INTRODUCTION

Most cardiac surgery is currently being performed under cardiopulmonary bypass (CBP). The purpose of CBP is to supply adequate Oxygen (O_2) to the tissues and to remove the carbon dioxide (CO_2) that is produced in the tissues from the body.[1, 2]

The use of cardiopulmonary bypass distinguishes cardiac surgery from other types of surgery. It also introduces a unique set of potential postoperative complications. These include vasospasm, altered platelet-endothelial cell interactions, and a generalized inflammatory response due to blood contacting the synthetic surfaces of the bypass equipment. The result is low flow in the microcirculation of the heart, brain, and other organs, which may lead to organ dysfunction.[3, 4]

Monitoring following cardiac surgery initially occurs in the intensive care unit (ICU). However, the use of clinical practice guidelines and clinical pathways, combined with improvements in cardiac surgical care, has decreased the length of stay in the intensive care unit [5]. Many patients are now ready to be transferred to "step-down" units within 24 hours of surgery.

Prediction of outcome immediately after complex cardiac surgery is difficult, as both measurements of conventional haemodynamic parameters and risk scoring system have been shown to be inadequate for prognostic purpose.[6, 7] Consequently attention has focused on the use of biochemical parameters which might reflect critical oxygen supply dependency [8] which is associated with increased risk of post operative complications that include:

Cardiac Dysfunction

Poor cardiac function during the early postoperative period is associated with an increased risk of death [9]. It is usually suspected when there is unexplained postoperative hypotension, tachycardia, or pulmonary edema. Evaluation of suspected cardiac dysfunction consists of the following. [10- 12]

Telemetry: Assess the patient's continuous telemetry to identify or exclude cardiac dysrhythmias.

Echocardiography: Perform transthoracic or transesophageal echocardiography to assess biventricular function, to look for residual or unexpected valvular disease, and to exclude pericardial tamponade.

Electrocardiography: Obtain a 12-lead electrocardiogram to look for myocardial ischemia and to assess in detail any dysrhythmias noted on telemetry.

These tests are likely to identify the cause of cardiac dysfunction.

A chest x-ray may be helpful in the rare instances when these tests do not find the cause of cardiac dysfunction, since it can identify non-cardiac causes of cardiac dysfunction.

The most common causes of cardiac dysfunction following cardiac surgery are mechanical complications, physiologic complications (inadequate preload, excessive afterload, and poor ventricular inotropy, dysrhythmias, and myocardial infarction).

Mechanical complications

Mechanical complications of cardiac surgery are usually detected by echocardiography. Examples include spasm or occlusion of a coronary artery graft, prosthetic valve paravalvular regurgitation, cardiac tamponade, hematoma, and systolic anterior motion of the mitral valve with left ventricular outflow tract obstruction. Treatment of the mechanical complications of cardiac surgery is usually surgical.

Not all mechanical complications of cardiac surgery involve the heart. Non-cardiac mechanical complications include pneumothorax, hemothorax, and endotracheal tube malposition. These complications can be readily identified on a chest x-ray. Pneumothorax and hemothorax often require tube thoracostomy, while endotracheal tube malposition requires repositioning.

Physiological complications

Once mechanical complications have been excluded, an initial decision should be made about whether the patient's cardiac dysfunction (ie, low cardiac output) is most likely due to an insufficient stroke volume or heart rate. If it is likely due to diminished stroke volume, then it should be determined whether this is likely due to inadequate left ventricular preload (ie, intravascular hypovolemia), excessive left ventricular afterload (ie, hypertension), and/or poor inotropy (ie, cardiomyopathy). Data from the echocardiogram can be used to inform these judgments. Treatment should be directed at the presumed abnormality, while the underlying cause is sought.

Inadequate Preload

The best measure of left ventricular preload is the left ventricular end diastolic volume (LVEDV). It can be estimated by echocardiography or certain invasive hemodynamic measures: the pulmonary artery occlusion pressure (if a pulmonary artery catheter is in place) or the left atrial pressure (if a left atrial catheter has been placed). These hemodynamic measurements approximate the left ventricular end diastolic pressure (LVEDP), from which assumptions about the LVEDV can be made.

Left ventricular preload may be inadequate during the immediate postoperative period because of loss of vasomotor tone, increased capillary permeability, intraoperative and postoperative blood loss, or high urine output due to hypothermia. In addition, left ventricular compliance is frequently reduced following cardiac surgery, producing diastolic dysfunction; a higher LVEDP is required to maintain a given preload in affected patients[13]. The reduced compliance is the result of postischemic injury and "myocardial stunning," which results in inadequate myocardial diastolic relaxation.

Inadequate preload should be corrected by administering intravascular volume. Such patients should be monitored closely because many will continue to exhibit signs of cardiac dysfunction even after their preload has been corrected. This suggests that there is

coexisting poor inotropy and therapy should be redirected toward the poor inotropy as described below.

Excessive after load

Postoperative hypertension is common; it can cause decreased stroke volume and increased myocardial oxygen demand [14,15]. The presumed etiology is systemic vasoconstriction, likely related to hypothermia induced during bypass [16]. The observation that rewarming does not closely correlate with resolution of the hypertension suggests that other factors may also be involved, such as humoral factors provoked by cardiopulmonary bypass [17,18] Consequences of systemic vasoconstriction include tissue hypoxia in the skeletal muscles and secondary metabolic acidosis.

