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## Editorial

# Postcardiac arrest ischemia/reperfusion pathophysiology and functional outcome: Can intra-aortic balloon counterpulsation confer any overall or patient-specific benefit?



Cardiac arrest results in cessation of systemic and pulmonary blood flow within 60 s, whole-body/cerebral ischemia, and intracellular adenosine triphosphate (ATP) depletion, followed by homeostasis disruption and imminent necrotic cell death.<sup>1–4</sup> Concurrently, there is increased systemic release of stress hormones and proinflammatory cytokines, platelet/coagulation cascade/complement/leukocyte activation, and impaired microvascular permeability.<sup>1–6</sup> Partial restoration of organ perfusion with basic/advanced life support and return of spontaneous circulation (ROSC) is associated with widespread tissue reperfusion injury.<sup>1–4</sup>

At myocardial tissue/cell level, injurious mechanisms contributing to postresuscitation myocardial dysfunction (PRMD) include (1) interstitial edema formation; (2) oxidative stress and nitric oxide depletion; (3) impaired or obstructed microvascular coronary reflow and low ATP levels; (4) intracellular/mitochondrial calcium overload and acidosis reversal causing hypercontracture and opening of the mitochondrial permeability transition pore, uncoupling of oxidative phosphorylation, and pro-apoptotic protein-/cytochrome C-induced activation of apoptotic pathways; and (5) upregulation of cell adhesion molecules and tissue neutrophil infiltration.<sup>1–6</sup> Additional myocardial injury may be caused by chest compressions, electrical shocks, and epinephrine, especially in cases of prolonged resuscitation.<sup>1,7</sup> Lastly, preexisting ischemic heart disease may exacerbate the effects of several of the aforementioned pathophysiological mechanisms.<sup>8</sup>

PRMD may comprise (1) systolic dysfunction indicated by reduced left ventricular (LV) ejection fraction/stroke volume, fractional shortening, outflow tract peak velocity, and velocity time integral;<sup>8,9</sup> and (2) diastolic dysfunction indicated by LV wall thickening (due to edema<sup>1</sup>), prolonged/impaired isovolumic relaxation, and increased medial mitral E/e' ratio.<sup>8,10</sup> PRMD may result in low cardiac index (e.g.  $<2.2 \text{ L min}^{-1} \text{ m}^{-2}$ ),<sup>11</sup> whereas the systemic ischemia/reperfusion response may be associated with intravascular volume depletion, impaired vasoregulation, and adrenal dysfunction.<sup>5</sup> This combined cardiogenic/vasodilatory shock may respond poorly to vasopressor/inotropic support and intravenous fluids and culminate into early postresuscitation multiple organ failure and death.<sup>8,11,12</sup> Furthermore, irrespective of early death occurrence, early postresuscitation hypotension and/or low diastolic arterial pressure due to PRMD and/or vasodilatory shock/adrenal dysfunction is associated with poor patient outcomes.<sup>13,14</sup>

Global cerebral ischemia/reperfusion is characterized by (1) rapid ATP depletion; (2) calcium cytosolic overload boosted by glutamate and aspartate, and cytotoxic cell swelling; (3) oxidative stress; (4) epinephrine/ $\alpha 1$  adrenergic-receptor-mediated reduction in microcirculatory blood flow and increased risk of microcirculatory reflow obstruction; (5) activation of apoptotic pathways; (6) secondary neuronal injury due to microglia activation and leukocyte infiltration into cerebral tissue; and (7) delayed ischemic neurodegeneration, with increased risk of cytotoxic brain edema.<sup>2–5,15,16</sup> Early post-resuscitation, cerebrovascular hemodynamics exhibit higher critical closing pressure (i.e. intraluminal pressure threshold for vessel collapse), increased resistance, and reduced macrovascular flow velocity.<sup>17</sup> Critical closing pressure reflects vascular smooth muscle tone plus intracranial pressure.<sup>17</sup> Effective prevention of early post-ROSC, secondary brain ischemia may require cerebral perfusion pressure to exceed 60–70 mmHg, corresponding to mean arterial pressure of 85–100 mmHg.<sup>18</sup> The subsequent, reperfusion-related drop in vascular resistance and the already impaired autoregulation may contribute to reactive hyperemia, thereby predisposing to vasogenic brain edema.<sup>16</sup>

