Emergency Medicine: Open Access
ISSN: 2165-7548

Devia-Jaramillo et al., Emergency Med 2013, 4:1
DOI: 10.4172/2165-7548.1000170

Review Article Open Access

Perfusion Measurement of the Septic Patient in the Emergency Department

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Abstract

Sepsis is a deadly disease, more complex and frequent every day, that requires management from different specialists. The emergency physician is the first and one of the most important physicians that has to deal with the septic critically ill patients, because an appropriate initial management is key to a favorable outcome.

In the emergency department it can be hard to predict which patients will become sicker just with information from the vital signs, and it's even harder to predict which patients will require a more intensive medical treatment. That is the reason why there must be more resources to measure tissue perfusion in an early and simple way in the emergency room, so that the emergency physician can manage to establish which patients requires earlier intervention to improve their perfusion state, despite not showing any clinically evident signs that help in the diagnosis of their current state.

The goal of this paper is to propose a diagnostic and therapeutic algorithm for the hypoperfused patient with septic shock in the emergency department.

Keywords: Sepsis; Emergency department; Hypoperfusion; Tissue perfusion

Introduction

The current approach to the septic patient starts with a concept developed in 1914 by Schottmueller [1]; he mentions in his work that the systemic manifestations of the sick patients are because of the presence of microorganisms (pathogens) in the blood stream. This concept allowed, since then, to guide the diagnostic and therapeutic efforts to focus on these newly found process of infection, and to study and understand the way to modify it, in order to avoid the tragic natural outcome of sepsis.

However, despite this effort, the amount of septic patients in the emergency department is rising, about 750000 cases are seen every year in the United States from the last 10 years data [2], about two thirds of them are admitted from the emergency department [3].

For Latin America there is a more severe statistic, Silva et al. [4] reports in Brazil an incidence of 59.7 for every 1000 patients, with a mortality rate between 24.2-54.2%. In Colombia, the situation is not too different, Rodriguez et al. [5], found mortality rates up to 45.6%, showing it as a public health problem, requiring educative interventions on the medical personnel, in order to raise awareness of this problematic situation.

There are diverse tissue perfusion markers, and they can be divided in clinical and laboratory markers (Table 1); however the emergency physician must always take into account that clinical parameters are late in their onset, and their presence is a reflex of advanced phases of hypo perfusion.

Many laboratory markers have been studied in order to detect the hypoperfused patient in its early state, the best known markers included gastric tonometry, central venous oxygen saturation, mixed venous oxygen saturation, arterial and venous lactate, microcirculatory study in different anatomical sites and oxygenation indexes.

Clinical	Laboratory
Level of awareness	Lactate (arterial or venous)
Urinary output	$ScvO_2$ or SvO_2 (central or mixed)
Skin characteristics (color, capillary refill, temperature)	Gastric tonometry
Hypotension	Microcirculatory studies
Vital signs	Oxygenation indexes
Breathing patterns	ABG–Metabolic acidosis

Table 1: Clinical and laboratory manifestations of hypo perfusion.

The emergency department, a place of rapid transit, with time constraints, progressive overcrowding and limited physical space, requires efficient indicators of early appearance and simple implementation in the system. That is why this article aims to show a proposal of early detection of hypoperfusion in the septic patient in the emergency room.

Developing an Algorithm

Metabolic acidosis can be the early marker of hypoperfusion, especially if it is because of lactic acidosis; lactate elevation has been shown to be a manifestation of shock in various pathological states [6]. This is the reason lactic acidosis is considered associated with shock in a septic patient despite normal vital signs.

Lactic acidosis constitutes a vital marker in the diagnosis of tissue hypoperfusion in the septic patient. There are 2 types of lactic acidosis [7]; type "A" is related to a mismatch between oxygen offer and demand in the cell, type "B" occurs with no evidence of tissue hypoperfusion, "B1" is related to renal or hepatic failure, "B2" is drug related (metformin), "B3" is present in the inborn errors of metabolism.

A simple calculation helps to establish the type of lactic acidosis; a lactate/pyruvate quotient greater than 20 is highly suggestive of type A lactic acidosis [8].

