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Measurement of tissue perfusion by oxygen transport patterns in experimental shock and in high-risk surgical patients

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Abstract. Survivors of high-risk general (noncardiac) surgery were observed to have cardiac index (CI) values averaging 4.5 l/min·m^2, oxygen delivery ($\dot{D}O_2$) of >600 ml/min·m^2, and oxygen consumption ($\dot{V}O_2$) of 170 ml/min·m^2. In contrast, these values were relatively normal in patients who subsequently died. A very early predictive index based on these observations was found to predict outcome in 94% of high-risk patients. The hypotheses that increased $\dot{D}O_2$ and $\dot{V}O_2$ in the survivors represent compensatory physiologic responses and that these values were appropriate therapeutic goals were tested in prospective randomized clinical trials and found to reduce mortality and morbidity significantly. The optimal goals were more easily attained with colloids, red cells, dobutamine, and vasodilators, according to their capacity to improve tissue perfusion, as reflected by increased flow and oxygen transport. The extremely complex interactions between $\dot{D}O_2$ and $\dot{V}O_2$ are reviewed.

Key words: Cardiac index – Oxygen delivery – Oxygen consumption – Surgical patients

Circulatory function can be determined by measuring cardiac and respiratory physiology by invasive catheterization, cardiac angiography, computed tomography, multiple-gated image acquisition, positron-emission tomography, magnetic resonance imaging, chest x-rays, and tests of blood gases and pulmonary function. Overall circulation, however, involves tissue perfusion as well as cardiac and respiratory functions. The overall function of the circulation may be defined as the transport of blood constituents, including oxygen, carbon dioxide, nutrients, and metabolic end-products from their site of origin to their site of utilization or elimination. The delivery of blood constituents to peripheral tissues is as much a part of the circulation as are the heart and lungs.

In the present review we evaluate the measured oxygen delivery ($\dot{D}O_2$) and oxygen consumption ($\dot{V}O_2$ to assess tissue perfusion in animal models and in critically ill postoperative patients.

Conventional evaluation of tissue perfusion

Diagnosis of shock in general and tissue perfusion in particular is subjective, nonspecific, and imprecise. Diagnostic tests, which reflect secondary and tertiary effects of shock on the circulation as a whole, include skin temperature and color, capillary blanching on pressure to the nail, mottling of the skin, cyanosis, pulse quality, and general appearance. The superficial aspects of the overall circulation, such as mean arterial pressure (MAP), heart rate (HR), pulse pressure, urine output, central venous pressure (CVP), hematocrit (Hct), distal pulses, myocardial ischemia, altered level of consciousness, and skin ischemia are also used to evaluate the overall tissue perfusion as well as local or regional tissue perfusion of limbs, kidney, and brain. Measurements of acidosis, base deficit, anion gap, and blood lactate levels provide more objective measures. These are not direct measures of tissue oxygen debt, but are secondary reflections of tissue hypoxia. The functional assessments of tissue perfusion are less precise and accurate than the measurements of cardiac and pulmonary functions.

Diagnosis and evaluation of shock syndromes

Descriptions of clinical shock are often unclear because the patient samples are nonhomogeneous or poorly defined. Often hypotension is the first clinically recognized manifestation of shock, but when hypotension is treated with vasopressors, the physiologic deficiencies may be obscured until lethal complications occur. Early measurements of MAP, HR, CVP, Hct, urine output, and arterial and mixed venous oxygen tension (PaO_2 and $P\bar{v}O_2$) in high-risk postoperative patients were poorly correlated with outcome [1–6]. These commonly monitored variables were restored to the normal range in 76% of the nonsurvivors and in 75% of the survivors [2]. They are

often late manifestations of shock and do not directly reflect the major circulatory functions. The conventionally monitored variables may be corrected by vasopressors, crystalloids, and diuretics without affecting outcome, and thus they are poor criteria for monitoring, predicting, or guiding treatment.

Hemodynamic and oxygen transport variables can be readily and repeatedly measurement using a systemic arterial catheter and a balloon-tipped pulmonary arterial (Swan-Ganz) catheter with measurements of arterial and venous pressures of the systemic and pulmonary circulations, cardiac output, arterial and mixed venous gases, and hemoglobin or Hct [1–10]. Measured and calculated hemodynamic variables include cardiac index (CI), systemic and pulmonary vascular resistance index (SVR and PVR), left and right ventricular stroke work (LVSW and RVSW), left and right cardiac work (LCW and RCW), O_2 delivery ($\dot{D}O_2$), O_2 consumption ($\dot{V}O_2$, and O_2 extraction [1, 3–6]. All flow and volume measurements are indexed to body surface area.

Patterns of oxygen delivery and oxygen consumption

Cain [11] studied $\dot{D}O_2$ and $\dot{V}O_2$ patterns after hemorrhage, anemia, and hypoxia in anesthetized dogs and described a period of decreasing $\dot{D}O_2$ when $\dot{V}O_2$ is maintained in a flow-independent stage. This is followed by a period in which further $\dot{D}O_2$ reductions reduces $\dot{V}O_2$ (the flow-dependent stage). This concept has been evaluated by Danek et al. [12] and Mohsenifar et al. [13] in patients with the adult respiratory distress syndrome (ARDS), by Shibutani et al. [14] in anesthetized cardiac patients after bypass surgery, and by Pepe and Culver [15] during positive end-expiratory pressure sufficient to reduce cardiac output. Cain [11] and his colleagues have presented a clear picture of a horizontal straight line describing the flow-independent stage of $\dot{V}O_2$ and an abrupt angle leading to a straight sloping line describing the flow-dependent phase of $\dot{V}O_2$. However, other studies have shown considerable variations in this $\dot{D}O_2/\dot{V}O_2$ pattern.

Patterns in experimental hemorrhagic shock

Figure 1 illustrates the physiologic pattern during the standardized Wiggers' model of hemorrhagic shock in anesthetized dogs. Marked reductions in arterial pressure, cardiac output, $\dot{D}O_2$, and $\dot{V}O_2$ occurred immediately after bleeding and was intensified during the hypotensive period. These measures were restored immediately after return of the shed blood, but subsequently deteriorated to very low values just prior to death. Figure 2 shows the mean $\dot{V}O_2 \pm$SEM values plotted against their corresponding $\dot{D}O_2$ values at each stage described in Fig. 1. The pattern suggests $\dot{V}O_2$-flow dependency throughout most of the course, but with a wide scatter of $\dot{V}O_2$ values in the various temporal stages.

