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Transoperative Hemodynamic Status and Delayed Graft Function: Analysis of 42 Consecutive Renal Transplantation

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ABSTRACT

Objective: Evaluate the correlation between transoperative hemodynamic status and development of delayed graft function (DGF) in patients undergoing kidney transplantation. **Methods:** We analyzed 42 consecutive renal transplants between May 2021 and May 2022 in a University Hospital. Four kinds of variables were assessed. Recipients variables: age, gender, race, type of dialysis, dialysis time before transplantation and residual diuresis. Donor variables: age, serum creatinine level, death cause, race, laterality of the kidney (right or left kidney), perfusion solution and Kidney Donor Profile Index (KDPI). Surgical variables: cold Ischemia time (CIT), vascular multiplicity, the surgeon, duration of surgery and blood pressure during the procedure. Immunological variables: Panel reactive antibodies (PRA), HLA mismatches and the need of induction therapy with antithymocyte globulin. **Results:** In univariate analysis, regarding recipients' factors, type of dialysis (hemodyalisis) (p=0.004) and absence of residual diuresis (p=0.011) were significant on the development of DGF. Among the donors, only the laterality of the kidney (right kidney) was statiscally significant (p=0.005). The cold ischemia time higher than 24 hours (p=0.022), systolic blood pressure (SBP) less than 130 mmHg at reperfusion (p<0.001), Mean Arterial Pressure (MAP) less than 80 mmHg at the reperfusion (p<0.001), and mean MAP post-reperfusion (p=0.049) were the significant surgical factors for DGF. Among immunological factors, the patients that received antithymocyte globulin as induction therapy more frequently developed DGF (p=0.036). Only MAP < 80 mmHg (p=0.004) and SBP < 130m mmHg (p=0.005) were independent risk factors for DGF. **Conclusion:** In this survey, optimal renal perfusion, avoiding fall in blood pressure in the transoperative period, especially after graft reperfusion, is crucial for the immediate functioning of the kidney.

Keywords: Kidney Transplantation. Delayed Graft Function. Risk Factors. Hemodynamics.

Status Hemodinâmico Transoperatório e Retardo da Função do Enxerto: Análise de 42 Transplantes Renais Consecutivos

RESUMO

Objetivo: Avaliar a correlação entre o estado hemodinâmico transoperatório e o desenvolvimento da função retardada do enxerto (FRE) em pacientes submetidos a transplante renal. Métodos: Foram analisados 42 transplantes renais consecutivos entre maio de 2021 e maio de 2022 em um Hospital Universitário. Quatro tipos de variáveis foram estudadas. Variáveis relacionadas ao receptor: idade, sexo, raça, tipo de diálise, tempo de diálise antes do transplante e diurese residual. Variáveis relacionadas ao doador: idade, nível de creatinina sérica, causa do óbito, raça, lateralidade do rim (rim direito ou esquerdo), solução de perfusão utilizada e Kidney Donor Profile Index (KDPI). Variáveis cirúrgicas: Tempo de Isquemia Fria (TIF), multiplicidade vascular, cirurgião, duração da cirurgia e pressão arterial durante o procedimento. Variáveis imunológicas: Painéis Reativos de Anticorpos (PRA), incompatibilidades de HLA e necessidade de terapia de indução com timoglobulina. Resultados: Em análise univariada, os fatores

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relacionados significativos foram: tipo de diálise (hemodiálise) (p=0,004) e ausência de diurese residual (p=0,011). Entre os doadores, apenas a lateralidade do rim (rim direito) foi estatisticamente significativa (p=0,005). O tempo de isquemia fria maior que 24 horas (p=0,022), pressão arterial sistólica (PAS) menor que 130 mmHg na reperfusão (p<0,001), pressão arterial média (PAM) menor que 80 mmHg na reperfusão (p<0,001), e a média das PAMs pós-reperfusão (p=0,049) foram os fatores cirúrgicos significativos. Dentre os fatores imunológicos, apenas o uso de timoglobulina foi significativo para FRE (p=0,036). Apenas PAM < 80 mmHg (p=0,004) e PAS < 130m mmHg (p=0,005) foram fatores de risco independentes para FRE. Conclusão: Em nosso estudo, a ótima perfusão renal, evitando a queda da pressão arterial no transoperatório, principalmente após a reperfusão do enxerto, demonstrou ser fundamental para o funcionamento imediato do rim.

