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2 Association between long-term change in arterial stiffness and 3 cardiovascular outcomes in kidney transplant recipients: 4 Insights from the TRANSARTE study

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19 **Abstract:** (1) Background: Increased arterial stiffness is associated with cardiovascular (CV) diseases in end-stage renal
20 disease patients and CV mortality remains higher in kidney transplantation (KT) recipients compared to general
21 population. KT is associated with an improvement of arterial stiffness in the early post-transplant period,
22 followed by a potential reworsening in the late period. In a cohort of KT patients, we evaluated the associations
23 of pulse wave velocity (PWV) measured at different time-points (pre-transplant, early and late post-transplant
24 periods) with CV morbi-mortality, as well as the evolution between these measurements with the CV morbi-
25 mortality. (2) Methods: 40 KT recipients with a 10-year follow-up were included. The association of PWV with
26 CV events was assessed with multivariable cox analysis. Backward linear regressions were conducted to identify
27 the determinants of PWV at 1-year and those of the long-term evolution of PWV after KT (delta PWV at 1 year –
28 latest PWV). (3) Results: The absence of arterial stiffening during long-term follow-up after KT is associated with
29 a lower CV outcomes rate [(HR for the delta PWV = 0.76 (0.58-0.98), p=0.036]. Age at KT is associated with the
30 worsening of arterial stiffness in the late post-transplantation period [β for the delta PWV = -0.104, p=0.031]. A
31 high PWV at one year was associated with a potential for recovery during follow-up [β = 0.744, p<0.0001]. (4)
32 Conclusion: The absence of PWV worsening in the late post-transplantation period was significantly associated
33 with a lower risk of CV events whereas early changes in PWV were not. Finding an intervention able to reduce
34 long-term PWV could improve the prognosis of KT recipients.

35 **Keywords:** arterial stiffness, cardiovascular diseases, kidney transplantation, pulse-wave velocity

36 1. Introduction

37 Cardiovascular (CV) diseases are the leading cause of death in patients in end-stage renal disease
38 (ESRD). After kidney transplantation (KT) and the restoration of renal function, the risk of CV
39 mortality remains high compared with the general population [1]. Increased PWV, a marker of arterial
40 stiffness, has been reported to be a strong risk factor of CV morbi-mortality in ESRD [2]. In KT, some
41 studies also reported this association [3, 4].

42 The mechanisms underlying arterial stiffness in KT are numerous, involving the pretransplant
43 history of patients (duration of ESRD or dialysis, and co-morbidities such as hypertension or
44 diabetes). Age also remains a key determinant of PWV in KT [5]. Nevertheless, data on the evolution
45 of PWV suggest a decrease in PWV during the first year after transplantation [6, 7] followed by an
46 increase in PWV after that point [1]. This long-term deterioration of PWV may indicate that factors

arising with transplantation, e.g. immunosuppressive drugs could have a detrimental impact on PWV [8]. It was also reported that that donor age was as an independent factor for PWV in KT with a deceased donor [9].”

Therefore, considering the potential improvement of arterial stiffness in the early post-transplantation period [6, 7], and the potential reworsening in the late-transplantation period [1], we aimed to evaluate the associations between CV morbi-mortality and PWV measured at different time-points (pre-transplantation, early post-transplantation, and late post-transplantation periods), as well as the evolution between these measurements with the CV morbi-mortality, in a cohort of kidney transplant patients. In this framework, we investigated the association of arterial stiffness with CV events in KT recipients from the monocentric TRANSARTE study (Transplantation and Arteries).

2. Materials and Methods

2.1. Study population

A detailed description of the TRANSARTE study have been published previously [7]. Briefly, 100 ESRD patients were recruited from the waiting list of the University Hospital of Nancy to characterize the evolution of arterial stiffness after KT in a population of ESRD patients. Among the kidney-transplanted patients, the present study was carried out on 40 renal transplant recipients with available predefined PWV measurements, as previously described [7]. The composite primary outcome of the study is CV event (defined by acute coronary syndrome, myocardial infarction, angioplasty, vascular angioplasty, coronary bypass, ischemic or hemorrhagic stroke, angioplasty of lower extremity arteries, amputation, and atrial fibrillation).