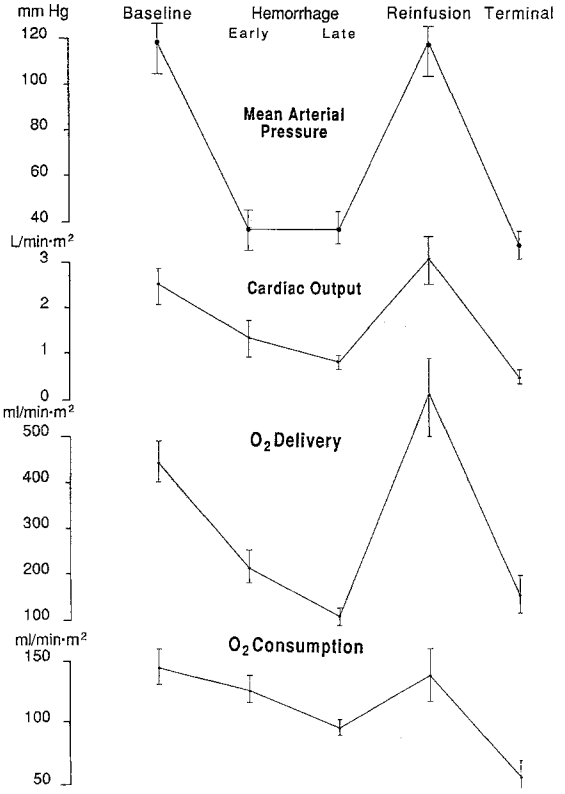

Fig. 1. Serial patterns of mean arterial pressure, cardiac output, and oxygen delivery and consumption in dogs subjected to the Wiggers' standardized hemorrhagic shock model. Mean (±SEM) values at baseline, immediately after hemorrhage, just before reinfusion of the shed blood, immediately after reinfusion of the shed blood, and just before death

Patterns in high-risk surgery

Figure 3 shows the CI, $\dot{D}O_2$, and $\dot{V}O_2$ in postoperative patients [6] to demonstrate the $\dot{D}O_2/\dot{V}O_2$ interactions in survivors and nonsurvivors throughout the various stages of the entire operative course. The $\dot{D}O_2/\dot{V}O_2$ relation-

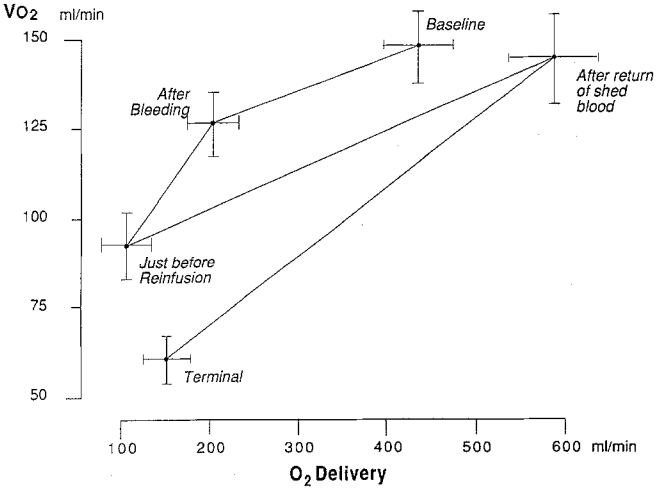

Fig. 2. $\dot{D}O_2$, $\dot{V}O_2$ relationship in hemorrhagic shock. Mean (±SEM) oxygen delivery and consumption in dogs at baseline, after bleeding, before and after reinfusion of the shed blood, and in the terminal state

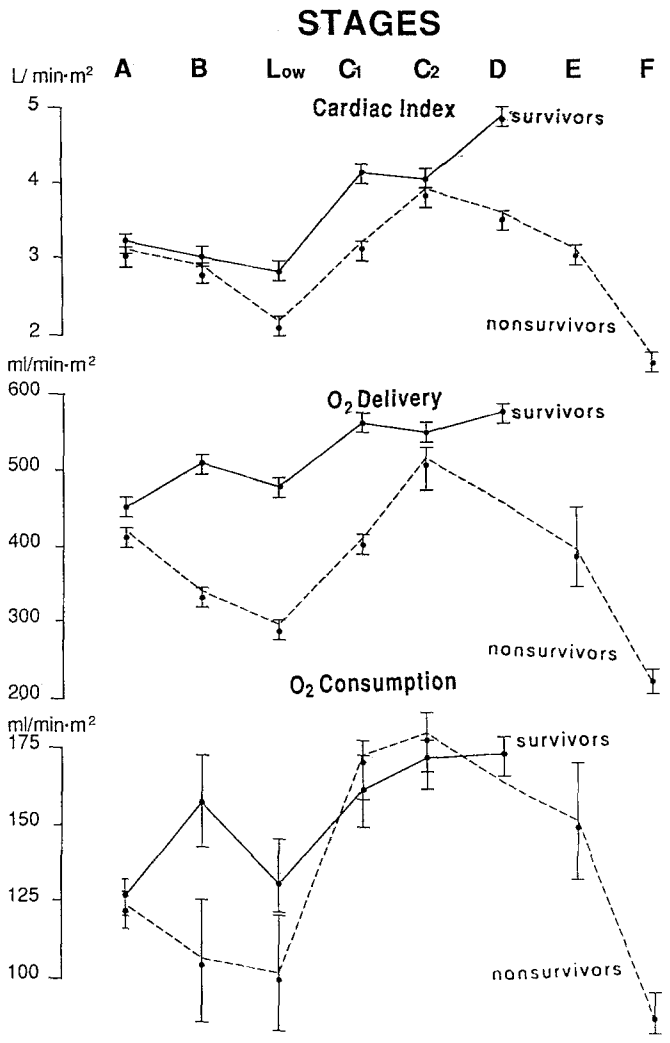

Fig. 3. Mean (±SEM) cardiac index and oxygen delivery and consumption in survivors and nonsurvivors throughout the perioperative period: stage A, preoperative; stage B, early intraoperative period; stage Low, hemodynamic crisis at the lowest mean arterial pressure (MAP); stage C_1, halfway to MAP recovery; stage C_2 full MAP recovery; stage D, stable period after recovery in survivors; stage E, preterminal period of nonsurvivors; stage F, terminal period of nonsurvivors. From Shoemaker et al. [6]

ships are widely diverse, depending on temporal factors and outcome. They are only roughly described by a sloping line consistent with a flow-dependent $\dot{V}O_2$ (Fig. 4). $\dot{V}O_2$ is maintained in the face of falling $\dot{D}O_2$ by many compensations, including changes in the rate of O_2 extraction and oxyhemoglobin dissociation, distribution of regional blood flow, local changes in microcirculatory flow, erythrocyte behavior, pH, CO_2, and cellular metabolic influences.