Descritores: Transplante Renal. Função Retardada do Enxerto. Fatores de Risco. Fenômenos Hemodinâmicos.

INTRODUCTION

Kidney Transplantation is the treatment of choice in patients with end-stage renal disease. It is associated with better quality of life, better cost/benefit ratio, and possibly longer survival. The Delayed graft function (DGF) is a common complication, and it leads to an increased risk of acute rejection and lower graft survival. In addition, it is associated to prolonged hospitalization time, cost increase and poorer results in long term. Is reasonable that we make effort to minimize this process, since graft longevity and patient survival are directly attached with its occurrence.[1–5]

The incidence of DGF varies across different regions in the world. USA reports 30%, European centers 30-35%. In Australia, the reported incidence of DGF is around 25%. Incidence of DGF in Brazilian centers range from 29% until 87%. We don't have a concern about the definition of DGF in literature, this may explain, in parts the disproportionally incidence.[2,6,7]

Many factors are associated with DGF. Donor factors: female sex, increased age, body mass index (BMI), donation after cardiac death, increased serum creatinine, cause of death, diabetes and hypertension. Recipients factors: male sex, black race, BMI, retransplantation, diabetes, duration and type of dialysis and residual diuresis. Surgery factors: warm and cold ischemia time, perioperative hemodynamics recipient managements, and immunological factors: HLA mismatches and sensitization.[7–11]

There are inconclusive evidences that hemodynamics factors can be associated with DGF. High levels of mean arterial pressure (MAP) at the time of reperfusion seems to be essential and good graft function is described in some studies when MAP is higher than 70mmHg to 108 mmHg.[11–16]

OBJECTIVE

The aim of this study is to evaluate de correlation between intraoperative hemodynamic status and development of DGF in patients undergoing kidney transplantation. Others risk-factors: donor, recipients, surgical and immunological variables were analyzed also.

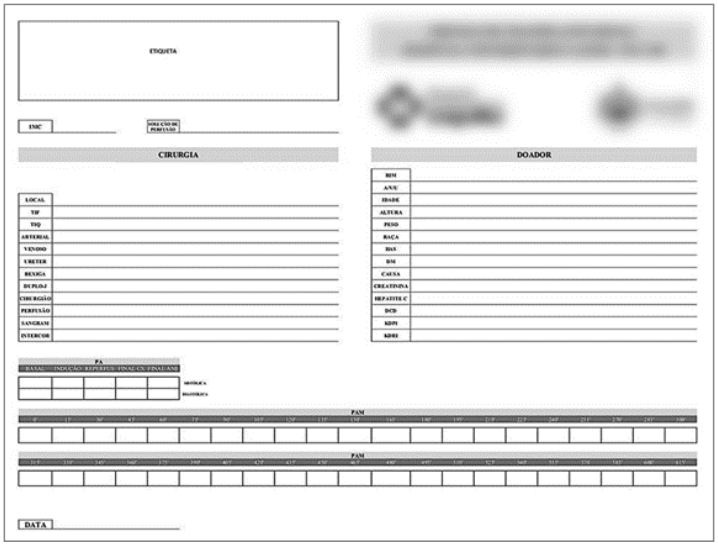
METHODS

This retrospective cohort study was approved by de local ethics committee, in Pontifical Catholic University of Paraná, Brazil (approval number 5.577.570). This paper was designed in accordance with the initiative for Strengthening the Reporting of Observational Studies in Epidemiology, STROBE, using the suggestive checklist for epidemiological cohort studies.[17] We analyzed 42 consecutive renal transplants between may 2021 and may 2022. We excluded five procedures (two venous thrombosis at the third day, both from the same cadaveric donor, one death by coronarian acute event and two living-donor transplantations). Priori sample size was not calculated due to the retrospective design of the study.

