INTRODUCTION

Kidney transplantation is the therapy of choice for patients with end-stage kidney disease (ESRD), but due to organ shortage, there are long waiting times across all age groups with severe repercussions on morbidity and mortality. Living kidney donation has been used to overcome this shortage, and even in older dialysis patients it remains the best treatment option. Traditionally, only healthy candidates, ie, candidates without chronic diseases such as hypertension and thus a very low baseline risk for renal or cardiovascular disease were considered suitable for donation. Older ESRD patients often present with older living kidney donor candidates who often suffer from hypertension, thus selecting a hypertensive candidate is quite common in older ESRD patients.

Association of donor hypertension and recipient renal function in living donor kidney transplantation: A single-center retrospective study

Thomas Dienemann1 | Jana Schellenberg1 | Katharina Heller1 | Christoph Daniel2 | Kerstin Amann2 | Karl Friedrich Hilgers1 | Mario Schiffer1 | Alexander Weidemann1,3

1Medizinische Klinik 4, Nephrologie und Hypertensiologie, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
2Abteilung für Nephropathologie, Pathologisches Institut, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
3Medizinische Klinik 1, Nephrologie, Transplantation und Internistische Intensivmedizin, Krankenhaus Köln Merheim, Klinikum der Universität Witten-Herdecke, Cologne, Germany

Abstract

Transplant centers now accept living donors with well-controlled hypertension. Little is known whether hypertension in living donors affects recipient's kidney function. We aimed to examine potential differences in kidneys from hypertensive donors compared to normotensive donors with respect to renal function over 36 months and histologic findings at transplantation (T0) and 12 months after transplantation (T1). Retrospective single-center analysis of 174 living donor-recipient pairs (age > 18; transplantation date 1/2008-3/2016). Hypertension in donors was defined as being on antihypertensive medication. All biopsies were assessed by the same blinded, experienced renal pathologist. Biopsies were scored for glomerulosclerosis, IFTA, and arteriosclerosis. Regression models were used to examine the relationship of donor hypertension with renal function and histologic changes. Hypertensive donors were significantly older than normotensive donors. Chronic changes such as tubular atrophy and atherosclerosis were more evident in kidneys from hypertensive donors at T0 as well as T1. Donor hypertension was independently associated with histologic changes at T0 and T1 but not with renal function over the follow period. Despite more pronounced histologic changes in kidneys from hypertensive living donors, these grafts exhibited a similar functional outcome. However, they subsequently might be at a greater risk and warrant thorough follow-up care.

KEYWORDS

donor hypertension, living donor renal transplantation, recipient renal function

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2019 The Authors. Clinical Transplantation published by John Wiley & Sons Ltd
Whereas, donor age and predonation estimated glomerular filtration rate (eGFR) have been known to be important predictors of recipient graft function, and little is known whether donor hypertension is associated with recipient renal function. In kidneys from deceased donors, hypertension is often a reason for not accepting the organ, due to fear of inferior graft function. Even an increased risk of death in recipients with a transplant from a hypertensive donor has been described. Only few studies have examined the consequences of the transplantation of a kidney from a hypertensive living donor for the recipient. A small study with 10 hypertensives and 17 age-matched normotensive donors showed a reduced number of glomeruli in preimplantation biopsies in hypertensive donors. A study from the Cleveland Clinic showed that donor blood pressure greater than 120 mm Hg in a single office measurement was independently associated with a lower eGFR in transplant recipients 2 years after transplantation, and a Japanese study demonstrated that donor renal artery vasculopathy but not donor hypertension was predictive of reduced allograft function after 12 months of follow-up.

In the present study, we attempted to elucidate the effect of donor hypertension on recipient renal function over a follow-up of 36 months. Additionally, we examined histologic changes in preimplant biopsies (t0) and one-year protocol biopsies (t1) attributable to hypertension in the living donor and correlated these findings to recipient eGFR.

2 | METHODS

2.1 | Study participants

Patients (aged ≥18 years) who received a living donor kidney allograft at the University Hospital of Erlangen between January 1, 2008 and January 31, 2016 comprised the study population of this retrospective study. The cohort included recipients who had a prior kidney transplant, another organ transplant, and recipients with kidneys from ABO incompatible donors. All donors were evaluated according to a presupervised protocol that remained unchanged during the entire study period. Potential donors with hypertension were accepted at our center if the following criteria were fulfilled: caucasian ethnicity, no end organ damage (eg, left ventricular hypertrophy, microalbuminuria, abnormal fundoscopy), and average blood pressure levels less than 135/85 mmHg on ambulatory blood pressure measurement (ABPM) under medication ≤2 antihypertensive drugs.

