

Hemodynamic goal-directed therapy. A review

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ABSTRACT

Patients can show arterial pressure and cardiac index within the normal range and still be in circulatory shock if oxygen and metabolic demand is increased or blood flow distribution is altered.

Lactate is produced in anaerobic environment to preserve cellular integrity and physicians use its blood concentration value as a reliable marker of tissue hypoxia and energy failure.

The authors review the recent literature on the importance of mixed venous oxygen saturation (SvO₂) as an early sign of inadequate DO₂ that precede the lactate production.

Keywords: Lactate, Goal directed therapy, Low cardiac output syndrome, Sepsis.

Cardiac Output (CO) is the primary determinant of global oxygen transport from the heart to the tissues since it represents the main contributor to the oxygen delivery (Table 1).

CO calculation has been used as the main parameter for hemodynamic monitoring since Swan and Ganz (1) introduced the pulmonary artery catheter (PAC) in clinical practice.

Physicians need to monitor hemodynamics of critically ill patients in order to optimize pre-load, after-load, and contractility by titrating fluids, diuretics, inotropes, and vasoactive drugs, as to achieve the best delivery of oxygen and metabolites to tissues.

PATHOPHYSIOLOGICAL IMPLICATIONS

Inadequate hemodynamics had been considered for a long time a clinical condition characterized by low arterial blood pressure and/or flow. This concept could be misleading if not related with that of oxygen demand and of blood flow distribution to tissues. Therefore, one patient can show arterial pressure and cardiac index (CI) within the normal range and still be in circulatory shock if oxygen and metabolic demand is increased or blood flow distribution is altered. Studies by Shoemaker et al. (2), at the end of eighties, have focused on the observation that critically ill patients who survived major surgery had higher DO₂ values than non-survivors. According to Shoemaker's results a *perioperative* optimization of DO₂ up to supra-normal values, was accompanied with reduced complications, duration of hospitalization, intensive care unit (ICU) length of stay, mechanical ventilation, and, therefore, overall costs.

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Table 1 - Hemodynamic parameters.

Hemodynamic Parameter	Calculation	Absolute range	Size-Adjusted range*
Delivery of oxygen (DO ₂)	$CO \times (1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2) \times 10$	900-1100 ml/min	520-600 ml/min/m ²
Oxygen consumption (VO ₂)	$CO \times (CaO_2 - CvO_2) \times 10$	200-270 ml/min	110-160 ml/min/m ²
Pulse Pressure Variation (PPV) %	$\frac{PP_{max} - PP_{min}}{PP_{max} + PP_{min}} / 2 \times 100$	< 10-15 %	
Systolic Pressure Variation (SPV) %	$\frac{SP_{max} - SP_{min}}{SP_{max} + SP_{min}} / 2 \times 100$	< 10-15 %	
Stroke Volume Variation (SVV) %	$\frac{SV_{max} - SV_{min}}{SV_{max} + SV_{min}} / 2 \times 100$	< 10-15 %	

Abbreviations: CO, Cardiac Output (l/min); Hb, hemoglobin concentration (g/dl); SaO₂, oxygen saturation in arterial blood; PaO₂, oxygen partial pressure in arterial blood (mmHg); CaO₂, arterial oxygen content ((1.34 x Hb x SaO₂) + (0.003 x PaO₂)); CvO₂, venous oxygen content ((1.34 x Hb x SvO₂) + (0.003 x PvO₂)); PP, Pulse Pressure; SP, Systolic Pressure; SV, Stroke Volume. *Size-adjusted values are the absolute values divided by the patient's body surface area in square meters (m²).

On the basis of these findings many investigators had been considering that values of CO and DO₂, previously believed “in normal range”, could be inadequate to fulfill the tissue oxygen needs.

Deep modifications in the cellular metabolic-energetic pathways occur when inadequate DO₂ is delivered to tissues (e.g. low CO states), whatever was the cause. Independently from cellular oxygen tension, in the cytoplasm, one mole of glucose is transformed into 2 moles of *pyruvate*. This reaction, needs 2 NAD⁺ molecules and results in the net production of 2 ATP and 2 NADH molecules for each molecule of glucose (poor energetic profit). If oxygen availability is adequate, the pyruvate within the mitochondrial matrix, is converted to *acetyl-CoA* and CO₂. Acetyl-CoA, by means of the *citric acid cycle* (or tricarboxylic acid cycle or Krebs cycle) is fully oxidized to CO₂ and H₂O, producing NADH that is oxidized by the electron transport chain (inner mitochondrial matrix) using oxygen as the final electron acceptor leading to a strong free energy production (net energy profit: 36 moles ATP/mole glucose).

Conversely, when dysoxia occurs (anaerobic conditions, low CO states), the Krebs

cycle and the electron transport chain cannot proceed and the metabolic pathways shift toward the conversion of glucose into pyruvate (net energy profit: 2 ATP). The *conditio sine qua non* the above mentioned reaction can occur is the presence of NAD⁺ (oxidized form of NADH) that is produced when pyruvate is converted into *lactate*. Hence, lactate is produced in anaerobic environment as to preserve cellular integrity and, physicians, can use its blood concentration value as a reliable marker of tissue hypoxia and energy failure (3). The metabolic shifting from a high energy production pathway, in presence of adequate oxygen, to a poor but rescuing option in anaerobic conditions helps, thanks to lactate, to maintain cellular vitality but, if prolonged over time, structural alterations of mitochondria occur with consequent cellular death.