The procedures were performed by only four different surgeons. All patients received methylprednisolone intraoperatively, followed by a triple oral immunosuppression with prednisone, mycophenolic acid and tacrolimus target to 5-8 ng/dl. Nine patients, with high risk of rejection, received antithymocyte globulin prior to kidney reperfusion.

DGF was defined by failure of creatinine to fall by 50% in the first week, or the dialysis necessity in the first week, excluding the first day postoperative dialyses to adjust hypervolemia or hyperkalemia. Four kinds of variables were assessed. Recipients variables: age, gender, race, type of dialysis, dialysis time before transplantation and residual diuresis. Donor variables: age, serum creatinine level, race, death cause, laterality of the kidney (right or left kidney), perfusion solution and Kidney Donor Profile Index (KDPI) (calculated at https://optn.trasplant.hrsa.gov/data/allocation-calculator/kdpi-calculator). Surgical variables: cold Ischemia time (CIT), the surgeon, vascular multiplicity, duration of surgery and blood pressure during the procedure. Immunological variables: Panel reactive antibodies (PRA), HLA mismatches and the need of induction therapy with antithymocyte globulin.

Blood pressure was assessed by an indwelling peripherical arterial catheter and carefully noted in a handwritten chart (Fig. 1) every 15 minutes during the surgery. We included both systolic blood pressure (SBP) and mean arterial pressure (MAP) in our assessment. MAP was calculated as: (diastolic blood pressure) + 1/3 (systolic blood pressure – diastolic blood pressure). The Mean MAP after reperfusion was calculated by a simple media of the MAPs noted in the handwritten charts.



Source: Elaborated by the authors.

Figure 1. Model of the handwritten chart adopted for data collection

The statistical analysis was performed using SPSS Statistics, version 28.0.1.1 (*IBM corp, Armonk, New York*). We dichotomized the cohort in two groups: Immediate graft function (IGF) as the control group and DGF group. Firstly, we applied the Komogorov-Smirnov test to check the normality of the continuous variables. The Student-T test were used on parametrical continuous variables and Mann-Whitney test on non-parametrical continuous variables. Chi-square test was used on categorical variables. Lastly, a multivariate analysis was performed by a stepwise logistic regression. All parameters that demonstrates significance in univariate analysis were included on multivariate analyses. A *p* value less than 0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 49.5 (20-75) years, with a predominance of male gender (61.5%) and white race (71.8%). Regarding the donors, the mean age was 44 years (10-65), mean serum creatinine was 0.91 (0.3-1.8 mg/dl), mean KDPI was 46% (4-83%) with a prevalence of the white race (76.3%) and left kidney (54.1%). Mean CIT was 1217 minutes (768-2110) and the mean duration of surgery was 228 minutes (165-300). 56.8% of the patients developed DGF. Other demographic data are listed in Table 1.

Table 2 shows the results of the univariate analysis of the patients that developed DGF and those with IGF. Regarding recipients, patients undergoing hemodyalisis (p=0.004) and absense of residual diuresis (p=0.011) were the factors that significantly impacts on DGF. Age, gender, race and time of dialysis before transplantation weren't statiscally significant on our evaluation. Among the donors, only the right kidney was statiscally significant (p=0.005). Age, serum creatinine, race, cause of death, perfusion solution and KDPI weren't significant.

Still in the univariate approach, the surgery factors that impacts the DGF were: the cold ischemia time higher than 24 hours (33.3% in the IGF group versus 75% in the DGF group - p=0.022), SBP less than 130 mmHg at the reperfusion time (21.4% in the IGF group versus 83.3% in the DGF group - p<0.001) and MAP less than 80 mmHg at the reperfusion (7.1% in the IGF group versus 61.1% in the DGF group - p<0.001). Exploring a little bit more the blood pressure, the quantitative analyses of the SBP after reperfusion (133.07 mmHg ± 15.80 mmHg in the IGF group versus 114.61 mmHg ± 17.65 mmHg in the DGF group – p=0.002) and the mean MAP after reperfusion (91.05 mmHg ± 9.45 mmHg in the IGF group versus 84.53 mmHg ± 11.31 mmHg in the DGF group – p =0.049) were associated to DGF also.

