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=609) in conjunction with pre-transplant characteristics and post-surgical outcomes, including DGF incidence, 60-day creatinine trends, and graft survival. 127 DGF events were captured in our cohort derived from a single academic medical center (57/276 NDDs, 65/150 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 Transplant procedure

The majority of procedures were performed by CN as the lead surgeon. Warm ischemia time was eliminated by wrapping the donor kidney in an ice pack during the anastomosis itself prior to parachuting the kidney into the iliac fossa. [Write down indications for biopsies in the post-transplant period.] [Write down any other details about the surgeries as required.]

2.3 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.

2.4 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 **??**).

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. Lastly, mean map triggering pressor use (graph D, fig. 2) is a value calculated from the average MAP at the use of pressor bolus, or the first MAP at the start of an pressor infusion. 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.

2.5 Missing data and outliers

Various forms of missing data were handled differently in analyses. Missing time series hemodynamic and medications data, or data that were reocrded deliberately at <5 minute intervals were forward filled from the last available value. Missing medication dosing information were manually reviewed with reasonable dose ranges selected by reviewers blinded to patient outcomes. Missing times of anastomosis were mean imputed per the averages for each donor source. All other missing data were excluded from respective analyses. Regarding outliers, all available data were manually inspected, and no specific outlier handling such as exclusion based on percentiles or otherwise was performed.

3 Results

3.1 Baseline characteristics

The patient cohort's general characteristics are outlined in table **??**. 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 MAP (88.9 ± 8.41 *vs.* 95.2 ± 7.3, p=0.10), although this was not statistically significant.

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

Fig. 3 depicts creatinine recovery post transplant between those maintaining an average MAP of greater than and lesser than 75 mmHg post anastomosis during their surgeries. Creatinine recovery was significantly different between these two groups only in the first seven days post-transplant in the DCD kidney recipients, 419.74 *vs.* 494.16, p<0.001. Average creatinine equalized early afterwards in the 14-60 day measurements. In NDD recipients, there was no statistically significant difference between the two groups in either early or late postoperative phases. Included in extended data (Fig. **??**) are a series of Kaplan-Meier curves showcasing 5-year graft survival across levels of hypotension in an analysis facetted across DCD, LD and NDD recipients. No significant difference or trend towards difference in long-term graft survival is noted in survival analysis.

3.5 Timing of pressors, IV fluids

In multiple logistic regression analysis on our cohort, we observed that post-anastomosis hypotension (specifically, average post-anastomosis MAP) represented an powerful determinant of DGF incidence as compared to typical predictors, including DCD/NDD status, and recipient age and sex. Post-anastomosis hypotension is noted again to be a greater risk factor for DGF in DCD kidneys over NDD kidneys. An interaction term was included in the multiple regression for phenylephrine and cumulative crystalloid infused during the surgery, and the marginal risk effects were plotted for mean, mean-SD, and mean+SD values of phenylephrine and cumulative IV fluid on the estimated relationship between hypotension and DGF incidence. We observe that there is an intersection point at 75 mmHg of the marginal effects risk curves for phenylephrine use and crystalloid dose. At MAPs lower than this intersection point, the model estimates that increasing doses of pressors and crystalloid lower the risk of DGF. However, at MAPs higher than 75, doses of pressors and cryatalloid higher than the mean were correlated with increased DGF incidence. The mean quantity of phenylephrine provided was 400 mcg, and the mean + 1 standard deviation dose of phenylephrine in included surgeries was approximately 1300 mcg. The mean quantity of crystalloid infused intraoperatively was 2500 mcg, and the mean $\pm$ 1 standard deviation dose for IV fluids in included surgeries was approximately 1500-3500 mcg.

Discussion

DGF is recognized as a common complication of solid organ transplantation requiring extensive inpatient management, especially in marginal donor kidneys. The pre-operative clinical donor and recipient risk factors, such as donor source and

terminal creatinine, recipient age and sex are well characterised, but the role of features of intraoperative management are less well investigated to this end.

Intraoperative blood pressure targets have previously been investigated in the domain of transplantation. Thomas et al.[10] identified an SBP target of 120 mmHg post-perfusion on the basis that 50% of patients in that study with BP lower than this experienced DGF. More recent retrospective single-center data from Kaufmann et al.[11] indicated, similar to our current analysis, that in DCDs maintaining post-anastomosis MAP<80 was associated with 2.4-fold increased risk for DGF.