2.2 | Variables of interest, exposure, outcomes, and definitions

Donor and recipient medical records were reviewed by trained abstractors to obtain information at the time of transplantation and over the course of follow-up. All recipients and donors underwent 24-hour ABPM (OnTrak, Spacelabs) during the donor evaluation process where mean systolic and mean diastolic blood pressure as well as the nocturnal dipping pattern were recorded. Recipient blood pressure at 1 year was the average of three office blood pressure measurements according to ESC/ESH guidelines. The exposure of interest, hypertensive donor (HTD), was defined as a donor who received antihypertensive medication or had abnormal blood pressures during the 24h-ABPM measurement. Elevated blood pressure was defined according to the 2018 European Society of Cardiology/European Society of Hypertension guidelines.

The clinical outcome was recipient renal function after 3 years. Secondary outcomes were donor renal function and chronic changes in kidney biopsy at time of donation (pre-implant biopsy) and 12 months after transplantation.

Renal function was assessed by the estimated glomerular filtration rate (eGFR) using the CKD-EPI equation with creatinine. Our center conducts preimplant biopsies and protocol biopsies 12 months after transplantation in all patients within a range of ±30 days toward the exact transplant date. Preimplantation biopsies are obtained during back table preparation. All biopsies were re-assessed for the study by the same dedicated renal pathologist blinded to donor hypertension status. Biopsies were scored for glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis, which was combined to a total renal chronicity score (TRCS) as proposed by Sethi et al. To increase reproducibility regarding the chronic changes not elicited by alloreactivity, both preimplant and protocol biopsies were scored with the same scoring system. Acute rejection was defined according to Banff criteria on a renal biopsy pathology report. Delayed graft function (DGF) was defined as ≥1 dialysis treatment(s) within the first 7 days after transplantation.

2.3 | Immunosuppression/Post-transplant care

At our center, the standard immunosuppressive regimen for living kidney donation consists of prednisone, mycophenolate, tacrolimus, and basiliximab. Cyclosporine was used in a minority of patients instead of tacrolimus due to participation in a study, positive HCV RNA or due to a pathological glucose tolerance. Recipients with immunological risk factors receive anti-thymocyte globulin (ATG) instead of basiliximab as induction therapy. Recipients from ABO incompatible kidneys additionally receive a combination of the anti-CD20 antibody rituximab, plasmapheresis, and anti-A/B antibody immunoadsorption according to a standardized protocol. In very few selected cases, steroids can be withdrawn in patients with excellent kidney function and no other risk factors at the discretion of the treating physician 12 months after transplantation.

2.4 | Statistical analysis

STATA 14 (StataCorp LP) was used for all statistical analyses. A P-value < .05 was considered statistically significant, and all tests were two tailed. Descriptive data are presented as means (SD) for continuous variables or frequencies for count data.

Student’s t-test and Mann-Whitney U were used for descriptive comparisons. A logistic regression model was used to identify causes for donor hypertension in our cohort (Model 1). A linear regression model was used to examine the association of donor renal function with donor blood pressure status (Model 2), and a generalized estimating equation model (GEE) was used to estimate the association of donor hypertension on recipient renal
function over 3 years (Model 4). The GEE model was used because of the repeated measures for eGFR at 1, 2, and 3 years and its robustness regarding the variance structure. Furthermore, a logistic regression model was used to assess the association of donor blood pressure status with chronic changes in biopsy specimens at time of transplantation (Model 3) and at 12 months after transplantation (Model 5). All models were a priori models, and covariates were selected on the basis of previous knowledge. Univariate analysis was not used. Because of its non-normal distribution, the total renal chronicity score (TRCS) was transformed into a dichotomous variable (minimal and mild chronic changes vs moderate and severe chronic changes) and then referred to as renal chronicity score (RCS). RCS T0 is the dichotomous total renal chronicity score for preimplant biopsies and RCS T1 for 12 months protocol biopsies, respectively. Covariates were chosen after review of literature and after careful assessment of correlation structures the following covariates were used: Model 1 included donor age, donor BMI, donor gender, donor smoking status, donor eGFR, and renal chronicity score (RCS T0). Model 2 included all variables of Model 1 except donor eGFR, donor age, and donor gender. Model 3 included all factors of Model 2, and additionally DONOR hypertension. Model 4 included recipient BMI, acute rejection, DGF, donor hypertension, donor BMI, HLA DR mismatch, type of calcineurin inhibitor, history of prior transplant, presence of DSA, post-transplant diabetes (PTDM), cytomegalovirus CMV or polyoma virus (BKV) (all within the first 12 months), ABO incompatibility, donor eGFR, and type of induction therapy.

