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Addressing inadequate blood flow during normothermic regional perfusion for in-situ donation after circulatory death grafts preservation

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Abstract

Donation after circulatory death (DCD) has emerged as attainable strategy to tackle the issue of organ shortage, expanding the donor pool. The DCD concept has been applied to the multiple declinations of circulatory arrest, as per the Modified Maastricht Classification. Notwithstanding, whichever the scenario, DCD donors experience a variable warm ischemia time whose correlation with graft dysfunction is ascertained. This applies to both "controlled" (cDCD) donors (i.e., the timespan from the withdrawal of life-sustaining therapies to the onset of in-situ perfusion), and "uncontrolled" DCD (uDCD) (i.e., the low-flow period during cardiopulmonary resuscitation – CPR). This sums up to the no-flow time from cardiac arrest to the start of CPR for uDCD donors, and to the no-touch period for both uDCDs and cDCDs. Static and hypothermic storage may not be appropriate for DCD grafts. In order to overcome this ischemic insult, extracorporeal membrane oxygenation devices are adopted to guarantee the in-situ grafts preservation by means of techniques such as the normothermic regional perfusion (NRP) which consists in a selective abdominal perfusion obtained via the endovascular or surgical occlusion of the thoracic aorta. The maintenance of an adequate pump flood throughout NRP is therefore a sine qua non to accomplish the DCD donation. The issue of insufficient pump flow during NRP is prevalent and clinically significant but its management remains technically challenging and not standardized. Hereby we propose a systematic algorithmic approach to address this relevant occurrence.

Keywords

perfusion, donation after circulatory death, extracorporeal membrane oxygenation, normothermic regional perfusion, flow inadequacy

Introduction

Donation after circulatory death (DCD) has emerged in the late nineties as attainable strategy to tackle the infamous issue of organ shortage, de facto expanding the donor pool.[1] The DCD concept has been applied to the multiple declinations of circulatory arrest, as per the Modified Maastricht Classification.[2] Notwithstanding, whichever the scenario, DCD relies on extracorporeal circulation technologies since donors experience a variable warm ischemia time (WIT), that is consistently associated with graft dysfunction.[3,4] This applies to both "controlled" DCD (cDCD) donors (i.e., timespan from the withdrawal of life-sustaining therapies to perfusion onset), and "uncontrolled" ones (uDCD) (i.e., low-flow

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period during cardiopulmonary resuscitation). This sums up to the "no-touch period" for both uDCDs and cDCDs, and to the no-flow time from cardiac arrest to the start of CPR for uDCD donors (Figure 1). Hence, the conventional methods for organ preservation such as static and hypothermic storage may not be appropriate for DCD grafts. In order to overcome the ischemic insult, extracorporeal membrane oxygenation (ECMO) devices are adopted to guarantee the in-situ grafts preservation. Among the existing perfusion techniques, normothermic regional perfusion (NRP) consists in a selective perfusion of the abdomen obtained occluding the thoracic aorta either internally (i.e., endovascular balloon occlusion of the aorta – EBOA) or externally (i.e., surgical cross-clamping). The maintenance of adequate pump flow throughout NRP is a *sine qua non* to accomplish the DCD donation.

The issue of insufficient pump flow during NRP is prevalent and clinically significant. However, its management remains technically challenging, not standardized, and do not necessarily resemble that of conventional venoarterial ECMO. Hereby we propose a systematic algorithmic approach to address this relevant occurrence (Figure 2).

Culprit ascertainment

Insufficient pump flow during NRP can be detected extemporaneously by visual-checking the ECMO console or by setting a low-flow alarm. A delayed and

