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Guidelines for potential multiple organ donors (adult). Part I. Overview and hemodynamic support

Diretrizes para manutenção de múltiplos órgãos no potencial doador adulto falecido. Parte I. Aspectos gerais e suporte hemodinâmico

ABSTRACT

There is a relative shortage of appropriate organs available for transplantation. The appropriate diagnosis of brain death, a suitable family approach and the maintenance of the deceased donor are fundamental in addressing this issue. The intensive care physician plays a key role in the maintenance of the deceased donor, thereby reducing losses and increasing the number of successful transplants.

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INTRODUCTION

For some patients, the only viable therapeutic option is organ transplantation. In recent years, Brazil, similar to other countries, has had a progressive increase in the gap between the number of organs available and the number of patients requiring a transplant.[1-3]

Brazilian medical authorities are struggling to minimize this gap. Many potential organs are lost due to failure in establishing the diagnosis of brain death, lack of a suitable family approach and appropriate maintenance of the potential deceased donor. Although the appropriate measures for maintenance of the deceased donor are obvious, a large portion of Brazilian intensive care units (ICUs) fail to value this matter appropriately, as evidenced by the almost absolute lack of a systematic approach to potential multiple-organ donors. Such an approach involves more than just technical questions. This approach includes an attention to humanity and citizenship and must include all players involved in the maintenance of a potential deceased donor. The intensive care physician should lead the team with respect to maintaining potential donors. The lack of more robust evidence concerning this subject highlights the relevance of formal guidance (although it is merely consensual in many respects); such guidance would provide minimal homogeneity with respect to the maintenance of a deceased donor. Standardized and prompt actions are clearly associated with an increase in the availability of transplantable organs available, a decrease in the number of donors lost due to cardiovascular failure and increased post-transplant survival.[2]

These guidelines are provided by the Associação de Medicina Intensiva Brasileira (AMIB) and Associação Brasileira de Transplantes de Órgãos (ABTO) and will be published in three different parts: 1) overview and hemodynamic support; 2) complementary interventions and 3) organ-specific recommendations.

OBJECTIVE

These guidelines are aimed at contributing to the institutional coordination of transplants and will provide "real world" guidelines that are appropriate to the Brazilian context as a reference for the uniform care of the deceased donor. Ultimately, this guide is aimed at increasing the quality and quantity of transplantable organs.

METHODOLOGY

Based on an extensive literature research conducted by the Writing and Planning Committee, which was comprised of young intensive care physicians and intensive medicine residents, preliminary questions were formulated and forwarded to all authors as a starting point for receiving suggestions, replacements and definitions of other questions.

The finally prepared questions were revised by the Executive Committee and were returned to the authors to develop the texts.

These questions guided the literature search, which was conducted using the P.I.C.O. methodology, where P stands for the target population, I for the intervention, C for the control or comparative group and O for the clinical outcome.

The retrieved articles were critically analyzed and categorized according to their grade of recommendation and strength of evidence in the following manner:

A: More consistent experimental or observational studies.

B: Less consistent experimental or observational studies.

C: Case reports (non-controlled studies).

D: Opinions lacking critical evaluation, based on consensus, physiological trials or animal models.

Given the paucity of evidence from trials involving deceased donors, many of these recommendations were based on analogies with other clinical conditions. Therefore, physiological, epidemiological and experimental considerations were used.

There were seven discussion subgroups, which are as follows: 1) overview; 2) hemodynamic support; 3) endocrine-metabolic management; 4) mechanical ventilation and pulmonary maintenance; 5) liver maintenance; 6) renal maintenance and 7) heart maintenance. Each subgroup had a coordinator who was responsible for stimulating and guiding the discussions via email messages. The texts from each subgroup were organized by the Writing and Planning Committee and presented for review by the Executive Committee and were returned for subgroup review. The full text was provided to all panel members and discussed in a meeting held during the XIV South-Brazilian Intensive Care Medicine Congress in May 2001 at Joinville, Santa Catarina, Brazil. The coordinators presented their recommendations, which were subsequently discussed. Given that a large portion of the recommendations had poor strength of evidence, the grade of recommendation was added based on the GRADE (Grading of Recommendation, Assessment, Development and Evaluation). This system grades the quality of recommendations as STRONG (should be done), WEAK (perhaps should be done) and NONSPECIFIC (there are no advantages or disadvantages). A strong recommendation means that the benefits of a given intervention outweigh its risks and burdens. A weak recommendation of a given intervention means that its benefits are likely to outweigh its risks and burdens; however, the group is not confident either because the evidence is not good enough or more studies on the subject are warranted. A nonspecific recommendation means that the group considers the benefits and risks and burdens to be balanced, making a case-by-case assessment advisable. A strong recommendation should be understood as 'recommended' and a weak recommendation as 'suggested'.