Model 5 included in addition to the covariates from Model 4 recipient age and gender and recipient blood pressure. To overcome possible problems with differences in size of donors and recipients, Model 4 was also modeled with the Cockroft-Gault equation for eGFR. Coefficients were generally not different (data not shown). Age and sex were not considered when eGFR was the dependent variable as they are used to estimate eGFR.

### RESULTS

#### 3.1 Cohort characteristics

During the study period, 188 living donor kidney transplantations were performed at our center. One donor-recipient pair was excluded because the recipient was <18 years old, 12 donor-recipient pairs were excluded due to preformed DSA of the recipient and 1 pair due to concomitant diabetes of the donor. Thus, the study cohort comprised 174 donor-recipient pairs. Out of these, 47 recipients received a kidney from an ABO incompatible donor, 17 underwent their second or third kidney transplantation. Three patients lost their graft shortly after surgery due to vascular issues. In the first year, one patient died of sepsis and one patient lost the graft due to humoral rejection. In the second year, one patient lost the graft due to BK nephropathy and another patient due to humoral rejection. No deaths or graft losses were observed in year three. The characteristics of donors and recipients stratified by donor hypertension are summarized in Table 1 and 2.

#### 3.2 Donors

Hypertensive donors (HTD) had a significantly higher BMI and were significantly older (BMI 27.1 ±3.1) vs 25.8 ±3.5, P < .022; Age 58.5 ±8.9) vs 53.3 ±8.5, P < .000) than normotensive donors (NTD) (Table 1).

| TABLE 1 Donor characteristics subdivided in normotensive donor vs hypertensive donor: Variables either presented as mean (SD) or absolute values (relative frequencies) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Donor age (years)                              | Normotensive donor: 53.3 ±8.5                      | Hypertensive donor: 58.8 ±8.9                      |
| Donor sex (male)                               | 43 (33.3%)                                         | 20 (47.4%)                                         |
| Donor BMI (kg/m²)                              | 25.8 ±3.5                                          | 27.1 ±3.1                                          |
| Donor smoking status (smoker)                  | 21 (16.2%)                                         | 8 (19.1%)                                          |
| Donor eGFR (mL/min)                            | 88.1 ±16.1                                         | 90.8 ±16.5                                         |
| Donor systolic BP (mm Hg)                      | 119.3 ±8.7                                         | 131.1 ±12.1                                        |
| Donor diastolic BP (mm Hg)                     | 71.9 ±6.6                                          | 76.9 ±8.0                                          |
| Donor nocturnal non-dipping                    | 0                                                 | 7 (16.7%)                                          |
| Donor mean # of antihypertensive drugs         | 0                                                 | 1.24 (±1.0)                                       |
| TRCS (mean) at transplantation                 | 0.56 (±0.90)                                       | 1.0 (±1.1)                                         |

Abbreviations: BMI, body mass index; BP, blood pressure; TRCS, total renal chronicity score.
71.9 mm Hg (±6.6), \( P < .000 \) (Table 2). Hypertensive donors were on a mean of 1.24 (±1.0) antihypertensive medications. 17% of hypertensive donors also showed no physiologic nocturnal dipping pattern. Donor eGFR was numerically higher in the HTD group, the difference was not significant (HTD vs NTD: 90.8 mL/min (±16.5) vs 88.1 mL/min (±16.1), \( P = .341 \)) (Table 1).

### 3.3 Recipients

Recipients from donors with hypertension suffered significantly more often from coronary artery disease (CAD) (14.3% vs 3.8%, \( P = .016 \)), and there were no recipients with diabetes mellitus in the recipient group from hypertensive donors (DM) (13% vs 0%,

| Kidney from | Normotensive donor | Hypertensive donor | \( P \)-value |
|------------|--------------------|--------------------|--------------|
| N          | 132                | 42                 |              |
| Age (y)    | 43.8 (±13.4)       | 47.5 (±13.6)       | 0.141        |
| Recipient sex (male) | 83 (63.9%) | 26 (61.9%) | 0.820        |
| BMI (kg/m²) | 25.0 (±4.0)       | 25.4 (±3.1)        | 0.625        |
| DM         | 13 (10.0%)         | 0 (0%)             | 0.032        |
| CAD        | 5 (3.8%)           | 6 (14.3%)          | 0.016        |
| Recipient hypertension | 29 (21.0%) | 13 (28.8%) | 0.276        |
| Recipient # of anti-hypertensives | 3.2 (±1.7) | 2.9 (±1.8) | 0.539        |
| PRA > 0%   | 8 (6.1%)           | 4 (9.5%)           | 0.457        |
| Dialysis vintage (mo) | 12.7 (±18.6) | 19.1 (±31.6) | 0.453        |
| Mean HLA mismatch | 3.7 (±1.7) | 3.7 (±1.8) | 0.835        |
| ABO incompatible | 37 (28.5%) | 10 (23.8%) | 0.557        |
| Mean CIT (h) | 1.8 (± 1.0)       | 1.6 (± 0.9)       | 0.487        |
| Mean WIT (min) | 38.5 (±21.1) | 34.5 (±9.8) | 0.444        |
| CNI: Tacrolimus | 119 (91.4%) | 37 (88.0%) | 0.505        |
| Induction: ATG | 19 (14.6%) | 6 (14.2%) | 0.952        |
| Prior kidney transplantation | 10 (7.7%) | 5 (11.9%) | 0.401        |