The specific strategies available to transplant anesthesia for targeting post-anastomosis hypotension remain controversial. Adjustment of vasopressors and fluid provision must balance the risk of underrescuscitation with the benefit of maintaining sufficient driving pressure in a post-ischemic donor kidney. Older studies in fluid administration in kidney transplantation advocated for maximum volume infusion[12–14]. However, this can lead to excess fluid infusion, which can damage the endothelial glycocalyx and lead to a fluid shift into the interstitial space[15]. Accordingly, more recent investigations, including a multicenter study, largely indicate the superiority of more moderate fluid regimens[11,15,16].

One novel finding in this study is the delineation of blood pressure ranges in which increased phenylephrine/vasopressor use or IV crystalloid use associates more heavily with DGF incidence through inspection of interaction terms analysis. In our cohort the use of increased doses of crystalloid and phenylephrine (at or above mean dose + 1 standard deviation) below a MAP of 75 associated with decreased DGF, but beyond a MAP of 75 mmHg was associated with increased DGF incidence, ultimately supporting the concept that while the use of pressors and fluids to drive blood pressure to an acceptable minimum is critical, the use of these medications to drive pressure higher than this target may not be appropriate.

Outside of the domain of transplantation, several studies have demonstrated intraoperative hypotension to be associated with myocardial injury, acute kidney injury, and mortality[17–19]. 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[20]. Furthermore, it states that that postoperative injury is a function of both time spent having hypotension and depth of hypotension, making various operationalizations of hypotension, such as intraoperative minimums of BP or time-weighted averages, end-points of particular interest[20]. Salmasi et al. while investigating the relationship between intraoperative hypotension and incidence of post-operative AKI through similar analysis of surgical time-series (excluding transplant surgeries), undertook multiple approaches to operationalize hypotension, looking at absolute and relative thresholds for BP[21]. In their study both absolute and relative thresholds had comparable ability to predict the incidence of AKI postoperatively, and that there was no clinically relevant interaction with preoperative patient baselines. In our cohort we were able to also investigate the prognostic ability for various measures of hypotension, including lowest and mean post-anastomosis MAP, including individualized blood pressure targets based on pre-operative recipient BP pre-procurement donor BP. The associations based on relative thresholds were no stronger than those based on absolute thresholds. In recipients of kidneys from live donors there appeared to be a trend towards improved predictive capacity when using percentage of donor baseline BP as a target for DGF prediction, but this analysis was limited due to the scant incidence of DGF in live donors. There was however an observed trend wherein patients with DGF on average had donors with higher baseline MAP (88.9 ± 8.41 *vs.* 95.2 ± 7.3, p=0.10), suggesting that there may be value in targeting higher blood pressures in recipients of kidneys from chronically hypertensive donors. Anesthetic management can thus likely be based on absolute intraoperative pressures without regard to preoperative donor and recipient pressure in DCDs and NDDs, although in LDs it may be advisable to set higher targets based on the donor BP.

The findings of this trial add to the evidence (or lack thereof) of benefits of personalizing care, especially in higher-risk recipients of DCD kidneys. 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.

Some strengths of this analysis include the emphasis on commonly measured intraoperative variables (SBP, DBP, MAP), and the use of averages on specific periods of granular time-series data in the analysis, improving internal validity. This analysis is, to our knowledge, the first to investigate specifically into specific dose ranges of vasopressors and IV fluids and the interaction between interventions and MAP. Furthermore, this study investigates multiple short as well as long-term outcomes, including 60-day serial creatinine and time to graft failure, and multiple methods of operationalizing hypotension in the post-anastomosis phase, uniquely enabled by the time-series nature of the analysis, increasing the internal validity of the study. The internal validity is also increased via the measurement of sustained averages of hemodynamic parameters throughout entire time periods of observations as opposed to single measurements taken after the point of anastomosis.

This analysis does carry multiple limitations. First, this is a retrospective analysis, largely hypothesis-generating rather than capable of establishing causality. Second, the analysis uses data entirely from a single center, impacting the external validity

and generalizability of the results. Any inferences on LD recipients are also limited as there were only 5 DGF events in this cohort. Finally, the hemodynamics in the post-emergence period were not captured for analysis.

