Towards establishing targets for goal-directed anesthesia in renal transplantation: a cohort analysis of high-saliency surgical time-courses.

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ABSTRACT

Delayed graft function (DGF) increases morbidity and mortality in kidney transplant recipients. Operative parameters, including hemodynamics and vasopressor and fluids use can impact perfusion to the newly transplanted kidney and influence the development of DGF, but there is limited evidence appropriate management strategies for this. We analyzed highly granular time-series intraoperative data from kidney transplant recipients (n=600) in conjunction with pre-transplant characteristics and post-surgical outcomes, including DGF incidence, 60-day creatinine trends, and graft survival. 121 DGF events were captured in our cohort derived from a single academic medical center (54/261 NDDs, 62/138 DCDs, 5/176 live donors). Post-anastomosis hypotension was primarily a risk factor for DGF in DCD kidneys, independent of conventional predictors of DGF. In our cohort, at a maintained average MAP of 90 mmHg post-anastomosis, DGF incidence in DCD kidneys was equal to NDD kidneys (20%), while at MAP<75, DGF rates rose threefold (60%). In analysis of long-term effects, serial creatinine measured to 60 days post-operatively and graft survival were largely equal between groups regardless of intraoperative hypotension level. Interaction analysis demonstrated that higher doses of vasopressors and IV fluids were associated with improved outcomes when used at MAPs of 75-80 mmHg or lower, but associated with increased DGF at MAPs above 75-80 mmHg. In conclusion, our analysis of granular surgical time-series has identified potential hemodynamic targets and vasopressor/fluid management strategies.

1 Introduction

Transplantation is widely regarded as the treatment of choice for patients with end-stage organ failure, with substantial improvements in morbidity and mortality in transplant recipients compared to dialysis[1,2]. As the demand for transplantation continues to increase, an increasing share of transplant volume is driven kidneys donated after circulatory death (DCDs)[3]. This has allowed for the transplantation of organs into a wider range of recipients, including older and more comorbid individuals, who derive mortality benefit[4]. However, the use of marginal donors for more marginal recipients carries increased risk of delayed graft function (DGF). DGF, defined specifically as the requirement for dialysis within a week of transplantation, is an early postoperative complication that can increase the morbidity and mortality for the recipient, and profoundly increases healthcare costs in proportion to the number of extra dialysis sessions needed[5,6].

While the incidence of DGF can be influenced by various factors, including recipient and donor characteristics[7], intraoperative parameters have also been suggested to play a role. Intraoperative parameters, including vasopressor medication use, fluid management, and patient hemodynamics are understood to impact perfusion to the newly transplanted kidney, and influence the development of DGF, but best evidence on this is limited[5]. Therefore, further study in optimizing anesthesia management during the transplant procedure by formulating specific targets for goal-directed anesthesia may help prevent DGF, which in turn would decrease reluctance to use marginal donor sources and improve patient outcomes.

We felt that anesthesia time series records (which are routinely recorded at our institution) were an underutilized resource in the literature inside and outside of transplantation, and carried great potential characterizing anesthesia courses in the highest fidelity possible. These time series comprised operative ventilatory parameters and hemodynamics, and also a full list of medications (including timing, doses, and infusion rates), including blood-pressure controlling medications such as vasopressors and IV fluids. We primarily questioned what blood pressures after the surgical milestone of vascular anastomosis (where the

transplanted kidney is fully connected to the recipient blood supply) were ideal for prevention of DGF. We also questioned whether there was value in personalized blood pressure targets, in terms of characterizing hypotension as relative to donor or recipient blood pressure baselines. Lastly, as the time series records contained detailed information about medication provision, we aimed to characterize special features of vasopressor and fluid provision, such as average blood pressure thresholds for the use of pressor boluses by the attending anesthesiologist, and how increasing cumulative doses of pressors and fluids influenced DGF risk incidence.

Existing studies in goal-directed therapy in anesthesia largely pertain to non-transplant populations[8,9]. However, transplantation in particular represents a high-stakes domain where the scarcity and vulnerability of ischemic donor organs demands careful avoidance of even mild organ damage. The identification of domain-specific goals using high-fidelity transplant-specific anesthesia time-series data, enables the potential to capture previously unrecognized clinical etiological features in DGF incidence, and ultimately to more effectively investigate how to prevent DGF.

2 Methods

2.1 Study design, setting, data sources

600 kidney transplant recipients were included from surgeries performed at a single major academic medical centre (Vancouver General Hospital, 2014-2020) based on availability of the anesthetic record, operative note, and discharge summary. Collected anesthetic records comprised all medications and fluids administered (including quantities, timing, and rate of administration), and hemodynamic and ventilatory parameters throughout the procedure, in five minute intervals. The examined intraoperative hemodynamic and ventilatory variables included heart rate, systolic and diastolic blood pressure, respiratory rate and tidal volume, end-tidal CO2, body temperature, concentration of inhaled anesthetic, and pulse oximetry. Information regarding major time points such as the start and completion of anastomosis were also obtained from post-operative notes. These time-series records were digitized for analysis (WebPlotDigitzer, version 4.6). Measured outcomes of renal graft function included DGF, defined as requirement for dialysis within one week of transplant, and serum creatinine at 1-7, 14, 30, 45, and 60 days post-transplant. Criteria for patient exclusion included all-cause mortality within one week of the transplant and having received a combined organ transplant. Furthermore, early graft dysfunction and dialysis requirement attributable to biopsy-proven rejection were not treated as DGF events.

2.2 Ethical approval and consent

This cohort study was approved by the University of British Columbia, Institutional Review Board (REB approval H18-02941). The study was exempt from informed consent as it is a review involving only retrospective data collection and analysis.

2.3 Statistical analysis

Feature extraction and data processing from digitized anesthetic records were undertaken using Python (version 3.8), and statistical analysis and figures were conducted and generated in R (version 4.2.0). Continuous variables are presented as mean values ± standard deviation, and categorical variables as percentages (%) unless indicated otherwise. Hypothesis testing between continuous variables were conducted using one-way ANOVA, and categorical or binary variables were compared using the chi-squared test (Table 1).

The analysis of hypotension in all figures except 1 is focused on the MAP values between reperfusion (after completion of anastomosis) and emergence, as this is the specific hemodynamic milieu to which a newly transplanted kidney is exposed. Analyses are also subdivided between DCD and NDD kidney recipients. Recipients receiving live donations were excluded from analyses in Figures 2, 3, and 4 due to the low incidence of DGF in this subgroup.

Direct time-series graphs of average MAP, IV fluid infusion rate, and frequency of pressor use (fig. 1) were generated via first ‘warping’ the time series for the above three intraoperative parameters, recorded at 5 minute intervals during surgeries. ‘Warping’ in this setting refers to stretching or squeezing the timecourse to a larger or smaller timeframe, while keeping the trends and range of parameter values identical. Warping was performed to equalize time series to coordinate the times of start of vascular anastomosis, end of anastomosis, and to emergence/end-of-operation, and the average time intervals for these milestones were calculated separately for DCDs, NDDs, and LDs. Average values at each 5 minute interval were plotted from these warped time series. A smoothed fit line was drawn over these average values per 5-minute interval to indicate trends in MAP, IV fluid rate, and pressor use in DCD, NDD, and LD recipients. Hypothesis testing was not conducted.