**Type of dialysis**

|                        | HD    | CAPD |
|------------------------|-------|------|
| Recipient systolic BP t0 (mm Hg) | 135.8 (± 14.3) | 135.5 (±18.2) |
| Recipient diastolic BP t0 (mm Hg) | 79.85 (±10.0) | 79.0 (±10.9) |
| Recipient systolic BP t1 (mm Hg) | 128.3 (±14.6) | 128.8 (±14.8) |
| Recipient diastolic BP t1 (mm Hg) | 76.6 (±13.2) | 76.6 (±11.3) |
| Recipient # of antihypertensive drugs t0 | 3.1 (±1.8) | 3.0 (± 1.5) |
| Recipient # of antihypertensive drugs t1 | 2.1 (±1.7) | 2.7 (±1.7) |

**Delayed graft function**

- 7 (5.0%) vs 2 (4.4%) (0.866)

**PTDM (first 12 mo)**

- 11 (8.4%) vs 3 (7.32%) (0.825)

**CMV Viremia (first 12 mo)**

- 8 (6.0%) vs 2 (5%) (0.802)

**BKV Viremia (first 12 mo)**

- 12 (9.0%) vs 5 (11.9%) (0.593)

**Acute rejection (first 12 mo)**

- 42 (31.1%) vs 19 (34.1%) (0.143)

**eGFR at 1 y**

- 53.3 (±174) vs 50.6 (±15.4) (0.413)

**eGFR at 2 y**

- 52.9 (±17.6) vs 51.4 (±14.8) (0.627)

**eGFR at 3 y**

- 51.1 (±16.3) vs 50.6 (±14.2) (0.852)

**TRCS (mean) after 1 y of follow-up**

- 1.6 (±1.5) vs 2.3 (±1.8) (0.000)

**Abbreviations:** ATG, anti-thymocyte globulin; BMI, body mass index; CAD, coronary artery disease; CIT, cold ischemia time; CNI, calcineurin inhibitor; DM, diabetes mellitus; ECD, expanded criteria donor; HLA, human leukocyte antigen; PRA, panel reactive antibody; PTDM, post-transplant diabetes mellitus; t0, time of transplant; t1, 12 mo post-transplant; TRCS, total renal chronicity score; WIT, warm ischemia time.
There were no differences regarding delayed graft function, acute rejection, post-transplant diabetes, detection of CMV, and BKV viremia between the groups. Systolic and diastolic blood pressure in recipients of both NTD and HTD did not differ at time of transplantation and 1 year after transplantation. The amount of antihypertensive medication in recipients at time of transplantation was similar in both groups (NTD vs HTD 3.2 (±1.9) vs 3.1 (±1.6), \( P = .866 \)). In contrast, 1 year after transplantation, NTD recipients—on average—needed significantly less antihypertensive medication to achieve an equal blood pressure (NTD vs HTD 2.1 (±1.7) vs 2.7(±1.7), \( P = .023 \)) (Table 2). Despite small numeric differences, eGFR in the two groups was not significantly different at 1, 2, or 3 years after transplantation.

### 3.4 Histologic changes at transplantation and at 1 year after transplantation

Preimplant biopsies were available in 127 recipients (96.2%) in the NTD group and in 40 recipients (95.2%) in the HTD group. Protocol biopsies at 12 months were available in 116 recipients ([out of 127]: 90.6%) in the NTD group and in 38 recipients ([out of 40]: 90.4%) in the HTD group. Severity of histologic changes increased on average in all recipients over time (Figures 1 and 2). Kidneys from hypertensive donors showed a faster increase in severity, however, the slope between the groups was not significantly different (Figure 3 Supplements). Glomeruli in preimplant biopsies from the NTD group showed almost no signs of sclerosis, while preimplant from the HTD group showed
mild glomerular changes like mesangial matrix expansions, which were comparable to changes observed 1 year after transplantation in the NTD group. The most distinct glomerular changes were observed in the 12-months biopsies of the HTD group including more prominent mesangial matrix expansion. Although the comparison of glomerular changes found in 12-months biopsies reached statistical significance between the NTD and HTD, overall the observed glomerular changes were relatively mild. Chronic lesions in individual renal tissue compartments are summarized in Table 3. Figure 4 provides typical changes in the before mentioned compartments in kidney from normotensive and hypertensive donors at T0 and T1. (Histologic changes are described in more detail in the supplements).