Among immunological factors, only the patients that received antithymocyte globulin as induction therapy impacted on DGF (6.2% in the IGF group versus 33.3% in the DGF group – p=0.036). The PRA and HLA mismatches didn't impact.

Table 1. Demographic description and operative data.

	n=37
Recipients	
Age (Years)	49.5 (20-75)
Male Gender	61.5%
White Race	71.8%
Type of Dialysis	
PD	34.2%
HD	55.3%
Preemptive	10.5%
Base disease	
Diabetes	36.9%
Hypertension	21.1%
Glomerulonephritis	21.1%
Others	21.1%
Dialysis time before transplantation (months)	18.5
Residual diuresis	84.2%
Donors	
Age	44 (10-65)
Creatinine level (mg/dl)	0.91 (0.3 - 1.8)
White race	76.3%
Cause of Death	
Stroke	51.4%
Head Trauma	39.5%
Others	9.2%
Right Kidney	45.9%
Perfusion solution	
Custodiol	86.5%
Euro-Collins	4.5%
IGL-1	9%
KDPI	46% (4-83%)
Surgery	
CIT (minutes)	1217 (788 - 2118)
Vessel multiplicity	32.4%
Surgeon	
A	13.5%
B	43.2%
C	29.8%
D	13.5%
Duration of Surgery (minutes)	228 (165-300)
Base SBP (mmHg)	165 (104 - 252)
Reperfusion SBP (mmHg)	122 (70 - 155)
Base MAP (mmHg)	115 (69 - 170)
Reperfusion MAP (mmHg)	86 (50 - 108)
DGF	56%
Immunity	
PRA	11% (0-92%)
MM	3.76 (1-5)
ATG	23.1%

Abbreviations: PD, Peritoneal Dialysis; HD, Hemodialysis; KDPI, Kidney Donor Profile Index; CIT, Cold Ischemia Time; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; DGF, Delayed Graft Function; PRA, Panel Reactive Antibodies; MM, Mismatches; ATG, antithymocyte globulin. Source: Elaborated by the authors.

Table 2. Univariate Analysis of Patient-Specific Risk Factors for Delayed Graft Function.

	IGF (n=16)	DGF (n=21)	Test	*p* Value
Recipients Factors				
Age (Years)	53.18±15.65	45.95±16.17	T-Student	0.09
Male Gender	8 (50%)	7 (33.3%)	Chi-Square	0.306
White Race	11 (73.3%)	15 (71.4%)	Chi-Square	0.571
Type of Dyalisis (HD, PD, PE).	7 / 4 / 4	4 / 17 / 0	Chi-Square	**0.004**
Dyalisis before transplantation (months)	15.57 15.90	20.57 15.14	Mann-Whitney	0.351
Residual Diuresis	15 (93.7%)	15 (71.4%)	Chi-Square	**0.011**
Donor Factors				
Age (Years)	38.78± 16.42	47.14± 14.59	Mann-Whitney	0.162
Creatinine (mg/dl)	0.9± 0.25	0.88± 0.33	T-Student	0.141
White Race	12 (85.7%)	16 (76.1%)	Chi-Square	0.192
Death Cause (Stroke / Head trauma / Others)	2 / 8 / 3	13 / 7 / 1	Chi-Square	0.119
Right Kidney	3 (21.4%)	14 (66.6%)	Chi-Square	**0.005**
Perfusion Solution (Custodiol, Collins, IGL-1)	8 / 1 / 0	10 / 0 /2	Chi-Square	0.266
KDPI	35.9± 30.88	53.65± 25.14	Mann-Whitney	0.156
Surgery Factors				
CIT > 24h	4 (33.3%)	9 (75%)	Chi-Square	**0.022**
CIT (minutes)	1160.83± 495.07	1283.42 ±451.42	Mann-Whitney	0.244
Surgeon (A / B / C / D)	3 / 4 / 5 / 2	2 / 10 / 6 / 3	Chi-Square	0.263
Vessel multiplicity	5 (35.7%)	7 (33.3%)	Chi-Square	0.172
Duration of Surgery (min)	221.79± 36.82	236.25± 40.43	T-Student	0.157
SBP <130mmHG at Repefusion	3(21.4%)	15(83.3%)	Chi-Square	**<0.001**
MAP <80 at reperfusion (mmHG)	1 (7.1%)	11(61.1%)	Chi-Square	**<0.001**
SBP at Reperfusion (mmHG)	133.07± 15.80	114.61± 17.65	T-Student	**0.002**
Mean MAP Post-Reperfusion (mmHG)	91.05± 9.45	84.53± 11.31	T-Student	**0.049**
Immunological factors				
PRA	15± 31.57	5± 18.5	Mann-Whitney	0.35
MM	3.66±1.23	3.85± 1.15	Mann-Whitney	0.776
ATG	1 (6.2%)	7 (33.3%)	Chi-Square	**0.036**