In fig. 2, incidence proportions of DGF are plotted across intervals of various measures post-anastomosis hypotension. Selected measures of hypotension included markers of 'absolute' and 'relative' hypotension. Absolute hypotension was operationalized in terms of an average MAP between completion of vascular anastomosis and emergence, and the lowest MAP recorded in the same time interval. Relative hypotension was operationalized the same, but the average MAP and lowest MAP were then expressed as a percentage of the recipient baseline MAP and the donor baseline MAP. Baseline recipient MAP data was calculated from the most recent documentation of pre-transplant evaluation with a SBP/DBP present. Baseline donor MAP were supine blood pressures collected from pre-procurement documentation in deceased donors, and from pre-operative standing blood pressures in living donors. Error bars indicating the 97.5th percentile confidence intervals for each hypotension interval's DGF incidence proportion are included for representation of significance in differences but no specific hypothesis testing was conducted. Concordance indexes for the receiver operating characteristic of each the predictive ability of each operationalization of hypotension for DGF in logistic regression (with only DCD/NDD status as a covariate) were calculated. Confidence intervals for calculated c-statistics were then generated via 100-fold bootstrap and plotted.

Longer-term outcomes outside of the first week post-transplantation were also assessed in fig. 3. Serial creatinine was measured daily from 1-7 days, and thereafter at 14, 30, 45, and 60 days. Welch's two-sample t-test was conducted to compare average creatinine in the first seven days post-transplant between patients with average post-anastomosis MAP of <75 and >75 mmHg.

Lastly, an logistic regression analysis was performed for the influence of average absolute post-anastomosis MAP on DGF, with interaction terms to investigate potential effect modification on this relationship from cumulative operative phenylephrine dose (the most frequently used vasopressor) and cumulative IV fluid infusion. The calculated logistic probability of DGF incidence are plotted for three values of the effect modifying variable, at the mean - 1SD dose (0 mcg for phenylephrine dose), the mean dose, and the mean + 1SD dose. Logistic regression analysis included donor type, recipient age, and sex as major covariates in the model.

3 Results

3.1 Baseline characteristics

The patient cohort's general characteristics are outlined in table 1. The incidence of DGF differed significantly between the three major donor categories. 121/575 DGF events were captured in our cohort overall (54/261 NDDs (20.7%), 62/138 DCDs (44.9%), 5/176 live donors (2.8%)). Age, sex distribution, and BMI between DCD patients with and without DGF, and NDD patients for the same were not significantly different, but did differ between subgroups. Average baseline MAP in DCDs and NDDs were not significantly lower in recipients with DGF than without. However, for live donors, average baseline recipient MAP was substantially lower in recipients with DGF (97.1 ± 11.3 *vs.* 81.7 ± 9.0, p=0.003). Regarding baseline donor MAPs, there were minimal differences within donor source subgroups, supine donor MAPs for DCD recipients were on average lower than NDD recipients. There was also an observed trend for live donor recipients, where patients with DGF on average had donors with higher baseline blood pressures (88.9 ± 8.41 *vs.* 95.2 ± 7.3, p=0.10).

Regarding intraoperative parameters, vasopressor medications were used more frequently in surgeries with DGF in all subgroups. The most commonly used vasopressor was phenylephrine, although the use of phenylephrine did not differ significantly within or between subgroups (p=0.217), as it did for ephedrine and norepinephrine (respectively the second and third most common vasopressor). Quantities of IV fluid infusion intraoperatively between groups did not differ significantly between groups either, either when expressed as a sum quantity or as rates accounting for bodyweight, although in all subgroups DGF recipients tended to receive higher quantities of fluid.

3.2 Visualizations of averaged operative time-series

In direct graphing of normalized time courses (fig. 1, recipients experiencing DGF had notably lower MAP throughout the entirety of their operation, including in the post-anastomosis phase, in DCD and LD recipients, but not significantly in NDD recipients. Pressor use was expectably elevated in DCD and LD recipients in DGF patients compared to non-DGF patients, corresponding with timeframes where MAP was depressed. In LD recipients, fluid infusion rate was similarly elevated. However, in DCD recipients, fluid rates were not increased as compared to non-DGF patients, indicating an overall preference for vasopressors in the control of perceived hypotension over further volume resuscitation. In NDD patients, while MAP and pressor use did not differ substantially at any operative time points, fluid infusion rate, especially near the average time of anastomosis, was elevated in NDD recipients.

3.3 Absolute *vs.* relative blood pressure thresholds

Fig. 2 represents multiple methods of operationalizing post anastomosis hypotension in absolute or relative terms based on recipient and donor baseline blood pressures, which are described in 2. All methods of describing hypotension demonstrate an overall increasing proportion in the incidence of DGF with lower MAPs in DCD recipients, but minimal similar hypotension susceptibililty was noted in NDD recipients. In comparison of concordance indexes for the discriminating ability of each method for predicting DGF, all methods performed similarly (concordance indexes ranging from 0.64 [0.6-0.7] (mean MAP as percentage of donor baseline MAP) to 0.7 [0.64-0.74] (lowest absolute MAP)).

3.4 Long-term outcomes

4. long term analyses: serial creatinines, Cox proportional hazards analysis with

3.5 Timing of pressors, IV fluids

In multiple logistic regression analysis on our cohort, we demonstrate that post-anastomosis [mean/minimum/aut/aut-twa/as pct donor baseline/as pct recipient baseline] blood pressures represented an outsized determinant of DGF incidence as compared to typical predictors including DCD/NDD status, age, sex, and donor terminal creatinine. All analyses were facetted between DCD and NDD recipients, indicating that post- vascular anastomosis hypotension was primarily a risk factor for DGF in DCD kidneys over NDD kidneys. Long-term outcomes analysis indicated that outside the first 7 days, serial creatinines measured to 60 days post-transplant were largely equal between recipients that had post-anastomosis hypotension versus those who were normotensive post-anastomosis. Time to graft loss in long-term follow-up was not different between the two groups. Finally, an interaction terms logistic regression analysis was undertaken for the influence of measures of hypotension on DGF between recipients who were given vasopressors medications and those who were not, indicating that pressors were best used at 70mmHg or lower, and that the use of pressors above targets of 75mmHg were associated with increased DGF from baseline.

2. time series direct graphs, or time-stretched graphs, and/or major time points graph

5. interaction terms graph with pressors, plus multiple regression table underneath to demonstrate p-values

Example text under a subsection. Bulleted lists may be used where appropriate, e.g.

Discussion

Several studies have demonstrated intraoperative hypotension to be associated with myocardial injury, acute kidney injury, and mortality[10–12]. Based on these studies, the 2019 Perioperative Quality Initiative consensus statement concluded with the notion that anesthesiologists should maintain a MAP threshold of greater than 60 to 70 mm Hg during surgery[13]. Furthermore, it states that that postoperative injury is a function of both time spent having hypotension and depth of hypotension, making the time-weighted average of hypotension an end point of particular interest[13]. Futier et al.[9] demonstrated in the INPRESS RCT that maintaining a higher MAP–largely with the use of vasopressor medications–during abdominal surgery reduced the risk of postoperative organ dysfunction.