Early patterns in postoperative patients with normal preoperative values

Recent studies [1, 3] have more precisely defined the early hemodynamic and oxygen transport patterns in terms of time elapsed in hours postoperatively (Fig. 5). In patients with normal preoperative baseline cardiorespiratory values, surgical trauma produced intraoperative physiologic deficits that in the immediate postoperative period led to increased CI, HR, temperature, mean pulmonary artery pressure (MPAP), and oxygen transport, especially in survivors. The early survivors' pattern differed greatly from that of the nonsurvivors: the survivors had greater myocardial performance (increased CI and flow-related variables) with lower CVP and wedge pressures (WP); lower pulmonary vasoconstriction (PVR and MPAP); greater increases in oxygen transport and metabolism with lower oxygen extraction rates and normal blood gases; greater Hct, blood volume, and red cell mass; and lower $P_{(A-a)}O_2$ and $\dot{Q}sp/\dot{Q}t$ values especially in the early postoperative period [1, 5]. These postoperative patterns occurred despite wide variations in the type of surgical illnesses and the surgical operations.

Reduced $\dot{V}O_2$, resulting in tissue hypoxia, was the common denominator in early postoperative high-risk patients [5, 16, 17]. Inadequate $\dot{V}O_2$, which is the earliest pathogenic event, occurring at or before the initial hypotensive crisis, leads to an oxygen debt that limits body metabolism and increases mortality and morbidity. Reduced or inadequate $\dot{V}O_2$ may be produced by low blood flow from cardiogenic or hemorrhagic shock, maldistribution of flow at the microcirculatory level from uneven vasoconstriction, and increased metabolic need from such conditions as sepsis, trauma, burns, or late-stage liver cirrhosis. The basic physiologic problem is the imbalance between oxygen supply ($\dot{D}O_2$) and demand ($\dot{V}O_2$). Thus reduced or inadequate $\dot{V}O_2$ is the common denominator of shock syndromes and the major determinant of outcome. There is a greater $\dot{V}O_2$ reduction in patients who develop organ failure than in those who do not and the O_2 debt is greater and more prolonged in patients who die than in those who survive [4, 5, 16–18].

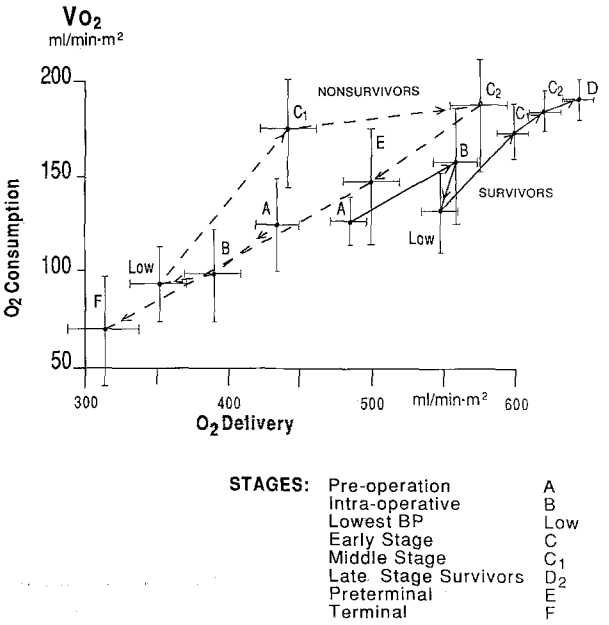

Fig. 4. Mean (±SEM) oxygen delivery and consumption in survivors and nonsurvivors (successive perioperative stages as in Fig. 3)

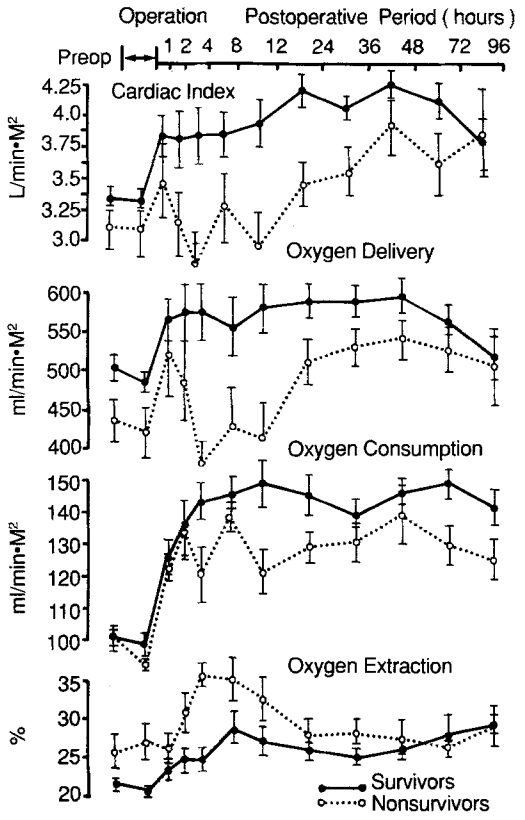

Fig. 5. Mean (±SEM) cardiac index and oxygen delivery, consumption, and extraction in 240 patients with preoperative normal cardiac index. Reproduced, with permission, from Bland et al. [1]

Patterns in patients with increased preoperative cardiac output

Preoperative patients with systemic manifestations of sepsis, severe stress from accidental injury, and advanced liver cirrhosis often had high cardiac output preoperatively. Survivors showed postoperative increases over their own baseline values in MAP, CI, $\dot{D}O_2$, and $\dot{V}O_2$, but only minimal changes in CVP, WP, MPAP, and PVR. In contrast, the nonsurvivors had little or no increases in CI, $\dot{D}O_2$, $\dot{V}O_2$, and flow-related variables despite higher CVP and WP. The PVR and $\dot{Q}sp/\dot{Q}t$ were also higher in the nonsurvivors. These patients started from higher baseline cardiac output values preoperatively, but the differences in the patterns of the survivors and nonsurvivors relative to their own baseline values were similar to those with normal preoperative values [4, 5].