Abbreviations: IGF, Immediate Graft Function; DGF, Delayed Graft Function; PD, Peritoneal Dialysis; HD, Hemodialysis; KDPI, Kidney Donor Profile Index; CIT, Cold Ischemia Time; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; PRA, Panel Reactive Antibodies; MM, Mismatches; ATG, antithymocyte globulin.
Source: Elaborated by the authors.

Table 3 shows the multivariate stepwise logistic regression analysis. In this scenario we observed that only MAP < 80 mmHg (p=0.004) and SBP < 130m mmHg (p=0.005) were independent risk factors for DGF. The antithymocyte globulin group does not sustained significance (p=0.05). as well as mean MAP after reperfusion (p=0.187), cold isquemia time > 24 hours (p=0.43) and absence of residual diuresis (p=0.996).

Table 3. Multivariate Stepwise Logistic Regression Analysis of Patient-Specific and Procedure Risk Factors for Delayed Graft Function.

	Chi-Square	Beta Value	p Value
MAP < 80 mmHg at Reperfusion	8.344	-43.688	0.004
SBP < 130 mmHg at Reperfusion	8.052	-22.468	0.005
ATG	3.833	20.733	0.05
Mean MAP Post-Reperfusion (mm Hg)	1.743	-0.218	0.187
CIT > 24h	0.622	-1.753	0.43
Residual Diuresis	0	2.516	0.996

Abbreviations: MAP: Mean Arterial Pressure; SBP: Systolic Blood Pressure; ATG: Antithymocyte globulin; CIT: Cold Ischemia Time.
Source: Elaborated by the authors.

DISCUSSION

The incidence of DGF in our cohort study was 56.8%, and is comparable to others brazilian centers. In a multicentric Brazilian recent study, the incidence of DGF was 54%, ranging from 29.9% to 87.7%. Many variables are cited as risk-factors for development of DGF, they are: age, male gender, diabetes, time on dialysis, retransplantation, absence of residual diuresis, preformed anti-HLA

donor-specific antibodies (DSA), HLA mismatches, donor age, donor serum creatinine, CIT, warm ischemia time, KDPI, ASA score and blood pressure (pre-operative, peri-operative and pos-operative).[6,10,18,19]

Most of these classic factors were analyzed in our study. Dialysis time before transplantation, KDPI and donor age, well-known risk factors for DGF, demonstrates differences between our two groups, but this was not statistically significant. Absence of residual diuresis, hemodialysis, right kidney, higher CIT, lower blood pressure after reperfusion, and induction therapy with antithymocyte globulin has demonstrated association with DGF, but only lower blood pressure after reperfusion was maintained as independent risk factor for DGF. The cut-off point for SBP was 130 mmHg and 80 mmHg for the MAP ($p<0.05$ for both).

Absence of residual diuresis, hemodialysis and use of ATG are certainly factors that impact on the patient's hemodynamic control. Perhaps this is the reason for the significance of such findings. Regarding the right kidney, it is demonstrated in literature poorer results in some living donor transplantation, but not in deceased ones. A recent reported systematic review has shown similarity comparing left e right laparoscopic living donor kidney transplantation in terms of safety, feasibility and DGF rates.[20] Another point to be discussed is the fact that all the right kidneys are implanted at the left iliac fossa in our service. Sometimes the left iliac vein is compressed by the right common iliac artery (Cockett Syndrome), which can impact in the perfusion of the kidneys. For this reason, some services opt for implants, always in the right fossa.