![Figure 3: Line of best fit between chronic histologic changes from T0 to T1](image)

|                | Normotensive | Hypertensive |
|----------------|--------------|--------------|
| Glomerulosclerosis | 0.08 (±0.28) | 0.16 (±0.48) | 0.14 (±0.46) | 0.37 (±0.78) |
| Interstitial fibrosis | 0.08 (±0.28) | 0.16 (±0.37) | 0.65 (±0.71) | 0.90 (±0.64) |
| Tubular atrophy    | 0.07 (±0.25) | 0.18 (±0.39) | 0.59 (±0.67) | 0.95 (±0.61) |
| Arteriosclerosis   | 0.26 (±0.44) | 0.48 (±0.50) | 0.36 (±0.48) | 0.51 (±0.55) |
| TRCS              | 0.50 (±0.75) | 0.97 (±1.10) | 1.75 (±1.5)  | 2.74 (±1.70) |

**TABLE 3** Histologic changes (mean (SD)) in recipients from normotensive and from hypertensive donors in preimplant biopsies (T0) and 12 mo protocol biopsies (T1)

Abbreviation: TRCS, total renal chronicity score.
3.5 | Regression analysis

3.5.1 | Donor hypertension (Model 1) and donor eGFR (Model 2)

Donor age was the only covariate associated with donor hypertension (OR 1.08, 95% CI (1.02 to 1.13), P = .002) whereas donor BMI showed a trend: OR 1.11, 95% CI (0.99 to 1.25), P = .069) (Table 4). Histologic changes from pre-implant biopsies were not associated with donor hypertension. Donor eGFR (Model 2) was not associated with any of the tested variables (Table 5 left).

3.5.2 | Renal chronicity score T0 (Model 3)

Donor hypertension was the only variable to be significantly associated with histologic changes in pre-implant biopsies (OR 2.49, 95% CI (0.89 to 7.28), P = .045) (Table 5 right).

3.5.3 | Recipient eGFR (Model 4)

The generalized estimating equation (GEE) model identified acute rejection and donor eGFR as independent predictors for renal function in recipients (acute rejection: coef. -6.91, 95% CI (-11.76 to -2.07), P = .011; donor eGFR: coef. 0.33, 95% CI (0.19 to 0.47), P = .000) (Table 6 left). Donor hypertension was not associated with recipient renal function over a follow-up of 3 years. BMI was also negatively associated with renal function; BKV, choice of calcineurin inhibitor, and induction therapy showed a trend (Table 6 left).

3.5.4 | Renal chronicity score T1 (Model 5)

Donor hypertension remained a significant predictor for histologic changes after 1 year.

(underlined text)

4 | DISCUSSION

While there are many studies focusing on donor outcomes after nephrectomy, very little is known about recipient renal function from hypertensive living kidney donors. In the present study, donor hypertension was not associated with recipient renal function over a follow-up of 3 years. Contrary to our result a study by Issa et al found a positive correlation between the recipient post-transplant creatinine and the binary variable of donor systolic blood pressure >120 mm Hg. However, a single systolic office blood pressure measurement was used and thus it is not clear whether these donors were truly hypertensive. Secondly, this study focused on identifying donor factors influencing graft outcomes and therefore did not include potential confounders such as acute rejection or presence of DSA. The absence of an association of donor hypertension and recipient renal function in the present study may be explained by relatively healthy donors with above average renal function. We did identify donor renal function and acute rejection to be independently associated with recipient renal function. The significant association with BMI was most likely due to the fact that the estimation formula is not adjusted for size, however, when using the Cockroft-Gault Formula to estimate GFR, coefficients remained similar (data not shown).

As a potential morphological correlate of donor hypertension, we obtained pre-implant biopsies (T0) and 12 month protocol biopsies (T1) from non-hypertensive (NTD) vs hypertensive (HTD) living donors. Representative pictures of PAS-(A-D, I-P) or Sirius red-stained (E-H) renal biopsies were shown demonstrating early glomerulosclerosis (A-D), interstitial fibrosis (E-H), tubular atrophy (I-L) and arteriosclerosis (M-P).