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Author contributions statement

RM and CN conceived the analyses. RM conducted the data analyses. RM 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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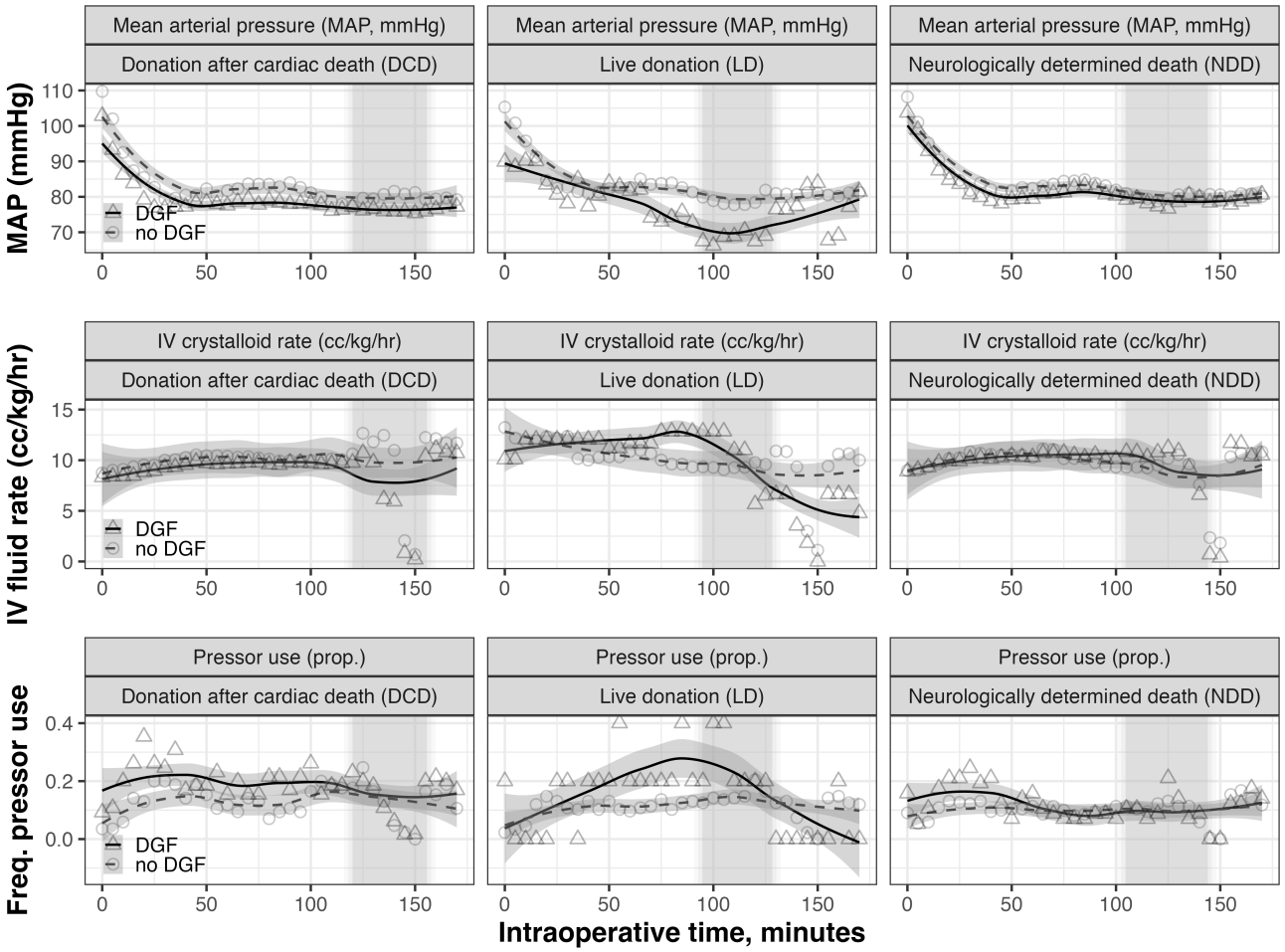