2.2. Measurement of PWV

PWV measurements were performed using the Complior[®] technique (ALAM medical), which simultaneously records arterial pulse waves at carotid and femoral sites. Propagation time (t) of the incident wave was measured through mechanotransducer probes, carotid-femoral distance (D) was evaluated with a tape measure, and PWV (m/s) was obtained by the formula $PWV = D * 0.8 / (t)$.

2.3. Statistical Analysis

Analyses were performed using R version 4.0.2 (R Development Core Team, Vienna, Austria). Means are presented with SD and median with 25th and 75th percentiles. P-values are considered significant if < 0.05 . Association of PWV with CV events was assessed using Cox models. Backward linear regression was performed to identify the determinants of PWV at 1-year and absolute changes in PWV post-transplantation (delta between PWV before transplantation and at 1-year, and between 1- and 4-years post-transplantation). Gender, age at transplantation, mean arterial blood pressure (MBP), hypercholesterolemia, diabetes mellitus, smoking, history of angina or myocardial infarction, previous strokes, CNI (Tacrolimus/ Cyclosporine) and cause of ESRD were considered as independent variables. In addition, PWV at one-year post-transplantation was considered in the model focusing on late change in PWV. All variables with a $p < 0.15$ in univariable analysis were used as candidate variables in the multivariable model prior to backward selection procedures.

3. Results

3.1. Baseline characteristics of patients

In the 40 patients receiving either a living (n=6) or a deceased (n=34) donor allograft, the median age at transplantation (years) was 53 [47-60]. 19 (47.5%) were female. Of the subjects, 5 (12.5%) were diabetic, 2 (5.0%) had history of angina or myocardial infarction and 2 (5.0%) had previous strokes. The mean pre-transplantation, 1-year post-transplantation and latest post-transplantation PWVs (m/s) (respectively measured at a median delay of 7 [2-11] months before KT, 13 [11-25] months after KT, and 52 [37-62] months after KT) were 8.9 ± 2.45 , 9.0 ± 2.8 and 8.9 ± 2.4 (m/s), respectively ($p=0.96$). The majority of patients received calcineurin inhibitors (CNI) (95%), most of them cyclosporine (55.3%). During the median follow-up period of 10.9 years, 12 patients died, 11 patients had a CV event and 6 patients returned in dialysis (Table 1).

Table 1. Baseline characteristics and outcomes of patients

	Overall population N=40
Baseline characteristics	
Female (%)	19 (47.5)
Age at transplantation (years)	53 [47-60]
Medical history	
Hypercholesterolemia (%)	20 (50.0)
Smoking (%)	16 (40.0)
Diabetes (%)	5 (12.5)
History of angina or myocardial infarction (%)	2 (5.0)
Previous Strokes (%)	2 (5.0)
Cause of ESRD (%)	
Diabetes	2 (5.0)
Glomerulopathy	7 (17.5)
Malformation	8 (20.0)
Polycystic kidney disease	10 (25.0)
Vascular	6 (15.0)
Other	7 (17.5)
Pre-transplantation dialysis (%)	30 (75.0)
Hemodialysis (%)	23 (76.7)
Peritoneal dialysis (%)	7 (23.3)
Dialysis duration (years)	2.7 [2.1-3.5]
Transplantation characteristics	
Calcineurin inhibitors (%)	38 (95.0)
Cyclosporine (%)	21 (55.3)
Tacrolimus (%)	17 (44.7)
Donor type	
Living donor (%)	6 (15.0)
Deceased donor (%)	34 (85.0)
Standard criteria donors (SCD)	17 (51.5)
Expanded-criteria donors (ECD)	16 (48.5)
Arterial stiffness characteristics	
Duration between pre-transplantation PWV and transplantation (months)	7 [2-11]
Pre-transplantation PWV (m/s)	8.9 ± 2.5
Pre-transplantation mean arterial blood pressure (mmHg)	101 ± 14
Duration between transplantation and 1-year post-transplantation PWV (months)	13 [11-25]
1-year post-transplantation PWV (m/s)	9.0 ± 2.8
1-year post-transplantation mean arterial blood pressure (mmHg)	94 ± 12