*FIGURE 4* Histopathological changes in pre-implant biopsies (t0) and 12 mo biopsies (t1) from non-hypertensive (NTD) vs hypertensive (HTD) living donors. Representative pictures of PAS-(A-D, I-P) or Sirius red-stained (E-H) renal biopsies were shown demonstrating early glomerulosclerosis (A-D), interstitial fibrosis (E-H), tubular atrophy (I-L) and arteriosclerosis (M-P).

*TABLE 4* Donor hypertension (Model 1, logistic regression)

| Donor characteristic | OR  (95% CI) | P-value |
|----------------------|-------------|---------|
| Donor age            | 1.08        | 1.02-1.13 | .002   |
| Donor BMI            | 1.11        | 0.99-1.25 | .069   |
| Donor female         | 0.59        | 0.26-1.33 | .206   |
| Donor smoker         | 1.35        | 0.45-3.96 | .576   |
| RCS T0               | 2.52        | 0.79-7.99 | .114   |

Abbreviation: RCS, renal chronicity score (none/mild vs moderate/severe) at transplantation.
TABLE 5  Donor eGFR (Model 2, linear regression) and renal chronicity score from pre-implant biopsy (Model 3, logistic regression)

| Donor eGFR | Renal chronicity score T0 |
|------------|---------------------------|
| Coefficient | 95% CI | P-value | OR | 95% CI | P-value |
| Donor hypertension | 2.63 | -3.46-8.74 | .395 | 2.49 | 0.89-7.28 | .045 |
| Donor BMI | .26 | -0.49-1.02 | .495 | 1.11 | 0.95-1.29 | .183 |
| Donor smoker | 1.38 | -5.62-8.40 | .696 | 2.69 | 0.80-8.99 | .106 |
| RCS T0 | 4.20 | -4.28-12.69 | .330 | - | - | - |
| Donor eGFR | - | - | - | 1.01 | 0.98-1.05 | .329 |

Abbreviations: -, not tested; RCS, renal chronicity score (none/mild vs moderate/severe) at transplantation.

TABLE 6  Univariate and multivariate results of Recipient eGFR (Model 4, GEE model) and renal chronicity score from 12 mo protocol biopsy (Model 5, logistic regression)

| Recipient eGFR | Renal chronicity score T1 |
|----------------|---------------------------|
| Coefficient | 95% CI | P-value | OR | 95% CI | P-value |
| Donor hypertension | .64 | -4.24-5.52 | .797 | 3.30 | 1.18-8.25 | .023 |
| Donor eGFR | .33 | 0.19-0.47 | .000 | - | - | - |
| Age | - | - | - | 1.00 | 0.97-1.04 | .568 |
| BMI | -.83 | -1.42-0.24 | .006 | 1.03 | 0.9-1.15 | .610 |
| Female | - | - | - | 1.03 | 0.44-2.36 | .942 |
| Recipient systolic BP | -.02 | -0.17-0.11 | .701 | 1.01 | 0.98-1.04 | .493 |
| Donor BMI | -.35 | -0.99-0.27 | .270 | 1.17 | 0.98-1.27 | .097 |
| Donor age | - | - | - | 0.99 | 0.94-1.04 | .865 |
| Acute rejection | -6.91 | -11.76-2.07 | .011 | 2.72 | 0.99-5.23 | .057 |
| DGF | -4.32 | -15.94-7.30 | .466 | 0.49 | 0.04-5.23 | .559 |
| PTDM | .024 | -7.02-7.75 | .948 | 3.05 | 0.51-17.99 | .216 |
| CMV | 4.22 | -4.46-12.91 | .340 | 0.57 | 0.10-3.08 | .519 |
| BKV | -6.74 | -13.84-0.35 | .063 | 4.53 | 0.82-24.80 | .081 |
| HLA DR MM (0 vs 1/ 0 vs 2) | .28 | -6.31-6.88 | .933 | 0.54 | 0.16-1.87 | .337 |
| Prior transplant | -2.86 | -11.40-5.67 | .511 | 0.40 | 0.05-2.92 | .367 |
| HLA antibody | -.55 | -7.30-6.19 | .871 | 0.31 | 0.07-1.31 | .114 |
| ABO incompatible | -1.43 | -6.48-3.26 | .579 | 0.72 | 0.28-1.87 | .508 |
| Calcineurin inhibitor | -6.52 | -13.32-0.27 | .060 | 0.57 | 0.11-2.81 | .493 |
| Induction | -5.81 | -11.9-0.36 | .065 | 0.83 | 0.21-3.25 | .799 |

Abbreviations: - = not tested, Calcineurin Inhibitor: Tacrolimus vs other, HLA DR MM: Human leukocyte antigen DR Mismatch 0 vs 1&2, de novo HLA antibody † (not necessarily donor specific), CMV †, BKV †, PTDM † († all within the first 12 mo), ABO incompatible: Donor was not ABO compatible to Recipient, Induction therapy Basiliximab vs other (ATG or none).