Patients judged to have excessive afterload should be treated with a vasodilator. Sodium nitroprusside is the vasodilator of choice to reduce excessive vasoconstriction in the immediate postoperative period. The blood pressure must be continuously monitored during therapy because vasoconstriction may improve quickly during rewarming from the hypothermia, leading to hypotension that requires immediate discontinuation of the sodium nitroprusside. Hypotension that persists despite the discontinuation of sodium nitroprusside should be initially treated with intravenous fluids, but may require vasopressors. Such hypotension is more common with normothermic bypass and longer cardiopulmonary bypass times, and less common in patients with diabetes, peripheral vascular disease, or a left ventricular ejection fraction of less than 40 percent [19, 20].

Some patients will continue to exhibit signs of cardiac dysfunction even after their afterload has been reduced. This suggests there is coexisting poor inotropy and therapy should be redirected toward the poor inotropy.

Poor inotropy

Impaired ventricular function is suggested if the echocardiogram shows poor ventricular contraction and a low ejection fraction. Postoperative ventricular function may be decreased due to intra-operative events, postoperative events, and/or hibernating myocardium. Examples include inadequate myocardial protection during cross-clamping of the aorta, ischemic myocardial injury during off-pump operations, uncorrected valvular lesions, reduced or inadequate intraoperative coronary blood flow, cardiac tamponade, or ischemia or infarction due to coronary artery air embolus, coronary graft vasospasm, or coronary graft thrombosis.

Patients with poor inotropy due to ischemia, poor inotropy plus inadequate preload, or poor inotropy plus excessive after load, respectively should initially have their ischemia corrected. Correction of the ischemia may improve inotropy, rendering an inotropic agent unnecessary. Correction of the inadequate preload makes it less likely that hypotension will occur if an inotropic agent is started (most inotropic agents cause vasodilation at low doses and, thus, hypotension is common immediately following initiation of the inotropic agent).

Patients with persistent poor inotropy despite correction of potential underlying causes require pharmacologic inotropic support to augment contractility. The patients who are most likely to benefit from inotropic support are those with a cardiac index less than

2.0 liters/minute/m^2 despite an optimized heart rate, rhythm, preload, afterload, and without evidence of tamponade.

Epinephrine is an effective inotrope following cardiac surgery, even though is rarely used as an inotrope in other settings. Epinephrine produces consistent increases in the cardiac output with variable effects on arterial blood pressure following cardiac surgery [21,22] Dopamine and dobutamine also increase cardiac output and heart rate, and appear to have efficacies similar to epinephrine [21]. Dobutamine produces greater reduction in left ventricular preload than dopamine and it augments coronary blood flow. However, the importance of the latter phenomenon is unclear, because surgically revascularized patients rarely exhibit ischemia in the absence of mechanical compromise of the coronary circulation.

Phosphodiesterase inhibitors such as inamrinone (formerly known as amrinone), milrinone, enoximone, and vesnarinone increase myocardial contractility, enhance myocardial relaxation, improve coronary blood flow, and reduce the systemic vascular resistance. The effect is to increase the cardiac index and decrease left ventricular preload and afterload, with minimal change in myocardial oxygen demand. Such agents are probably beneficial when used briefly following cardiac surgery, despite concerns that they may increase mortality when used in chronic heart failure [23,24].

Patients with profound ventricular dysfunction who are unable to wean from cardiopulmonary bypass despite the use of inotropic drugs often require the addition of mechanical assist devices, such as an intraaortic balloon pump or ventricular assist device, until native ventricular function recovers from the stresses of surgery and cardiopulmonary bypass. These devices reduce ventricular wall stress and augment coronary and systemic perfusion.

Dysrhythmias

The trauma of cardiac surgery predisposes patients to atrial and ventricular arrhythmias:

- Atrial fibrillation: Atrial fibrillation can disturb normal atrio-ventricular synchrony and result in a 15 to 25 percent reduction in cardiac output [25]. Initial management involves slowing the ventricular heart rate using negative chronotropic agents.
- The optimal heart rate usually occurs at rates between 80 and 100 beats per minute [26] once the ventricular heart rate is controlled, restoration of sinus rhythm with electrical or pharmacologic cardioversion may be considered.
- Postoperative prophylactic therapy with beta blockers or amiodarone can help prevent postoperative atrial fibrillation and may have a role in the management of some patients.
- Ventricular arrhythmias: The hemodynamic instability of patients with ventricular arrhythmias is variable and depends upon the rate of the tachyarrhythmia and left ventricular systolic and diastolic function. Sustained ventricular tachyarrhythmias should be promptly converted chemically or electrically.

- Bradyarrhythmias: Bradyarrhythmias are particularly common after valve surgery and are probably a consequence of direct surgical injury and local edema. If the bradycardia is symptomatic, temporary electrical pacing may be required. In some cases, permanent pacing may be necessary.