Description of the evidence collection method

The primary resource that was used for the search was MEDLINE, which was accessed via the PubMed service. The search was based on the P.I.C.O. methodology. Using the MeSH interface (Medical Subject Heading), the following key words were used: (organ donor OR donor management OR brain death AND recommendation OR consensus), (brain-death organ donor AND hypothermia), (organ donor OR donor management OR organ donor maintenance OR brain death AND central venous oxygen saturation OR mixed venous oxygen saturation OR venous oximetry AND outcome), (organ donor OR donor management OR organ donor maintenance OR brain death AND carbon dioxide OR CO_2 gradient OR PCO_2 difference OR central venous-arterial carbon dioxide tension gradient OR mixed venous-arterial), (brain death OR organ donor maintenance OR donor management AND pulmonary artery catheter OR resuscitation), (organ donor OR donor management OR brain death AND hemodynamics OR vasoactive drugs OR fluids), (organ donor OR brain death AND cardiac output OR

fluid challenger OR hemodynamic monitoring OR tissue perfusion OR hemodynamic support). Secondary sources included the Cochrane, Ovid and Trip databases.

OVERVIEW

Is there such an optimal time to maintain viable the organs of a deceased donor? What is considered essential to maintain the deceased donor during this time?

After brain death (BD) is diagnosed and organ donation is consented to by the family, every effort should be made to transplant the organs as quickly as possible (**D**).[1] Organs from deceased donors are commonly lost due to the time wasted prior to organ removal either because of delays in diagnosis or administrative and/or assistential factors (**C**).[2] Regarding assistance, unfortunately, few organ donors are optimally managed by the team responsible for the maintenance of the deceased donor (**C**).[2]

Fast and aggressive maintenance measures are fundamental to providing oxygen to the tissues (DO_2), maintaining organ functions based on clear therapeutic targets and reversing eventual organ dysfunction. Delayed DO_2 restoration is associated with an increased inflammatory response, which may render certain organs useless (**C**)[4](**B**).[5] Between 12 and 24 hours is considered appropriate for bureaucratic procedures and reversal of eventual organ dysfunction (**D**).[1] During this time, quick, aggressive and coordinated actions are required to reverse or stop cardiovascular dysfunction, oxygen deficits, eventual bacterial infections, hypothermia, fluid and electrolytic disorders, metabolic/endocrine disorders, renal or liver disorders, coagulation disorders and any other treatable organ disorder (**C**).[2]

The wide range of different therapeutic measures adopted by different services or even within the same site renders the use of a best practices model for maintenance of the deceased donor difficult, thereby reducing the number of donations and quality of the transplanted organs (**D**).[3] However, uniform and aggressive measures to maintain the potential deceased donor increases the potential number of donors (19%), increases the actual number of donors (82%), reduces the number of donors lost due to hemodynamic instability (87%) and increases the number of actual donations (71%) (**C**).[2] Similarly, Straznicka et al. have shown that aggressive management of lung donors who were initially categorized as unacceptable resulted in an increased number of lungs available for transplantation with excellent 1-year survival (**C**).[6]

Recommendations

- Maintain organ function, correct organ dysfunction and accelerate the removal of organs for transplant within 12 to 24 hours from the diagnosis of BD (**D**).[1] **Strong Recommendation**.

- Prevention and aggressive, coordinated and simultaneous correction of all organ dysfunction. Provide hemodynamic stability, correct oxygen deficits, treat bacterial infections, reverse hypothermia, watch for and correct metabolic disorders (especially hypernatremia), treat endocrine, renal and hepatic changes, correct coagulation disorders and correct any other reversible organ dysfunction (**C**).[2,6] **Strong Recommendation**.

What are the body temperature limits at which the donor should be maintained? How should clinicians heat the patient?

Body temperature regulation is fundamental for the maintenance of key biological processes. Body temperature is regulated by the hypothalamus based on information from the hypothalamus, spinal cord, brain, skin and deep tissue thermoreceptors. This system has afferent pathways, modulating centers and efferent pathways, which regulate thermal homeostasis under normal conditions.

Core temperature in healthy adults ranges from 36ºC to 37.5ºC (**B**).[7] With BD, the ability of the hypothalamus to thermoregulate ceases. Consequently, hypothermia progressively ensues, and the body temperature equilibrates to that of room temperature.

Temperature monitoring is essential for the early detection of hypothermia (**C**).[8] The central temperature may be measured from the pulmonary artery, esophagus, eardrum or nasopharynx. Oral, axillary and rectal temperatures are not recommended.