Duration between transplantation and the latest post-transplantation PWV (months)	52 [37-62]
The latest post-transplantation PWV (m/s)	8.9 ± 2.4
The latest post-transplantation mean arterial blood pressure (mmHg)	91 ± 12
Post-transplantation characteristics	
eGFR at one year	48.5 [40.5-54.3]
eGFR at the last contact	
All patients	48.0 [25.8-53.8]
Not back to dialysis patients	48.5 [42.3-56.8]
Follow-up time (years)	10.9 [8.2-12.0]
Back to dialysis or preemptive retransplantation (%)	6 (15.0)
Death (%)	12 (30.0)
CV events post-transplantation (%)	11 (27.5)

96 Data presented as mean ± standard deviation; number (percent); and median [interquartile range].

97 Abbreviations: ESRD, end-stage renal disease; PWV; pulse wave velocity; eGFR; estimated glomerular filtration rate; CV,
98 cardiovascular.

99 CV events post-transplantation, the composite primary outcome of the study, is defined by acute coronary syndrome,
100 myocardial infarction, angioplasty, vascular angioplasty, coronary bypass, ischemic or hemorrhagic stroke, angioplasty of
101 lower extremity arteries, amputation, and atrial fibrillation.

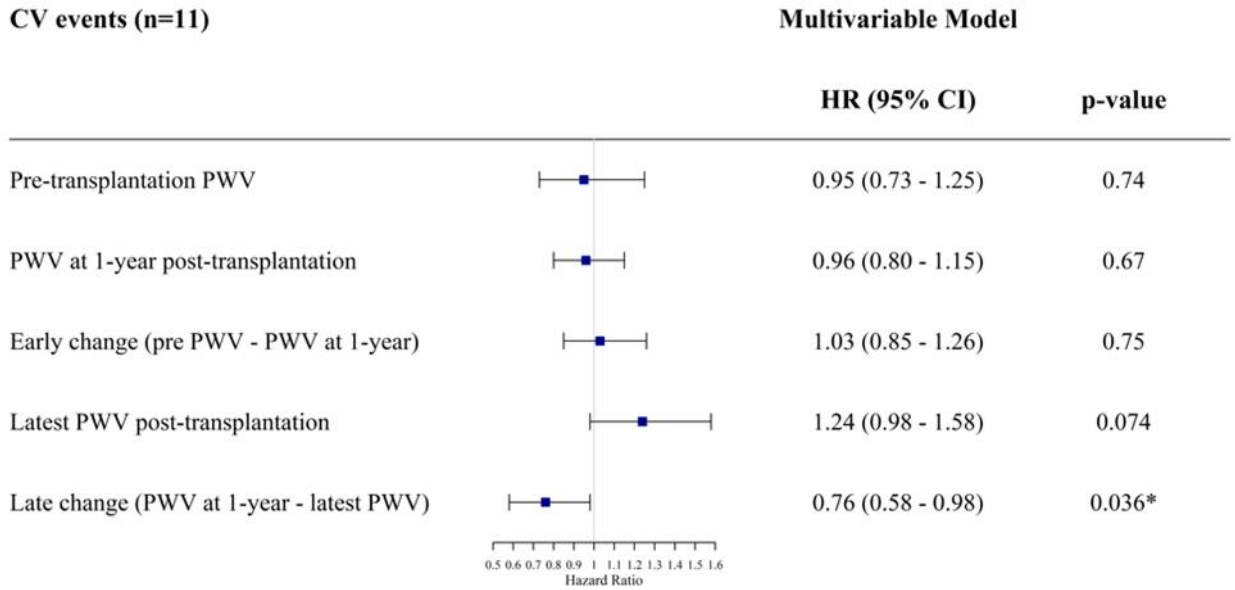
102 3.2. Association of PWV with CV events

103 In multivariable analysis adjusted for PWV post-transplantation at 1-year and age at transplantation,
104 the absence of arterial worsening in the late post-transplantation period was significantly associated
105 with a lower risk of CV events [(HR for the delta PWV at 1 year – latest PWV = 0.76 (0.58-0.98)]. On
106 the contrary, the evolution of PWV between the pre-transplant period and the early post-
107 transplantation period, as well as the PWV at 1 year, was not significantly associated with CV morbi-
108 mortality (Figure 1). The complete output of the Cox models is provided in Supplementary Table S1.