Lactate can be measured in an arterial or venous blood sample; there

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Received November 20, 2013; **Accepted** December 26, 2013; **Published** December 28, 2013

Citation: Devia-Jaramillo G, Castro-Canoa J, Valverde-Galván E (2013) Perfusion Measurement of the Septic Patient in the Emergency Department. Emergency Med 4: 170. doi:10.4172/2165-7548.1000170

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is an adequate correlation between the two samples [0.94 [95% IC, 0.91-0.96]] [9], being greater the value from the venous sample. However, a trauma patient's study showed no statistical difference between the arterial or venous value [10], therefore the initial approach would be to try and get an arterial sample, but if it isn't easy to accomplish, a venous sample is a viable option.

The lactate value is of great importance in the initial workup of the septic patient; a result of 4 mmol/l is considered a reliable maker of hypoperfusion and is the starting point in the early goal directed therapy for the septic patient, despite normal vital signs in an otherwise clinically stable patient [11]. This value, however, has been a matter of debate, Mikkelsen et al. [12]. Found in their paper that lactate values, either associated with hypotension or not, is an independent mortality predictor starting with values of >2.5 mmol/l.

The mortality rate in this study for patients with a lactate value of less than 2.5 mmol/L was of 8.7% without hypotension, and 15.4% with hypotension. Lactate values between 2.5 and 4 mmol/L had mortality rates of 16.4-31.8% without hypotension, and 37-46.9% in patients with hypotension.

There is recent observational evidence of high mortality rates, close to 60%, with lactate values of >2 mmol/L and multiple organ failure [13]. Although more evidence is needed, it is reasonable to start suspecting tissue hypoperfusion with lactate values as low as 2mmol/l, lowering the threshold to start an early and more intensive treatment.

Another useful tool in the hypoperfusion search is the measurement of central venous oxygen saturation [$ScvO_2$], which reflects disequilibrium between oxygen offer and consumption in a cellular level [DO_2/VO_2]; an abnormally low or high level of $ScvO_2$ reflects this disequilibrium [14]. There is evidence that $ScvO_2$ <70% or >90% is associated with high mortality rates.

Rivers and cols in their study used continuous monitoring of $ScvO_2$, and keeping values close to 70% through Early Goal Directed Therapy (Volume replenishment, vasopressors, blood products, and inotropes) reduced hospital mortality from 46.5% to 30.5% in all septic patients [15]. Values beneath 70% or above 90% were prognostic of higher mortality [16].

When the lactate and the $ScvO_2$ are compared as resuscitation goals, a low concordance between the two is found. If the lactate clearance is lower than 10% after the initial resuscitation efforts the mortality rates is as high as 40%, whilst $ScvO_2$ lower than 70% have mortality rates of 11% [17]. That is the reason none of this markers is used alone, but together to complement each other.

The calculation of the arterial-central venous CO_2 difference [p[cv-a]CO_2] is also used in the patient with suspected hypoperfusion, differences higher than 6 mmHg suggest a disequilibrium in the cellular O_2 offer-consumption relationship. It can also suggest early hypoperfusion in patients with normal $ScvO_2$ [18].

Our first proposal is an algorithm for the early recognition of the hypoperfused patient with sepsis. It starts with lactate measurement; if the value is more than 2 mmol/L the next step is to determine if the type of lactate elevation [type A: a lactate/pyruvate quotientof more than 20]. The next marker, trough a central venous line, is the measurement of $ScvO_2$ [<70% or >90%] and at the same time, with that result, the calculation of the [p[cv-a]CO_2] (Figure 1).