To maintain organ viability for transplantation, a temperature above 35ºC should be maintained (ideally between 36ºC and 37.5ºC), with the goal of preventing undesirable effects (e.g., coagulopathy, hemodynamic instability), which may impair the transplant organ's viability (**B**).[9]

The best way to maintain body temperature is by preventing hypothermia using measures to prevent heat loss. The environment and the bed, as well as the infused fluids, should be heated. Once hypothermia set in, it is difficult to reverse (**C**).[8,10] Re-heating measures to be adopted include the following:

- Passive external heating: increasing the room temperature and of the use of blankets (**C**).[9,10]

- Active external heating: immersion in hot water, heating lamps and heated air blankets. Peripheral

vasodilation is an inconvenience, as it may lead to 'reheating shock' and a consequent drop in the central temperature (**C**).[9]

- Active internal heating: infusion of heated fluids (saline solution heated at 43ºC via a central venous line at 150-200 mL/hour), mechanical ventilator gas humidification and heating (42-46ºC) and stomach and coloni irrigation with heated crystalloid solutions. Vesical, pleural and peritoneal irrigation should not be performed in organ donors (**C**)[9,10](**D**).[11]

- Extracorporeal blood reheating: hemodialysis or extracorporeal circulation devices (**C**).[9]

Recommendations

- Maintain the central temperature above 35ºC. Ideally, the temperature should be kept between 36ºC and 37.5ºC (**B**).[9] **Strong Recommendation.**

- Check the central temperature (**D**).[7,9] **Strong Recommendation**.

- Prevent hypothermia from the beginning of potential donor management in the following ways (**C**):[8] heat the room air; heat the mechanical ventilator gas (42-46ºC); use thermal blankets; infuse the patient with heated fluids (43ºC). **Strong Recommendation**.

- Reverse hypothermia using the above mentioned measures, gastric and colonic irrigation with heated solutions (**C**).[9,10] Infusion of 43ºC crystalloids via a central venous line at a 150-200 mL/hour rate. **Strong Recommendation**.

- Do not perform vesical or peritoneal irrigation in organ donors (**C**).[9,10] **Strong Recommendation**.

Which laboratory tests should be collected and at which intervals? Which reference values should be used and for which indications?

Laboratory tests should include blood typing, blood count, electrolytes, renal and liver function tests, amylase, cardiac enzymes, arterial blood gas, lactate, coagulation studies and serology (**D**).[12] Blood and urine cultures should be collected for all potential donors (**C**).[13]

Abnormal levels of sodium, potassium, magnesium, calcium and phosphorus may result from large urinary losses. These ions have many physiological roles within the cell; therefore, changes in their serum concentrations deserve vigorous interventions. Monitoring during the correction of these ions should include serial dosages, every 6 hours (**D**).[14,15]

The severity of hemodynamic instability and hydroelectrolytic disorders should dictate the frequency of blood gas and lactate tests (**D**).[16] Blood count and coagulogram should be conducted every 6 hours, due to the risk of a potential coagulopathy (**D**).[1] The indication and intervals for many blood chemistry tests are organ-specific. In cases of potential heart donors, cardiac enzymes (CKMB and/or troponin) should be repeated every 24 hours (**D**).[12] For liver donors, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (TB) and prothrombin time (PT) should be collected at least every 24 hours (**D**).[12] For kidney donors, creatinine and urea should be repeated every 24 hours (**D**).[1] Hyperamylasemia or hyperglycemia alone are not contraindications for pancreas donation, except in cases in which there has been direct pancreatic trauma, pancreatitis or history of diabetes in the donor (**C**).[17]

Recommendations

- Periodic blood chemistry tests should be conducted with the aim of normalizing physiological parameters for all laboratory tests (**D**).[16] **Strong Recommendation**.

- Repeat electrolyte and blood gas panels should be sent at least every 6 hours (**D**).[14,15] **Strong Recommendation**.

- Other tests to be collected are specific to the organ that is being transplanted. They are as follows (**D**):[12,14,15] CKMB and/or troponin every 24 hours (heart donor) (**D**) [12] – **Weak Recommendation** – AST, ALT, PT, TB at least every 24 hours (liver donor) – **Weak Recommendation** (**D**);[12] blood urea nitrogen and creatinine every 24 hours (kidney donor) (**D**).[1] **Strong Recommendation**.

- Two blood cultures and a urine culture should be performed in all potential donors by the beginning of the BD protocol (**C**),[13] and the results should be provided to the transplanting teams. **Strong Recommendation**.

- Request PT, APTT and fibrinogen only with bleeding disorders.[12] **Strong Recommendation**.

HEMODYNAMIC SUPPORT

Should invasive mean blood pressure (MBP) monitoring be used?

Hemodynamic instability is the primary challenge for the maintenance of a potential donor, as hypotension is common and leads to reduced organ perfusion (**D**).[18,19] Noninvasive blood pressure measurements are inaccurate in the setting of shock (**B**).[20-22] There is a significant difference between noninvasive and direct blood pressure measurements, especially when systemic vascular resistance is increased (**D**).[23] Invasive blood pressure is a safe and essential guide for hemodynamic therapy (**B**)[24](**D**)[25] and is recommended by several international organs for the maintenance of a potential donor (**D**).[1,18,26,27] In addition, arterial access makes

serial blood gas measurements easier and allows for the use of dynamic fluid-responsiveness parameters, such as respiratory variation in arterial pulse (ΔPp).