In the current study, indicators of both long and short term organ dysfunction (delayed graft function, 60-day serial creatinine, time to graft failure) as a result of various forms of hypotension (absolute and relative–to both donor andrecpient BP baselines–thresholds of low MAP) were investigated. This relationship was investigated a step further through interaction terms analysis for whether the use and timing of vasopressors intraoperatively influenced the incidence of DGF.

1. Does hypotension intraoperatively increase DGF incidence?

Yes

2. Do individualized blood pressure targets based on pressure thresholds from the patient's baseline result in better prediction of DGF events? What about based on pressure thresholds from the donor's baseline?

The issue of what comprises a minimal acceptable blood pressure in anesthetized patients has been the point of controversy for years,

The associations based on relative thresholds were no stronger than those based on absolute thresholds. Furthermore, there was no clinically important interaction with preoperative pressure. Anesthetic management can thus be based on intraoperative pressures without regard to preoperative pressure.

The findings of this trial add to the evidence of benefits of personalizing care, especially in high-risk surgical patients.9 To our knowledge, this is the first study to investigate the effects of individualizing blood pressure management according to patients' preoperative values, and the study differs from others that either examined the relationship between different blood pressure thresholds and outcome or used predefined fixed blood pressure targets. The recent SEPSISPAM trial found no mortality difference in patients with septic shock who underwent resuscitation targeting a mean arterial pressure of either 65 to 70 mm Hg or 80 to 85 mm Hg35; however, patients with chronic hypertension in the high target group had less kidney injury.

3. What trigger hypotension threshold for vasopressor use and increased fluid use is most associated with reduced DGF incidence?

Adjustment of vasopressors and fluid provision must balance the risk of underrescuscitation withe the benefit of maintaining sufficient driving pressure in

Moderate pressor strategy:

Moderate fluid strategy:

MAP >93 mm Hg and perioperative fluid administration <2500 mL were associated with greater graft survival[14]. In contrast to previous literature in the domain, we did not note differences in graft survival with various methods of operationalizing hypotension, with varied MAP cutoffs (analysis not shown).

Older studies in fluid administration in kidney transplantation advocated for maximum volume infusion[15–17]

However, this can lead to excess fluid infusion, which can damage the endothelial glycocalyx and lead to a fluid shift into the interstitial space [14]. For several years, during kidney transplantation, a liberal fluid-therapy attitude was recommended, with infusion rate values ranging from 10–15 mL/kg/h to 30–40 mL/kg/h with a CVP of 8–12 mmHg, in order to promote early function recovery of implanted grafts [14,15,16,17]. Over the last few years, this attitude has been downsized in favor of less aggressive fluid therapy, and infusion is now driven by relatively accurate hemodynamic indicators (CVP, mean arterial pressure [MAP]) characterized by an infusion rate of 10–15 mL/kg/h with a target CVP of 7–9 mmHg. This has resulted in a reduction in cardiovascular complications with good graft survival [18].

Limitations: 1. causality 2. inferences on LD recipients with DGF are limited as there were only 5 events in this cohort.

References

1. Wolfe, R. A. *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *New Engl. journal medicine* **341**, 1725–1730 (1999).
2. Abecassis, M. *et al.* Kidney transplantation as primary therapy for end-stage renal disease: a national kidney foundation/kidney disease outcomes quality initiative (nkf/kdoqi™) conference. *Clin. journal Am. Soc. Nephrol. CJASN* **3**, 471 (2008).
3. Annual statistics on organ replacement in canada, 2011 to 2020 (2020).
4. Jay, C. L. *et al.* Survival benefit in older patients associated with earlier transplant with high kdpi kidneys. *Transplantation* **101**, 867 (2017).
5. Kasiske, B. L. *et al.* Delayed graft function in renal transplantation: definition, epidemiology, and management. *Am. J. Kidney Dis.* **41**, S1–S8 (2003).
6. Kim, D. W. *et al.* Financial impact of delayed graft function in kidney transplantation. *Clin. transplantation* **34**, e14022 (2020).
7. Heering, P. *et al.* Risk factors for delayed graft function: a multicenter analysis. *Am. journal transplantation* **2**, 879–888 (2002).
8. Saugel, B., Michard, F. & Scheeren, T. W. Goal-directed therapy: hit early and personalize! *J. clinical monitoring computing* **32**, 375–377 (2018).
9. Futier, E. *et al.* Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *Jama* **318**, 1346–1357 (2017).
10. Bijker, J. B. *et al.* Intraoperative hypotension and 1-year mortality after noncardiac surgery. *The J. Am. Soc. Anesthesiol.* **111**, 1217–1226 (2009).

11. Hallqvist, L., Granath, F., Huldt, E. & Bell, M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery. *Eur. journal anaesthesiology* **35**, 273–279 (2018).

12. Sun, L. Y., Wijeysundera, D. N., Tait, G. A. & Beattie, W. S. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology* **123**, 515–523 (2015).

13. Sessler, D. I. *et al.* Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br. journal anaesthesia* **122**, 563–574 (2019).

14. Campos, L. *et al.* Do intraoperative hemodynamic factors of the recipient influence renal graft function? In *Transplantation proceedings*, vol. 44, 1800–1803 (Elsevier, 2012).

15. Wagener, G. *et al.* Fluid management during kidney transplantation: a consensus statement of the committee on transplant anesthesia of the american society of anesthesiologists. *Transplantation* **105**, 1677–1684 (2021).

16. Carlier, M. *et al.* Confirmation of the crucial role of the recipient's maximal hydration on early diuresis of the human cadaver renal allograft. *Transplantation* **36**, 455 (1983).

17. Thomsen, H. S., Løkkegaard, H. & Munck, O. Influence of normal central venous pressure on onset of function in renal allografts. *Scand. journal urology nephrology* **21**, 143–145 (1987).

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Author contributions statement

RM and CN conceived the analyses. RM conducted the data analyses. RM, ATN, and CN drafted the manuscript. RM, ATN, EE, and AN collected data. All authors reviewed the manuscript prior to submission.

Additional information

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The corresponding author is responsible for submitting a competing interests statement on behalf of all authors of the paper. This statement must be included in the submitted article file.

