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RESEARCH NOTE

WILEY

Hemodynamics and urinary excretion of kidney-injury biomarkers in pediatric kidney transplantation

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1 | INTRODUCTION

Pediatric kidney transplantation with adult donor and young acceptor requires significant increases in the acceptor's cardiac output (CO) to optimize donor kidney perfusion. Insufficient blood flow and pressure to the relatively large donor kidney may risk hypoperfusion and cause kidney injury.[1] Therefore, perioperative supraphysiological hemodynamic targets are recommended, although there is no consensus about which variables to target and what value these targets should have.[2] Liberal administration of fluids, vasopressors, and inotropes are used to increase CO and blood pressure. This strategy, however, risks fluid overload and vasoconstriction potentially limiting graft perfusion. Early postoperative kidney injury can be detected by urinary excretion of novel kidney-injury biomarkers, but their relation to perioperative hemodynamic values is unknown.[3] Therefore, we performed a pilot study aimed to investigate the relation between perioperative hemodynamic values and donor kidney urinary excretion of acute kidney-injury biomarkers in pediatric kidney transplantation with large donor–acceptor size mismatch.

2 | METHODS

Following institutional review board approval and trial registration (Trial NL6666/NTR6900) patients were enrolled at the Radboud University Medical Center between December 2017 and April 2021. Written informed consent was obtained. Standardized anesthesia management followed the local protocol, including a target cardiac index >3.5 L/min/m^2 and mean arterial pressure (MAP) >65 mmHg postreperfusion (Appendix S1). Patient demographics, perioperative fluid administration, urine output, and kidney function were collected. CO (Transpulmonary Thermodilution technique; PiCCO), central venous pressure (CVP), MAP, norepinephrine, and dobutamine infusion rates were recorded at one and 4 h postreperfusion (t1 and t4). Urine samples from the donor kidney were collected from t4 until 3 days postoperative at 8–12 h intervals and analyzed with commercially available ELISA kits to determine KIM-1, NGAL, LFABP, IGFBP-7, and TIMP-2 concentrations. Concentrations were multiplied with donor kidney urine production during a 2-h interval around each sampling time to calculate absolute biomarker excretion. For each biomarker, area under the curve (AUC) during the first three postoperative days was calculated to define total donor kidney biomarker excretion.

Abbreviations: AUC, area under curve; BSA, body surface area; CO, cardiac output; CVP, central venous pressure; IQR, interquartile range; MAP, mean arterial pressure.

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Continuous variables were summarized as median and interquartile ranges. Pearson correlations of each biomarker AUC with CO, CVP, MAP, and norepinephrine infusion rates were calculated with log-transformed data using R version 4.3.3.

3 | RESULTS

Fifteen patients were included with median [IQR] age 6 [5–8] years, weight 21 [16–25] kg, and donor–acceptor BSA mismatch of 2.4 [2.1–3.0]. All acceptors had diuresis within 1 h after reperfusion of the donor kidney and good renal function at hospital discharge. Demographic and perioperative data are summarized in Table 1.

We found several trends: (1) a higher CO related to attenuated excretion of all tested kidney-injury biomarkers, (2) higher levels of CVP and norepinephrine infusion rates related to increased IGFBP-7 and TIMP-2 excretion, and (3) MAP related to KIM-1 excretion. In contrast to CO, the last two correlations were not unidirectional between the biomarkers (Figure 1).

TABLE 1 Patient demographics and perioperative variables.

	Median [IQR]	*N*
Acceptor age (years)	6 [5–8]	15
Acceptor weight (kg)	21 [16–25]	15
Cold ischemia time (min)	176 [149–202]	15
Warm ischemia time (min)	28 [23–34]	15
CO_t1 (L/min)	3.6 [3.2–4.6]	14
CO_t4 (L/min)	4.0 [3.4–5.1]	14
MAP_t1 (mmHg)	74 [66–79]	15
MAP_t4 (mmHg)	76 [69–83]	15
CVP_t1 (mmHg)	8 [2–8]	11
CVP_t4 (mmHg)	5 [1–8]	11
Nor_t1 (μg/kg/min)	0.2 [0.1–0.3]	15
Nor_t4 (μg/kg/min)	0.13 [0.04–0.5]	15
Dobutamine_t1 (μg/kg/min)	2.3	1
Dobutamine_t4 (μg/kg/min)	2.3	1
Fluids total (mL/kg)	61 [46–71]	15
eGFR at discharge	101 [71–117]	15

Note: Patient characteristics, kidney function and perioperative hemodynamic values, fluids, and vasopressor infusion rates. Variables are summarized as median [25th–75th percentile].

Abbreviations: CO, cardiac output; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; Nor, norepinephrine.

4 | DISCUSSION

Our data support the hypothesis that an increased CO is required to limit postreperfusion donor kidney injury in pediatric kidney transplantation with large donor–acceptor size mismatch. However, they also suggest that excessive therapy to reach a supraphysiological CO, like a high CVP and vasopressor infusion rates, might be associated with early donor kidney injury. This corresponds with the reported associations between CVP-guided fluid therapy, fluid overload, and morbidity in critically ill children, and might argue against the often advocated high CVP in perioperative protocols in pediatric kidney transplantation.[4,5]

Clearly, cause–effect relationships cannot be deduced from associations. Other limitations of our study include the small sample size and the protocolized target cardiac index and MAP, which prevented a perioperative low CO-state and hypotension thereby limiting the range of these parameters. Lastly, sedatives and ventilator support could be stopped a few hours after the kidney transplantation in several children. Subsequently, vasopressor support could often be stopped as well, after which the CO monitor was removed. Consequently, the variance in the availability of cardiac output and CVP measurements in the early postoperative period was too large to include these measurements in the analysis.