Patterns in patients with low cardiac output preoperatively

Critically ill patients with low cardiac output and congestive failure or hypovolemic shock preoperatively usually had the classic findings of low cardiac output, high WP, hypotension, reduced $\dot{D}O_2$, and low $\dot{V}O_2$. In the early postoperative period, the average CI, $\dot{D}O_2$, and $\dot{V}O_2$ values in most survivors increased. In contrast, the nonsurvivors had lower CI, $\dot{D}O_2$, and $\dot{V}O_2$ despite high WP; they also had significantly increased PVR and $\dot{Q}sp/\dot{Q}t$ [4, 5] relative to their own baseline values. Thus survivors compensated for intraoperative tissue hypoxia with increased CI, $\dot{D}O_2$, and $\dot{V}O_2$, but nonsurvivors poorly compensated for these deficits.

Short-duration monitoring of $\dot{D}O_2$ and $\dot{V}O_2$ relationships

Data collected over relatively long periods during critical illness may not clearly show the simple linear horizontal relationship of $\dot{D}O_2$ to $\dot{V}O_2$ described by Cain [11]. Thus we studied short-term monitored events during rapidly changing periods that were usually about an hour or less. Of 100 monitored events consisting of >20% changes in flow, pulmonary function, or peripheral tissue oxygenation, we found 51 instances of a pattern of increasing $\dot{D}O_2$ and $\dot{V}O_2$ associated with a horizontal plateau period. Altogether there were 833 pairs of $\dot{D}O_2$ and $\dot{V}O_2$ values. Figure 6 shows these data during the so-called flow-dependent slope of the $\dot{D}O_2/\dot{V}O_2$ curve and Fig. 7 shows the data obtained during the relatively horizontal component of this curve. As may be seen, there are wide variabilities suggesting that the flow-dependent/independent $\dot{V}O_2$ is not a simple relationship. For example, it may take different times for unevenly distributed metarteriolar capillary networks to be restored to full function. When these delays occur, the plateau may slope upward. Moreover, an oxygen debt as it is resupplied my produce a transient increase with a new plateau, or a biphasic response, or a plateau that slopes downward. Furthermore, the mechanisms that contribute to the $\dot{D}O_2/\dot{V}O_2$ configuration during the hemorrhagic shock or critical illness may not be operative during therapeutic correction of these conditions. Finally, clearly defined horizontal and sloping components presume that all regions, organs, and tissues are developing the same circulatory problems simultaneously. It may be hazardous to extrapolate this simplistic $\dot{D}O_2/\dot{V}O_2$ concept observed in very special experi-

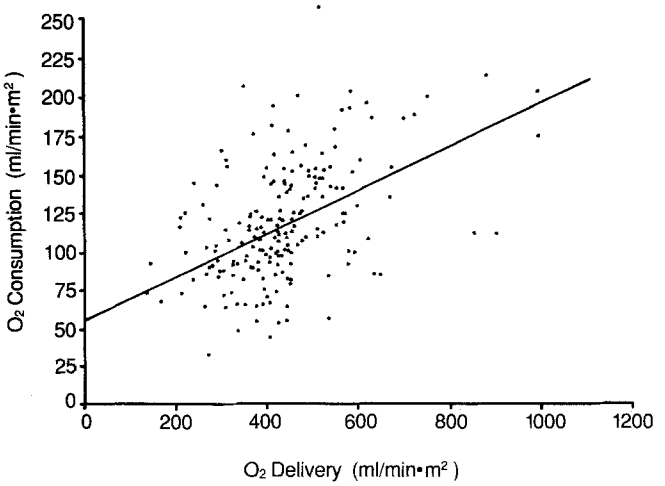

Fig. 6. Oxygen delivery and consumption in 51 consecutively monitored patients with sudden changes in monitored oxygen delivery values: $r = 0.50$; slope 0.14; intercept 59

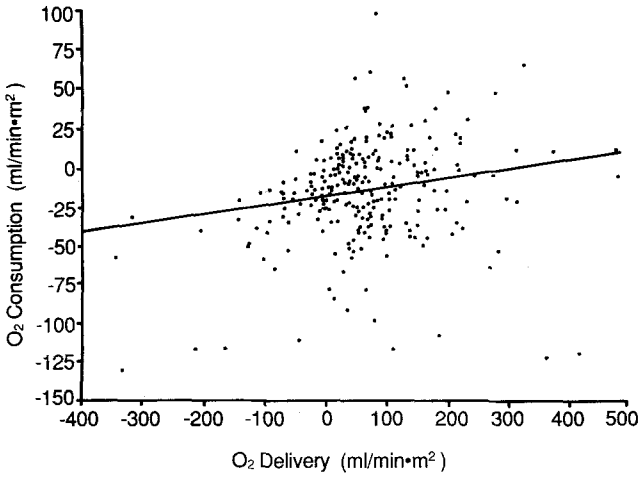

Fig. 7. Oxygen delivery and consumption in 51 consecutively monitored patients during the plateau period when oxygen consumption was relatively constant as delivery values changed markedly: $r = 0.19$; slope 0.06; intercept -17

mental and anesthetized conditions to more general circulatory problems in complex clinical circumstances of critical illness.

Therapeutic principles based on oxygen transport patterns

Early prognostic indicators, which differ from conventional subjective criteria of shock, approach the complex physiologic problems with an objective empirical analysis, no preconceptions, and only minimal assumptions. The criteria for therapeutic goals were determined from observed values in critically ill surgical patients who survived and compared with those in patients who subsequently died. A simplified predictor was recently developed based on empirically observed values of each cardiorespiratory variable at serial time intervals postoperatively, and found to be correct in 94% of high-risk patients [1, 3]. The accuracy of these predictors has been corroborated by others [19].