Figure 1. Graphs of average intraoperative time courses for mean arterial pressures, IV crystalloid infusion rates, and frequency of pressor use. MAP (mmHg), IV rate per bodyweight (cc/kg/hr), and use of pressors were measured in 5 minute intervals. The time series were 'warped' (i.e. compressed or stretched 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	85	65	176	5	221	57	
Recipient pre-transplant parameters							
Age (years)	58.88 (12.37)	59.26 (12.07)	50.14 (15.16)	45.72 (11.34)	53.61 (14.00)	57.04 (11.34)	<0.001
Sex = M	51 (60.0)	44 (67.7)	111 (63.1)	2 (40.0)	140 (63.3)	41 (71.9)	0.567
Race/Ethnicity							<0.001
Black	4 (4.7)	0 (0.0)	1 (0.6)	0 (0.0)	3 (1.4)	1 (1.8)	
East Asian	20 (23.5)	21 (32.3)	34 (19.3)	0 (0.0)	57 (25.8)	17 (29.8)	
Hispanic	0 (0.0)	1 (1.5)	2 (1.1)	0 (0.0)	4 (1.8)	4 (7.0)	
Indigenous	3 (3.5)	0 (0.0)	5 (2.8)	0 (0.0)	6 (2.7)	1 (1.8)	
Other	2 (2.4)	1 (1.5)	0 (0.0)	0 (0.0)	5 (2.3)	0 (0.0)	
Pacific Islander	0 (0.0)	4 (6.2)	0 (0.0)	0 (0.0)	3 (1.4)	0 (0.0)	
South Asian	19 (22.4)	13 (20.0)	22 (12.5)	1 (20.0)	59 (26.7)	16 (28.1)	
White	36 (42.4)	23 (35.4)	110 (62.5)	4 (80.0)	82 (37.1)	18 (31.6)	
BMI (kg/m^2)	26.05 (4.86)	26.71 (5.44)	26.33 (5.27)	24.98 (6.81)	26.02 (5.29)	27.66 (5.46)	0.382
Cause of ESRD							0.008
DN	24 (28.2)	27 (41.5)	46 (26.1)	1 (20.0)	63 (28.5)	25 (43.9)	
GN	21 (24.7)	23 (35.4)	68 (38.6)	2 (40.0)	67 (30.3)	17 (29.8)	
HTN	18 (21.2)	5 (7.7)	12 (6.8)	1 (20.0)	32 (14.5)	7 (12.3)	
other	14 (16.5)	1 (1.5)	31 (17.6)	1 (20.0)	32 (14.5)	5 (8.8)	
PCKD	6 (7.1)	9 (13.8)	17 (9.7)	0 (0.0)	18 (8.1)	2 (3.5)	
unknown	2 (2.4)	0 (0.0)	2 (1.1)	0 (0.0)	9 (4.1)	1 (1.8)	
Dialysis mode							<0.001
HD	48 (56.5)	49 (75.4)	59 (33.5)	5 (100.0)	131 (59.3)	47 (82.5)	
PD	29 (34.1)	11 (16.9)	53 (30.1)	0 (0.0)	74 (33.5)	5 (8.8)	
predialysis	8 (9.4)	5 (7.7)	64 (36.4)	0 (0.0)	16 (7.2)	5 (8.8)	
Dialysis vintage (years)	3.58 (2.66)	3.96 (3.92)	1.10 (1.69)	1.83 (1.24)	3.32 (2.75)	3.96 (3.25)	<0.001
Comorbid DM = 1	37 (43.5)	39 (60.0)	74 (42.0)	2 (50.0)	101 (45.7)	34 (59.6)	0.066
Comorbid HTN = 1	67 (78.8)	52 (80.0)	139 (79.0)	2 (40.0)	168 (76.0)	42 (73.7)	0.388
Systolic BP (mmHg)	133.67 (20.71)	134.45 (17.30)	134.57 (17.64)	117.00 (15.65)	131.38 (16.82)	134.83 (20.90)	0.166
Diastolic BP (mmHg)	78.37 (11.41)	76.73 (11.58)	78.36 (11.10)	64.00 (8.94)	77.54 (10.94)	74.30 (12.66)	0.024
MAP (mmHg)	96.67 (12.13)	95.90 (11.39)	96.99 (11.33)	81.67 (8.98)	95.46 (11.16)	94.51 (13.43)	0.061
Panel reactive antibody (%)	33.26 (37.12)	32.04 (34.22)	25.85 (30.61)	65.95 (39.30)	28.87 (34.06)	29.94 (35.75)	0.109
Donor pre-transplant parameters							
Age (years)	43.16 (16.60)	51.06 (13.70)	50.65 (12.30)	52.20 (9.42)	40.48 (15.09)	42.59 (15.76)	<0.001
Sex = 1	42 (66.7)	38 (70.4)	54 (39.1)	1 (20.0)	95 (64.2)	23 (50.0)	<0.001
Left kidney = 1	37 (58.7)	26 (48.1)	137 (99.3)	5 (100.0)	74 (50.0)	19 (41.3)	<0.001
Comorbid DM = 1	5 (8.6)	4 (7.7)	0 (0.0)	0 (NaN)	12 (8.5)	7 (15.2)	NaN