Myocardial infarction

Perioperative myocardial infarction (MI), defined as new Q waves on the postoperative electrocardiogram, occurs in 4 to 5 percent of patients undergoing coronary artery bypass grafting (CABG) [27,28]. It is usually due to poor distal perfusion after grafting of the more proximal coronary arteries. The incidence of perioperative MI after other types of cardiac surgery is uncertain. It is important for clinicians to realize that the diagnostic accuracy of elevations in the serum creatine kinase (CK), CK-MB, and troponin is reduced after cardiac surgery because the enzymes are released as a routine sequela of the procedure.

Haematological Dysfunction

Patients who undergo cardiac surgery are at increased risk for both bleeding and thrombosis.

Bleeding

Postoperative bleeding is common, with severe bleeding (requiring transfusion of >10 units of packed red blood cells) occurring in 3 to 5 percent of patients who have undergone cardiopulmonary bypass [29]. Such extensive bleeding is usually due to one or more of the following factors: incomplete surgical hemostasis, residual heparin effect after cardiopulmonary bypass, clotting factor depletion, hypothermia, postoperative hypotension, hemodilution (dilutional thrombocytopenia and coagulopathy), or platelet abnormalities (platelet dysfunction and thrombocytopenia) [30].

Postoperative bleeding frequently requires fresh frozen plasma and platelets to correct the coagulation abnormalities. Transfusion of packed red blood cells may also be necessary to replace blood loss. Extensive bleeding can be mitigated in some cases by the administration of the antifibrinolytic agent, epsilon-aminocaproic acid[31,32].

Thrombosis

Patients who undergo cardiopulmonary bypass appear to be at increased risk of developing thrombosis, probably due to increased platelet activity. This was demonstrated by a trial that randomly assigned 80 patients to undergo CABG with or without cardiopulmonary bypass [33]. Platelet activity during the early postoperative period was higher among patients who underwent cardiopulmonary bypass than among those who did not. This platelet activity may be resistant to aspirin, as suggested by another study that reported that the antiplatelet effect of aspirin was impaired after CABG with cardiopulmonary bypass, but not after CABG without cardiopulmonary bypass [34].

It has been hypothesized that the aspirin resistance noted in these studies may be due to the increased platelet turnover that follows cardiopulmonary bypass. Data looking at the long-term outcome of patient`s who develop aspirin resistance after cardiopulmonary bypass are lacking. However, there is evidence that the platelets of patients who develop

graft thrombosis are more likely to be resistant to aspirin than patients without thrombotic events. [35] Pharmacological approaches to improve antithrombotic therapy in patients to develop aspirin resistance after CABG are being explored.

Pulmonary Dysfunction

Pulmonary dysfunction is a significant cause of morbidity following cardiac surgery. Common types of pulmonary dysfunction include the following:

- Pleural effusion**:** Pleural effusions are common postoperative findings in patients who undergo various cardiac surgical procedures [36]. Most are a consequence of the surgery itself (nonspecific pleural effusions) and follow a benign course. However, pleural effusions may also occur with post-cardiac injury syndrome (PCIS) or may be the initial manifestation of a potentially serious complicating event.

- Pneumonia**:** Sternotomy and thoracotomy incisions produce pain, which impairs the ability to cough and breathe deeply. This increases the risk of pneumonia.

- Atelectasis**:** Atelectasis occurs in up to 70 percent of patients following cardiac surgery, usually as a result of single lung ventilation and intentional lung collapse during the surgery [37,38]. Management consists of incentive spirometry and early physical mobilization.

- Decreased thoracic compliance**:** Chest wall and lung compliance decrease postoperatively. This effect peaks approximately three days after surgery and may complicate the extubation of patients, especially those with underlying lung disease.

- Difficulty weaning**:** Some patients prove difficult to wean from mechanical ventilation following cardiac surgery. The prognosis of such patients varies widely across series, but is not uniformly poor. As an example, a series of 124 patients who received greater than seven days of mechanical ventilation following cardiac surgery found that 85 percent of the patients survived until discharge and 99 percent of the survivors were successfully weaned from mechanical ventilation [39].

- Diaphragmatic dysfunction**:** Phrenic nerve injury during surgery is rare, but may cause diaphragmatic dysfunction or paralysis if it occurs.

- Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS**):** ALI and ARDS are types of hypoxemic respiratory failure characterized by acute onset, bilateral infiltrates, a decreased ratio of arterial oxygen tension to fraction of inspired oxygen, and lack of evidence of elevated left atrial pressure. They differ only in the severity of hypoxemia, with ARDS being more severe than ALI. ALI and ARDS complicate less than two percent of cardiac surgeries that used cardiopulmonary bypass [40].