109 3.3. Determinants of PWV using backward linear regression

110 The backward multivariate regression analyses identified age at KT and diabetes were significantly
111 associated with an increased arterial stiffness at 1-year post-transplantation ($\beta=0.013$, $p=0.006$ and
112 $\beta=0.509$, $p<0.0001$, respectively). Age at KT was also associated with the worsening of arterial stiffness
113 in the late post-transplantation period, even after adjusting for PWV at 1-year [β for the delta (PWV at
114 1 year – PWV at 4 years = -0.104, $p=0.031$]. A higher PWV at 1-year was associated with PWV decrease
115 over the late post-transplantation period [$\beta=0.744$, $p<0.0001$] (Figure 1). Importantly, MBP was not
116 retained as a significant factor in the selection process. A detailed description of the backward
117 regression model is provided in Supplementary Table S2.

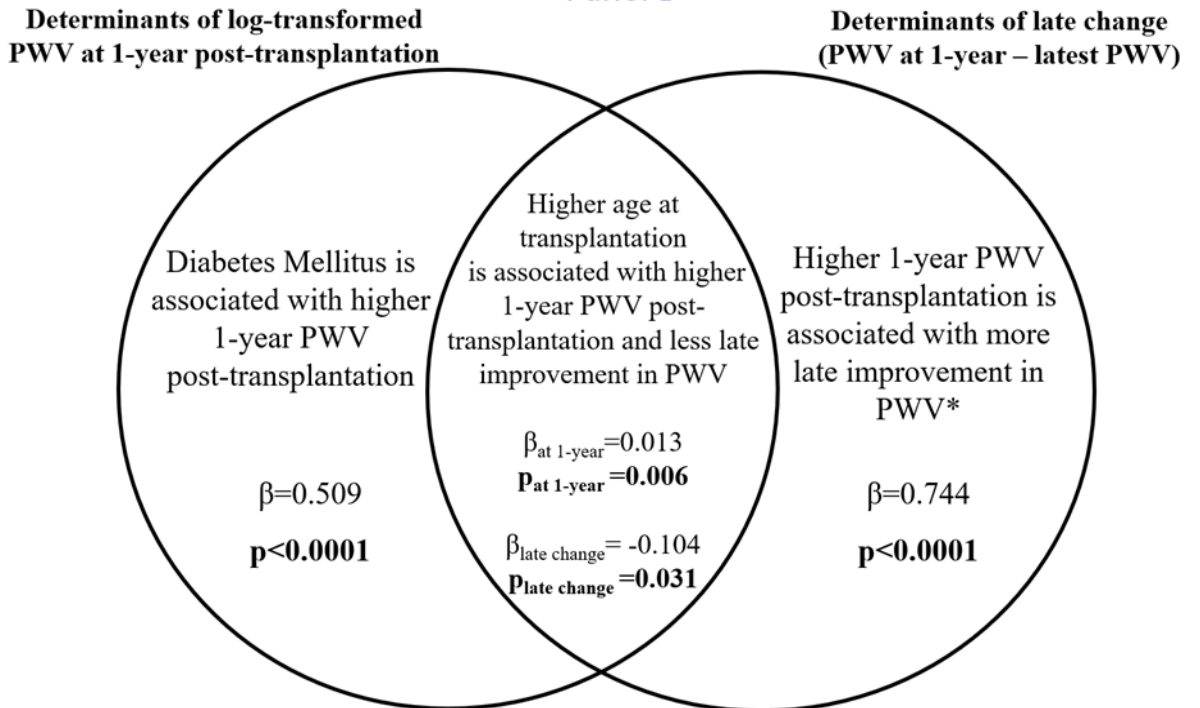
Panel A



*p-value <0.05;
 All models were adjusted for age at transplantation;
 PWV change was adjusted for the baseline PWV on top of age at transplantation

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Panel B



Age at transplantation: PWV at 1-year was put into the model of late change in PWV as independent variable.