Comorbid HTN = 1	12 (21.1)	17 (32.7)	1 (50.0)	0 (NaN)	22 (15.9)	12 (27.3)	NaN
Terminal creatinine	79.67 (56.41)	85.15 (57.37)	74.20 (15.77)	72.40 (3.36)	95.90 (82.45)	140.18 (147.56)	<0.001
Systolic BP (mmHg)	128.30 (21.59)	135.00 (24.57)	118.29 (13.21)	117.50 (10.61)	137.27 (18.15)	135.39 (18.04)	<0.001
Diastolic BP (mmHg)	70.37 (13.01)	69.02 (12.68)	74.49 (7.91)	84.00 (5.66)	75.55 (13.24)	75.00 (12.13)	0.004
MAP (mmHg)	89.68 (14.52)	91.01 (15.41)	88.92 (8.41)	95.17 (7.31)	96.12 (13.02)	95.13 (12.36)	0.001
ECD = 1	18 (24.0)	15 (26.3)	0 (0.0)	0 (0.0)	34 (16.2)	10 (18.9)	<0.001
Surgical timelines							
Operative time (min)	209.54 (40.78)	226.82 (42.76)	184.17 (40.39)	254.20 (93.93)	201.70 (39.66)	217.39 (48.24)	<0.001
Cold ischemia time (min)	680.42 (477.80)	669.74 (347.76)	249.53 (104.65)	363.40 (182.46)	538.01 (249.37)	622.11 (313.78)	<0.001
Anastomosis time (min)	34.78 (10.46)	36.27 (7.10)	34.29 (12.75)	47.75 (6.95)	34.25 (9.84)	36.34 (7.71)	0.098
Blood loss (mL)	193.42 (193.53)	195.12 (235.53)	148.89 (224.63)	400.00 (360.56)	145.13 (107.90)	149.26 (85.83)	0.091
Hemodynamic parameters							
Avg. SBP whole op.	121.06 (13.03)	117.64 (11.90)	120.69 (13.36)	110.41 (23.05)	122.13 (12.75)	120.88 (13.01)	0.097
Avg. SBP after anast.	118.77 (13.23)	115.21 (11.64)	120.79 (17.66)	112.09 (23.97)	120.20 (12.92)	118.59 (13.33)	0.099
Avg. SBP whole op.	62.81 (7.62)	59.05 (6.77)	63.60 (7.74)	59.58 (9.32)	63.44 (7.42)	61.21 (6.94)	<0.001
Avg. DBP after anast.	60.76 (7.52)	57.02 (6.37)	61.51 (8.50)	59.20 (9.21)	60.76 (7.31)	58.99 (6.95)	0.002
Avg. MAP whole op.	82.22 (8.14)	78.58 (7.33)	82.53 (8.57)	76.52 (13.35)	83.00 (8.03)	81.10 (7.88)	0.003
Avg. MAP after anast.	80.10 (8.06)	76.42 (6.78)	81.03 (10.38)	76.83 (13.83)	80.56 (7.82)	78.86 (7.90)	0.006
Avg. HR whole op.	67.70 (9.11)	66.81 (10.75)	70.04 (10.85)	77.18 (8.09)	69.20 (9.64)	65.72 (10.67)	0.012
Avg. HR after anast.	67.72 (9.16)	67.38 (11.68)	70.39 (12.07)	82.10 (12.00)	69.74 (10.97)	66.61 (11.13)	0.010
Area under MAP=75	7.60 (9.71)	9.29 (12.04)	7.62 (8.55)	12.24 (15.96)	7.12 (8.26)	6.89 (6.77)	0.462
Medications and fluids							
Ephedrine used = 1	41 (48.2)	41 (63.1)	71 (40.3)	1 (20.0)	100 (45.2)	31 (54.4)	0.024
Phenylephrine used = 1	42 (49.4)	37 (56.9)	78 (44.3)	4 (80.0)	101 (45.7)	29 (50.9)	0.327
Norepinephrine used = 1	15 (17.6)	13 (20.0)	4 (2.3)	2 (40.0)	19 (8.6)	8 (14.0)	<0.001
Vasopressin used = 1	0 (0.0)	3 (4.6)	2 (1.1)	0 (0.0)	1 (0.5)	2 (3.5)	0.073
Any pressor used = 1	61 (71.8)	56 (86.2)	110 (62.5)	4 (80.0)	145 (65.6)	44 (77.2)	0.007
Avg. MAP at pressor use	75.00 (8.25)	73.80 (9.72)	76.13 (10.23)	73.84 (14.97)	77.24 (10.46)	78.29 (11.75)	0.186
IV fluids total	2677.33 (1055.70)	2652.63 (1033.99)	2377.54 (1237.48)	2556.50 (1585.25)	2406.23 (1074.43)	2692.34 (1254.21)	0.140
IV fluids (cc/kg/min)	0.96 (0.38)	0.86 (0.38)	0.87 (0.40)	0.68 (0.34)	0.89 (0.44)	0.96 (0.48)	0.530