Recommendation

- Use invasive blood pressure monitoring for all potential deceased donors (**D**).[23] **Strong Recommendation**.

Should intracranial hypertension-related arterial hypertension (sympathetic storming) be treated? Which pressure levels should be tolerated? What are the drugs of choice?

During the process of BD, several physiological changes are seen in response to lost brainstem functions. One of the most significant changes is hemodynamic instability, which occurs in two phases (**D**).[28,29] The initial phase is related to adrenergic hyperactivity and is clinically noted by tachycardia, hypertension and increased systemic vascular resistance, in addition to increased myocardial oxygen consumption. Typically, systolic blood pressure is more increased than diastolic pressure (**C**).[30] This phase is called 'sympathetic storming' and lasts approximately 20 to 30 minutes; it is followed by hypotension (**D**).[12,16,28,29,31,32]

Despite the fact that the increased systemic vascular resistance during sympathetic storming is associated with the hypoperfusion of intra-abdominal organs, (**D**)[1,12,33] myocardial ischemia and arrhythmias (**D**),[12,34,35] a number of experts prefer a conservative approach (no administration of hypotensive drugs), due to an increased trend toward hypotension after BD is established (**D**).[36] However, a mean blood pressure (MBP) above 95 mmHg or systolic blood pressure (SBP) above 160 mmHg for longer than 160 minutes may increase the risk of intra-abdominal organ hypoperfusion and may impact the function of the transplanted organ (**D**).[37] Intravenous drug therapy should be used in these cases (**D**).[36] Sodium nitroprusside and esmolol are the preferred drugs, as they are effective, easily titrated and short-acting (**D**).[1,36]

Recommendations

- Sympathetic-storming related arterial hypertension must be treated (**D**).[36] **Strong Recommendation**.

- Start drug therapy for sustained (30 or more minutes or the presence of target organ injury due to hypertension) hypertension (SBP > 180 mmHg and diastolic blood pressure [DBP] > 120 mmHg or MBP > 95 mmHg) (**D**).[1,36] **Strong Recommendation**.

- The suggested drugs include sodium nitroprusside or short-acting beta-blockers (esmolol) (**D**).[1,36] **Strong Recommendation**.

Which minimal pressure target should be reached for a potential deceased donor?

Catecholamine stocks are depleted following the initial sympathetic storming, which results in vasodilation and hypotension (**D**).[28,29] In addition, hypovolemia can result, possibly secondary to osmotic diuresis from hyperglycemia or mannitol administration, incomplete volume expansion or diabetes insipidus. Concomitant ventricular dysfunction as a cause of hypotension should be considered and may result from myocardial contusion, electrolytic disturbances, pulmonary hypertension and neurogenic myocardial depression. Therefore, hypotension, which is the most frequently encountered issue among potentially deceased donors, may be caused by vasodilation, hypovolemia and myocardial depression. Also, the resulting hypoperfusion is the primary cause for losing these donors, as well as for impaired transplanted organs. There is no available evidence concerning the best target blood pressure levels for potential multiple-organ donors. However, there are recommendations available for pressure targets, which range from 60 mmHg to 80 mmHg MBP and 90 mmHg to 100 mmHg SBP (**D**)[1,23,25,27](**B**).[5] However, normalizing MBP is not a guarantee of restored tissue perfusion; therefore, in addition to MBP normalization, tissue perfusion markers should always be monitored (**D**).[23]

Recommendation

- Maintain MBP above 65 mmHg or SBP above 90 mmHg (**D**)[1,23,25,27](**B**).[5] **Strong Recommendation**.

Which therapeutic measures should be used to reach the minimal pressure target?

Hypovolemia is the primary cause of hemodynamic instability in potential donors, and aggressive volume replacement is the first measure to be adopted. However, determining when volume resuscitation is sufficient is challenging. Insufficient replacement can result in inappropriate tissue perfusion, systemic inflammatory activation, organ dysfunction and reduced quality of transplant organs (**B**).[5] However, unnecessary fluid administration may cause acute lung edema and impair the viability of the pulmonary tissue for transplantation (**C**)[6](**D**).[38] Therefore, both insufficient and excessive fluid infusion may harm transplant organs and impact post-transplantation survival of transplant organs. The use of appropriate methods for the precise and rapid identification of volume deficits is fundamental to minimizing tissue damage related to decreased perfusion while concomitantly preventing iatrogenic fluid overload (**B**)[5](**C**)[6](**D**).[38]