Patients undergoing cardiac surgery for structural or congenital heart disease frequently have pulmonary hypertension, which can complicate postoperative management. As an example, pulmonary complications (eg, pneumonia, atelectasis) may cause hypoxic vasoconstriction, worsened pulmonary hypertension, and hypoxemia. The result may be hypoxemia that seems out of proportion to the severity of the pulmonary complication. Inhaled nitric oxide (NO) causes selective pulmonary vasodilation and, therefore, can mitigate the exacerbation of pulmonary hypertension and stabilize

hemodynamically compromised patients with severe pulmonary hypertension. It cannot be used long-term, but may be useful while the acute process that led to the deterioration is reversed. Inhaled NO requires a special device to administer and weaning it can cause rebound pulmonary hypertension. Oral Sildenafil may facilitate inhaled NO withdrawal by preventing rebound pulmonary hypertension in patients who have failed previous attempts to wean of inhaled NO. [41, 42]

Neurologic Dysfunction

The incidence of postoperative neurologic sequelae after coronary artery bypass graft surgery (CABG) is approximately 2 to 6 percent, with the frequency increasing among older patients [43]. A prospective cohort study followed 2108 patients undergoing CABG for postoperative neurologic complications[44], the complications were placed into two categories: type I neurological complications were defined as focal injury (eg, stroke), stupor, or coma at discharge, while type II neurological complications were defined as deterioration in intellectual function, memory deficits, or seizures. The incidence of all adverse cerebral events was six percent. Patients with cerebral complications had higher in-hospital mortality, longer hospitalizations, and a higher rate of requiring discharge to a chronic care facility than did those without neurologic sequelae. Type I complications occurred in three percent, primarily consisting of nonfatal strokes. Type II complications also occurred in three percent and consisted primarily of deterioration in intellectual function.

Delirium is one of the most common neurological complications occured after cardiac surgery, it is a transient and fluctuating organic mental syndrome of acute onset, characterized by a global impairment of cognitive functions, a reduced level of consciousness, attentional abnormalities, increased or decreased psychomotor activity and a disordered sleep-awake cycle. Cardiac surgery with cardiopulmonary bypass has traditionally been associated with a particularly high rate of postoperative delirium, supposed to be due to cytotoxic oedema induced by cerebral microemboli, hypoperfusion or haemodilution. This pshychiatric complication is associated with increased morbidity, high mortality, prolonged hospital stay and poor functional recovery.

Early recognition of neurological complications is important. Although treatment is largely supportive, prompt initiation of therapy may prevent worsening of the complications.

Neurological complications following cardiac surgery may be a result of a variety of processes. These include atheroembolism of aortic debris, embolism of left atrial or left ventricular thrombus, cerebral hypoperfusion, air embolism, and microembolism of granulocyte aggregates, fibrin, and platelets .[45]

Renal Dysfunction

Acute renal failure occurs in up to 30 percent of patients who have undergone cardiac surgery, when defined as a 50 percent increase in the serum creatinine concentration above baseline [46]. It is severe enough to require dialysis in 1 to 5 percent of patients and it appears to be associated with increased mortality [47].

- Risk factors: Postoperative risk factors for acute renal failure include poor cardiac performance and peri-operative hemodynamic instability [38,47]. Risk factors that cannot be controlled post-operatively include advanced atherosclerotic vascular disease, reduced creatinine clearance, a long duration of cardiopulmonary bypass, and the use of radiocontrast agents immediately before surgery.
- Mechanism: Mechanisms of perioperative renal failure include renal artery vasoconstriction, hypothermia, loss of pulsatile flow during cardiopulmonary bypass, and atheroembolic disease.
- Prevention: The best preventive strategy is to optimize renal perfusion (ie, avoid hypotension and hypovolemia) and to avoid potentially nephrotoxic agents (eg, aminoglycoside antibiotics, angiotensin converting enzyme inhibitors, and radiologic contrast agents) in the immediate postoperative period. There is no clear evidence supporting the efficacy of pharmacologic therapy (eg, low-dose dopamine, loop diuretics) to prevent acute renal failure after major surgery. In addition there is some concern about toxicity (eg, arrhythmias, myocardial ischemia, and intestinal ischemia with dopamine).
- Treatment: There is no convincing evidence of benefit from early and/or aggressive dialysis, and there is some concern that renal function might be impaired by this approach [48]. Thus, the decision to perform dialysis generally should be based upon the presence of uremic symptoms, fluid overload, or electrolyte abnormalities, rather than a specific blood urea nitrogen or serum creatinine concentration.

Prediction of outcome immediately after complex cardiac surgery is difficult, as both measurements of conventional haemodynamic parameters and risk scoring system have been shown to be inadequate for prognostic purpose [49,50], consequently attention has focused on the use of biochemical parameters which might reflect critical oxygen supply dependency.[51]

Identification of predictors of morbidity and mortality is an important issue for the optimal management of patients with cardiac pathologies. Monitoring of blood gases may detect inadequate tissue oxygenation, also lactate is a product of anerobic metabolism that reflects tissue hypoperfusion.[52-55]

Number of alternative techniques have been proposed to measure cardiac output with varying degree of accuracy, accessibility, and ease of use [56]. One such method consist of calculating cardiac output based upon the measurement of mixed venous-arterial partial pressure of carbon dioxide difference ($P_{v-a}CO_2$).[57]

The mixed venous-arterial PCO_2 difference ($P_{v-a}CO_2$) is determined by subtracting the peripheral arterial carbon dioxide (P_aCO_2) from the mixed venous carbon dioxide (P_vCO_2). Obtaining a mixed venous-arterial carbon dioxide difference ($P_{v-a}CO_2$) requires access to the pulmonary artery circulation and thus has limitation similar to pulmonary artery catheter (PAC). Furthermore, if a pulmonary artery catheter is in place, cardiac output can be obtained by thermodilution, and the clinical utility of an alternative method of measurement is diminished. In contrast, central venous access is more frequently and easily obtained, yet no direct measure of cardiac output can be calculated. The substitution of a central venous carbon dioxide partial pressure ($P_{cv}CO_2$) may yield a similar inverse relationship to cardiac output.[58] If this relationship could be obtained by substitution of

central venous $P_{cv}CO_2$, cardiac output could be calculated by more feasible and rapid fashion which is central venous-arterial carbon dioxide gradient (ΔPCO2).