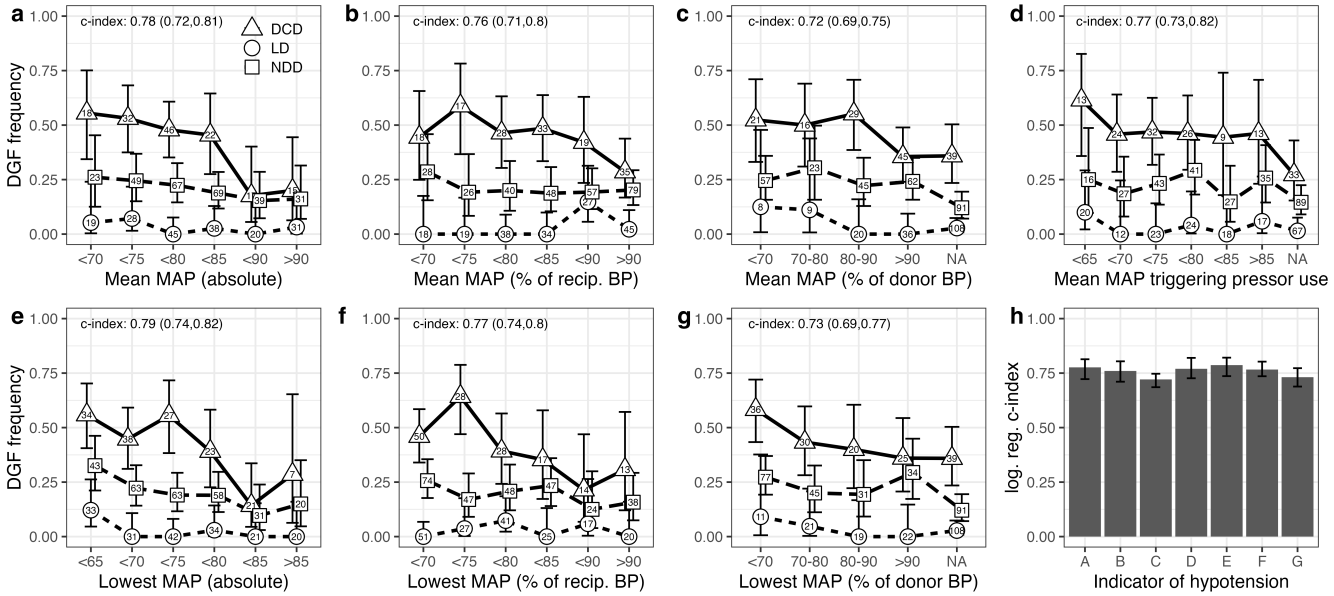


Figure 2. Incidence proportions of delayed graft function (DGF, y-axis) in association with various measures of absolute and relative hypotension, post-vascular anastomosis, in NDD (squares), DCD (triangles), and LD (circles) grafts. Graphs in the first row (A, B, C) plot average MAP in the entire post 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/LD/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.