Therapeutic goals defined empirically from the median values for each physiologic variable of the survivors of life-threatening postoperative critical illness were: (a) CI 50% greater than normal (4.5 l/min·m^2), (b) $\dot{D}O_2$ greater than normal (>600 ml/min·m^2), (c) $\dot{V}O_2$ about 30% greater than normal (170 ml/min·m^2), and (d) blood volume 500 ml in excess of the norm (3.2 l/m^2 for males, 2.8 l/m^2 for females) [1–5, 7, 8]. These increased values are compensatory reactions needed to supply the increased metabolic requirements associated with tissue repair. The gross physiologic compensations to tissue hypoxia include increased HR, myocardial contractility, stroke volume, cardiac output, and $\dot{D}O_2$; hyperpnea; tachypnea; increased O_2 extraction rate; and altered vascular tone. The decompensations include hypotension, bradycardia, and collapse. Severely traumatized, cirrhotic, and septic patients may require even greater increases in $\dot{D}O_2$ and $\dot{V}O_2$ [1, 3–5].

A branch-chain decision tree or clinical algorithm for high-risk surgical patients and assignment of priorities was designed from decision rules based on predictor outcome data from several clinical trials of various therapeutic agents [4, 20].

Fluid resuscitation: choice of fluid regimens

The strategy is first to give fluid volume vigorously without exceeding WP of 18 mmHg. Blood is used when Hct falls below 34%. The decision to use colloids instead of crystalloids in the high-risk surgical patients was based on prospective studies comparing these agents, and because it is easier to attain and maintain optimal goals with colloids [5]. The relative effectiveness of 1 l of lactated Ringer's solution was compared with 25 g of 25% albumin (100 ml) in a prospective random-order, cross-over study in surgical patients with early shock lung [21]. Albumin increased mean (±SE) plasma volume 465±47 ml by shifting over 350 ml of water from the interstitial compartment to the intravascular space; albumin also increased CI, MAP, LVSW, $\dot{D}O_2$, and $\dot{V}O_2$; lung function did not deteriorate, but in many instances actually improved. By contrast, 1 l of Ringer's lactate given to the same patients expanded plasma volume only 194±18 ml at its peak, which occurred at the end of the infusion. Over 80% of the infused crystalloid almost immediately equilibrated into the interstitial water; the small proportion of fluid that remained in the plasma then decreased exponentially [21]. The pulmonary shunt and $\dot{V}O_2$ worsened after Ringer's lactate administration.

The hemodynamic and oxygen transport responses to fluid therapy were directly proportional to plasma volume expansion: colloids expanded plasma volumes and thereby improved hemodynamics and oxygen transport, but crystalloids principally expanded interstitial volume [22–30]. They may improve plasma volume if massive amounts are tolerated [31].

In Fig. 8, the changes in $\dot{D}O_2$ plotted against the corresponding change in $\dot{V}O_2$ are shown halfway through the infusions, at the end of the infusions, and 15, 30, 45, and 60 min after the infusions. The changes in $\dot{V}O_2$ are also plotted against the changes in plasma volume (PV) as measured by labeled albumin [21] for both agents. The $\dot{D}O_2$ and $\dot{V}O_2$ values increased during infusion of the concentrated albumin and for 45 min after infusion; then there was a small $\dot{V}O_2$ reduction at 60 min. The $\dot{V}O_2$/PV pattern was similar to the $\dot{D}O_2/\dot{V}O_2$ pattern, which suggests that the increased volume was the direct result of albumin which secondarily increased flow, $\dot{D}O_2$, and $\dot{V}O_2$.

In contrast, the Ringer's lactate produced a transient PV increase of only 200 ml and small increases in $\dot{D}O_2$, but reductions in $\dot{V}O_2$. A similar pattern of changes in $\dot{V}O_2$ versus changes in PV was observed. The reduced $\dot{V}O_2$ could not be attributed to flow dependency since flow and volume increased somewhat. The decreased $\dot{V}O_2$ may be better explained by the reduced tissue PO_2 demonstrated by Heughan et al. [32] after expansion of interstitial space by crystalloids. The increased interstitial

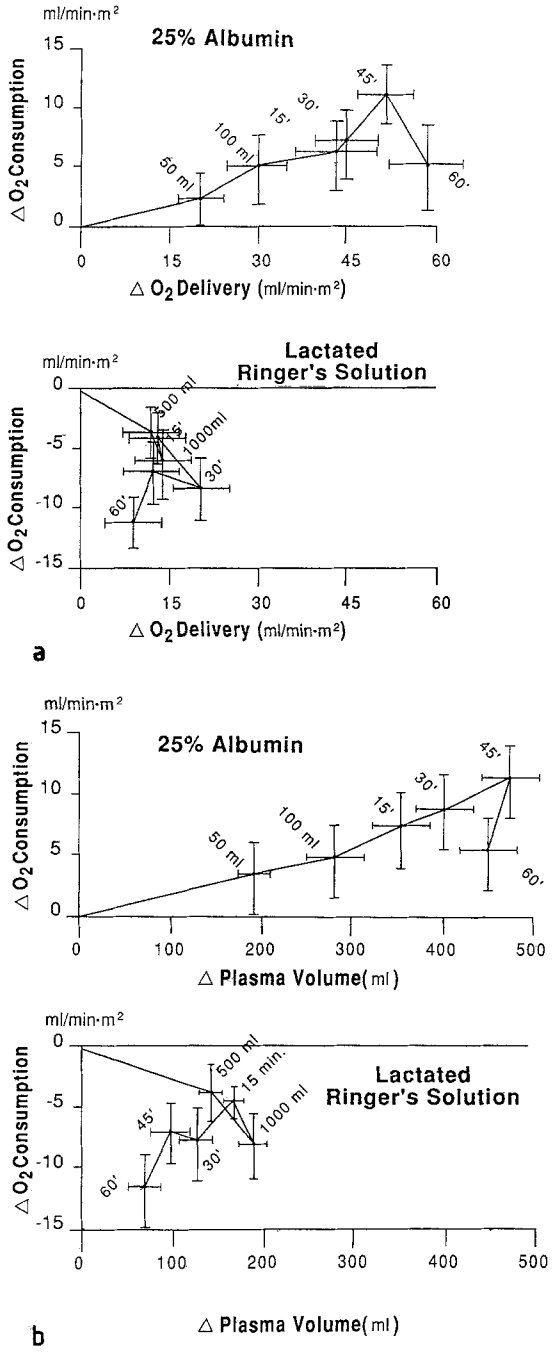

Fig. 8a, b. Mean (±SEM) changes in oxygen delivery (**a**) and consumption and in plasma volume (**b**) during and after infusion of 100 ml of 25% albumin of 1000 ml of lactated Ringer's solution. Values are shown for halfway through the infusion (50 ml or 500 ml), at the end of the infusion (100 ml or 1000 ml), and at 15, 30, 45, and 60 min after the end of the infusion

water expansion increases the length of the diffusion pathway for oxygen and may limit tissue oxygenation.

