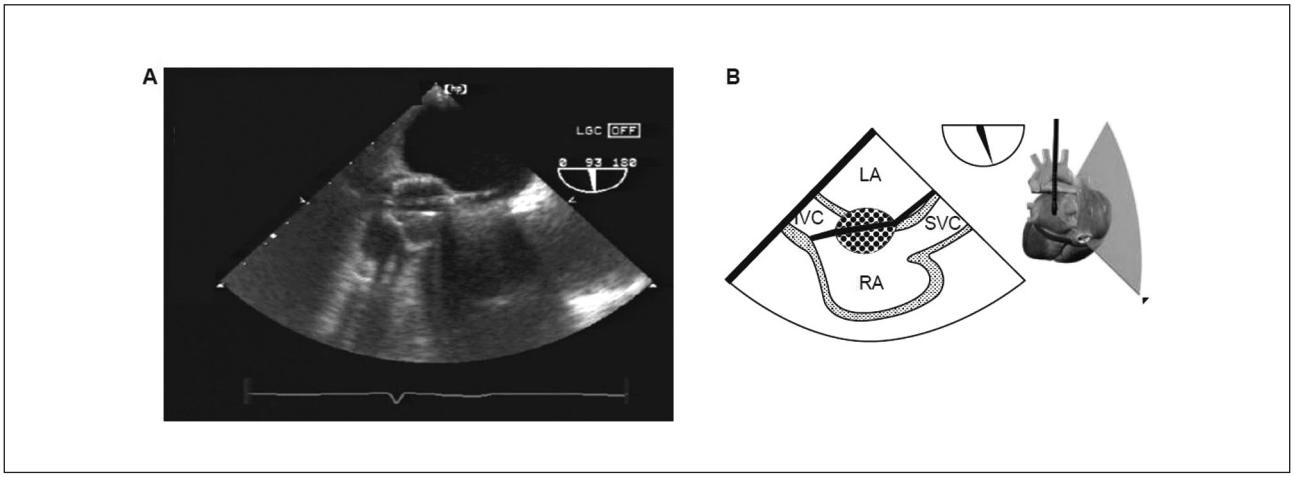

Figure 6. Retrograde cardioplegia cannula: (A, B) Bicaval view showing the retrograde cardioplegia cannula positioned toward the atrial septum through the patent foramen ovale (photo courtesy of Dr Baqir Qizilbash with permission of Denault et al[96])
Note: IVC = inferior vena cava; LA = left atrium; RA = right atrium; SVC = superior vena cava.