Prevention, detection and correction of tissue hypoxia are the main goals of the management of critically ill patients. A broad use of monitoring tools and parameters has been reported to help clinicians in the management of patients with circulatory failure [59]. Among them, the difference between venous blood carbon dioxide tension (P_VCO_2) and arterial carbon dioxide tension ($PaCO_2$), called ΔPCO_2 has been proposed to better characterize the relationship between systemic blood flow and global metabolic needs [60-62], as it provides information that is not provided by other parameters [63]. However, a correct interpretation of ΔPCO_2 at the bedside requires perfect knowledge of its physiological meaning.

Physiological background

Production of carbon dioxide

Under normoxic conditions, CO_2 is normally produced in the cells through the Krebs cycle. CO_2 is thereby a normal terminal product of oxidative metabolism. The CO_2 production (VCO_2) is directly related to the global oxygen consumption by the relation: $VCO_2 = R \times VO_2$ where R is the respiratory quotient. R may vary from 0.7 to 1 depending on the predominant metabolism condition. When lipids are the main energetic sources, R is near from 0.7 but it becomes close to 1 when carbohydrates are the main energetic sources. For a given VO_2, VCO_2 is expected to increase until 30 % when an injection of glucose is given[64]. Therefore, CO_2 production should increase either with higher oxidative metabolism or for a given VO_2, when the feeding regimen is replaced by a high carbohydrate intake regimen.

Under hypoxic conditions, CO_2 can be generated into the cells through buffering of excessively produced protons by local HCO_3 ions. Protons are generated by 2 mechanisms[65].

- Excessive production of lactic acid owing to an acceleration of anaerobic glycolysis, since pyruvate is no longer cleared by the Krebs cycle.

- Hydrolysis of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) that occurs in conditions of anaerobiosis.

Anaerobic decarboxylation of some substrates produced by intermediate metabolism (α ketoglutarate or oxaloacetate) is another potential but minor source of CO_2 production during hypoxia [65].

Transport of CO_2

The CO_2 is transported in the blood through three forms:

Dissolved CO_2 (10%), bicarbonate (60%) and associated with proteins as carbamino compounds (30%). Because only the dissolved form participates to blood CO_2 tension (PCO_2) and because CO_2 is approximately 20-30 times more solouble than O_2, the dissolved form plays a significant role in the CO_2 transport. However, in the blood, CO_2 is mainly carried as bicarbonates ions formed through the following reaction: $CO_2 + H_2O \leftrightarrow$

$H_2CO_3 \leftrightarrow HCO_3^- + H^+$. The CO_2 produced through the metabolic pathway diffuses into the tissue capillary blood and enters into the red blood cell. As a lipophilic molecule, CO_2 rapidly diffuses through the lipid bilayer of the red blood cell membrane[66]. Inside the red blood cell, diffusion of CO_2 is slowed down by the high concentration of hemoglobin. During the first step of the reaction, inside the red blood cell, carbonic anhydrase catalyses CO_2 hydration, and most CO_2 is converted to HCO_3 and H^+. The acceleration of CO_2 hydration-dehydration by erythrocytic carbonic anhydrase is essential for an efficient CO_2 transport. The capacity of hemoglobin to fix CO_2 depends on its oxidation state. This phenomenon, called "Haldane effect", illustrates the fact that CO_2 has a greater affinity with reduced hemoglobin than with oxygenated hemoglobin [67]. Thus, unloading oxygen in peripheral capillaries facilitates the loading of CO_2 while oxygenation enhances the unloading of CO_2 in the lung.

Finally, the carbamino compounds are formed by combining the CO_2 with the terminal NH_3 groups of proteins, especially with the globin of hemoglobin. Here again, the reaction is favored by deoxygenation of hemoglobin.

Elimination of CO_2

The three forms of CO_2 produced by the body metabolism are carried by the blood flow to alveolar circulation and then eliminated by pulmonary ventilation. Gas exchanges occur through the alveolo-capillary barrier. The CO_2 is eliminated by passive diffusion from the capillaries to the alveoli. The flow depends on the difference of gas tension between the two phases.

Relationship between the blood CO_2 Content (CCO_2) and PCO_2

With respect to the relationship between CCO_2 and PCO_2, which is almost linear over the physiological range, it has been proposed to measure the value of PCO_2 as a surrogate for CCO_2 for assessing veno-arterial CO_2 difference at the bedside [68]. However, the relationship between CCO_2 and PCO_2 is curvilinear rather than linear and is influenced by the degree of metabolic acidosis, the hematocrit and the SaO_2[69,70].

Determinants of ΔPCO_2

The Fick equation applied to CO_2 shows that in steady-state, the CO_2 excretion equals the product of cardiac output by the difference between central venous blood CCO_2 (C_VCO_2) and arterial blood CCO_2($CACO_2$): VCO_2 = cardiac output × ($CVCO_2 – CaCO_2$).