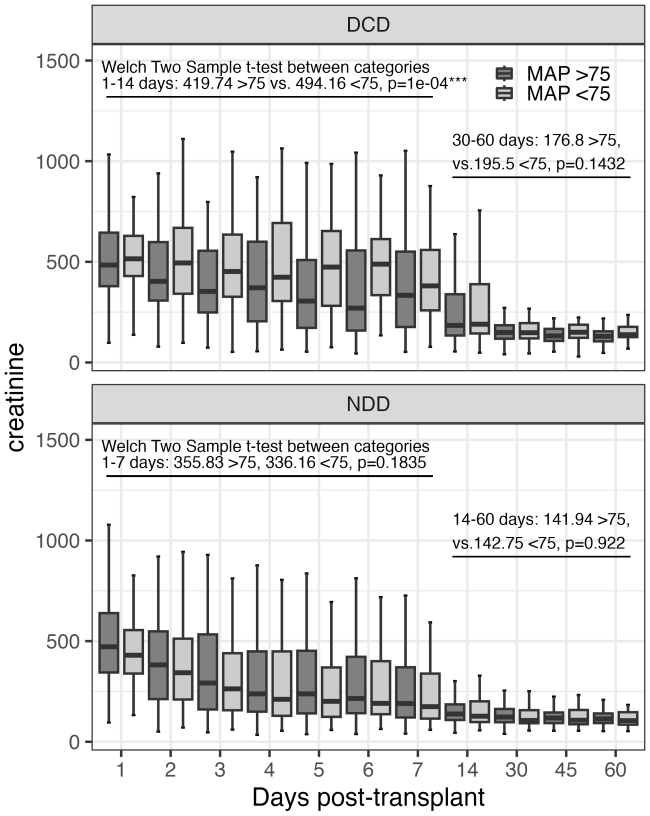
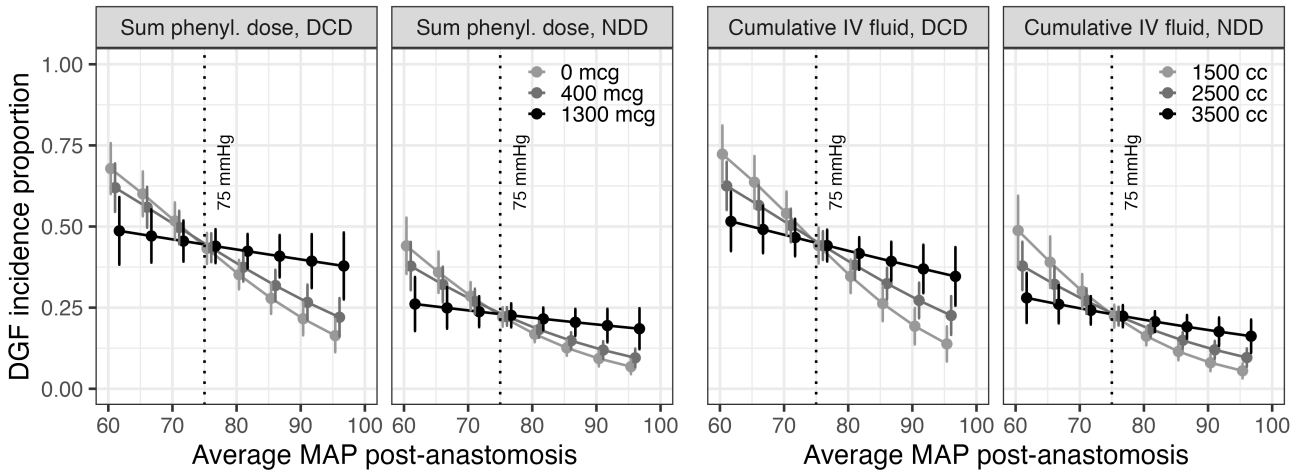


Figure 3. Chart of serum creatinine (sCr) serially measured from 1 to 60 days post transplant, facetted between DCD and NDD kidney recipients. Welch's two sample t-tests are performed for differences in average sCr between recipients who maintained an average MAP above 75 mmHg post anastomosis, and recipients 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)	0.93 [0.90, 0.97]	<0.001
Sum phenyl. (100 mcg)	0.72 [0.54, 0.94]	0.021
Donor type (NDD)	0.37 [0.24, 0.59]	<0.001
Recipient age (years)	1.01 [1.00, 1.03]	0.125
Recipient sex (M)	1.52 [0.95, 2.48]	0.087
MAP*phenyl	1.00 [1.00, 1.01]	0.015