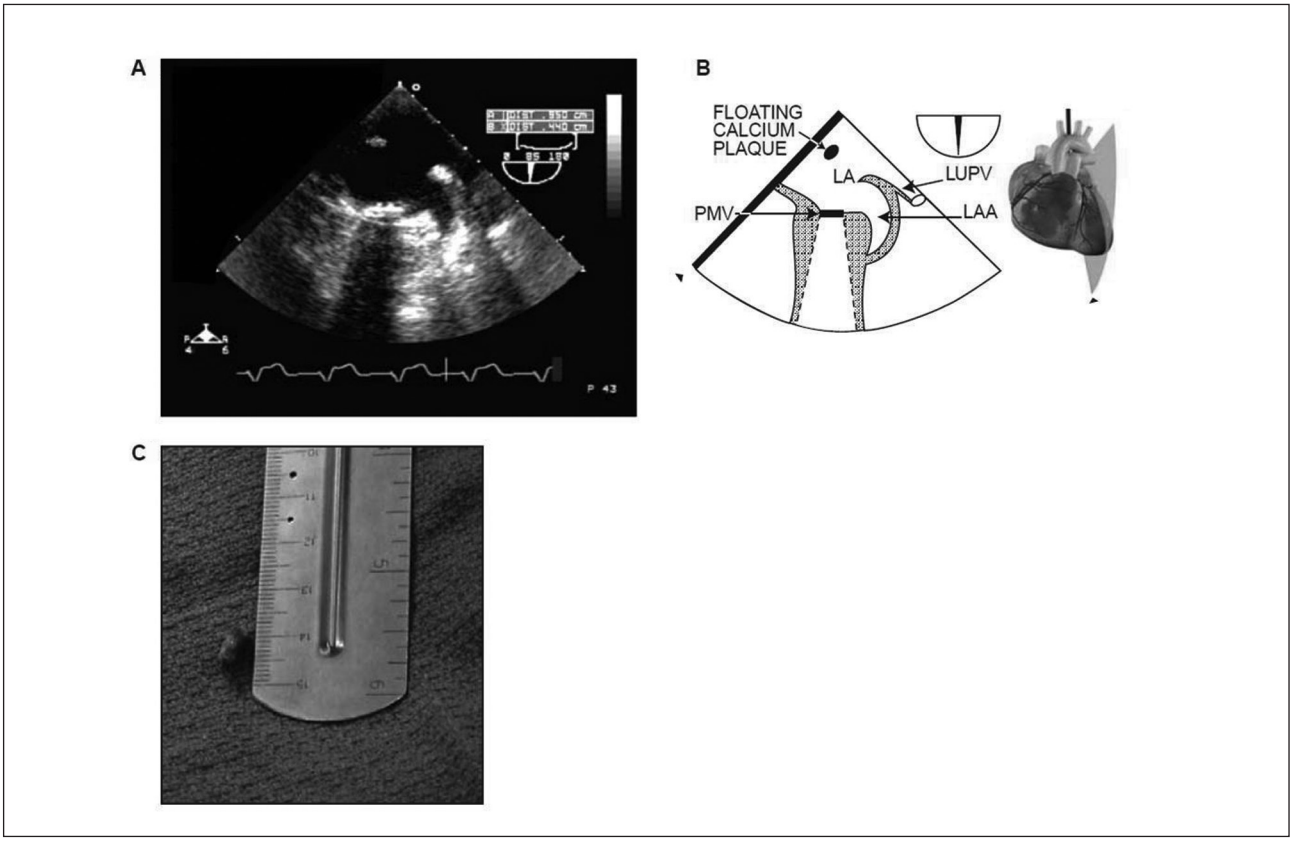

Figure 7. Calcium emboli in valvular surgery: a 70-year-old man who underwent coronary revascularization and combined aortic and mitral valve replacement. (A, B) As weaning from cardiopulmonary bypass (CPB) proceeded, floating material was detected in the left atrium (LA) from this midesophageal 2-chamber view. The attending surgeon went back immediately to full CPB. (C) This material was a 4×1 mm^2 floating calcium plaque, which was removed. The patient had no postoperative neurological complications (with permission of Denault et al[96])
Note: LAA = left-atrial appendage; LUPV = left upper pulmonary vein; PMV = prosthetic mitral valve.