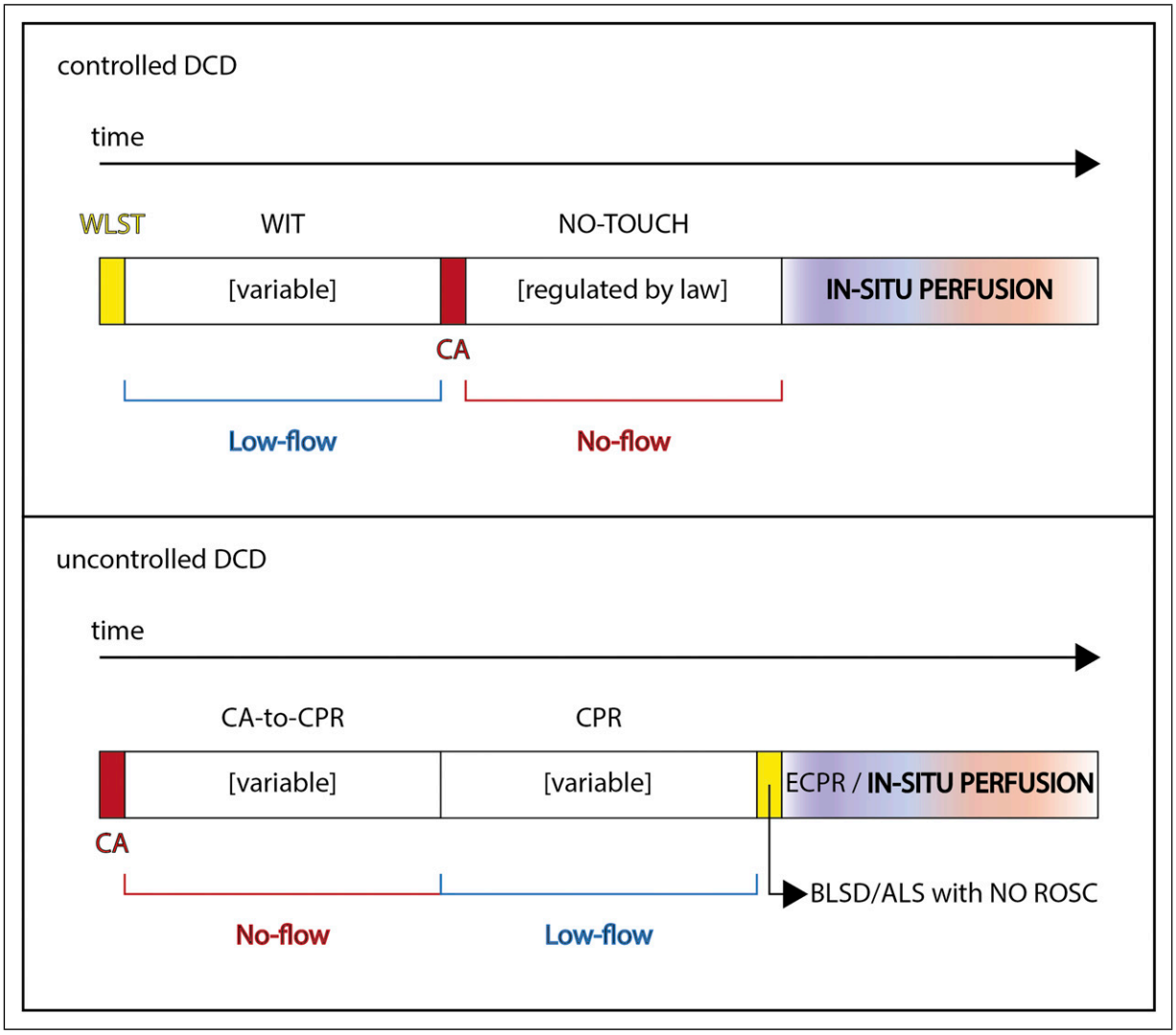

Figure 1. Controlled and uncontrolled DCD timelines, low- and no-flow periods. ALS: advanced life support; BLSD: basic life support and defibrillation; CA: cardiac arrest; CRP: cardiopulmonary resuscitation; ECPR: extracorporeal cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; WIT: warm ischemia time; WLST: withdrawal of life sustaining therapy.