	OR [95% conf. int.]	p-value
Avg. MAP (5 mmHg)	0.88 [0.82, 0.95]	0.001
Sum IVF (100 mL)	0.80 [0.65, 0.98]	0.029
Donor type (NDD)	0.37 [0.23, 0.57]	<0.001
Recipient age (years)	1.01 [0.99, 1.03]	0.211
Recipient sex (M)	1.46 [0.91, 2.36]	0.122
MAP*IVF	1.00 [1.00, 1.01]	0.024

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.

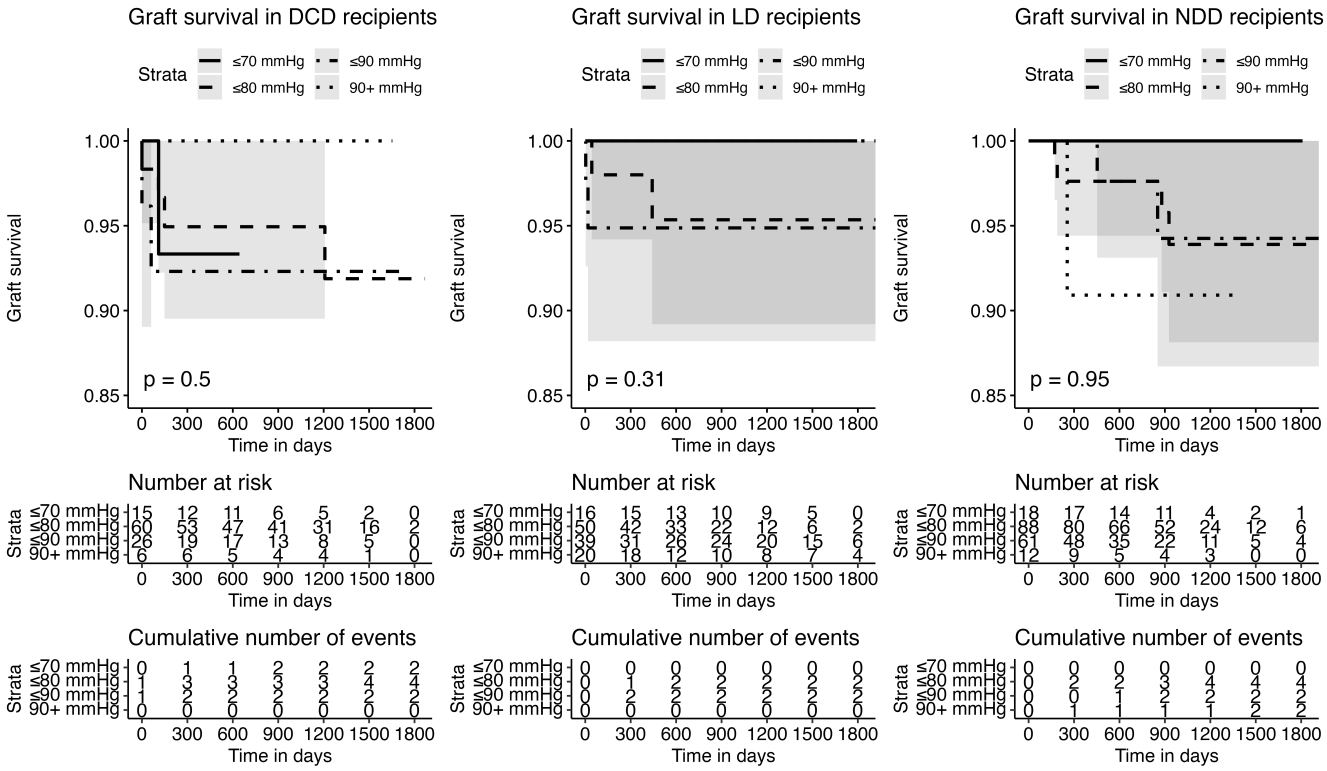


Figure 5. Extended data: Kaplan-Meier survival curves for graft survival across categories of post-anastomosis hypotension as measured by average MAP. Analysis is facetted between DCD and NDD recipients. P-values account for trend across ordered categories. Error ribbons indicate 95% confidence interval for the hazard estimate.