Choi et al could show an association of more severe histologic changes with donor age and, similar to the present study, no difference in donor renal function, however, only four donors (3.3%) were hypertensive and mean donor age was 40 years, approximately 15 years younger than the donors in our cohort. In the study by Chauhan et al, donor age and donor systolic blood pressure were the only significant factors associated with moderate or severe histologic changes. In this study, donors with histologic changes were on average of 7 years younger and systolic office blood pressure measurements were 7 mm Hg lower.

As in previous studies, histologic findings from T0 biopsies did not predict recipient renal function. However, in combination, the cited studies only included 17 hypertensive donors.

In the present study, hypertensive donors (HTD) had a significantly higher systolic and diastolic blood pressure than normotensive donors (NTD), despite antihypertensive treatment. The median
number of anti-hypertensive medication in these donors was 1, but donors were still in the “high normal” group according to the current ESC guidelines on hypertension. Recipients from normotensive donors required significantly fewer anti-hypertensive drugs after 12 months. Although the notion is intriguing, this study was not designed to support evidence of a blood pressure-lowering effect from a transplant from a normotensive donor, which has been described before.

Despite a probable biological link between donor hypertension and recipient renal function, comparable to the mechanisms in native kidneys, there are multiple explanations for why we could not observe an association between donor hypertension and recipient renal function. First and most importantly, post-donation events such as acute rejection and immunosuppressive therapy may outweigh the adverse impact of donor hypertension. Second, hypertension in our donors may have been fairly well controlled and, third, the resulting histologic changes could have been too mild for a functional impairment. A significant positive correlation in histologic changes over time and a significant negative correlation of recipient eGFR with increasing histologic changes after 12 months demonstrate internal validity of our data. It could be argued that chronic histologic changes at 12 months may be a more sensitive marker for early damage than renal function. The observation that histologic changes are associated with blood pressure but not with age may be due to the simple explanation that age is a risk factor for hypertension but not all older donors in our cohort were hypertensive.

We acknowledge several limitations. Due to its retrospective single-center design, there may be residual confounding and it may have limited generalizability. The chronicity score by Sethi et al was developed in native kidneys and may not be fully applicable to kidney allografts. However, the classification for chronic changes such as interstitial fibrosis and tubular atrophy are almost identical to ci and ct from the Banff classification. Furthermore, we did not assess proteinuria as an additional marker of renal injury in recipients because it is subject to high variability due to factors such as primary cause of disease, residual diuresis from native kidneys, and RAAS blockade. We did not have data on immunosuppressive medication after 12 months. Additionally, information on immunosuppressant levels was not available. Although it is generally accepted that optimal calcineurin-inhibitor target levels reduce the risk for acute rejection, the effect is not always clearly seen in epidemiologic studies due to the interval between the beginning of a rejection episode and the ascertainment of the immunosuppressant level, as well as for suspected non-calcineurin driven mechanisms. Data on duration of hypertension in donors did not exist; we would expect an association between hypertension history and renal histologic changes.

This study adds to current knowledge as we could show that recipients from living hypertensive donors with a mean age of nearly 60 years and significant chronic histologic changes on renal biopsy showed equal renal function compared to recipients from normotensive donors over a follow-up of 36 months. To our knowledge, this is the largest study to examine the association of donor hypertension and renal function in living donor kidney transplant recipients.