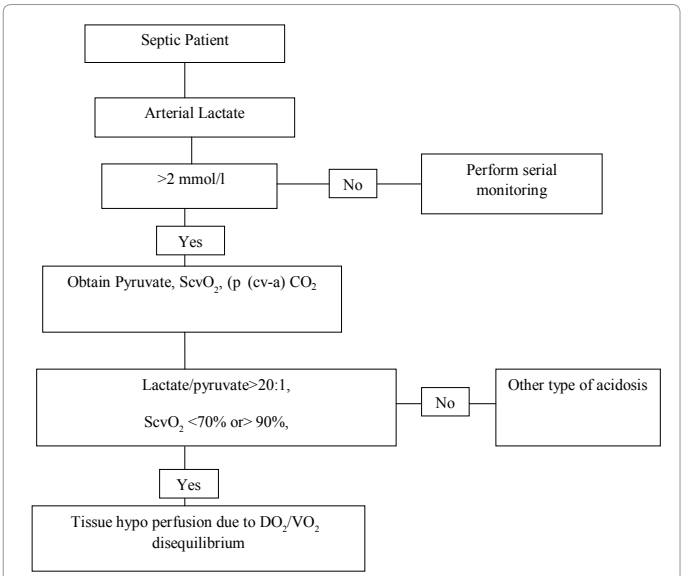

Figure 1: Early recognition of the hypo perfused patient, $ScvO_2$: Central venous oxygen saturation, (p (cv-a) CO_2): Arterial-central venous CO_2 difference.

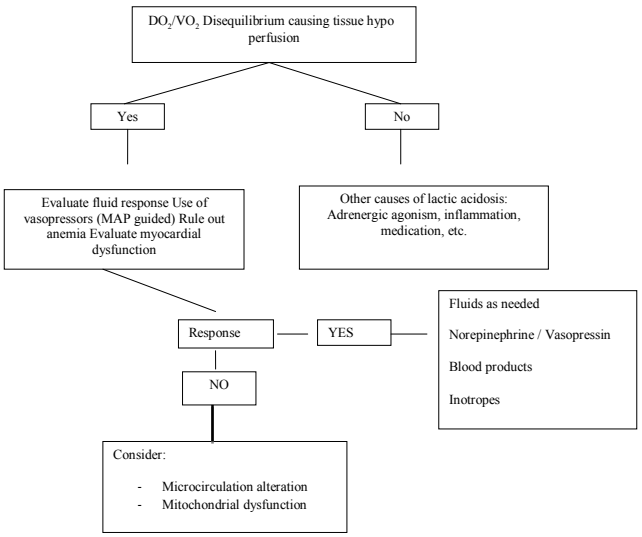

Figure 2: Treatment algorithm.

Treating the Hypoperfusion

Our second proposal (Figure 2) is about the therapeutic options and approach based in the findings of the patient hypoperfusion, once the septic patient is evaluated and documented with hypoperfusion, secondary to disequilibrium in the DO_2/VO_2, it must be investigated where we can intervene in order to resolve this equilibrium.

The first variable to treat is blood pressure; the Medial Arterial Pressure (MAP) recommended for the management of the patient with septic shock must be higher than 65 mmHg, since lower pressures can affect tissue perfusion [9]. Higher than normal suggested pressures can deteriorate the clinical outcome of septic patients [19], while the recommended MAP must be higher than 65 mmHg, and a strategy to achieve it is the use of vasopressors, the use of this drugs for pressures higher than 70 mmHg are not likely to be associated with an improved survival of septic patients [20,21]. The physician must be aware of these values in order to avoid the excessive use of catecholamine infusions, and to avoid the presence of episodes of MAP lower than 60 mmHg, given that more than one episode increases the risk of death 2.96 [CI

95% 1.06-10.36, p=0.04], therefore the MAP goal for the septic patient is between 60 and 70 mmHg. Although recent papers suggest that a higher MAP in certain individuals can improve the cardiac output, and promotes lactate clearance [22].

The use of vasopressors must be done in a timely manner; delays in the start of vasopressors can increase mortality [23], the choice of vasopressor will depend on the clinical situation of the patient. Dopamine is associated with a higher rate of adverse events when compared with Norepinephrine, leading to an increased mortality [24]. When compared, vasopressin showed no differences against norepinephrine in terms of mortality reduction or adverse effects, however, there is a small diminish in mortality rate in the subgroup of less severe sepsis when using a small dose of vasopressin- 0.1 units/minute [26.5% vs. 35.7%, p=0.05] [25].

The use of vasopressin would seem to be useful not only as it improves the value of blood pressure, it also improves the relative deficit of vasopressin in septic shock [26], and it has also been described as a hormonal replacement therapy [27].

Other vasopressors like phenylephrine have different mechanism of action and are not commonly used in the emergency department.