Vasopressor and inotrope support should be based

on a physiologic rationale, as no definitive studies are available on this subject. If a minimal blood pressure (BP) is not reached following appropriate volume expansion, vasopressor or inotropic drugs should be started. Infusing these drugs without appropriate volume replacement may result in arrhythmias, worsened hypotension (in the case of dobutamine) or exaggerated vasoconstriction followed by multi-organ ischemia (**D**).[1,23,38,39]

Recommendations

- Infuse 20 to 30 mL/kg crystalloid solution (heated at 43ºC) within 30 minutes. This procedure is the first step for controlling blood pressure (**D**).[38,39] **Strong Recommendation**.
- Base the subsequent volume infusions on metabolic oxygenation parameters (**D**)[23] and on an evaluation of volume responsiveness (**B**).[5] **Strong Recommendation**.
- Infuse vasopressor or inotropic drugs, preferably after infusing 20 to 30 mL/kg (**D**).[23] **Strong Recommendation**.
- Start vasopressor drugs prior to completing volume expansion if MBP < 40 mmHg or SBP < 70 mmHg.[23,38,39] **Strong Recommendation**.

Are the parameters used to assess appropriate volume replacement (as central venous pressure [CVP], pulmonary capillary wedge pressure [PCWP], hemodynamic variables) useful during hemodynamic resuscitation of potential organ donors?

Aggressive volume resuscitation is essential for the maintenance of the deceased donor. However, with heart dysfunction or for euvolemic patients (**D**),[16] fluid infusion may result in fluid overload and impair the quality of organs, e.g., the lung (**C**).[6,40] In addition, adding vasopressors alone without appropriate volume expansion may impact tissue perfusion and thus the quality of the transplantable organs. Therefore, in the setting of hypotension and/or hypoperfusion, the cardiovascular ability to assimilate additional volume must be evaluated based on an analysis of the cardiovascular volume responsiveness.

Consensus statements recommend that CVP should be monitored for every deceased donor. However, in a study involving 805 deceased donors, CVP failed to affect the quality of the transplanted organs (**C**).[41] A recent meta-analysis evaluating several studies in severely ill patients populations concluded that values of CVP/PCWP between 8 and 12 mmHg are not able to discriminate responsive from non-responsive subjects (sensitivity and specificity ~50%) (**B**).[42] However, consensus statements recommend that low CVP/PCWP values (< 4 mmHg) warrant volume infusion under careful CVP monitoring in unstable subjects (**D**).[23] Measurement of CVP or PCWP variation following 500 to 100 mL crystalloid infusion within 15 to 30 minutes is more reliable than isolated measurements. Volume infusion should be stopped if a ≥ 2 mmHg increase is observed (**C**).[23,42-44]

During mechanical ventilation without heart arrhythmias, dynamic methods, such as arterial pulse variation (ΔPp), allow for the reliable evaluation of cardiovascular responsiveness (both sensitivity and specificity ~95%) (**C**).[45] Potential deceased donors who are responsive to volume (ΔPp > 13%) have increased levels of IL-6 and TNF-alpha when compared with non-responsive candidates (ΔPp < 13%). This inflammation implies the organs from more responsive subjects may be less useful for transplantation (1.8 ± 0.9 versus 3.7 ± 2.5; p = 0.034). These results suggest that volume expansion guided by more accurate parameters may facilitate the retrieval of healthier grafts (**B**).[5] Pulse plethysmography variation (ΔPplet) is a quick and noninvasive alternative to ΔPp and consists of measuring the amplitude of the pulse oximetry track record (**B**).[46-51]

Recommendations

- Dynamic parameters should be used for volume responsiveness assessment (**B**).[5] **Strong Recommendation.**
- Infuse 500 to 1000 mL of volume whenever signs of hypoperfusion and CVP < 4 mmHg are detected (**D**).[23] CVP alone should not be used as a guide for volume replacement (**D**).[42] **Strong Recommendation.**
- Stop infusions if the patient is unresponsive to volume (based on dynamic parameters or is CVP variation is > 2 mmHg) after infusing 500 to 1000 mL crystalloid solution (**D**).[44] **Strong Recommendation.**

Which vasopressor and inotropic agent(s) should be used for hemodynamic resuscitation in potential organ donors? Are there preferred agents? Are there maximal doses?

Noradrenaline, epinephrine or dopamine may be used and adjusted to maintain the target blood pressure and overall tissue flow with the goal of increasing the feasibility of transplanting different organs. There is no maximal dose or drug of choice (**B**).[52-54] However, there are concerns related to the use of catecholamines (e.g., noradrenaline) and, especially, high-dose beta-agonistic therapy (e.g., dopamine and dobutamine) in potential heart donors, as they apparently reduce the chances of successful heart transplantation (**B**).[53-58] Beta-agonistic therapy should be particularly considered for cases of low cardiac flow and secondary hypoperfusion (**B**).[59] There are no randomized clinical trials supporting one choice of vasopressor drugs

over another for organ donors.