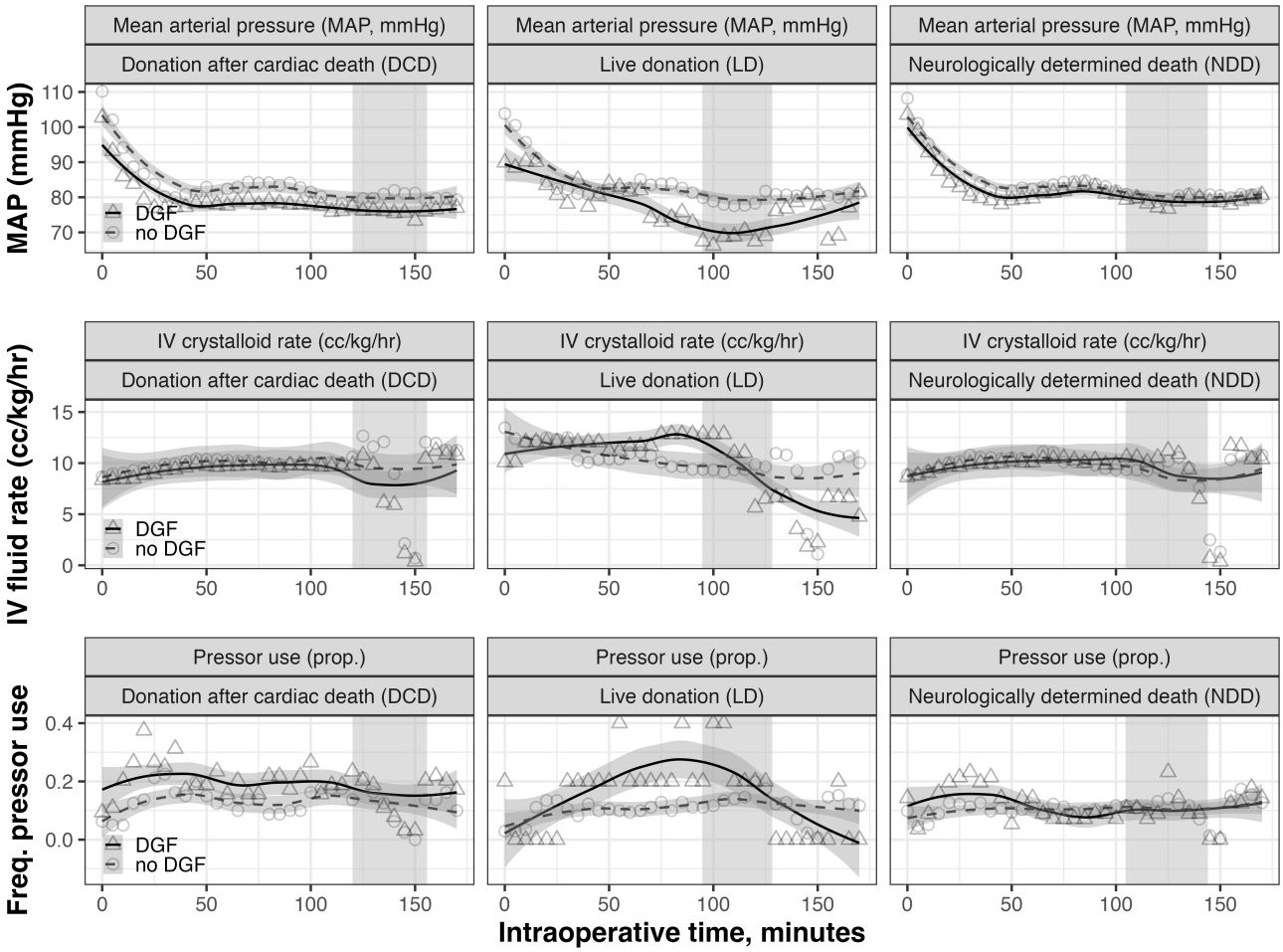


Figure 1. Graphs of average intraoperative time courses for mean arterial pressures, IV crystalloid infusion rates, and frequency of pressor use. MAP (mmHg), IV rate per bodyweight (cc/kg/hr), and use of pressors were measured in 5 minute intervals. The time series were 'warped' (i.e. compressed or stretched with interpolation) to have the time series' line up at the average start time of anastomosis, average end time of anastomosis, and average time of procedure end (calculated individually for DCD, NDD, and LD recipients). These averages for DGF/non-DGF patients (triangles and circles respectively, with transparency) were directly plotted and smoothing functions were drawn through plotted points. Error ribbons reflect the 95% confidence interval for the standard error of the smoothing function. Graphs are faceted between DCD, LD, and NDD kidney recipients. Greyed area indicates average time of vascular anastomosis in each major recipient group. Pressors included in this analysis included phenylephrine, ephedrine, norepinephrine, and vasopressin. Frequency of pressor use indicates the proportion of all surgeries wherein a pressor was used at the specific time point. Graphs are truncated at 2.5 hours of operative time and do not specifically reflect depicted parameters at the average time of emergence.