Quantitative analysis of blood pressures after reperfusion, as well as mean MAP after reperfusion, until the end of surgery, were also statiscally significant in the univariate analysis. We have seen in the literature that MAP < 70 mmHg in the first 24 postoperative hours are strongly associated with DGF and this corroborate to our finding.[15]

The blood pressure as a risk-factor for DGF was reported for some authors along the last years. Aulakh et al.,[13] in a retrospective study analyzing 100 consecutive renal transplantations, reported good graft function when MAP was higher than 95 mmHg at reperfusion. Gingell-Littlejohn et al.,[15] retrospectively studying 149 renal transplantations, shown association with DGF when MAP was below 70 mmHg in peri-operative time ($p=0.005$).

Campos et al.,[14] in a large retrospective study, including 1966 patients, reported better outcomes regarding DGF, in cases where MAP was superior than 93 mmHg, in reperfusion time ($p=0.04$). In spite of the large cohort, this study has a 29-year follow-up, and so many significant peri and post-operative management was applied in this time, so, the conclusion must be carefully interpreted.[14] Snoeijs et al.,[21] also in a retrospective study with 177 non heart beating donor (NHBD) kidney transplantation, reported intraoperative average systolic blood pressure below 110 mmHg (OR 2.6 - $p = 0.03$) as independent risk-factors associated to DGF, even in NHBD kidney transplantation. Toth et al, in a prospective cohort study, shown association between low blood pressure and DGF. It was 121 patients with MAP 108 +/- 26 mmHg ($p < 0.01$) 5 minutes before revascularization.[12]

Despite our small sample, the study demonstrates the importance of perioperative hemodynamic management and its impact on early graft function. We failed to demonstrate in the multivariate regression some well-known risk factors for DGF (male gender, KDPI, donor age and dialysis time before surgery), and probably once more, the small sample size is the reason.

The standardization in the collection of MAPs through the annotations in our handwritten chart and the peripheral invasive monitoring in all patients, makes the methodology more reliable, since many times, in medical records, we would not find the necessary details for the development of this analysis.

Our study is not a randomized clinical trial, and perhaps this type of study has ethical obstacles to be carried out, since many studies support good hemodynamic parameters as predictors of good results. There are few studies that fail to demonstrate such an association, and the vast majority of them used central venous pressure as the hemodynamic control parameter, but not de MAP.[14,22]

The MAP cut-off point in renal reperfusion is still unclear, since studies show large amplitudes in their findings (70-108 mmHg), in this way, more studies about this theme are comported with the objective to set a target-point for the MAP after reperfusion, as well as the time that this target should be carried out1.[2–15,21]

Another unclear point that we consider relevant, is the way which blood pressure are controlled in the perioperative period. High doses of vasoactive drugs, as well as the use of colloids, albumin and crystalloids > 3000ml, are also associated with poorer results. Adjustment should be fine and individualized, considering the patient's cardiac reserve, as well as adequate hemostatic control. Anesthesiologists and surgeons, working together for this purpose, will certainly achieve better results.[23,24]

CONCLUSION

In this survey, optimal renal perfusion, avoiding fall in blood pressure in the perioperative period, especially after graft reperfusion, is crucial for the immediate functioning of the kidney. Therefore, therapies aimed on hemodynamic control in properly monitored patients, may prove to be beneficial in reducing the rates of DGF.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Hokazono SR; **Conception and design:** Pimpao BF; **Data analysis and interpretation:** Pimpao BF; **Article writing:** Pimpao BF; **Critical revision:** Hokazono SR, Meyer F, Fraga R; **Final approval:** Pimpao BF.

AVAILABILITY OF RESEARCH DATA

Data will be provided upon request;

CONFLICT OF INTEREST

Nothing to declare

FUNDING

Not applicable

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Nothing to declare

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