Cardiovascular risk assessment in children and young adults following kidney transplantation (NKFI-ID: 124549)

Cardiovascular (CV) morbidity is one of the leading causes of mortality in patients with chronic kidney disease (CKD). The CV risk is three magnitudes higher as in the general population, and it decreases, but remains two magnitudes higher after successful kidney transplantation. The data are similar in children although the risk factors are in part different from those of the adult population. Thus, one may not apply directly the results of adult studies on CV risk assessment to the pediatric population and pediatric studies are needed.

Our group was the first to develop age and height normalized reference values for assessing arterial stiffness based on pulse wave velocity (PWV) in children. We have shown in pilot studies, that PWV is related to the uremic vintage and kidney function, the metabolic bone disease and body composition in children on dialysis and after kidney transplantation (KTX).

The project aimed

1. To complete our work on validating the surface distance measurement used in establishing our database of healthy children by a sub-study using intra-arterial distance assessment by MRI

2. To use the unique opportunity to follow up our renal transplant patient cohort 8 to 10 years after kidney transplantation and comparing their actual data to those measured at entry into the study.

3. In the cross-sectional part of the study we recruited a new cohort of KTX patients to include complementary data based on a larger study population. This part of the study was planned to evaluate echocardiographic imaging more in detail, based on the technique of speckle tracking echocardiography to asses subclinical myocardial dysfunction and its determinants in kidney transplanted children with stable renal function.

1. Distance Measurement for Pulse Wave Velocity Estimation in Pediatric Age: Comparison with Intra-arterial Path Length

Background and aims

Central pulse wave velocity (PWV) is a marker of arterial stiffness and is calculated by dividing the pulse wave travel distance by the transit time. However, there is no consensus as to the ideal distance measurement in children.

The aim of our study was to identify the more reliable method to assess the distance measurement in the pediatric age.

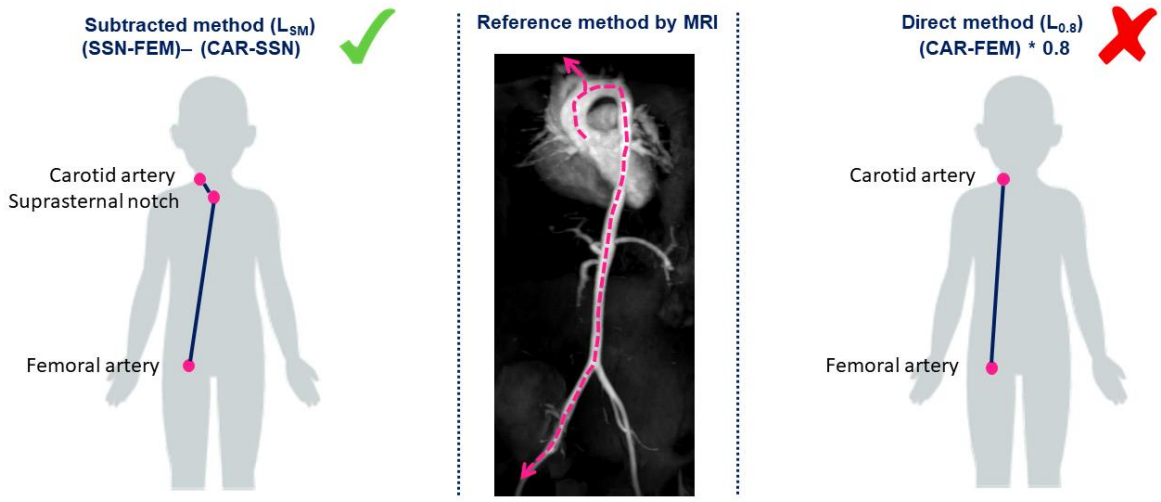
Methods

Carotid-femoral PWV was measured by applanation tonometry in 988 healthy children aged 6.5–19.9 years. Two different surface distances were assessed: the subtraction method, representing the distance from the suprasternal notch to the femoral artery minus the distance from the carotid artery to the suprasternal notch, and the direct method, which is recommended in the adult guidelines, consisting of 80% of the distance from the carotid artery to the femoral artery. Both methods were compared with the actual path length determined by magnetic resonance imaging (MRI) in 31 children.

Results

Subtraction and the direct method were significantly correlated in patients <14 years of age and the corresponding PWV values showed good agreement. In children aged ≥14 years, a significant difference between the two methods was found: subtraction - direct distance = -45 ± 28 mm, with a significant difference in the resulting PWV values = -0.57 ± 0.35 m/s ($p < 0.0001$). This result was confirmed by MRI, showing a 10% overestimation in distance measurement by the direct method in subjects aged ≥14 years, resulting in a significantly higher PWV. (Fig. 1.)

Figure 1.



Conclusions

These data suggest a greater reliability of the subtractive method of distance measurement compared to the direct method in children.

2. Follow-up of Blood pressure, Arterial Stiffness and GFR in Pediatric Kidney Transplant Recipients

Pediatric kidney transplant recipients (KTX) were studied for longitudinal changes in blood pressure (BP), arterial stiffness by pulse wave velocity (PWV) and graft function.