	DCD recipients		LD recipients		NDD recipients		
	No DGF	DGF	No DGF	DGF	No DGF	DGF	p
n	80	64	171	5	213	56	
Recipient pre-transplant parameters							
Age (years)	58.24 (12.44)	59.15 (12.13)	50.09 (15.13)	45.72 (11.34)	53.48 (13.95)	56.92 (11.40)	<0.001
Sex = M	48 (60.0)	43 (67.2)	108 (63.2)	2 (40.0)	132 (62.0)	40 (71.4)	0.591
BMI (kg/m^2)	25.95 (4.87)	26.72 (5.48)	26.23 (5.27)	24.98 (6.81)	26.04 (5.32)	27.64 (5.45)	0.391
Cause of ESRD							0.010
DN	22 (27.5)	27 (42.2)	44 (25.7)	1 (20.0)	62 (29.1)	25 (44.6)	
GN	20 (25.0)	22 (34.4)	66 (38.6)	2 (40.0)	66 (31.0)	16 (28.6)	
HTN	17 (21.2)	5 (7.8)	12 (7.0)	1 (20.0)	31 (14.6)	8 (14.3)	
PCKD	6 (7.5)	9 (14.1)	17 (9.9)	0 (0.0)	17 (8.0)	2 (3.6)	
other	13 (16.2)	1 (1.6)	30 (17.5)	1 (20.0)	29 (13.6)	4 (7.1)	
unknown	2 (2.5)	0 (0.0)	2 (1.2)	0 (0.0)	8 (3.8)	1 (1.8)	
Dialysis mode							<0.001
HD	44 (55.0)	49 (76.6)	58 (33.9)	5 (100.0)	126 (59.2)	46 (82.1)	
PD	29 (36.2)	11 (17.2)	53 (31.0)	0 (0.0)	72 (33.8)	5 (8.9)	
predialysis	7 (8.8)	4 (6.2)	60 (35.1)	0 (0.0)	15 (7.0)	5 (8.9)	
Dialysis vintage (years)	3.68 (2.69)	4.02 (3.92)	1.12 (1.71)	1.83 (1.24)	3.34 (2.76)	3.97 (3.28)	<0.001
Comorbid DM = 1	33 (41.2)	39 (60.9)	72 (42.1)	2 (50.0)	97 (45.5)	35 (62.5)	0.021
Comorbid HTN = 1	63 (78.8)	51 (79.7)	135 (78.9)	2 (40.0)	161 (75.6)	42 (75.0)	0.415
Systolic BP (mmHg)	133.55 (21.09)	134.36 (17.43)	134.48 (17.40)	117.00 (15.65)	131.11 (16.65)	134.21 (20.11)	0.161
Diastolic BP (mmHg)	78.17 (11.55)	76.68 (11.67)	78.52 (11.13)	64.00 (8.94)	77.29 (11.01)	74.19 (12.89)	0.022
MAP (mmHg)	96.55 (12.45)	95.83 (11.47)	97.06 (11.27)	81.67 (8.98)	95.22 (11.20)	94.26 (13.44)	0.048
Panel reactive antibody (%)	34.69 (37.66)	30.94 (33.47)	26.07 (30.73)	65.95 (39.30)	29.57 (34.35)	29.97 (36.13)	0.105
Donor pre-transplant parameters							
Age (years)	43.26 (16.72)	51.06 (13.70)	50.65 (12.35)	52.20 (9.42)	40.52 (15.13)	42.59 (15.76)	<0.001
Sex = 1	41 (66.1)	38 (70.4)	53 (38.7)	1 (20.0)	95 (64.6)	23 (50.0)	<0.001
Left kidney = 1	37 (59.7)	26 (48.1)	136 (99.3)	5 (100.0)	73 (49.7)	19 (41.3)	<0.001
Comorbid DM = 1	5 (8.8)	4 (7.7)	0 (0.0)	0 (NaN)	12 (8.5)	7 (15.2)	NaN
Comorbid HTN = 1	12 (21.4)	17 (32.7)	1 (50.0)	0 (NaN)	22 (16.1)	12 (27.3)	NaN
Terminal creatinine	80.37 (56.61)	85.15 (57.37)	74.11 (15.80)	72.40 (3.36)	95.93 (82.74)	140.18 (147.56)	<0.001
Systolic BP (mmHg)	128.59 (21.65)	135.00 (24.57)	118.29 (13.21)	117.50 (10.61)	137.24 (18.22)	135.39 (18.04)	<0.001
Diastolic BP (mmHg)	70.51 (13.07)	69.02 (12.68)	74.49 (7.91)	84.00 (5.66)	75.46 (13.25)	75.00 (12.13)	0.005
MAP (mmHg)	89.87 (14.57)	91.01 (15.41)	88.92 (8.41)	95.17 (7.31)	96.05 (13.04)	95.13 (12.36)	0.001
Extended criteria donor = 1	16 (24.2)	14 (25.5)	0 (0.0)	0 (NaN)	34 (16.8)	9 (17.3)	NaN
Surgical timelines							
Operative time (min)	212.15 (37.59)	226.80 (43.10)	184.32 (40.29)	254.20 (93.93)	202.16 (40.21)	219.61 (45.07)	<0.001
Cold ischemia time (min)	699.91 (485.33)	675.30 (347.59)	245.19 (95.03)	363.40 (182.46)	542.36 (251.30)	625.21 (315.60)	<0.001
Anastomosis time (min)	34.35 (8.59)	36.20 (7.15)	34.04 (12.42)	47.75 (6.95)	34.38 (9.99)	36.35 (7.79)	0.078
Blood loss (mL)	190.54 (195.38)	195.12 (235.53)	148.89 (224.63)	400.00 (360.56)	144.66 (108.24)	150.71 (84.99)	0.100
Hemodynamic parameters							
Avg. SBP whole op.	121.44 (13.19)	117.51 (11.94)	120.50 (13.37)	110.41 (23.05)	122.05 (12.62)	121.20 (13.02)	0.089
Avg. SBP after anast.	118.81 (13.40)	114.86 (11.38)	120.71 (17.73)	112.09 (23.97)	120.00 (12.68)	118.88 (13.48)	0.092
Avg. SBP whole op.	63.19 (7.57)	58.97 (6.79)	63.49 (7.74)	59.58 (9.32)	63.44 (7.50)	61.06 (6.84)	<0.001
Avg. DBP after anast.	60.99 (7.63)	56.85 (6.28)	61.40 (8.51)	59.20 (9.21)	60.74 (7.35)	58.74 (6.90)	0.001
Avg. MAP whole op.	82.60 (8.22)	78.49 (7.35)	82.39 (8.56)	76.52 (13.35)	82.97 (8.03)	81.10 (7.82)	0.003
Avg. MAP after anast.	80.27 (8.25)	76.19 (6.57)	80.93 (10.39)	76.83 (13.83)	80.48 (7.75)	78.78 (7.95)	0.005
Avg. HR whole op.	67.72 (9.28)	66.91 (10.80)	70.19 (10.93)	77.18 (8.09)	69.10 (9.63)	65.60 (10.79)	0.011
Avg. HR after anast.	67.71 (9.34)	67.54 (11.70)	70.51 (12.15)	82.10 (12.00)	69.68 (10.96)	66.38 (11.29)	0.009
Area under MAP=75	7.73 (9.91)	9.41 (12.09)	7.70 (8.64)	12.24 (15.96)	7.33 (8.34)	6.84 (6.84)	0.494
Medications and fluids							
Ephedrine used = 1	39 (48.8)	41 (64.1)	69 (40.4)	1 (20.0)	99 (46.5)	30 (53.6)	0.023
Phenylephrine used = 1	40 (50.0)	37 (57.8)	75 (43.9)	4 (80.0)	99 (46.5)	30 (53.6)	0.246
Norepinephrine used = 1	11 (13.8)	11 (17.2)	3 (1.8)	2 (40.0)	14 (6.6)	5 (8.9)	<0.001
Vasopressin used = 1	0 (0.0)	3 (4.7)	2 (1.2)	0 (0.0)	1 (0.5)	2 (3.6)	0.081
Any pressor used = 1	58 (72.5)	56 (87.5)	106 (62.0)	4 (80.0)	142 (66.7)	44 (78.6)	0.003
Avg. MAP at pressor use	75.61 (8.50)	73.83 (9.66)	76.18 (10.15)	73.91 (14.92)	77.50 (10.54)	77.06 (10.99)	0.303
IV fluids total	2644.37 (1062.19)	2662.82 (1038.87)	2388.94 (1253.69)	2556.50 (1585.25)	2387.85 (1076.12)	2680.60 (1234.33)	0.189
IV fluids (cc/kg/min)	0.94 (0.37)	0.86 (0.38)	0.88 (0.40)	0.68 (0.34)	0.89 (0.44)	0.95 (0.49)	0.761

Table 1. All values are expressed as mean (sd) unless indicated otherwise for binary variables (%). All hypothesis tests are conducted via regular ANOVA for continuous variables and chi-squared test for categorical variables.

