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The clinical relevance of pediatric post-cardiac arrest myocardial dysfunction and hemodynamic instability

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It has long been appreciated that myocardial stunning is one of the components of post-cardiac arrest organ dysfunction even in the absence of atherosclerotic disease or cardiac etiology for the arrest.¹ In pediatric out-of-hospital cardiac arrest (OHCA), a prior smaller study (n=24) found elevations in troponin I and decreases in echocardiographic (ECHO) measures of systolic function, specifically shortening fraction (SF) and ejection fraction (EF), were inversely proportional.² Higher troponin and diminished SF/EF were present in non-survivors.² Similarly adult studies have demonstrated reduced EF in non-survivors vs. survivors of OHCA of both cardiac and non-cardiac etiology.^{1,3} Shock or hemodynamic instability, whether defined as lower arterial pH or need for greater vasopressors/inotropes, is also strongly associated with mortality after pediatric OHCA.⁴ What remains unclear is the association between post-resuscitation myocardial dysfunction with shock or hemodynamic instability. A crucial concept in post-arrest cardiovascular instability is the relative contributions of the cardiac and the vascular components.^{5,6}

In this month's issue of Pediatric Critical Care Medicine, Conlon and colleagues examine the association between myocardial dysfunction measured by ECHO within the initial 24h post-resuscitation with mortality.⁷ This is the largest cohort of pediatric OHCA thus far for which early ECHO data is available (n=58). The information provided on measures of myocardial dysfunction and shock is revealing and somewhat surprising. It should be noted that 7 children (18%) died of apparent cardiovascular collapse in most cases due to refractory shock. Thus although brain injury clearly remains paramount in shaping outcomes after pediatric OHCA, cardiovascular death remains an important cause of death. Surprisingly, decreased LV systolic function was *NOT* associated with cardiovascular death (OR = 0.8 [0.15, 4/18], p=0.79). Moreover, in the entire cohort where 39 children died, LV

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systolic ($p=0.29$) and diastolic ($p=0.12$) dysfunction again failed to be associated with mortality (Table 4). The factors that were associated with mortality were those indicating hemodynamic instability or shock: tachycardia ($p=0.03$), elevated lactate ($p=0.005$) and increased use of vasopressors/inotropes ($p=0.02$). Although heart rate, elevated lactate and the use of vasopressors/inotropes can all be associated with myocardial dysfunction, none of them were associated with decreased LV systolic function by ECHO.

This begs the question how good of a measure of post-OHCA LV systolic function is the qualitative assessment by ECHO compared with other methods. Although decreased LV systolic function by ECHO was associated with higher troponin, as noted previously in pediatric OHCA,² it was not associated with tachycardia, hypotension, higher vasopressor/inotrope use, elevated lactate or increased acidosis, elevated central venous pressure, lower ScvO₂ or higher B-type natriuretic peptide (Table 2). In other words LV systolic dysfunction by ECHO failed to correlate with the expected physiology of myocardial dysfunction, biochemical abnormalities seen with myocardial dysfunction, the presence of shock or the ultimate outcome. In a multivariable regression, LV systolic dysfunction by ECHO was associated with mortality only when an interaction term for vasopressor inotropic score was included. As the authors point out, this association was only present in the absence of hemodynamic instability defined by need for a vasopressor or inotrope. Thus it appears that in the setting of hemodynamic instability, the need for increased vasopressor or inotropic support rather than LV systolic dysfunction by ECHO is most strongly associated with death.

One should be cautious in interpreting these results as a lack of relationship between refractory circulatory failure, or more broadly hemodynamic instability, and myocardial dysfunction. In adults with septic shock, EF by ECHO corresponded poorly to cardiac output by pulmonary artery catheter, arguably the gold standard of myocardial function, when EF was $> 35\%$. Based on the reported SF in this study (Table 2), most of the study population would fall into the EF $> 35\%$ group. Thus use of qualitative assessment of LV systolic function by ECHO though validated in some settings (see author's references 14–17) may not be ideal after OHCA as a large number of patients with “normal” myocardial function by EF indeed may have significant cardiogenic shock on the basis of cardiac output. In addition there is clearly a component of hypotension and shock after OHCA that persists beyond the recovery of myocardial function even when measured using cardiac output. This has been ascribed to superimposed vasodilation.⁵ The work of Adrie and colleagues in adult OHCA demonstrates significant elevations in cytokines, similar to levels seen in patients with septic shock,⁶ which may account for this distributive vs. cardiogenic post-OHCA shock. In Adrie's study, plasma cytokine elevations and shock measured as elevated lactate were significantly higher in non-survivors compared to survivors whereas LV EF by ECHO was identical regardless of outcome.

Conlon and colleagues *a priori* hypothesized that decreased LV systolic function by ECHO would be associated with increased mortality.⁷ This hypothesis led to the *a priori* inclusion of LV systolic function into the multiple regression model whose outcome was mortality when this variable would normally have been excluded on the basis of its p -value (0.29). Clearly it is important to have hypotheses in performing research but when this results in

modification of the analysis one risks the introduction of bias. Vasopressor inotropic score met the unbiased inclusion criteria ($p < 0.1$ in univariate regression) and was independently associated with mortality in the multiple regression model. This finding put in the context of the existing literature on pediatric OHCA⁴ supports the notion that hemodynamic instability is associated with mortality. More research is needed to determine the relative contributions of myocardial dysfunction and vasodilation to hemodynamic instability and the optimal methods to measure these. This knowledge is crucial before attempting to permit formulation of appropriate interventions aimed at improving outcomes.

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