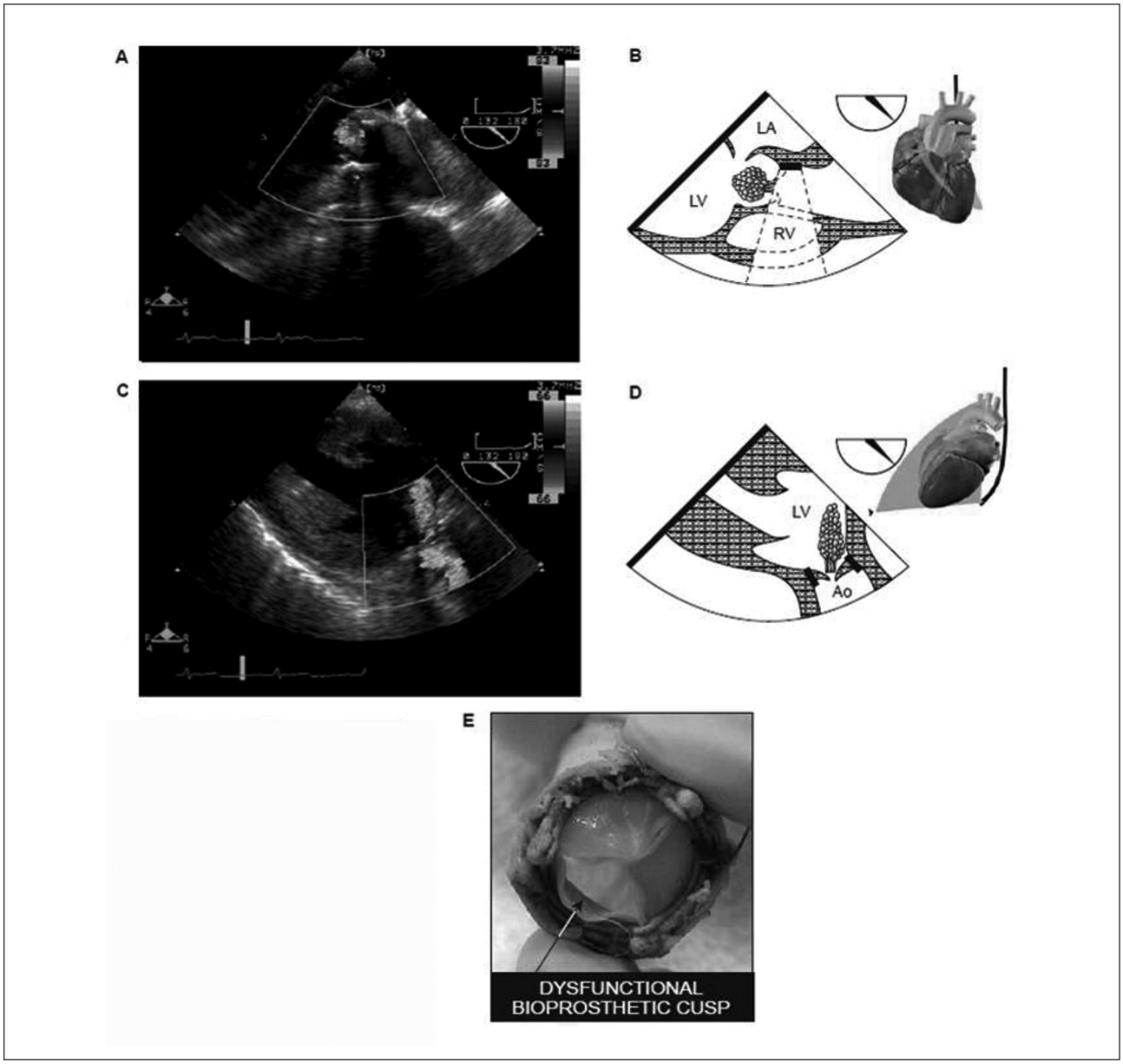

Figure 8. Dysfunctional AoV bioprosthesis after AVR: a 60-year-old man was reoperated after valve replacement (AVR) for periprosthetic aortic regurgitation (AR). (A-D) After the procedure, abnormal significant AR is still visible on the midesophageal long axis and deep transgastric views. The new bioprosthesis was removed and replaced by another one. (E) On examination of the defective bioprosthesis, abnormal motion of one of the leaflets was noted (photo E courtesy of Dr Tack Ki Leung, with permission of Denault et al[96])
Note: Ao = aorta; AoV = aortic valve; LA = left atrium; LV = left ventricle; RV = right ventricle.

monitor and to diagnose conditions that could result in difficult separation from CPB and that could be modified through a medical or surgical approach. Tables 2 and 3 summarize studies in which the primary end point was hemodynamic instability or difficult weaning from CPB after cardiac surgery.

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

Table 2. Studies on Difficult Separation From CPB and Postoperative Inotropes

Authors	Year	N	Death	Population	Single Versus Multicentered	Timing of Inotropic Administration	Method	Primary End Point	Prevalence
Royster et al[9]	1991	128	5 (3.9)	CABG	S	OR and ICU	Retrospective	Inotropic support	58 (45%)
Davila-Roman et al[2]	1995	75	34 (44%)	LCOS	S	> 48 Hours after OR	Retrospective	LCOS	NA
Rao et al[30]	1996	4558	109 (2.4)	All	S	ICU	Retrospective	LCOS	412 (9.1%)
Butterworth et al[15]	1998	149	9 (6%)	Valve	S	OR and ICU	RCT post hoc	Inotropic support	78 (52%)
Groban et al[22]	2002	381	7 (1.8%)	CABG	S	OR and ICU	RCT post hoc	Inotropic support	142 (37.2%)
Muller et al[21]	2002	1471	33 (2.2%)	All	S	OR and ICU	Retrospective	Inotropic support	476 (32,4%)
McKinlay et al[26]	2004	1009	NA	All	S	OR	Retrospective	Inotropic support	50 (52%)
Tsukui et al[25]	2004	151	3 (1.9)	All	S	OR and ICU	Prospective	Inotropic support	71 (47%)
Kumbhani et al[72]	2005	247	9 (3.6)	All	S	OR	Retrospective	Inotropic support	50 (20.2%)
Heringlake et al[73]	2005	20	NA	CABG	S	OR	Microdialysis	Inotropic support	6 (30%)
Maganti et al[32]	2005	2255	66 (2.9%)	AVR	S	OR and ICU	Retrospective	LCOS	87 (3.9%)
Robitaille et al[27]	2006	1439	50 (3.5%)	All	S	OR and ICU	Retrospective	Inotropic support	876 (61%)
Surgenor et al[33]	2006	8004	NA	CABG	M	OR and ICU	Prospective	LOF	644 (8.1%)
Weis et al[68]	2006	1558	34 (2.2%)	All	S	ICU	Prospective	Vasopressor dependence	425 (27%)
Ahmed et al[66]	2009	97	10 (10.3)	CABG-AVR	S	OR	Retrospective	Inotropic support	50 (52%)