	DCD recipients				LD recipients				NDD recipients				
	SCD, no DGF	SCD, DGF	ECD, no DGF	ECD, DGF	SCD, no DGF	SCD, DGF	ECD, no DGF	ECD, DGF	SCD, no DGF	SCD, DGF	ECD, no DGF	ECD, DGF	p
n	50	41	16	14	64	0	0	0	168	43	34	9	
Recipient pre-transplant parameters													
Age (years)	55.12 (13.47)	57.99 (11.15)	65.20 (5.19)	67.99 (6.08)	50.46 (15.19)	-	-	-	51.89 (13.38)	55.80 (11.06)	62.40 (12.47)	63.81 (7.55)	<0.001
Sex = M	31 (62.0)	30 (73.2)	10 (62.5)	9 (64.3)	40 (62.5)	-	-	-	106 (63.1)	29 (67.4)	20 (58.8)	7 (77.8)	NaN
BMI (kg/m^2)	25.65 (4.74)	26.88 (5.09)	26.97 (5.51)	26.56 (4.93)	25.55 (5.10)	-	-	-	26.15 (5.41)	27.61 (5.71)	25.35 (3.21)	28.68 (5.13)	0.355
Cause of ESRD						-	-	-					NaN
DN	16 (32.0)	17 (41.5)	4 (25.0)	9 (64.3)	17 (26.6)	-	-	-	46 (27.4)	18 (41.9)	15 (44.1)	5 (55.6)	
GN	8 (16.0)	15 (36.6)	5 (31.2)	2 (14.3)	25 (39.1)	-	-	-	52 (31.0)	13 (30.2)	10 (29.4)	2 (22.2)	
HTN	11 (22.0)	2 (4.9)	2 (12.5)	1 (7.1)	3 (4.7)	-	-	-	26 (15.5)	8 (18.6)	3 (8.8)	0 (0.0)	
other	10 (20.0)	1 (2.4)	3 (18.8)	0 (0.0)	11 (17.2)	-	-	-	22 (13.1)	3 (7.0)	5 (14.7)	0 (0.0)	
PCKD	4 (8.0)	6 (14.6)	1 (6.2)	2 (14.3)	6 (9.4)	-	-	-	16 (9.5)	1 (2.3)	1 (2.9)	1 (11.1)	
unknown	1 (2.0)	0 (0.0)	1 (6.2)	0 (0.0)	2 (3.1)	-	-	-	6 (3.6)	0 (0.0)	0 (0.0)	1 (11.1)	
Dialysis mode						-	-	-					NaN
HD	25 (50.0)	31 (75.6)	10 (62.5)	12 (85.7)	26 (40.6)	-	-	-	100 (59.5)	35 (81.4)	20 (58.8)	8 (88.9)	
PD	21 (42.0)	6 (14.6)	3 (18.8)	2 (14.3)	23 (35.9)	-	-	-	55 (32.7)	4 (9.3)	13 (38.2)	1 (11.1)	
predialysis	4 (8.0)	4 (9.8)	3 (18.8)	0 (0.0)	15 (23.4)	-	-	-	13 (7.7)	4 (9.3)	1 (2.9)	0 (0.0)	
Dialysis vintage (years)	3.33 (2.27)	3.51 (3.80)	3.54 (3.26)	5.00 (2.75)	1.77 (2.36)	-	-	-	3.19 (2.52)	4.13 (3.50)	3.85 (2.89)	4.14 (2.62)	<0.001
Comorbid DM = 1	22 (44.0)	24 (58.5)	7 (43.8)	11 (78.6)	24 (37.5)	-	-	-	72 (42.9)	27 (62.8)	21 (61.8)	7 (77.8)	NaN
Comorbid HTN = 1	42 (84.0)	32 (78.0)	10 (62.5)	12 (85.7)	43 (67.2)	-	-	-	127 (75.6)	32 (74.4)	26 (76.5)	7 (77.8)	NaN
Systolic BP (mmHg)	133.71 (19.98)	132.34 (13.58)	137.40 (16.95)	142.14 (26.05)	133.39 (18.90)	-	-	-	130.91 (15.44)	135.98 (19.59)	129.53 (19.72)	120.88 (20.78)	0.122
Diastolic BP (mmHg)	78.58 (12.24)	74.95 (8.43)	80.07 (8.42)	78.64 (17.10)	80.03 (11.11)	-	-	-	78.31 (10.56)	75.03 (12.86)	71.31 (11.69)	68.38 (14.18)	0.003
MAP (mmHg)	96.88 (12.46)	94.15 (7.69)	98.92 (8.39)	99.81 (18.92)	97.60 (12.00)	-	-	-	95.80 (10.85)	95.32 (13.11)	90.97 (11.80)	86.89 (14.66)	0.034
Panel reactive antibody (%)	29.94 (35.82)	28.32 (30.13)	37.14 (36.87)	28.36 (34.44)	24.24 (30.57)	-	-	-	26.93 (32.27)	29.18 (36.25)	37.34 (38.64)	33.07 (41.34)	0.769
Donor pre-transplant parameters													
Age (years)	38.25 (16.78)	49.15 (12.49)	59.88 (6.40)	61.92 (8.47)	50.05 (12.85)	-	-	-	37.59 (13.70)	38.17 (12.80)	53.57 (15.65)	63.12 (13.77)	<0.001
Sex = 1	29 (72.5)	24 (72.7)	4 (50.0)	9 (75.0)	25 (40.3)	-	-	-	76 (66.1)	18 (51.4)	12 (52.2)	3 (37.5)	NaN
Left kidney = 1	29 (72.5)	15 (45.5)	4 (50.0)	6 (50.0)	62 (100.0)	-	-	-	59 (51.8)	15 (42.9)	9 (37.5)	3 (37.5)	NaN
Comorbid DM = 1	1 (2.9)	3 (9.7)	2 (25.0)	0 (0.0)	0 (0.0)	-	-	-	9 (8.0)	5 (14.3)	2 (10.0)	1 (12.5)	NaN
Comorbid HTN = 1	4 (11.8)	7 (22.6)	3 (37.5)	6 (50.0)	0 (0.0)	-	-	-	9 (8.3)	8 (23.5)	11 (55.0)	2 (28.6)	NaN
Terminal creatinine	73.87 (60.00)	75.71 (36.26)	105.25 (59.50)	81.92 (53.12)	73.05 (16.25)	-	-	-	96.58 (86.90)	153.72 (165.44)	84.24 (45.90)	89.25 (20.89)	0.001
Systolic BP (mmHg)	129.22 (21.23)	137.20 (24.69)	133.12 (24.90)	132.58 (23.08)	117.30 (10.20)	-	-	-	136.79 (18.84)	135.34 (17.67)	141.55 (16.25)	128.50 (18.39)	0.001