Vasopressin is a hormone that can be used both as a vasopressor and for the management of diabetes insipidus. Organ donors requiring vasopressors are frequently deplete of vasopressin.[60] In a number of cases, vasopressin may provide pressure stability and allow for the discontinuation of catecholamines (**B**).[61-63] A hormone replacement test can be conducted at any time in a hemodynamically unstable organ donor. Hormone replacement may include, in addition to vasopressin, thyroid and corticosteroid hormones.[59]

Recommendations

- Start vasopressor catecholamines (noradrenaline, adrenaline or dopamine) to maintain MBP > 65 mmHg or SBP > 90 mmHg (**D**).[23] There is no dose limit (**C**).[52-54] **Strong Recommendation.**

- Use vasopressin whenever vasopressor drugs are indicated (1 U bolus followed by continued 0.5 to 2.4 U/hour infusions). Gradually discontinue the catecholamine infusion if BP is stabilized with vasopressin infusion (**B**).[61-63] **Strong Recommendation.**

- Start dobutamine if heart contractility is impaired (clinical evidence of ventricular dysfunction or EF < 40% or CI < 2.5 L/min/m^2) with signs of hypoperfusion. High-dose beta-agonistic therapy (10 µg/kg/min) may jeopardize heart transplant success but is not a contraindication to it (**D**).[59] **Strong Recommendation.**

Should central venous saturation ($ScvO_2$) be a target during hemodynamic resuscitation of a potential organ donor?

Venous oxygen saturation, either mixed (SvO_2) or central ($ScvO_2$), reflects the oxygen available/consumption balance and is directly correlated with cardiac output (CO) (**C**)[64] Both low and high values on admission to the ICU are associated with increased mortality rates.[65]

In patients with brain death, the venous saturation, as measured at the jugular bulb (reflecting brain oxygen metabolism), is increased, thereby contributing to increased $ScvO_2$ (as measured at vena cava superior or right atrium) (**C**).[66] There are no target $ScvO_2$ hemodynamic resuscitation trials available, nor are there observational studies that have assessed its levels of association with improved transplant organ quality. One citation is available (**D**)[67], which states that there are no studies showing 'normal' values in this setting, given the potential impact of reduced brain oxygen consumption. Therefore, until these values are identified, a $ScvO_2$ level cannot be recommended for the assessment of tissue oxygenation or as a resuscitation target.

In septic patients, as previously explained, restoring $ScvO_2$ to levels that are closer to normal has been associated with improved prognosis. In these patients, lactate clearance would have a similarly beneficial impact. Of note, this restoration should occur within the first several hours of the septic insult.

Recommendations

- There is no established cut-off for deceased donor $ScvO_2$ (**D**).[67] Low $ScvO_2$ values (<70%) may be indicative of hypoperfusion, and its serial evaluation may be an additional method for the follow-up of hemodynamic resuscitation (**D**).[67] **Weak Recommendation.**

- Target-guided hemodynamic recovery should be started early and independently of the target. The time of the intervention, rather than the target, drives outcomes (**D**).[68] **Strong Recommendation.**

Should lactate be a target during hemodynamic resuscitation of potential organ donors?

Target-guided resuscitation is important for the maintenance of organ function. Such resuscitation includes obtaining hemodynamic targets to improve the oxygen supply available to tissues prior to the development of multi-organ dysfunction (**A**).[69,70] Blood lactate (either venous or arterial) is correlated with the hemodynamic recovery of severely ill patients. However, few studies have evaluated target blood lactate concentrations in the resuscitation of critically ill patients, and its usefulness remains unclear. Several observations have shown that blood lactate clearance is associated with successful hemodynamic resuscitation in sepsis or trauma patients (**B**).[64-66,71] Two trials have evaluated the usefulness of blood lactate clearance as a target for the resuscitation of septic patients (**B**).[72,73] One of these trials compared resuscitation guided by venous saturation versus blood lactate, and both were shown equivalent for the assessed outcomes. A second trial evaluated lactate-guided resuscitation with standard care. The adjusted results analysis showed reduced mortality associated with more intensive use of fluids and nitroglycerin. However, there are no studies that have assessed blood lactate in the hemodynamic management of organ donors, which is a patient population that may have different energy metabolism.

Recommendation

- Lactate should not be used as a therapeutic target. Values above 2 mmol/dL may be indicative of hypoperfusion; therefore, serial follow-up may be used as an additional metabolic parameter (**D**).[1] **Weak Recommendation.**

Should the venous-arterial CO_2 gradient be a target during hemodynamic resuscitation of potential organ donors?