***PWV at 1-year post-transplantation was used alone in the model.**

Figure 1. (a) Forest plot of the association between pulse wave velocity (PWV) and cardiovascular (CV) events; (b) the determinants of PWV using backward linear regression.

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4. Discussion

Despite the improvement of renal function conferred by KT, CV mortality remains higher in KT recipients compared with the general population. In KT, some studies demonstrated that an increased arterial stiffness was associated with CV mortality [3, 4]. Nevertheless, the evolution of arterial stiffness is complex after KT; some studies reported an early improvement [5, 6], and others reported a long-term reworsening [1]. Vascular remodeling is complex and involves alterations of extracellular matrix by uremic toxins which are not fully reversed by KT [6]. Moreover, immunosuppressive therapy is associated with hypertension, diabetes or dyslipidemia and may indirectly or directly impact the vascular system.

The present study focuses on the association between CV morbi-mortality and the PWV measured at different time-point, as well as the evolution of the PWV through time. Of note, despite the low number of patients, we had for the first time the opportunity to measure the arterial stiffness in the pre-KT, the early post KT, and the late post KT periods. Moreover, we analyzed CV outcomes after a ten-year follow-up period.

In a study on 220 kidney transplant recipients, carotid-femoral PWV evaluated at 3 and 12 months after KT was significantly associated with morbi-mortality 5.5 years after KT, whereas delta of PWV between month-12 and month-3 was not [8]. However, the present study added that an increased PWV between month-12 and month-48 is associated with CV events (adjusted for PWV at 1-year after KT and age at KT) in kidney recipients 10 years after KT. This suggests the impact of non-traditional factors in the late post KT period, probably related to immunosuppressive therapy.

Unsurprisingly, age is associated with increased PWV at one year, but also with less improvement in the long-term post-transplantation period. Ignace et al. previously reported that older patients had a higher improvement of PWV in the early post-transplantation period at 3 months post KT [9]. We can hypothesize that despite this early improvement, arteries from older patients are more prone to deterioration related to immunosuppressive regimens after a long-term exposition.

On the contrary, increased PWV at one year is associated with increased potential improvement in the long-term post-transplantation period. One can hypothesize that arterial stiffness mainly related to CKD but not age has a greater potential of recovery after KT, and that the susceptibility of the vascular system to immunosuppressive therapy is less pronounced among the youngest patients with ESRD.

It is worth mentioning that, similarly to the results of Kolonko et al. [10], history of diabetes mellitus was a significant determinant of PWV 1-year after transplantation in the present study. Of note, diabetes mellitus was not related to the worsening of PWV change post transplantation, suggesting the stability of PWV in diabetic patients after 1-year of KT. Indeed, it was evident that patients with greater age, diabetes mellitus and higher PWV at baseline had an increased PWV at 1-year after transplantation [11, 12].

5. Limitations

This study is a single-center study with a small sample size. This prevented the use of more advance statistical analysis such as splines to determine the most adequate prognostic PWV thresholds or the addition of some possibly important covariates in the multivariable analysis. However, we assessed ESRD-related arterial stiffness over a long period of time in a peculiar population of kidney transplanted patients, something that has not been reported previously. Further long-term studies should be conducted better ascertain the long-term changes in PWV following KT.

There was no preemptive KT in this cohort. Therefore, it was not possible to include the residual renal function before KT to assess its potential impact on the evolution of arterial stiffness after KT.

6. Conclusions

In this analysis, the absence of pulse wave velocity (PWV) worsening in the late post-transplantation period was significantly associated with a lower risk of CV events. In contrast, the change of PWV observed early during the post transplantation period was not associated with CV events.

In summary, the present study suggests that the worsening of aortic stiffness in the late post KT period has a negative impact on the long-term CV morbi-mortality. Ultimately, finding an intervention able to reduce PWV could improve the prognosis of KT recipients.

Supplementary Materials: The following are available online, Table S1: Association of pulse wave velocity (PWV) with CV events; Table S2: Determinants of absolute changes in pulse wave velocity (PWV) post-transplantation (PWV at 1-year – latest PWV) using backward linear regression.

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