Intensive care givers have learned that when mixed venous oxygen saturation ((SvO₂), i.e. the oxygen saturation of blood sampled in the pulmonary artery (blood coming from both superior and inferior vena cava)) drops under normal values (normal values > 70 %), DO₂ is suspected to be inadequate. SvO₂ although very sen-

sitive is a non-specific marker of low CO because depends on several factors, other than flow (CO), it depends on arterial saturation (respiratory function), cells metabolism, and hemoglobin concentration. When DO_2 falls, the cell still maintains its needed oxygen consumption (VO_2) by means of an increase in oxygen uptake thus causing a reduction of SvO_2 . Therefore, SvO_2 values under 70 % can represent an early sign of inadequate DO_2 that precede the lactate production.

When the duration of dysoxia persists longer or if microcirculation disorders occur, such as capillary shunts, preventing normal distribution of blood to tissues, the SvO_2 value can even return to normal values suggesting that mitochondria can't uptake any more oxygen. Since the duration of dysoxia is associated to the magnitude of cell injury, the earlier is the intervention, the greater is the physiological response to treatment and the better is the outcome.

PURPOSE OF HEMODYNAMIC MONITORING

In the study by Shoemaker et al. (2), an early hemodynamic goal-directed therapy (GDT), aimed to maintain an elevated DO_2 , were applied very early similarly to Rivers et al. (4) who described that, in emergency room, the cardio-circulatory status of septic patients, was supported according to a close algorithm. In their study group, Rivers et al. observed a significant reduction in mortality and morbidity vs. controls and concluded that "*Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock*".

In a previous randomized multicentric study designed on the basis of Shoemaker's observations, Gattinoni et al. (5), randomized patients in two study groups other than

control group. In fact, GDT was decided on the basis of CI in one group and SvO_2 in the other. Otherwise from Shoemakers' investigation, this study did not come to similar results and the authors concluded that "*Hemodynamic therapy aimed at achieving supra-normal values for the cardiac index or normal values for mixed venous oxygen saturation does not reduce morbidity or mortality among critically ill patients*".

One of the main differences between the studies by Gattinoni and Rivers is the TIME elapsed from the patient hospitalization and the inclusion in a hemodynamic GDT group. In the Rivers' study the median time from arrival at the emergency department to enrollment was only 50.5 minutes (Standard Therapy Group) and 59 minutes (Early GDT Group) respectively. Moreover the median value of central venous oxygen saturation ($ScVO_2$); saturation in oxygen of blood sampled in the superior vena cava or right atrium, considered in this study as a surrogate of SvO_2) in the patients of Rivers' study was almost 50 %, a value that strongly suggests a severe hemodynamic impairment. The mean value of SvO_2 in the patients of Gattinoni's study was only slightly lower than 70 % (67.3 ± 10.5 % in the Control Group; 68.2 ± 9.7 % in the Cardiac Index Group; 69.7 ± 10.5 % in the Oxygen Saturation Group) suggesting that too much time was elapsed until the initiation of the hemodynamic GDT.

The benefit from a hemodynamic GDT was recently reconsidered in two trials carried out in major surgery setting by Pearse et al. (6) and by Lopes et al. (7).

In the randomized controlled study by Pearse, high risk general surgical patients, were treated according to a close post-operative GDT ($DO_2I \geq 600$ ml/min/m²), sustained with fluids and inotropes or standard treatment (Controls). Otherwise from the previous studies, CO was measured by means of pulse power analysis (lithium

indicator dilution) instead of PAC. In the study by Pearse et al. (6), patients in the study group, developed fewer complications and had a lower duration of hospital stay when compared with controls even if no significant difference in mortality was observed.

In the study by Lopes et al. (7), in patients undergoing high risk surgery, the hemodynamic therapy was instituted minimizing the Pulse Pressure Variation (PPV) (Table 1), the cyclic variations induced by positive pressure ventilation in PP ($P_{\max} - P_{\min}$). Briefly, positive pressure ventilation when applied to a patient at rest and with no spontaneous respiratory effort is associated with a cyclic increase in right atrial pressure during the inflation. Since right atrial pressure is the back-pressure to venous return, if upstream venous pressures do not simultaneously increase then right ventricular (RV) filling will also decrease in a cyclic fashion. This cyclic variation in RV filling will induce a cyclic variation in left ventricular (LV) filling if both RV and LV are preload responsive.

This cyclic variation in LV filling will induce a cyclic variation in LV SV and arterial PP if the patient is preload responsive. Since the primary determinant of arterial PP is SV, PPV has been shown to predict preload responsiveness (Cardiac Index augmentation of at least 15% after 500-mL volume bolus) when exceeded 10-15% (8, 9). In the study by Lopes et al. (7), minimizing PPV to 10% or less by means of volume loading, a lower incidence of complications, a lower duration of mechanical ventilation, and hospital stay, and a lower (not statistically different) mortality was observed in the hemodynamic GDT Group in respect to Controls.

Recently, Jacob et al. (10) published a review concerning the importance of fluid management during vascular surgery, a surgery burdened by a considerable mor-

bidity and mortality (11). A strict monitoring of volemia and an early correction of hypovolemic states may contribute to prevent organ dysfunction due to low perfusion. Nevertheless, it is well recognized, that neither the pulmonary artery occlusion pressure nor the central venous pressure accurately predicts ventricular preload or cardiac performance, either in critically ill patients or in normal volunteers (12). Jacobs et al., confirm that dynamic measures are superior than "static" markers of preload concluding that patients who undergo vascular surgery may benefit from a close monitoring and treatment of hypovolemia with a GDT approach in which early timing is a key factor.

(Early) hemodynamic goal-directed therapy has always been recognized as a key factor for successful management of the critically ill, hemodynamically unstable and high risk surgical patients.

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