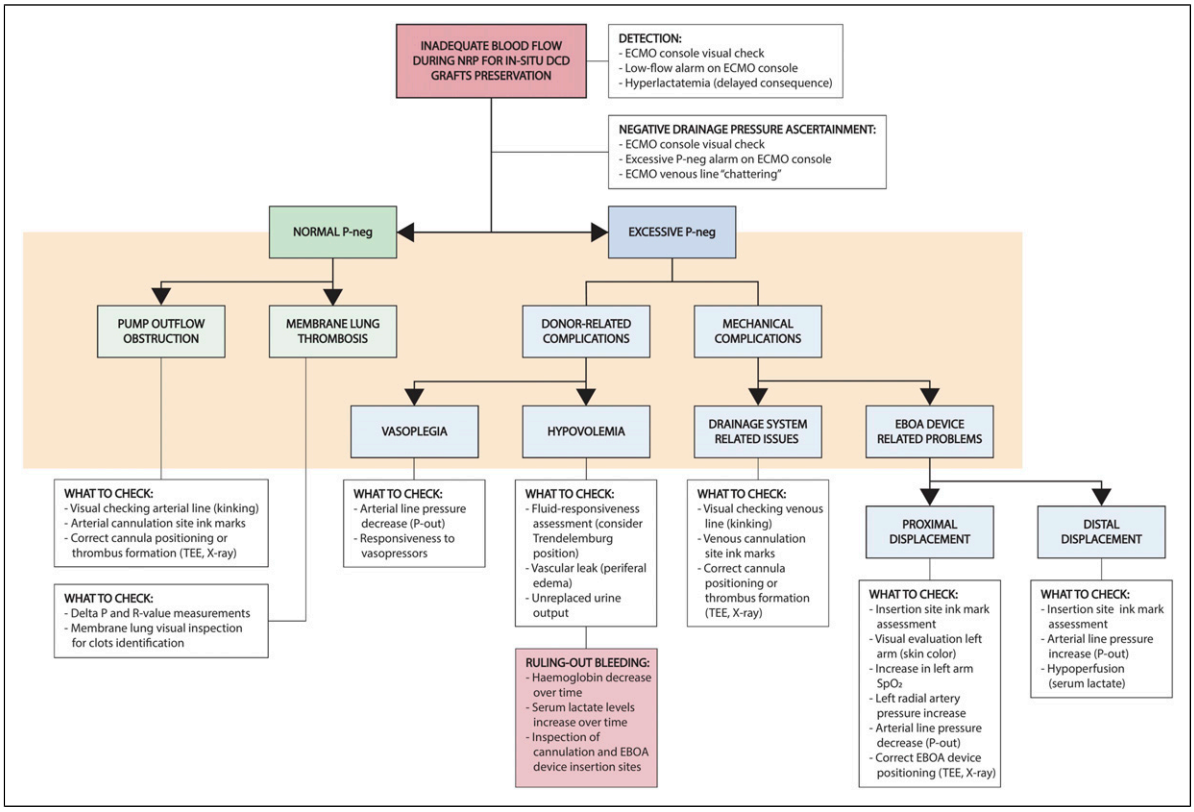

Figure 2. Algorithmic approach to address the issue of inadequate blood flow during NRP for in-situ DCD grafts preservation. Yellow rectangle: plausible causes of NRP flow insufficiency.

indirect detection is also a contingency: an increasing serum lactate concentration over-time is indeed a clear sign of hypoperfusion. However, being lactate an end product of glycolysis under conditions of total or partial anaerobia (i.e., formed from pyruvate mediated by lactate dehydrogenase), the ischemic damage preexist the increase in lactate concentration, making this delayed detection very undesirable.

Drainage insufficiency and pump outflow-related issues are two sides of the same coin that is the inadequacy of pump flood, possibly precipitating towards suboptimal in-situ organ preservation, and graft dysfunction. Clinicians must discern between these two main scenarios in order to further gather the underlying causative factor (or the combination of causes), and address it. In this sense, a drainage pressure-directed ascertainment may immediately rule out either an outflow-related complication or a drainage problem (i.e., characterized by variable degrees of excessively negative drainage pressure). All the more so since an excessively negative pressure is undemanding to be identified by just visual-checking the ECMO console, by setting an appropriate alarm, or simply noticing a movement of the tubing: a phenomenon variably termed "chatter," "chugging", or "kicking." Furthermore, this phenomenon is clinically relevant per se, given the renowned association between excessive negative pressure and entities like cavitation and hemolysis.[5]

Insufficient venous return

A reduced pump preload can result from either donor-related or mechanical, device-related, causes.

Donor-related drainage issues

Two are the major donor-related concerns: vasoplegia and hypovolemia. Vasoplegia increases vasculature capacitance, thus redistributing circulating volume, and reducing venous drainage. This phenomenon is usually difficult to identify while using closed systems like ECMO, whereas its occurrence cannot pass unnoticed when using an open system like conventional cardiopulmonary bypass, in cardiac surgery setting (i.e., lowering of blood level in the reservoir). Vasoplegia commonly occur during NRP, and can be tackled resorting to alpha-adrenergic pharmacologic agents (i.e., noradrenaline). Indeed, a low arterial line pressure

(P-out) results from vasoplegia. Second and more important is the phenomenon of hypovolemia that implicates fluid extravasation, bleeding complications, or unreplaced urine output. While vasoplegia treatment is somehow straightforward, the management of hypovolemia depends on its cause. Bleeding must be immediately ruled out and resolved, as it impose an unpredictable and possibly catastrophic ischemic injury due to its synergistic effect that lowers both NRP flow and oxygen delivery, and that may manifest only after reperfusion in the recipient. Bleeding is commonly due to problems with femoral cannulation or with the external cross-clamp of the Aorta, ergo these sites must be promptly and carefully checked. This point represents a substantial distinction between NRP and ECMO, since cross-clamp is inherent of in situ abdominal perfusion procedures. Finally, internal bleeding can be difficult to detect, thus a thorough monitoring of hemoglobin levels is mandatory during NRP.