Based on the Fick physiological principle, central or mixed venous-arterial CO_2 gradient has a behavior that is opposite that of cardiac output and other overall perfusion parameters; however, the mechanism underlying this finding is unclear (**D**)[74](**B**).[75] The time-related behavior of hemodynamics and tissue CO_2 tension (intramuscular) have been described in brain death; however, no prospective trials are available showing a relationship between guided interventions and successful organs harvest (**B**).[76] No trials are available that clarify the relevance of the central or mixed CO_2 venous-arterial gradient for deceased donors. The CO_2 jugular (bulb)-arterial gradient, also a venous-arterial gradient, has diagnostic relevance exclusively for the diagnosis of brain hypoperfusion and brain death (**B**)[77](**D**).[74]

Recommendation

- Do not use the CO_2 venous-arterial gradient as a therapeutic target for deceased potential donor, although serial assessments may be used as an additional metabolic parameter (**D**).[67] **Strong Recommendation**.

When should echocardiography be requested during hemodynamic resuscitation of a potential organ donor?

In the initial stages, hemodynamic monitoring should include an arterial line, an assessment of fluid-responsiveness and tissue perfusion. However, following the initial volume expansion, doubts concerning actual myocardial function and the donor's ability to tolerate additional volume infusion remain. Additional fluid infusion may lead to hypervolemia, which may jeopardize the viability of lungs for transplant. In addition, the empiric use of inotropes may be disastrous, as they may worsen hypotension in patients who are hypovolemic, and they may precipitate heart arrhythmias (**D**).[16,78]

In patients who are severely unstable despite initial volume expansion and who are requiring progressively more vasoactive drugs, minimal parameter-based hemodynamic monitoring may be insufficient (**D**)[16,27,75,79](**B**).[76]

Although the use of serial echocardiography for the guidance of hemodynamic therapy in unstable patients has not yet been fully studied (**C**)[79](**D**),[1] it is an easy, quick and noninvasive method for hemodynamic monitoring that provides serial evaluations of hemodynamic interventions aimed at the correction of circulatory changes in a potential donor (**C**).[79] Studies have shown an agreement between the echocardiography- and thermodilution-measured cardiac output. In addition, echocardiography provides assessments of fluid responsiveness based on changes in the diameter of the vena cava (**D**).[80,81]

Recommendation

- Echocardiography is indicated whenever initial hemodynamic resuscitation guided by regular hemodynamic monitoring fails (i.e., volume, vasopressor, inotropes) (**D**).[1,27] **Weak Recommendation**.

When during hemodynamic resuscitation of a potential organ donor is a pulmonary artery catheter indicated? What are the targets?

Hemodynamic monitoring using a pulmonary artery catheter is indicated if the initial hemodynamic resuscitation fails (**D**).[82] Most clinical trials and expert consensus on maintenance of a deceased donor suggest using pulmonary artery catheters, although few specific studies are available. Depending on the organ to be transplanted, the use of a pulmonary catheter is based on the type of organ failure to be either prevented or treated. However, no prognostic studies are available in this setting (**D**).[26]

Early routine pulmonary artery catheterization, performed when echocardiography shows ventricular dysfunction (low ejection fraction) or when pre-defined hemodynamic targets fail to be reached (MBP > 65 mmHg or SBP > 90 mmHg, heart rate between 100 and 120 bpm), improves organ availability by 12% to 30% (**B**).[83,84] For all papers, the therapeutic targets were close to normal reference values (**B**).[83,84]

A recent trial showed that 26.7% more organs were appropriate for heart transplant when pulmonary artery catheter monitoring was added during the maintenance of deceased donors. In this trial, the targets were as follows: SBP > 90 mmHg; pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg; cardiac index ≥ 2.5 L/min/m^2 (**B**).[85] None of the deceased donor maintenance studies that have established targets discusses whether these targets should be reached using fluids, vasoactive drugs, hormones or procedures.

Recommendations

- Early pulmonary artery catheter monitoring should be performed if echocardiographic ventricular dysfunction (ejection fraction<40%) is present or if regularly monitored hemodynamics (MBP, HR, urinary output) do not normalize (**B**).[83-85] **Strong Recommendation**.

- Targets: SBP>90 mmHg or MBP>65 mmHg, cardiac index ≥ 2.5 L/min/m^2 (**B**).[85] **Strong Recommendation**.

How should heart arrhythmias be prevented in a deceased donor? How should they be treated when they do occur?