As mentioned above, under physiological conditions, CCO_2 can be substituted by PCO_2 ($PCO_2 = k \times CCO_2$) so that ΔPCO_2 equals $k \times (C_VCO_2 – C_aCO_2)$.

Thus, VCO_2can be calculated from modified Fick equation:

$$\Delta PCO_2 = (k \times VCO_2) / \text{cardiac output}$$

Where *k* is a factor defining the relation between PCO_2 and CCO_2. Because of the curvilinear relationship between PCO_2 and CCO_2, *k* increases with venous hypercapnia. Additionally, metabolic acidosis results in a shift in the PCO2/CCO_2 relationship such that *k* should markedly increase with metabolic acidosis and tissue hypoxia.

The relationship between cardiac output and ΔPCO_2 is explained by the CO_2 stagnation phenomenon that increases P_VCO_2 relatively to P_aCO_2 at the peripheral venous level. Thus a low cardiac output and hence a low efferent venous blood flow should decrease the CO_2 clearance rate and should result in an increased ΔPCO_2 for a given VCO_2. In experimental studies in which cardiac output was gradually reduced, under conditions of stable VO_2 and VCO_2 [71,72], ΔPCO_2 was observed to increase along with the decrease in cardiac output. Conversely, a high cardiac output and hence a high efferent venous blood flow should increase the CO_2 clearance rate and should result in a decreased ΔPCO_2 for a given VCO_2. Accordingly, in a clinical study performed in normolactatemic patients with cardiac insufficiency, the increase in cardiac index from 1.6 to 2.2 L min^{-1} m^{-2} was associated with a decrease in ΔPCO_2 from 9 to 5 mmHg, while VO_2 (and probably VCO_2) was unchanged [62].

Clinical use of veno-arterial PCO_2 differences

Central venous blood: arterial blood PCO_2 difference (ΔPCO_2).

ΔPCO_2 can be calculated after simultaneous sampling of arterial blood (P_aCO_2) and of central venous blood (P_VCO_2). Under normal conditions, ΔPCO_2 ranges from 2 to 6 mmHg [73].

Can ΔPCO_2 be used as a marker of tissue hypoxia?

Striking increase in ΔPCO_2 were observed in cardiac arrest-resuscitated animals or patients [74,75]. These findings were ascribed to the reduced blood flow during resuscitation and to the development of anaerobic metabolism following cardiac –respiratory arrest. Adrogue et al.[76] also reported a ΔPCO_2 greater in patients with circulatory failure than in those without circulatory failure. From these observations, it has been postulated that anaerobic CO_2 production may play a major role in the widening of ΔPCO_2 under conditions of tissue hypoxia. However, for the reasons detailed below, ΔPCO_2 cannot serve as a marker of tissue hypoxia or anaerobiosis [63].

Indeed, in the case of tissue hypoxia, the determinants of ΔPCO_2 can change in opposite directions so that ΔPCO_2 can increase, decrease or remain unchanged.

As mentioned above, *k* increases in the case of tissue hypoxia, at least because of the development of local metabolic acidosis that shifts the curvilinear relation between CCO_2 and PCO_2. In an animal study where tissue hypoxia was induced by cardiac tamponade, independent measurements of ΔPCO_2, cardiac output and VCO_2 allowed to analyze the change in *k* with hypoxia [71]. A striking rise (six folds) of *k* was observed after induction of tissue hypoxia [71]. On the other hand, the total VCO_2 should decrease in the presence of tissue hypoxia. In the above- mentioned study [71], below a critical level of oxygen delivery (DO_2), the further decrease in cardiac output and DO_2 resulted in progressive decrease in VCO_2 along with progressive decrease in VO2 (O_2 supply dependent period). Both VO_2 and VCO_2 were derived from expired gas analysis. Similar results were reported by Groeneveld et al. [72] in a model of tissue hypoxia created by application of incremental levels of PEEP in pigs.

The decrease in VCO_2 during tissue hypoxia strongly suggest that the increased "anaerobic" production of CO_2 does not compensate for the decreased "aerobic" CO_2 production. Because VCO_2 must decrease and *k* must increase during tissue hypoxia, the resultant effect on ΔPCO_2 will mainly depend on the third determinant, i.e. the cardiac output [63]. Therefore, two situations should be distinguished: tissue hypoxia with reduced blood flow and tissue hypoxia with maintained or high blood flow.

Tissue hypoxia with low cardiac output:

Low cardiac output states are frequently encountered in critically ill patients (e.g. congestive heart failure, reduced blood volume). In such situations, $PvCO_2$ increases relatively to $PaCO_2$ in relation to venous stagnation phenomenon. In this regard, higher than normal ΔPCO_2 values (mean value: 9 mmHg) have been reported in patients with congestive heart failure and low cardiac index (mean value: 1.6 L min^{-1} m^{-2}) but normal lactate[62].