Effects of various volume therapies on $\dot{D}O_2$ and $\dot{V}O_2$

We have performed 400 fluid therapy interventions in 211 patients with early ARDS occurring postoperatively and with sepsis [22]. The results showed significant increases in hemodynamic and oxygen transport after colloid infu-

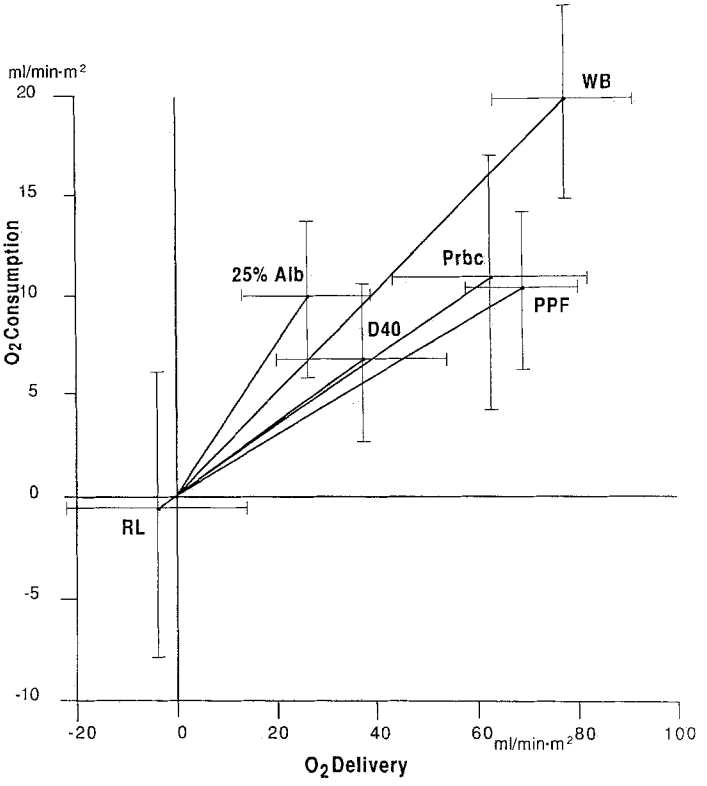

Fig. 9. Effects of various plasma expanders on $\dot{D}O_2$ and $\dot{V}O_2$. Mean (±SEM) changes in oxygen delivery and consumption after 1 U of whole blood (WB), 100 ml of 25% albumin (25% Alb), 500 ml of dextran-40 (D-40), 2 U of packed red cells (*Prbc*), 500 ml of plasma protein fraction (*PPF*), and 1000 ml of lactated Ringer's solution (*RL*)

sions, but insignificant changes, except in arterial pressure, after Ringer's lactate. Figure 9 shows the effects of 86 whole-blood transfusions, 32 packed red-cell transfusions of 2 U each, 82 infusions of 500 ml of plasma protein fraction, 73 infusions of 100 ml of 25% albumin, 92 infusions of 500 ml of dextran-40, and 35 infusions of 1000 ml of lactated Ringer's solution plotted as changes in $\dot{D}O_2$ versus changes in $\dot{V}O_2$. Most of these agents, except Ringer's lactate, produced appreciable and statistically significant increases in both $\dot{D}O_2$ and $\dot{V}O_2$ [22]. The slope of the $\dot{D}O_2/\dot{V}O_2$ relationship suggests that the increasing $\dot{V}O_2$ was flow related, despite the fact that the $\dot{D}O_2$ was usually in the range of 400 to 600 ml/min·m^2.

Inotropic agents

After the maximum effect of fluid therapy had been obtained, the patients were given dobutamine, a synthetic catechol with inotropic properties, starting at 2 μg/kg and increasing until the optimal goals for CI, $\dot{D}O_2$, and $\dot{V}O_2$ were reached. Figure 10 shows significant increases in CI and stroke index, cardiac and stroke work, HR, $\dot{D}O_2$, and $\dot{V}O_2$ after dobutamine, as well as decreases in systemic and pulmonary vascular resistance and intravascular pressures, including MAP, MPAP, CVP, and WP [32]. Blood gases, pH, and $\dot{Q}st/\dot{Q}t$ were not significantly changed. Dobutamine primarily increases myocardial contractility by its β_2 effect, but it also improves

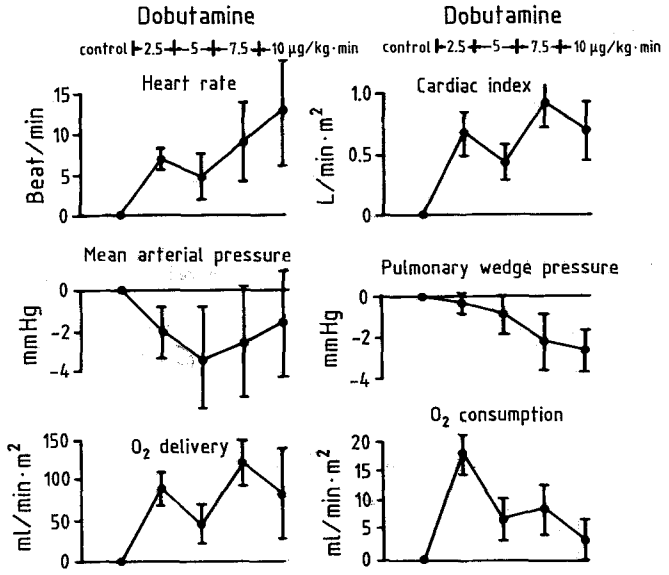

Fig. 10. Mean (±SEM) changes in heart rate, mean arterial pressure, oxygen delivery cardiac index, wedge pressure, and oxygen, consumption in response to dobutamine in 43 studies of 34 critically ill general (non-cardiac) surgical patients. From Shoemaker et al. [33]

tissue perfusion by its β_2 effect, which vasodilates peripheral metarteriolar-capillary networks previously vasoconstricted, and improves the distribution of flow and oxygen consumption [33, 34].