Because only few research has been done on the interplay between hemodynamics and early donor kidney injury in pediatric kidney transplantation, our results should be interpreted as hypothesis-generating. These results warrant future investigations to determine to what extent hemodynamic therapy relates to clinical consequences, and which biomarkers are most sensitive to detect early donor kidney injury in pediatric kidney transplantation.

In conclusion, the prevention of early donor kidney injury in kidney transplantation with large donor–acceptor size mismatch might benefit from an increased CO. However, careful titration of fluids and vasopressors seems crucial to prevent overtreatment which might cause postreperfusion kidney injury.

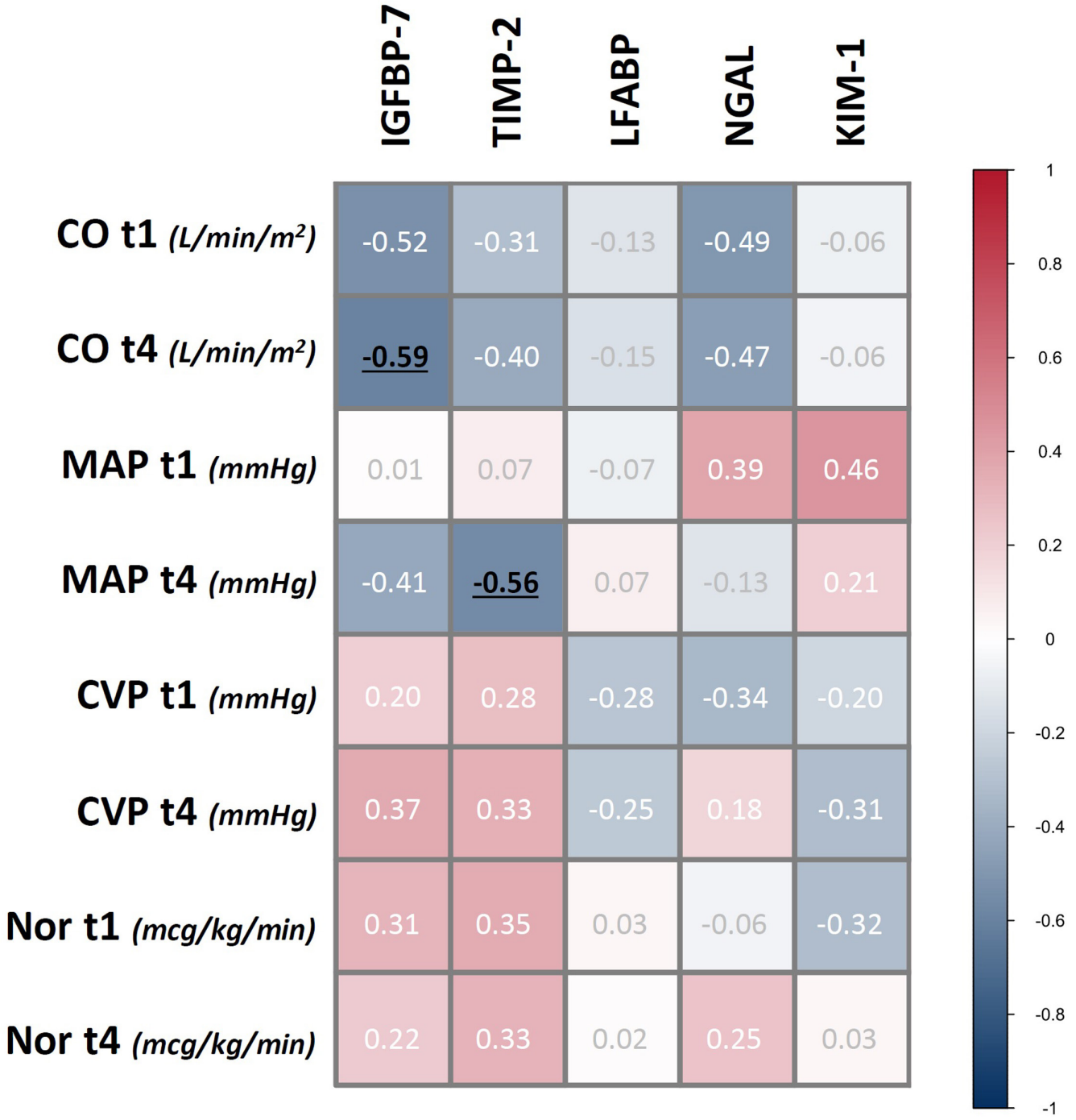

FIGURE 1 Correlogram of total splint biomarker production and hemodynamic variables. Pearson correlation coefficients of log-transformed data are displayed. Positive correlations are displayed in red, negative correlations are displayed in blue. Significant correlations ($p < .05$) are displayed in bold font. CO, cardiac output; CVP, central venous pressure; MAP, mean arterial pressure; Nor, Norepinephrine.

CONFLICT OF INTEREST STATEMENT

Author AZ received lecture fees and an unrestricted research grant from BioMerieux.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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