In experimental studies where tissue hypoxia was induced by reducing blood flow, high values of ΔPCO_2 were also found [71,72,77]. In addition to the venous stagnation phenomenon, the increase of ΔPCO_2 was explained by the fact that *k* also increases with decreased cardiac output. Indeed, decreased cardiac output results in an increase in $CvCO_2$, which is particularly marked for the lowest range of cardiac output. Because of the curvilinear relation between CCO_2 and PCO_2, this should result in a greater increase in $PvCO_2$ than in C_vCO_2. Thus, in such conditions, ΔPCO_2 can dramatically increase in spite of the decrease in VCO_2 as observed in experimental studies [71,72,77].

Tissue hypoxia with maintained or high cardiac output:

In many septic patients, tissue hypoxia can coexist with maintained or even high cardiac output. Tissue hypoxia is here ascribed to severe disturbances at the micro circulatory level [78] and/or at the cellular level [79]. In such situations, the global CO_2 produced by aerobic metabolism should decrease dramatically while the "anaerobic" VCO_2 should increase. Whatever the resultant VCO_2, the high efferent venous blood flow could be sufficient to wash out the resultant global CO_2 generation from the perfused peripheral tissues and hence, ΔPCO_2 should not increase.

Results from clinical studies in septic patients have supported this hypothesis. [61] found that most patients with septic shock had a $\Delta PCO_2 \leq 6$ mmHg (mean value: 4 mmHg). The cardiac index obtained from this subgroup of patients was significally higher than that obtained in the sub group of patients with a $\Delta PCO_2 > 6$ mmHg. Interestingly, the two subgroups did not differ in terms of blood lactate and VO_2. Although VCO_2 and VO_2 were not measured directly, these data suggest that differences in CO_2 production did not occur for differences in ΔPCO_2. In other words, many patients had a normal ΔPCO_2 despite tissue hypoxia, probably because their high systemic blood flow had easily removed the CO_2 produced at the periphery. Clearly, these latter studies [60, 61] have underlined the poor sensitivity of ΔPCO_2 to detect global tissue hypoxia, since ΔPCO_2 was normal in most patients with septic shock except with those with low cardiac output. Normal or low ΔPCO_2 were also reported in a study including ten hypotensive patients with fulminant hepatic failure. These patients were assumed to have significant tissue hypoxia, as they demonstrated an increase in VO_2 after prostacyclin infusion [80]. The major finding was that during baseline, ΔPCO_2 was very low (less than 3 mmHg). This was probably explained by a low VCO_2 as suggested by the low VO_2 (119 mL min^{-1} m^{-2}) easily removed by very high systemic blood flow (mean cardiac index: 5.4 L min^{-1} m^{-2}). These findings underline the fact that tissue hypoxia under conditions of high flow states should rather result in decreased than increased ΔPCO_2.

The major role of the cardiac output in the widening of ΔPCO_2 was nicely demonstrated in animal studies comparing changes in ΔPCO_2 in ischemic hypoxia and in hypoxic hypoxia [81,82]. Hypoxic hypoxia was created either by a progressive reduction of inspired oxygen concentration in pigs [81] or by progressive instillation of hypochloric acid in sheep [82]. In both studies, cardiac output remained unchanged in the hypoxic hypoxia group [81,82]. In both studies, ΔPCO_2 increased in the ischemic hypoxia group whereas it remained unchanged in the hypoxic hypoxia group [81,82]. Similar results were reported in a model of vascularly isolated dog hind limb. Indeed, ΔPCO_2 significantly increased when limb hypoxia was induced by ischemia while it remained unchanged when hypoxia was induced by hypoxemia (with maintained blood flow) [83]. It is interesting to note that the

limb CO_2 production dropped in both groups of animals below the critical level of DO_2. In the hypoxic hypoxia group, this finding along with the maintained limb blood flow strongly suggests that *k* actually increased during hypoxia.

All these experimental [81-83] and clinical [60,61,80] studies have confirmed that during tissue hypoxia ΔPCO_2 can be either high or normal depending on the cardiac output. A mathematical model analysis also confirmed that cardiac output represents the major determinant in the elevation of ΔPCO_2 [84]. Thus, a normal ΔPCO_2 does not exclude the absence of tissue hypoxia. This is what should happen in high blood flow shock states. On the other hand, ΔPCO_2 is elevated in cases of low cardiac output in the absence of tissue hypoxia.

ΔPCO_2 as a marker of adequacy of cardiac output to remove the CO_2 produced by the metabolism

As developed above, ΔPCO_2 cannot serve as a reliable marker of tissue hypoxia. However, ΔPCO_2 can be considered as a marker of adequacy of the venous blood flow (i.e. cardiac output) to remove the total CO_2 produced by the peripheral tissues.

The clinical implications of this concept can be summarized as follows:

- An increased ΔPCO_2 ($\geq$ 6 mmHg) may suggest that cardiac output is not high enough with respect to the global metabolic conditions.
- Under suspected hypoxic conditions (increased blood lactate), the presence of a high ΔPCO_2 could be done of the arguments that would incite the clinician to increase cardiac output in attempt to reduce tissue hypoxia.
- Under aerobic conditions (normal blood lactate), the presence of a high ΔPCO_2 suggests that systemic blood flow is not high enough, even if cardiac output is in the normal range. This condition can be associated with an increased oxygen demand and hence increased CO_2 production. However, whether further increasing cardiac output can prevent short term subsequent risks of onset of tissue hypoxia actually remains to be proven.