The effects of dobutamine were observed in hypovolemic patients before and after a fluid load consisting of 1000 ml of 5% albumin. Figure 11 shows marked reduction in MAP levels, but after the fluids the patients responded to the same dose of dobutamine with no decrease in MAP and greater improvement in flow and $\dot{D}O_2$. Since hypovolemic patients are sensitive to vasodilators, the hypovolemia must be corrected before vasocilators are given. Although inotropic stimulation of the tired heart may be needed therapeutically, stimulation of the tired empty heart may be disastrous. When dobutamine produces sudden severe hypotension, this reaction may be reversed with rapid administration of plasma expanders [33].

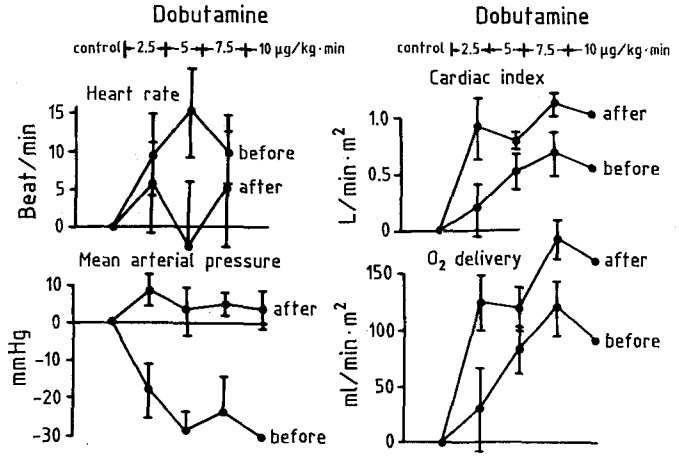

Fig. 11. Mean (±SEM) changes in heart rate, mean arterial pressure, cardiac index, and oxygen delivery in response to dobutamine at various doses in three hypvolemic patients before and after volume load. From Shoemaker et al. [33]

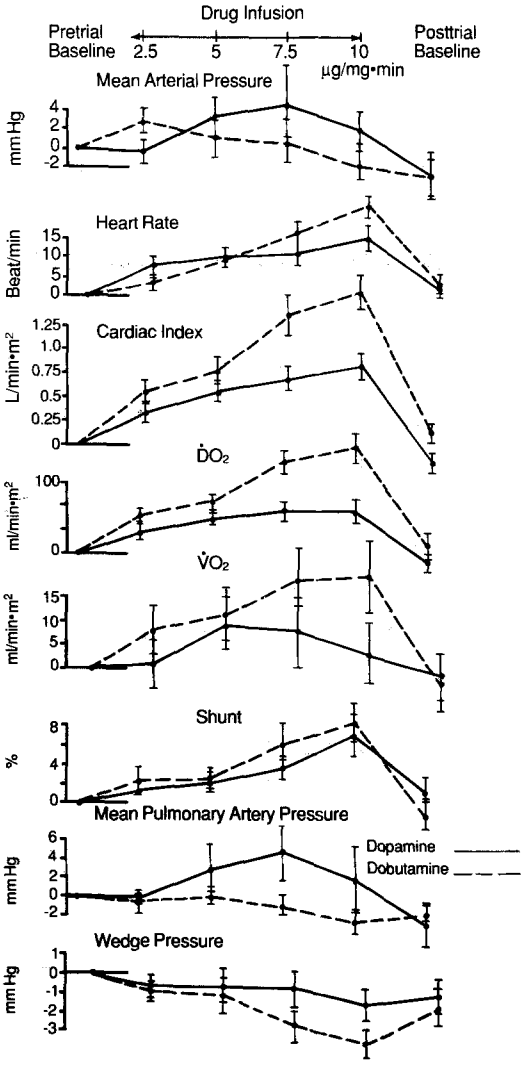

Fig. 12. Hemodynamic and oxygen transport effects of dobutamine and dopamine in 25 critically ill patients. From Shoemaker et al. [34]

The effects of dobutamine were also compared with those of dopamine in 25 critically ill, postoperative general surgical patients in a prospective, randomized, crossover study (Figs. 12 and 13). Dobutamine produced greater increases in HR, CI, stroke work, $\dot{D}O_2$ and $\dot{V}O_2$ than did dopamine. Moreover, dobutamine decreased WP, allowing more fluids to be given at lower WP. In general, the flow and oxygen transport effects of the two drugs were most marked in patients during the first 72 hours postoperatively.

Vasodilators

If the patient has high MAP and SVR, vasodilation with nitroglycerin, nitroprusside, labetalol, or prostaglandin E_1 should be considered; the appropriate dose is obtained by titration to improve CI, $\dot{D}O_2$ and $\dot{V}O_2$ without producing hypotension, defined as MAP < 80 mmHg and

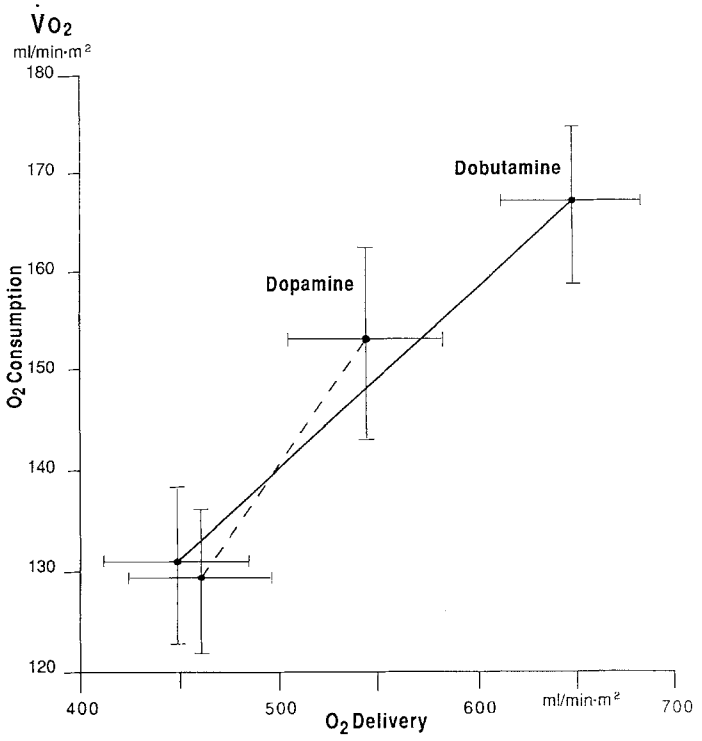

Fig. 13. Mean (±SEM) oxygen delivery and consumption before and after administration of comparable doses of dopamine and dobutamine. From Shoemaker et al. [34]

systolic blood pressure <110 mmHg. Vasodilators are primarily directed at improving tissue perfusion and oxygenation by dilating metarteriolar-capillary networks in order to provide increased flow, more evenly distributed flow, and better tissue oxygenation [35].

