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EDITORIAL COMMENT

Breaking Under Pressure

Cardiorenal Syndrome and Elevated Central Venous Pressures in Children With Heart Disease

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The term "cardiorenal syndrome" (CRS) delineates the intricate relationship between poor cardiac performance and kidney dysfunction, which can be associated with a wide range of congenital and acquired heart diseases including orthotopic heart transplantation.[1] CRS is caused primarily by compromised renal perfusion, derangements in the neurohormonal axis, and venous congestion, but it is also associated with systemic inflammation and the use of nephrotoxic agents.[2] Understanding the specific pathophysiological drivers is an important step in efforts to prevent or mitigate CRS, which is strongly associated with increased morbidity and mortality.[3] Poor right ventricular compliance and venous congestion are emerging as strong contributors to CRS and may present a modifiable risk factor for future interventions.[4] Central venous pressure (CVP) is used as a clinically relevant surrogate for venous congestion, which is often considered an independent variable or in the context of a composite renal perfusion pressure.[5] While higher CVP has been associated with adult cardiac patients with chronic renal dysfunction[6] and acute kidney injury in children,[7] its role in the progression of CRS in children with chronic cardiac disease has not been explored.

In this issue of *JACC: Advances*, Olsen et al[8] investigate the important relationship between CVP and kidney function in pediatric patients with cardiovascular disease undergoing routine cardiac catheterization In order to reduce potential confounding, they focused on a narrow subgroup composed exclusively of those with biventricular physiology without any intracardiac shunts. After controlling for cardiac index, arterial-venous oxygen difference, and left and right ventricular function, an elevated CVP was found to be an independent risk factor for a lower estimated glomerular filtration rate (eGFR) and worsening renal function over time. This inverse relationship was demonstrated for CVP above 6 mm Hg in a linear fashion and remained consistent across numerous statistical approaches. In contrast to the traditional conceptual framework of organ injury, no relationship was found between eGFR or worsening kidney function, and adequate systemic cardiac output (surrogate for oxygen delivery). Similarly, medication use was not associated with either outcome.

The mechanism by which CVP contributes to kidney injury was not elucidated in this study but may be due to the importance of hydrostatic pressures and fluid dynamics. Elevated CVP without a concomitant rise in systemic blood pressure will result in lower kidney perfusion pressure. A link between lower perfusion pressure and acute kidney injury has been previously established.[9] In numerous pathological states of vasodilation (eg, sepsis), kidney dysfunction progresses despite adequate or heightened cardiac output and is attributed to reduced perfusion pressure or exposure to nephrotoxic agents.[10] However, despite no association between systolic blood pressure and eGFR being found, this theory could not be explored as neither perfusion pressure nor mean arterial blood pressure were considered in the analysis.

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Fractional polynomial modeling revealed a complex correlation between CVP and kidney function, with a weak (positive) correlation found when CVP was lower than 6 mm Hg. The finding may represent acute kidney dysfunction due to fasting and dehydration in a susceptible population. The etiology of this inflection point, however, is not clearly understood and merits further investigation.

Transplant patients accounted for nearly half of the participants and had a lower eGFR than the remaining group. The importance of CVP to kidney injury suffered by transplant patients may differ from that of other pediatric cardiac diseases. These patients are exposed to a multitude of risk factors not experienced by other subgroups, including previous cardiopulmonary bypass,[11] pre-existing kidney injuries from the pretransplant state,[12] and nephrotoxic medications required for graft preservation.[13] Subgroup analysis demonstrated a similar response with comparable trajectory and inflection points, and transplant status dropped from significance when placed in the multivariable model with CVP. This suggests that the CVP-CRS relationship did not differ in transplant recipients; however, consideration for the potential of sampling and selection bias is required.

There are significant challenges to using spot CVP measurements to investigate the role of venous congestion and kidney dysfunction. First, a single CVP measurement may fail to capture the true venous physiology as it is highly load-dependent, which may be significantly altered during catheterization (patients are fasted and on positive pressure ventilation).[14] Second, catheterizations are invasive, and repeat investigations are unwarranted; as such, noninvasive measurements would be required to appreciate the impact of prolonged exposures and provide ongoing surveillance. Renal Doppler have recently been employed to measure vascular resistive indices, which have correlated well with worsening kidney function in postoperative cardiovascular surgical patients.[15] Novel use of bioimpedance vector analysis may also show promise in assessing venous congestion at the bedside.[16] Use of these or similar technologies can be easily implemented at the bedside and should be adopted in future study designs if they can be shown to correlate well with CVP measurements.

In summary, Olsen et al[8] have raised awareness about the potential deleterious impact of venous congestion and elevated CVP on acute and chronic renal function in pediatric cardiac patients. For children who fall within the restricted study inclusion, particularly following heart transplantation, routine catheterization may identify a high-risk subgroup that may benefit from closer surveillance and developing renal protective management strategies. These findings challenge the prevailing paradigm that renal function is determined primarily by cardiac output and will require validation through larger studies that include those with ventricular dysfunction and account for other sources of nephrotoxicity.

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REFERENCES

1. Choudhry S, Dharnidharka VR, Castleberry CD, et al. End-stage renal disease after pediatric heart transplantation: a 25-year national cohort study. *J Heart Lung Transplant*. 2018;37(2):217–224.

2. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2019;139(16):e840–e878.

3. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527–1539.

4. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions. *J Am Coll Cardiol*. 2008;51(13):1268–1274.

5. Sun R, Guo Q, Wang J, et al. Central venous pressure and acute kidney injury in critically ill patients with multiple comorbidities: a large retrospective cohort study. *BMC Nephrol*. 2022;23(1):83.

6. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009;53(7):582–588.

7. Alali A, Acosta S, Ahmed M, et al. Postoperative physiological parameters associated with severe acute kidney injury after pediatric heart transplant. *Pediatr Transplant*. 2022;26(5):e14267.

8. Olsen J, Tunuguntla H, Alali A, et al. Central venous pressure and impaired renal function in children and young adults with cardiovascular disease. *JACC Adv*. 2024;3:100995.

9. Ostermann M, Hall A, Crichton S. Low mean perfusion pressure is a risk factor for progression of

acute kidney injury in critically ill patients – a retrospective analysis. *BMC Nephrol*. 2017;18(1):151.

10. Wong BT, Chan MJ, Glassford NJ, et al. Mean arterial pressure and mean perfusion pressure deficit in septic acute kidney injury. *J Crit Care*. 2015;30(5):975-981.

11. Kumar AB, Suneja M, Riou B. Cardiopulmonary bypass-associated acute kidney injury. *Anesthesiology*. 2011;114(4):964-970.

12. Cho JS, Shim JK, Lee S, et al. Chronic progression of cardiac surgery associated acute kidney injury: intermediary role of acute kidney disease. *J Thorac Cardiovasc Surg*. 2021;161(2):681-688.e3.

13. Bloom RD, Doyle AM. Kidney disease after heart and lung transplantation. *Am J Transplant*. 2006;6(4):671-679.

14. Gelman S, Warner DS, Warner MA. Venous function and central venous pressure. *Anesthesiology*. 2008;108(4):735-748.

15. Hermansen JL, Pettey G, Sørensen HT, et al. Perioperative Doppler measurements of renal perfusion are associated with acute kidney injury in patients undergoing cardiac surgery. *Sci Rep*. 2021;11(1):19738.

16. Parrinello G, Paterna S, Di Pasquale P, et al. The usefulness of bioelectrical impedance analysis in differentiating dyspnea due to decompensated heart failure. *J Card Fail*. 2008;14(8):676-686.

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