Heart arrhythmias in deceased potential organs donors are frequent and represent a major challenge for the intensive care physician (**D**).[25,26,86] Heart arrhythmias may cause reduced heart output and hemodynamic instability. The cause of arrhythmias is multi-factorial, although the most frequent causes include hypovolemia, hypotension, hypothermia, the use of catecholamine drugs, myocardial contusion, acid-base disorders and electrolyte disturbances. All types of arrhythmias can be found in this population, including supraventricular and ventricular tachycardias to conduction disorders with associated bradycardia (**D**).[12,36] These arrhythmias are related to ischemia of the brain stem and sympathetic hyperactivity (sympathetic storming), which results in conduction system necrosis and myocardial injury (**D**).[18,86] Other causes may include metabolic and electrolyte imbalances, such as hyperkalemia and hypomagnesemia, which are common in cases of brain death. Other contributing factors may include sympathomimetic drugs, which may be required for hemodynamic control (**D**).[12,26] Prophylaxis and early therapy should include correction of the reversible factors, as mentioned above (**D**).[26] Specific therapy should comply with cardiology societies' recommendations (**D**).[1,12,18,36] Therefore, tachyarrhythmias that cause hemodynamic instability should be treated with synchronized electric cardioversion (**B**).[87-89] Without hemodynamic impairment, the recommended therapy for ventricular tachyarrhythmias includes the use of amiodarone, procainamide or lidocaine (**C**).[87] For supraventricular tachyarrhythmias, it is recommended that adenosine, verapamil, diltiazem or amiodarone be used (**A**).[88,89] In cases of brain death, bradyarrhythmias may be resistant to atropine, due to the lack of vagal activity; therefore, we recommend using adrenaline, dopamine or isoproterenol (**D**).[18,90,91] When persistent and associated with hypotension or low output, bradyarrhythmias should be treated with a transvenous pacemaker (**D**).[90] Previous family consent should be granted for all procedures required either for maintenance or removal of organs. A number of authors suggest that the families should be also informed when cardiorespiratory resuscitation may be required and the relevant consent obtained (**C**).[91]

Recommendations

- Prevent and treat heart arrhythmias by correcting reversible causes, e.g., electrolyte and acid-base disorders, hypovolemia, hypotension, hypothermia, excessive/inappropriate administration of catecholamines (**D**).[26] **Strong Recommendation**.

- Treat cardiorespiratory arrest (CRA) and tachyarrhythmias in compliance with the American Heart Association guidelines (**D**).[26,86] **Strong Recommendation**.

- Do not use atropine for therapy of bradyarrhythmias. **Strong Recommendation** (**D**).[18,90,91]

- Treat bradyarrhythmias (without hemodynamic instability) using adrenaline (2-10 μg/min), dopamine (50-10 μg/kg/min) or isoproterenol (2-10 μg/kg/min) (**D**).[18,90,91] **Strong Recommendation**.

- Treat bradyarrhythmias (with low output or hypotension) with a provisional transcutaneous pacemaker followed by tranvenous pacing (**D**).[90] **Strong Recommendation**.

After cardiac arrest in a potential deceased donor, when should transfer to the operating room to remove viable organs be considered? If the operating room or a surgery team are not available, is there any alternative for maintaining organ perfusion?

With previous family consent, immediate referral to the operating room should be considered while maintaining chest compression ('heart massage'). Chest compressions using an automated compressor may make transfer easier. There are two alternatives for the maintenance of organ viability. The first alternative is the insertion of a double-balloon catheter via the femoral artery during cardiopulmonary resuscitation (CPR), as a means by which to preserve the kidneys. This catheter allows for removal of the blood and an infusion of preservative solutions into both kidneys. The second alternative consists of a femorofemoral bypass followed by induction of hypothermia and membrane oxygenation (**D**).[92]

Recommendations

- Immediately start CPR maneuvers and transfer the patient to the operating room for removal of viable organs (**D**).[92] **Strong Recommendation.**

- Consider installing a double-balloon catheter for renal preservation or starting extracorporeal circulation via femoral access, if transfer to the operating room or a transfer team are not available (**D**).[92] **Weak Recommendation.**

Is there an indication for high dose heparin (500 U/kg) during cardiac resuscitation? When is it indicated?

Administration of high-dose heparin has been recommended for organ donors who are in cardiac arrest and should be given early during CPR maneuvers (**D**).[91,92]

Recommendation

- Give 500 IU/kg sodium heparin early during CPR

maneuvers when immediate removal and/or perfusion is being considered (**D**).[91,92] **Strong Recommendation.**

RESUMO

A desproporção entre a grande demanda por transplantes de órgãos e a baixa realização de transplantes é um grave problema de saúde pública. O reconhecimento da morte encefálica, a adequada abordagem da família e a manutenção clínica do doador falecido são fundamentais para a diminuição desta desproporção. Neste cenário, o intensivista tem importância central e a aplicação do conjunto de informações disponíveis para manutenção do potencial doador falecido está claramente associada à redução de perdas de doadores e ao aumento da qualidade e da efetivação de transplantes.

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Guidelines for potential multiple organ donors

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6. Renal maintenance
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Participants: Anderson Ricardo Roman Gonçalves, Marilda Mazzali, Valter Duro Garcia.

7. Heart maintenance
Coordinator: Cristiano Franke
Participants: Alfredo Fiorelli, Ben-Hur Ferraz Neto, Fernando Suparreghi Dias, Frederico Bruzzi, Marcelo Maia.