Vasopressors

If fluids, inotropic agents, and vasodilators fail to achieve optimal goals, vasopressors such as dopamine or norepinephrine are given in the smallest possible dose needed to maintain MAP at or slightly above 80 mmHg and systolic pressure at or slightly above 110 mmHg in patients who were previously normotensive. In hypertensive patients, 80% to 90% of preillness values are used as goals. Vasopressors are given last because they increase lactic acidosis, pulmonary artery pressure, pulmonary vascular resistance, pulmonary shunt, CVP, and WP. Vasopressors also improve MAP and thereby maintain coronary and cerebral blood flow, but they may compromise peripheral tissue perfusion [34].

Empirically defined therapeutic goals

The therapeutic plan was tested in prospective clinical trials of 275 consecutive high-risk patients: the therapeutic goal was normal CI, $\dot{D}O_2$, and $\dot{V}O_2$ values in the control group and supranormal values in the protocol group [5]. Mortality was 12.5% in the protocol patients and 35% in the control group; there were also significant reductions in morbidity in the protocol group. In a prospective, randomized trial of this concept, three groups of patients were studied; one group was managed with a central venous pressure (CVP) catheter, one with a pulmonary artery (PA) catheter using values in the normal range as goals of therapy, and one with a PA catheter using the supranormal values as goals of therapy. Mortality did not differ significantly between the CVP and PA groups with normal values as goals. In contrast, use of the pulmonary artery catheter with supranormal optimal goals led to marked and significantly reduced mortality and morbidity (Table 1) [5].

Conclusions

The patterns of oxygen transport variables provide a sensitive method for evaluating tissue perfusion during the course of critical illness as well as before and after therapeutic interventions. Objective evaluation of hemodynamic and oxygen transport monitoring has revealed distinct differences in the patterns of the survivors and nonsurvivors. Essentially, circulatory function in general and tissue perfusion in particular may be described by the transport of oxygen and other blood constituents: $\dot{D}O_2$ is the single best measure of the overall function of the circulation, the supply side of the problem; $\dot{V}O_2$ reflects the rate of body metabolism, i.e., the rate that oxygen is actually taken up by the tissues, which is not necessarily the rate that is needed. These oxygen transport variables were found to be strongly related to survival: they provide the capacity to predict outcome. Moreover, the interactions of $\dot{D}O_2$ and $\dot{V}O_2$ may be used as criteria to evaluate the adequacy of tissue perfusion and the effectiveness of treatment.

Although $\dot{V}O_2$ may be rate-limited by $\dot{D}O_2$ the interaction between these two variables is complex and not adequately explained by a simple horizontal line representing flow-independent $\dot{V}O_2$ and a sloping line representing flow-dependent $\dot{V}O_2$. $\dot{V}O_2$ represents oxygen uptake, not the metabolic need. Increased $\dot{V}O_2$ when $\dot{D}O_2$ is augmented indicates that there has been an oxygen debt that has been at least partly restored by therapeutic increase in $\dot{D}O_2$. However, the oxygen debt or flow-dependent $\dot{V}O_2$ may not be immediately corrected. Our data suggest there is some degree maldistributions that limit $\dot{V}O_2$ throughout critical illness in postoperative and septic patients. Treatment that drives $\dot{D}O_2$ to values above 1000 ml/min·m^2 may be required to optimize $\dot{V}O_2$. The $\dot{D}O_2/\dot{V}O_2$ relationships provide objective criteria for treatment in both postoperative and septic patients in whom estimates of metabolic and circulatory requirements are unavailable or uncertain. If a treatment increases $\dot{D}O_2$ and $\dot{V}O_2$, it may be continued if further $\dot{D}O_2$ increases lead to additional improvement in $\dot{V}O_2$.

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Table 1. Mobidity, mortality, and treatment costs in nonrandomized patients and in patients randomized to a central venous pressure (CVP) catheter, with a pulmonary artery (PA) catheter and normal values as the therapeutic goal (controls), and with a PA catheter and supranormal values as the therapeutic goal (protocol), and postoperative vital organ failure and nonvital organ complications

	Nonrandomized ($n = 45$)	CVP ($n = 30$)	PA-control ($n = 30$)	PA-protocol ($n = 28$)
Age (years)	56.9±25	55.2±30	53.4±2.5	56.4±3.1
Men/women (%)	45/55	64/36	39/61	72/25
Hospital days	21.9± 1.7	22.2± 2.8	25.2±3.4	19.3±2.4
ICU days	14.0[1.7	11.5± 1.7	15.8±3.1[a]	10.2±1.6[a]
Ventilator days	6.5± 1.3	4.6± 1.4	9.4±3.4[a]	2.3±0.5[a]
Intraoperative deaths	0	0	1	0
Postoperative deaths	17 (38%)	7 (23%)	10 (33%)[b]	1 (4%)[b]
Organ failures	42	22	31[b]	1[b]
Other complications	9	9	8	10
Average cost	$31438	$30748	$37335	$27665
Average cost per survivor	$50525	$40106	$58950	$28690
Vital organ failure				
Repiratory failure	11	7	9	1
Renal failure	10	7	7	0
Sepsis and septic shock	11	6	9	0
Acute myocardial infarction/failure	6	0	2	0
Hepatic failure	2	2	2	0
Disseminated intravascular coagulation	2	0	2	0
Novital organ complications				
Pulmonary edema	2	2	3	2
Pleural effusion	2	2	3	3
Wound infection	2	1	2	1
Evisceration	0	1	0	0
Intraabdominal abscess	1	1	0	0
Postoperative hemorrhage	1	1	0	1
Pancreatitis	0	0	0	1
Gastric outlet obstruction	0	1	0	1
Urinary tract infection	0	0	0	1
Cerebral infarct	1	0	0	0

[a] $p < 0.05$
[b] $p < 0.01$

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