The emergency physician must establish whether the intravascular volume is adequate, or if the patient may need more intravenous fluids, i.e. if the patient is a "fluid responder". Markers and predictors of fluid responsiveness are found in the literature, with variable controversy in their use, among them there is the measurement of Central Venous Pressure (CVP) [15], the ultrasonographic measurement of inferior vena cava index [28], the calculation of the variability of systolic pressure with the respiratory movements [29], and the response to the passive leg raise [30], among others. In case of requiring fluid support it is convenient the use of crystalloid boluses [9]; in case of requiring large amounts of intravenous fluids, the use of intravenous albumin can be considered [31], this is specially helpful if the patient has a known low albumin level [32].

Another variable to control during the management of the hypoperfused patient is the hemoglobin level, with goal values between 7-9 gr/dL, or more than 9 gr/dL in cases of myocardial ischemia, severe hypoxemia, acute hemorrhage, coronary artery disease, and lactic acidosis. Goals from which is useful to transfuse packed red blood cells [9].

The next step should be to assess myocardial contractility with echocardiography [33,34], or with cardiac biomarkers like troponin [35]. In case of documenting a contractility defect it's recommended the use of inotropic support, starting with dobutamine [31], however, milrinone [36] or levosimendan [37] can be considered if the clinical context of the patient allows for it.

If these measures do not improve the patient perfusion the emergency physician should start to assess the micro vascular state of the patient with diverse instruments that allow the measurement of the flow and micro vascular contraction [38] or even consider a pure mitochondrial dysfunction, being this a bad prognostic diagnosis [39].

In case of suspecting a myocardial dysfunction, this is not only derived from a cellular oxygen debt, since it can be present even in states of tissue normoxemia [40]. This is because of the multiple mechanisms of mitochondrial dysfunction, like substrate deficit, enzymatic blockage and cellular membrane damage [41], independent of the hemodynamic and microcirculatory state [42].

In summary, treatment strategies to control mitochondrial dysfunction include improving the use of oxygen, ATP generation, electron flux transport system, oxidative stress, membrane integrity and a decrease in inflammatory and apoptotic signals [43]. All these therapies have a long way to go before being routinely recommended. A fundamental aspect of mitochondrial dysfunction is oxidative stress in sepsis, from an imbalance between the production of Reactive Oxygen Species (ROS) and antioxidant mechanisms [44]. Therefore makes sense to target an antioxidant therapy to balance this mismatch. However, it should be selective mitochondrial antioxidants since it has previously been found that a non-selective therapy is not useful [45]. This selective antioxidant therapy may be administered exogenously though compounds or endogenously by promoting the endogenous antioxidants [46].

MitoQ, MitoE and melatonin are known antioxidants and their administration in animal models with sepsis like states [endothelial damage with LPS induction, and PgG in mice] can diminish the cytokine response [47,48], they even showed an improvement in the mitochondrial respiration, improvement in oxidative stress and diminish of the levels of interlekin 6 compared with mice in the control group [49].

Finally it should be noted that in the sepsis induced mitochondrial dysfunction there is an increased production of nitric oxide, secondary to the induced form of the type II nitric oxide synthase [becoming another therapeutic target], and inhibiting the Neural isoform [NOS] so far with arguable results [50,51].

When comparing a selective inhibitor of the iNOS [the BYK191023] with norepinephrine in a sheep model with septic shock, there was an improved gas exchange, mesenteric blood flow, microcirculation, pulmonary artery pressure and lactate levels with the iNOS inhibitor, and even better results with both drugs combined in maintaining blood pressure and renal blood flow [52].

In case of lactic acidosis without evidence of DO_2/VO_2 disequilibrium the treating physician should think about other entities such as adrenergic agonism [beta 2 agonist inhaled or intravenous], hepatic failure, and other drugs [53].

Conclusion

Sepsis is a frequent and deadly disease, even more so in developing countries, the emergency physician must be one of the leaders of early recognition and management of this disease. The mechanism behind its high mortality is the local at first and then systemic hypoperfusion processes. This paper tries to propose an algorithm for the active search of laboratory signs of hypoperfusion, such as lactate, lactate/pyruvate index, central venous O_2 saturation, and [p[cv-a]CO_2], for the early detection of the hypoperfused patient before the clinical manifestations of the disease. Once recognized it should be discerned which is the variable compromising the tissue perfusion: O_2 delivery, volume status, blood components, vasopressors or inotropes, and finally mitochondrial directed therapy.

All of this in order to resolve the disequilibrium between O_2 offer and demand, and to diminish sepsis and septic shock related mortality.

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