In a patient with a high initial value of ΔPCO_2, following the time-course of ΔPCO_2 can also be helpful to assess the global metabolic effects of a therapeutic intervention aiming at increasing cardiac output. Under conditions of oxygen supply-dependency, an increase in the cardiac output must be accompanied by increase in VO_2 and in VCO_2 so that ΔPCO_2 is expected to decrease to a lesser extent than in the case of oxygen supply-independence.

Consequently, relatively unchanged ΔPCO_2 with therapy would not mean that the therapy has failed. In this case, the therapeutic agent would be rather maintained and its dose even increased until obtaining a frank decrease in ΔPCO_2 that would indicate that the critical level of DO_2 has been actually overcome. Otherwise, ΔPCO_2 can also be helpful to choose the appropriate dose of a therapeutic agent known to have thermogenic effects. For instance, β-agonists agents may exert thermogenic effects and therefore are able to increase both VO_2 and VCO_2. Accordingly, ΔPCO_2 as an index of the VCO_2/ cardic output ratio was shown to detect changes in oxygen demand accompanying dobutamine-induced

changes in cardiac output [62]. In this regard, ΔPCO_2 together with mixed venous oxygen saturation (SvO_2) [85] may help to titrate dobutamine therapy.

A normal ΔPCO_2, ($\leq$ 6 mmHg) suggests that cardiac output is high enough to wash out the global CO_2 generation from the perfused peripheral tissues. Although not proven, this suggests that cardiac output elevation cannot be a priority in this therapeutic strategy even in the presence of tissue hypoxia. In this regard, it must be remembered that increasing cardiac output to supranormal values was not demonstrated to be beneficial in critically ill patients [86, 87].

Combined analysis of ΔPCO_2 and oxygen-derived parameters

From the Fick principle, two equations can be written:

$$VCO_2 \times k = \text{cardiac output} \times \Delta PCO_2$$

VO_2 = cardiac output × $C_{A-V}O_2$ where $C_{A-V}O_2$ is the arterial-venous difference in O_2 content (i.e. arterial blood oxygen content-mixed venous blood oxygen content).

During tissue hypoxia, *k* increases [63] while VCO_2 decreases less than VO_2 [88-91] because the generation of anaerobic CO_2. Therefore the ($VCO_2 \times k$) / VO_2 ratio should increase during tissue hypoxia. Since the ($VCO_2 \times k$) / VO_2 ratio equals the ΔPCO_2 / $C_{A-V}O_2$ ratio (after eliminating cardiac output presents on both the numerator and the denominator), the ΔPCO_2 / $C_{A-V}O_2$ ratio should increase during hypoxic conditions and thus could be used to detect global anaerobic metabolism in patients monitored with a pulmonary artery catheter. In a series of 89 critically ill patients (148 measurements), a close correlation was found between blood lactate concentration and ΔPCO_2 / $C_{A-V}O_2$ ratio. Therefore, ΔPCO_2 / $C_{A-V}O_2$ ratio could be a helpful parameter to detect global anaerobic metabolism. It's simple calculation would be useful for clinicians while interpreting pulmonary artery catheter data.

Difference between central venous blood PCO_2 ($PcvO_2$) and $PaCO_2$

Nowadays, the pulmonary artery catheter is less used than in the past in critically ill patients [92] so that mixed venous-arterial CO_2 gradient is infrequently obtained at bedside. Since a central venous catheter is inserted in almost critically ill patients with hemodynamic instability, the central venous blood oxygen saturation ($ScvO_2$) is frequently used as a surrogate of SvO_2. The $ScvO_2$ has been proposed as a relevant target in the early phase of hemodynamic resuscitation of severe sepsis and septic shock [93]. It has also been proposed to use the difference between $PcvCO_2$ and $PaCO_2$ instead of mixed venous-arterial CO_2 difference [94]. Accordingly, a good agreement between mixed venous-arterial CO_2 difference and $PcvCO_2$-$PaCO_2$ was reported in a series of 83 critically ill patients [94]. Vallee et al. [95] studying 50 septic shock patients in whom a $ScvO_2$ higher than 70 % has been achieved, found that 50 % of them had a $P_{CV}CO_2$ - $P_a CO_2$ (ΔPCO_2) > 6 mmHg. In those patients, lactate tended to be higher and cardiac output tended to be lower than in patients with a $\Delta PCO_2 \leq 6$ mmHg. Analysis of the data of this study suggests that the presence of a $S_{CV}O_2 \geq 70$ % with a $\Delta PCO_2 > 6$ mmHg reveals a persistent inadequate hemodynamic status and that increasing the cardiac output could be a good therapeutic option [95]. The study concluded that $S_{CV}O_2$ may not be sufficient to guide therapy and that when the 70 % $S_{CV}O_2$ goal value is reached, the presence of $\Delta PCO_2 > 6$ mmHg might be a

useful tool to identify patients who still remain inadequately resuscitated [95]. Interestingly, in a population of high-risk surgery patients, it was observed that a high $S_{CV}O_2$ (≥ 70 %) did not necessarily preclude the occurrence of postoperative complications but the presence of a ΔPCO_2 value > 6 mmHg was more often associated with complications.[96, 97]