In conclusion, our data show that controlled hypertension in otherwise healthy donors is not associated with recipient renal function over a follow-up of 3 years irrespective of biopsy findings at procurement. Although these grafts exhibit similar functional outcomes, the histological changes at the outset and the progression of chronicity parameters were significant. This could imply that these grafts are at risk for deterioration later on. Thus, patients receiving such grafts should be closely monitored and could potentially benefit from certain immunosuppressive (ie, calcineurin inhibitor-free) regimens. Future studies with larger cohorts are needed to elucidate whether transplant recipients from hypertensive donors do require more intense blood pressure lowering. Moreover, our data suggest that during donor screening and pre-donation efforts should be increased to treat hypertension sufficiently. As hypertension is likely to aggravate post-donation, our finding that renal structural changes are already present at donation irrespective of measured renal function should prompt centers to maximize efforts to reduce and treat additional risk factors in donors during post-donation follow-up care. Only if this is ensured, we can safely accept well-selected hypertensive donors as a means to decrease current shortage of organ donors.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTIONS
Thomas Dienemann: Responsible for study design, the acquisition, analysis, and interpretation of data. Furthermore, drafting and revision of the manuscript and final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Jana Schellenberg: Substantial contribution to the acquisition of data for the work and critical revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. Katharina Heller: Responsible for study design, the acquisition, analysis, and interpretation of data. Furthermore, drafting and revision of the manuscript and final approval of the version to be published. Agrees to be accountable for all aspects of the work. Christoph Daniel: Substantial contribution to the acquisition of data for the work and critical revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. Karl Friedrich Hilgers: Substantial contribution to the acquisition of data for the work and critical revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. Mario M. Schiffer: Substantial contribution to the acquisition of data for the work and critical
revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work.

Alexander Weidemann: Substantial contribution to the conception and design of the manuscript, substantial contribution to the revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work.

REFERENCES

1. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA. 1993;270(11):1339-1343.

2. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725-1730.

3. Organización Sanitaria de la Sociedad Europea. Nefrologia: publicación oficial de la Sociedad Española. Nefrologia. 2010;30:1-105.

4. Lentine KL, Kasiske BL, Levey AS, et al. Clinical practice guideline on the evaluation and care of living kidney donors. Transplantation. 2017;101(8 Suppl 1):S1-S109.

5. Issa N, Stephany B, Fatica R, et al. Association between pre-existing arteriosclerotic in-renal function in living-kidney transplantation: A single-center retrospective study. Clin Transplant. 2013;27(5):1039-1045.

6. Mohan S, Campenot E, Chiles MC, et al. Association between predonation hypertension with glomerular function. Transpl Int. 2015;28(10):1172-1178.

7. Li B, Cairns JA, Robb ML, et al. Effect of donor age and parent-to-child transplant on living-related donor kidney transplantation: a single center’s experience of 236 cases. Ren Fail. 2015;37(6):1007-1012.

8. Qiu J, Wang C, Liang X, et al. Effect of donor age and parent-to-child transplant on living-related donor kidney transplantation using flexible parametric modelling. BMC Nephrol. 2016;17(1):51.

9. Sofue T, Inui M, Kiyomoto H, et al. Pre-existing arteriosclerotic intimal thickening in living-donor kidneys reflects allograft function. Am J Nephrol. 2012;36(2):127-135.

10. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-3104.

11. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

12. Sethi S, D’Agati VD, Nast CC, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. Kidney Int. 2017;91(4):787-789.

13. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant. 2018;18(2):293-307.

14. Chaumont M, Racapé J, Broeders N, et al. Delayed Graft Function in Kidney Transplants: Time Evolution, Role of Acute Rejection, Risk Factors, and Impact on Patient and Graft Outcome. Journal of transplantation. 2015;2015:163757.

15. Irish WD, Ilsley JN, Schnitzler MA, Feng S, Brennan DC. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. Am J Transplant. 2010;10(10):2279-2286.

16. Doshi MD, Garg N, Reese PP, Parikh CR. Recipient risk factors associated with delayed graft function: a paired kidney analysis. Transplantation. 2011;91(6):666-671.

17. Teixtor SC, Taler SJ, Driscoll N, et al. Blood pressure and renal function after kidney donation from hypertensive living donors. Transplantation. 2004;78(2):276-282.

18. Choi KH, Yang SC, Joo DJ, et al. Do the abnormal results of an implantation biopsy as a surrogate to evaluate selection criteria for living kidney donors. Transplantation. 2013;96(11):975-980.

19. Wu E-H, Wojciechowski D, Chandran S, et al. Prevalence of abdominal aortic calcifications in older living renal donors and its effect on graft function and histology. Transplant Proc. 2014;46(2):359-362.

20. Seccia TM, Caroccia B, Calo LA. Hypertensive nephropathy. Moving from classic to emerging pathogenetic mechanisms. J Hypertens. 2017;35(2):205-212.

21. Rodrigo E, Segundo DS, Fernández-Fresneda G, et al. Within-donor kidney transplantation renal biopsy affect the donor renal function? Transplant Proc. 2010;42(10):2279-2286.

22. How to cite this article: Dienemann T, Schellenberg J, Keller K, et al. Association of donor hypertension and recipient renal function in living donor kidney transplantation: A single-center retrospective study. Clin Transplant. 2019;33:e13697. https://doi.org/10.1111/ctr.13697