Diastolic BP (mmHg)	70.97 (12.81)	70.87 (12.69)	69.50 (19.67)	66.08 (13.59)	73.83 (6.89)	-	-	-	75.50 (12.84)	76.17 (11.78)	75.20 (15.26)	67.38 (10.39)	0.083
MAP (mmHg)	90.39 (14.78)	92.98 (15.60)	90.71 (19.19)	88.25 (15.51)	88.32 (7.24)	-	-	-	95.93 (13.11)	95.90 (11.96)	97.32 (13.62)	87.75 (12.17)	0.056
Surgical timelines													
ECD = 1	0 (0.0)	0 (0.0)	16 (100.0)	14 (100.0)	0 (0.0)	-	-	-	0 (0.0)	0 (0.0)	34 (100.0)	9 (100.0)	NaN
Operative time (min)	213.48 (36.89)	223.59 (41.49)	207.19 (29.87)	225.36 (30.97)	193.09 (42.05)	-	-	-	201.12 (40.01)	213.98 (38.96)	202.88 (32.71)	246.78 (65.96)	<0.001
Cold ischemia time (min)	638.62 (319.24)	677.88 (356.48)	790.56 (901.23)	626.71 (310.60)	234.23 (101.13)	-	-	-	547.17 (249.94)	544.79 (242.60)	537.44 (222.27)	845.67 (408.27)	<0.001
Anastomosis time (min)	33.60 (7.86)	35.22 (7.56)	35.80 (11.37)	37.55 (5.22)	32.74 (12.08)	-	-	-	33.33 (6.79)	34.79 (6.96)	40.59 (18.78)	42.29 (10.03)	0.003
Hemodynamic parameters													
Blood loss (mL)	203.33 (210.88)	160.00 (101.20)	135.71 (98.80)	333.33 (460.30)	121.35 (87.06)	-	-	-	147.68 (114.87)	149.14 (87.24)	133.33 (72.76)	158.33 (80.10)	0.008
Avg. SBP whole op.	123.56 (14.24)	119.21 (11.94)	120.56 (9.69)	114.08 (11.13)	122.34 (16.41)	-	-	-	121.38 (12.30)	119.74 (12.71)	126.96 (13.61)	127.34 (13.86)	0.055
Avg. SBP after anast.	121.39 (14.04)	117.09 (10.46)	117.13 (10.93)	110.15 (11.17)	122.98 (24.15)	-	-	-	119.98 (12.05)	117.58 (13.77)	122.40 (14.64)	124.40 (11.88)	0.080
Avg. SBP whole op.	64.14 (7.82)	59.36 (7.31)	62.06 (6.78)	58.70 (6.93)	64.58 (7.65)	-	-	-	63.66 (7.68)	60.91 (6.20)	62.79 (6.07)	63.03 (10.21)	0.003
Avg. DBP after anast.	62.12 (7.55)	57.06 (6.41)	60.03 (6.61)	57.53 (6.87)	62.26 (9.30)	-	-	-	61.14 (7.59)	58.67 (6.73)	59.42 (5.65)	61.07 (7.64)	0.007
Avg. MAP whole op.	83.94 (8.89)	79.31 (7.68)	81.56 (5.63)	77.16 (7.71)	83.84 (8.90)	-	-	-	82.89 (8.15)	80.52 (7.31)	84.18 (7.18)	84.46 (10.90)	0.009
Avg. MAP after anast.	81.87 (8.31)	77.07 (6.41)	79.06 (6.54)	75.07 (7.77)	82.50 (12.05)	-	-	-	80.73 (7.76)	78.31 (7.98)	80.42 (7.05)	82.18 (7.96)	0.008
Avg. HR whole op.	67.75 (10.17)	66.43 (9.76)	65.08 (5.39)	69.13 (13.36)	69.89 (10.98)	-	-	-	69.76 (9.42)	66.02 (10.57)	66.34 (9.91)	67.19 (10.70)	0.152
Avg. HR after anast.	67.50 (9.62)	67.13 (10.14)	65.47 (5.74)	68.38 (15.59)	71.63 (13.42)	-	-	-	70.44 (10.74)	66.40 (10.35)	66.04 (10.86)	69.59 (13.61)	0.064
Medications and fluids													
Area under MAP=75	9.14 (11.48)	10.05 (13.12)	5.77 (6.57)	8.14 (12.01)	5.94 (5.59)	-	-	-	7.00 (7.38)	6.64 (6.36)	6.65 (6.14)	8.16 (10.05)	0.284
Ephedrine used = 1	23 (46.0)	27 (65.9)	7 (43.8)	8 (57.1)	26 (40.6)	-	-	-	82 (48.8)	23 (53.5)	13 (38.2)	3 (33.3)	NaN
Phenylephrine used = 1	26 (52.0)	26 (63.4)	4 (25.0)	7 (50.0)	23 (35.9)	-	-	-	77 (45.8)	22 (51.2)	17 (50.0)	5 (55.6)	NaN
Norepinephrine used = 1	7 (14.0)	7 (17.1)	3 (18.8)	4 (28.6)	1 (1.6)	-	-	-	11 (6.5)	2 (4.7)	3 (8.8)	3 (33.3)	NaN
Vasopressin used = 1	0 (0.0)	3 (7.3)	0 (0.0)	0 (0.0)	1 (1.6)	-	-	-	0 (0.0)	2 (4.7)	1 (2.9)	0 (0.0)	NaN
Any pressor used = 1	35 (70.0)	36 (87.8)	10 (62.5)	13 (92.9)	37 (57.8)	-	-	-	112 (66.7)	33 (76.7)	23 (67.6)	7 (77.8)	NaN
Avg. MAP at pressor use	75.41 (7.74)	75.23 (9.59)	74.82 (7.63)	72.20 (10.26)	77.60 (9.28)	-	-	-	77.23 (10.25)	77.21 (11.49)	78.88 (10.40)	79.52 (11.07)	0.556
IV fluids total	2554.76 (1098.72)	2586.19 (1000.22)	2728.33 (1123.84)	2898.87 (1224.56)	2465.42 (1091.86)	-	-	-	2275.74 (1066.86)	2508.08 (1194.18)	2916.67 (941.13)	3114.42 (1023.21)	0.021
IV fluids (cc/kg/min)	0.93 (0.35)	0.85 (0.34)	0.98 (0.42)	0.83 (0.40)	0.91 (0.37)	-	-	-	0.84 (0.43)	0.93 (0.46)	1.13 (0.42)	0.78 (0.31)	0.092