A key mechanism of secondary ischemic injury, i.e. persistent, PRMD-associated peripheral organ and cerebral hypoperfusion,<sup>14</sup> may be effectively addressable by intra-aortic balloon pump (IABP) counterpulsation.<sup>19</sup> The IABP increases diastolic arterial and coronary perfusion pressure, unloads the LV, decreases myocardial oxygen consumption, and increases cardiac output, mean arterial and cerebral perfusion pressure, and cerebral, macrocirculatory blood flow.<sup>19,20</sup> Therefore, post-ROSC IABP use might be associated with improved survival and neurologic outcome after out-of-hospital cardiac arrest.<sup>19</sup> This hypothesis was tested but not verified in a Japanese, multicenter, prospective, observational, propensity score-matched study published in the journal's current issue.<sup>21</sup> Compared cohorts were well-matched as regards potentially effect-modifying, peri-arrest characteristics/interventions such as (1) age, time from call to hospital arrival, and rhythm (shockable/non-shockable or presence of pulse); (2) "presence or absence" of witnessed arrest, bystander resuscitation, public access defibrillation, dispatcher instruction, tracheal intubation, and cardiac cause of arrest; and (3) "use or no use" of adrenaline/antiarrhythmics, percutaneous coronary

intervention, targeted temperature management, and extracorporeal membrane oxygenation (ECMO).<sup>21</sup> The primary analysis showed no association between IABP use and 30-day survival/good neurological outcome. Subgroup analyses according to arrest cause, rhythm, and PCI yielded similar results.<sup>21</sup> Similar results were reported by a Korean, propensity score-matched analysis of IABP use in patients resuscitated from cardiac arrest due to myocardial infarction/cardiogenic shock.<sup>22</sup> Furthermore, observational studies and randomized clinical trials (RCTs) in non-cardiac arrest patients with severe ischemic heart disease, acute myocardial infarction, and cardiogenic shock have failed to produce clear evidence in favor of IABP use.<sup>20,22</sup>

In patients with PRMD and vasodilatory shock, the possible lack of IABP efficacy could be explained by (1) the IABP inability to counteract the above-described pre-ROSC pathophysiology — IABPs are normally inserted in the presence of “native” LV function<sup>20</sup>; (2) the probably limited IABP augmentation of post-ROSC cardiac output (e.g. < 0.5 L/min)<sup>20,21</sup>; and (3) the previously documented absence of an IABP effect on microvascular perfusion,<sup>21–23</sup> this may also imply no IABP benefit in postresuscitation restoration of coronary and cerebral microvascular flow. In contrast, veno-arterial ECMO can provide systemic circulatory flows of 6 L/min before ROSC,<sup>20,24</sup> this may restore microvascular perfusion,<sup>25</sup> and prevent secondary, post-ROSC, ischemic insults. A systematic review and meta-analysis of cohort studies suggested ECMO superiority compared to (1) conventional treatment in cardiac arrest; and (2) IABP use in cardiogenic shock.<sup>26</sup> However, the authors of a more recent systematic review of observational studies of ECMO in cardiac arrest concluded that overall risk of bias due to confounding was critical, and that heterogeneity across studies precluded the conduct of meaningful meta-analyses; results of ongoing RCTs are awaited.<sup>27</sup>

To our knowledge, nonrandomized, propensity score-matched, comparative observational data on IABP use in cardiac arrest are relatively scarce.<sup>19,21,22</sup> Also, reported results are heterogeneous: as noted above, two studies reported no IABP-associated benefit,<sup>21,22</sup> whereas one study reported association of IABP use with good neurological outcome at discharge.<sup>19</sup> Interestingly, a large, American, observational analysis reported higher survival to discharge for IABP use vs. no use after out-of-hospital cardiac arrest.<sup>28</sup> Despite propensity score-matching, observational studies may still exhibit a high risk of bias due to limited adjustment.<sup>27</sup> For instance, Kishimori et al. acknowledged that they could not adjust for pre-arrest ischemic heart disease or heart failure, and pre-IABP insertion hemodynamic status and support.<sup>21</sup> Therefore, their IABP cohort might have included sicker patients with worse prognosis. Also, there was no report of (1) specific triggers for IABP use (e.g. presumed cardiac cause of arrest and postresuscitation shock with LV ejection fraction <30%,<sup>12,19</sup> and admission arterial blood lactate of >6.0 mmol/L, or lactate-to-albumin ratio >2.8)<sup>29,30</sup>; or (2) specific timing of IABP insertion; in high risk PCI, preprocedural IABP use may confer a long-term mortality benefit.<sup>31</sup> Lastly, approximately 44% of the IABP cohort patients received ECMO;<sup>21</sup> in these patients, it is unclear whether the IABP was used as adjunct to ECMO for LV venting,<sup>20</sup> or as main rescue intervention; ECMO-treated patients were excluded from the Korean study.<sup>22</sup>

Combined targeting of multiple injurious mechanisms of possibly varying and patient-specific importance may improve cardiac arrest outcomes.<sup>4,5</sup> As in the case of ECMO,<sup>27</sup> RCTs with rigorous eligibility criteria (e.g. exclusion of ECMO-treated patients), and well-pre-planned subgroup analyses (e.g. according to pre-IABP insertion LV function and vasopressor/inotropic support level) are required to conclude on IABP

usefulness as part of an effective/protocolized treatment strategy of patients with PRMD and shock.

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