The issues of unreplaced urine output and fluid leakage share a common treatment that trivially consists in volume replacement: definitely not a trivial point to be discussed, especially in the scenario of a DCD procedure. These two occurrences differ qualitatively and quantitatively, *ergo* their clinical weights are different. In fact, the urine output must be monitored and replaced as appropriate (even if it normally constitutes scarce amounts during NRP) whereas fluid leakage is a very consistent drawback of DCD in-situ organ preservation. Perhaps, choosing a more oncotic fluid (i.e., albumin or colloids) may better contrast the hydrostatic pressure that, together with the impaired endothelium secondary to the death-related processes and the superimposed inflammatory stress from the extracorporeal device, concurs to the overt vascular hyperpermeability. However, controversies about the use of colloid solutions especially with regards to their effect on kidney function well depicts the lack of evidenced-based consensus.[6,7] Finally, clinicians should cautiously monitor for signs of cutaneous edema (i.e., "pitting") which can direct the diagnostic process.

Device-related drainage issues

The device-related occurrences that can negatively impact the pump preload concern the drainage system (i.e., venous cannula and venous line), and the EBOA device, if used. Both these complications are highly frequent; thus, clinicians must be aware of some banal expedients that may allow to rapidly identify and resolve complications. Aside of the capacitance of the vasculature, it is likely that mechanical factors limit the venous return: for instance, kinking of the venous line must be prevented by carefully supervising the tubing, especially while mobilizing the donor during NRP. This complication is as frequent as opportunely straightforward to be managed by manipulating the drainage line. Venous return is also dependent on the position of the cannula, that can also result inadequate (mostly after mobilization the donor). Marking the correct position of the cannula with a line on the skin is extremely useful to adjust the cannula insertion depth quickly and effectively, particularly when conventional tools are not promptly available (i.e., during transport). However, transesophageal echography (TEE) and X-ray assessments unquestionably represent the gold standard to analyze and eventually correct the positioning of cannulas, all the more so since these imaging techniques also allows the evaluation of possible obstructions of cannulas and tubing (i.e., clots).

Furthermore, TEE and X-ray assessments guarantee the correct positioning of the EBOA device. In fact, while surgical – external – cross-clamping of the thoracic Aorta determines a firm occlusion of the vessel, the EBOA device is very likely to experience inadequate movements throughout NRP, especially while mobilizing the donor – as for both cannulas and lines. Securing the EBOA device on the skin and marking its correct position (as for the venous cannula) may help to rapidly address this problem. Other expedients to recognize an EBOA malposition exist: the detection of increased (or increasing) left radial artery pressure or an increased oxygen saturation disclose the proximal migration of the device up to the left subclavian artery, whereas a distal migration is more elusory to be detected. In this sense, a rise of the arterial line pressure (P-out) may throw particular suspicion on this occurrence. Moreover, a delayed and indirect EBOA malposition detection via an increased serum lactate concentration is possible but undesirable, as previously debated.

Pump outflow-related issues

Aside of the pump preload, a reduced NRP flow can also result from a problem localized after the pump itself. This group of complications is not characterized by an excessively negative drainage pressure. The increase in arterial line pressure (P-out) could be seen instead, or better yet, a specific alarm can be set. For instance, the arterial line can get easily kinked if not adequately supervised, with high-risk scenarios being the mobilization of the donor and transport. Similarly to the kinking of the venous line, this occurrence should be prevented, and can be identified and fixed in

the same manner. An augmented P-out can also manifest in case of arterial cannula malposition or thrombus obstruction, both these conditions must be immediately evaluated by resorting to the same techniques above discussed (i.e., ink marker, ultrasonography, and X-ray), and opportunely resolved.

Another factor that can decrease NRP flow is the thrombosis of the membrane lung (ML). ML clotting is indeed a terrific complication that, just like uncontrolled bleeding, exerts a synergistic action decreasing both NRP flow and oxygen delivery. For this reason, anticoagulation protocols are universally adopted. The continuous monitoring of the "*delta-P*" (i.e., the difference between the pressure measured before the ML, and the one measured after the ML) and the "*R value*" (i.e., that indexes the *delta-P* for the pump flow), is a valuable strategy attaining to prevent this occurrence, or at least to early recognized it. A visual inspection of the ML by using a light source can also allow the detection of clots albeit this finding could be tardive.

Conclusions

With the increase of DCD donations worldwide, it is predictable that the resort to extracorporeal technologies will expand. Considering the marginality of DCD grafts, it is mandatory to guarantee a reliable in-situ preservation (i.e., perfusion and oxygenation). Complex and inherent technical issues (different from VA ECMO) are likely to negatively impact grafts' quality thus lead to dysfunction in the recipient. It is essential to adopt a systematic approach for the management of inadequate blood flow during NRP for in-situ DCD grafts preservation in order to improve patient outcomes.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Prof. Lorusso is a consultant for Medtronic and LivaNova and is on the medical advisory board for Eroses (all honoraria are paid at the University). No other authors report conflicts of interest.

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