Note: 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.

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[29] 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 RV systolic dysfunction, a known factor for negative outcome after cardiac surgery,[1,2,76] with mortality ranging from 44% to 86%.[1,2] Mortality is also associated with an increase in the use of vasoactive drugs. Muller et al[21] studied 1471 patients undergoing various types of cardiac surgery and found that 81.2% of the nonsurvivors received inotropes compared with 18.2% of survivors ($P < .01$). In the 2 studies from Toronto that included 4558 patients undergoing coronary revascularization and 2255 isolated AVR patients,[30,32] the operative mortality for coronary revascularization was 19 times higher (16.9% vs 0.9%; $P = .001$) in patients undergoing coronary revascularization and 25 times higher in patients with AVR (38% vs 1.5%; $P < .001$) 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.[97]

NIRS can be used to monitor local tissue perfusion during cardiac surgery[98] but has also been used as a monitor of tissue perfusion in various types of shock states.[95,99,100] Monitoring with NIRS provides a noninvasive measure of local tissue perfusion. It is particularly useful during nonpulsatile flow conditions such as CPB or cardiac arrest. In 2 recent randomized trials, cerebral oximetry monitoring has been associated with shorter recovery room and hospital stays following noncardiac surgery[101] and with a decrease in major organ dysfunction and in intensive care unit length of stay after cardiac surgery,[102] thus, providing the rationale for its use. Significant brain desaturation (Figure 9) can be observed in hemodynamically unstable patients or in those experiencing difficult separation from

Table 3. Risk Factor for Difficult Separation From CPB and Postoperative Inotropes

Author	Age	Gender	CHF	Renal Disease	CAD	Reoperation	Urgent/ Emergency	LVEDP	LVEF	CPB or CX Duration	Transfusions	Other Factors
Royster et al[9]	X	X	Cardiac enlargement					X	X	X		
Davila-Roman et al[2]					Recent MI							
Rao et al[30]	X	X			Previous MI, left main	X	X		X			Left main CAD and triple Vx, diabetes
Butterworth et al[15]	X		CHF						X			Anesthesiologist
Groban et al[22]	X	X			Hx angina				X	X		
Muller et al[21]	X		CHF and NYHA > 2		No. of MIs					X		COPD, CABG
McKinlay et al[26]						X			X	X		WMSI by TEE, CABG + MVR, MR 3-4/4
Tsukui et al[25]										X	X	Use of IABP
Kumbhani et al[72]									X			pH_{37c} at 5 or 10 minutes of reperfusion
Heringlake et al[73]												Myocardial lactate
Maganti et al[32]	X	X		X					X			Year of operation, preoperative shock
Robitaille et al[27]	X	X	CHF							X		Preoperative neurological disease, IABP, MAP/MPAP
Surgenor et al[33]		X	CHF	X		Prior CABG	X		X		X	Reduced hematocrit, WBC ≥ 12
Weis et al[68]									X	X		Interleukin 6 concentration
Ahmed et al[66]				X				X	X			Cardiac index

Note: 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 infarc MPAP = mean pulmonary artery pressure; MR = mitral regurgitation; MVR = mitral valve replacement or repair; NYHA = New York Heart Association; TEE = transesophageal echocardiography; Vx = vessels; WBC = white blood cell; WMSI = wall motion score index.