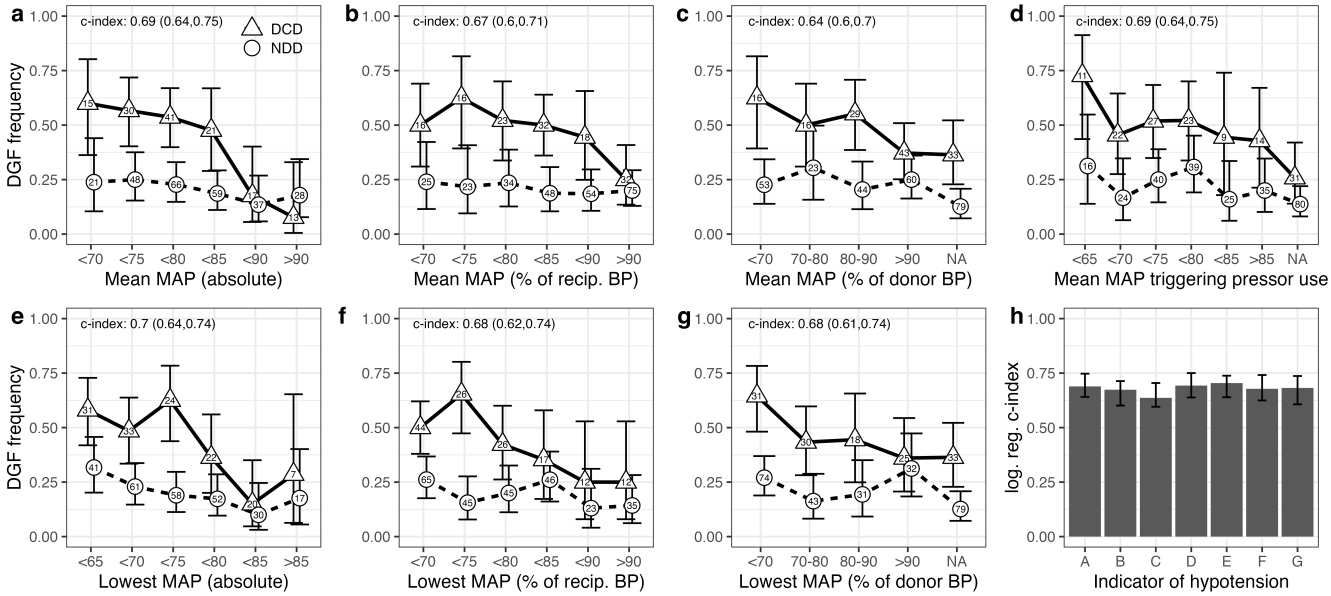


Figure 2. Incidence proportions of delayed graft function (DGF, y-axis) in association with various measures of absolute and relative hypotension, post-vascular anastomosis, in NDD (circles) and DCD (triangles) grafts. Graphs in the first row (A, B, C) plot average MAP in the entire post anastomosis phase, and graphs in the second row (E, F, G) plot the lowest MAP in the post anastomosis phase. Graphs in the first column (A, E) plot “absolute" hypotension; graphs in the second column (B, F) plot “relative" hypotension, as a percentage of the recipient’s baseline blood pressure (BP); graphs in the third column (C, G) plot hypotension relative to donor BP donor prior to procurement. (Missing data are placed in the NA category on the x-axis.) Graph D separately measures the average MAP when pressors were initiated (if not initiated, they are placed in the NA category), and the DGF incidence proportion for various values of the average “trigger threshold". Numbers inside the point markers indicate the number of patients (sample size) contributing to the estimate for the data point. Error bars indicate the 90% confidence interval for the estimate. Graph H plots the concordance indexes calculated from logistic regression with the hypotension indicator as the independent variable, DCD/NDD status as a covariate, and DGF incidence as the outcome. Confidence intervals for *H* are 97.5th percentile intervals generated via 100-fold bootstrap. All methods of operationalizing hypotension for analysis perform equally well for predicting DGF in bootstrapped concordance analysis, with overlapping confidence intervals in graph H.

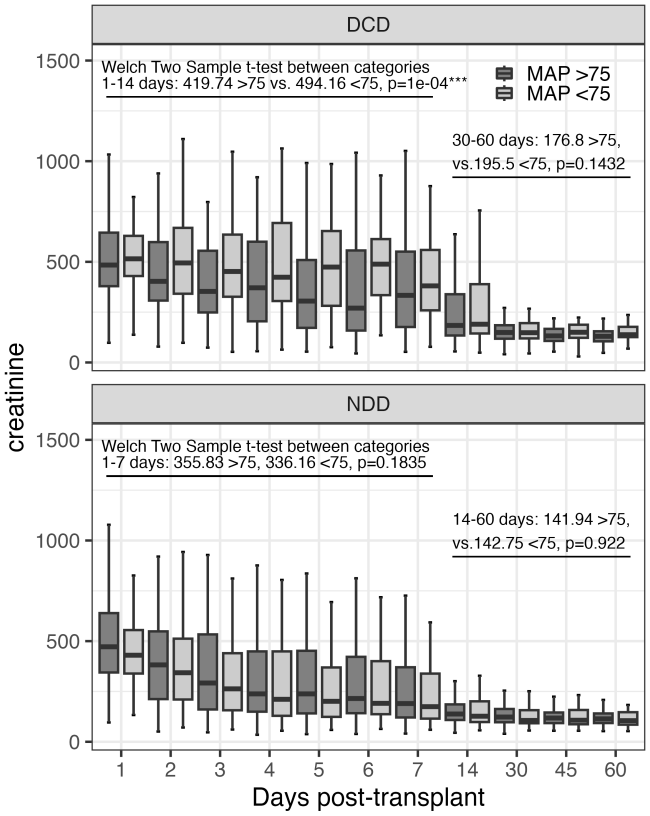
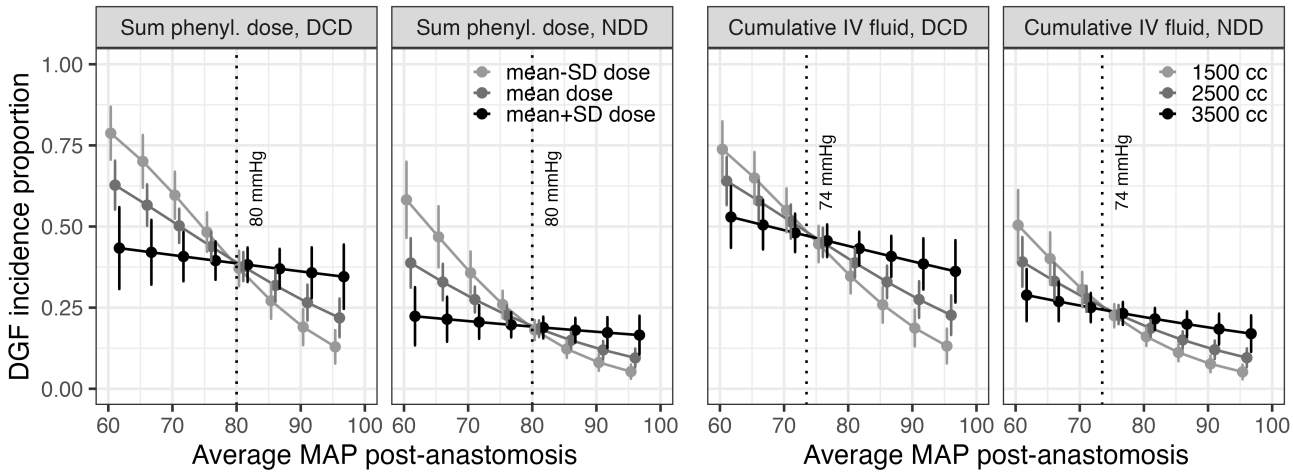


Figure 3. Chart of serum creatinine (sCr) serially measured from 1 to 60 days post transplant, facetted between DCD and NDD kidney recipients. Welch's two sample t-tests are performed for differences in average sCr between recipients who maintained an average MAP above 75 mmHg post anastomosis, and recipients who fell below this pressure goal. T-tests are conducted separately for average sCr in the 1-7 day range, and average creatinine between days 14, 30, 45, and 60. There is a significant difference in average sCr early post-transplant in DCD recipients (419.7 in MAP<75 vs. 494.16 in MAP>75, $p<0.001$) in the first seven days, but this difference does not persist later post-transplant, 14-60 days. Error bars indicate minimum/maximum ranges.



	OR [95% conf. int.]	p-value
Avg. MAP (5 mmHg)	0.94 [0.90, 0.97]	<0.001
Sum phenyl. (100 mcg)	0.83 [0.69, 0.96]	0.022
Donor type (NDD)	0.38 [0.24, 0.60]	<0.001
Recipient age (years)	1.02 [1.00, 1.04]	0.074
Recipient sex (M)	1.53 [0.95, 2.50]	0.086
MAP*phenyl	1.00 [1.00, 1.00]	0.020

	OR [95% conf. int.]	p-value
Avg. MAP (5 mmHg)	0.88 [0.81, 0.95]	0.001
Sum IVF (100 mL)	0.79 [0.63, 0.97]	0.027
Donor type (NDD)	0.36 [0.23, 0.57]	<0.001
Recipient age (years)	1.01 [0.99, 1.03]	0.171
Recipient sex (M)	1.46 [0.91, 2.38]	0.123
MAP*IVF	1.00 [1.00, 1.01]	0.021

Figure 4. Multiple logistic regression with interaction terms. This analysis depicts the modifiying effect of intraoperative cumulative phenylephrine dose and cumulative IV crystalloid on the relationship between average post-anastomosis MAP and incidence of DGF. Intersection between modified risk curves is indicated by dotted line. Analysis facetted between DCD and NDD recipients. Intercept omitted from multiple logistic regression summary output for clarity. Error bars indicate SEM for the DGF proportion estimate.