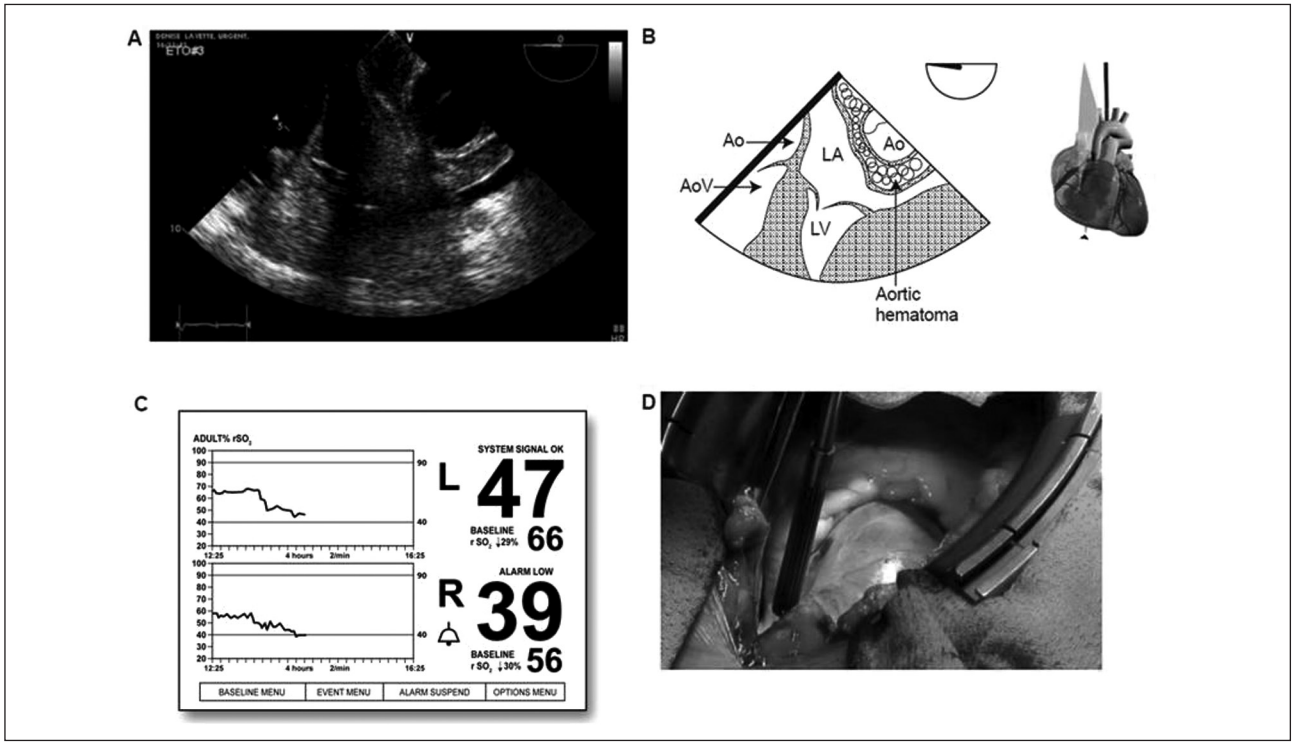

Figure 9. Hemodynamic instability and brain desaturation: (A, B) Midesophageal view showing an aortic hematoma compressing the left atrium (LA), creating an acute localized tamponade. (C) The onset of the hematoma was associated with hemodynamic instability and an abrupt reduction in the brain oximetry signal (arrow). (D) Intraoperative aspect of the aortic dissection (with permission of Denault et al[96])
Note: Ao = aorta; AoV = aortic valve; LV = left ventricle, RV = right ventricle.

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.[103] Transient hypoperfusion following a low-flow state may cause injury to the gut mucosa, allowing bacterial translocation and endotoxemia.[104] In some patients, if this condition persists, it can further develop into shock and multiorgan failure.[105] This mechanism could explain the observed association between brain desaturation and multiorgan dysfunction.[102]

In conclusion difficult separation from CPB is a critical complication in cardiac surgery. There is a clear association between difficult separation from CPB, and morbidity and mortality. The extent to which difficult separation from CPB is an independent predictor of mortality and could be used as a surrogate end point in cardiac surgery remains to be determined.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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