Patients and methods

Fifty-two KTX patients (22 males) were included; office BP (OBP) and 24h BP monitoring (ABPM) as well as PWV were assessed together with glycemic and lipid parameters and glomerular filtration rate (GFR) at 2.4[1.0-4.7] (T_1) and 9.3[6.3-11.8] years (T_2) after transplantation (median [range]).

Results

Hypertension was present in 67% and 75% of patients at T_1 and T_2, respectively. Controlled hypertension was documented in 37% and 44% by OBP and 40% and 43% by ABPM.

Nocturnal hypertension was present in 35% and 30% at T_1 and T_2; 24% and 32% of the patients had masked hypertension, while white coat hypertension was present in 16% and 21% at T_1 and T_2, respectively. Blood pressure by ABPM correlated significantly with GFR and PWV at T_2, (Fig. 1.a and 1.b.) while PWV also correlated significantly with T_2 cholesterol levels. Patients with uncontrolled hypertension by ABPM had a significant decrease in GFR (Fig. 2.). Anemia and increased HOMAi were present in approximately 20% of patients at T_1 and T_2.

Figure 1.

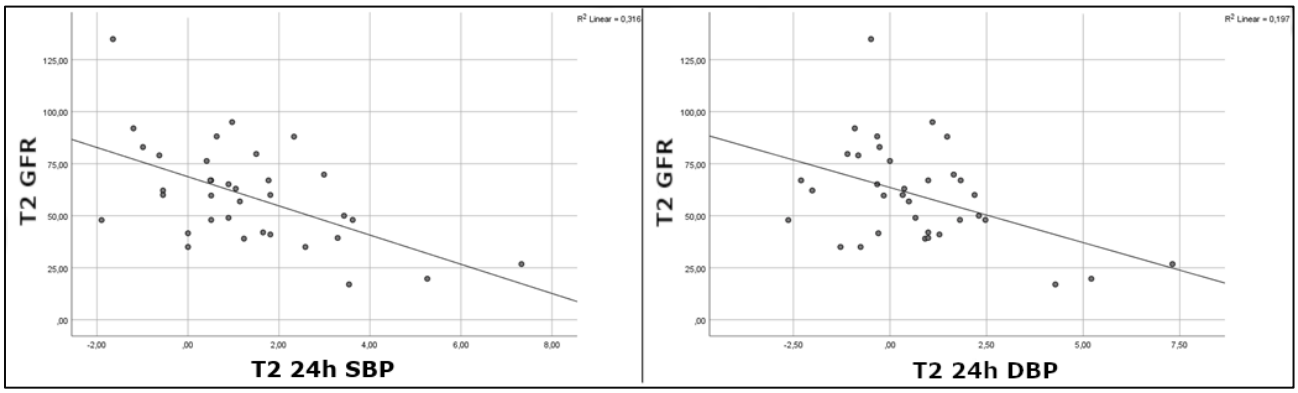


Figure 1a.: Correlation of 24h ABPM blood pressure values and GFR at the second follow-up.
GFR: glomerular filtration rate
SBP systolic blood pressure
DBP: diastolic blood pressure

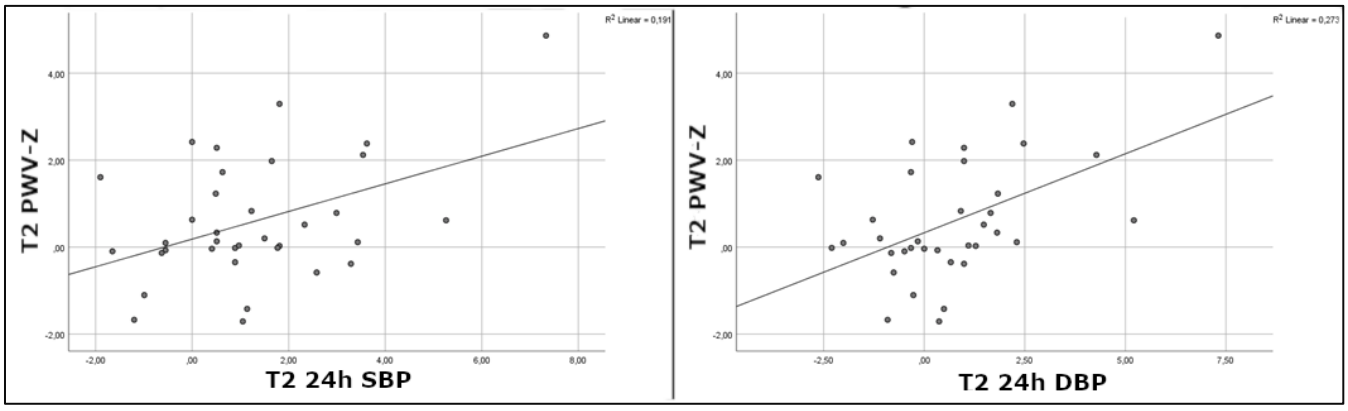
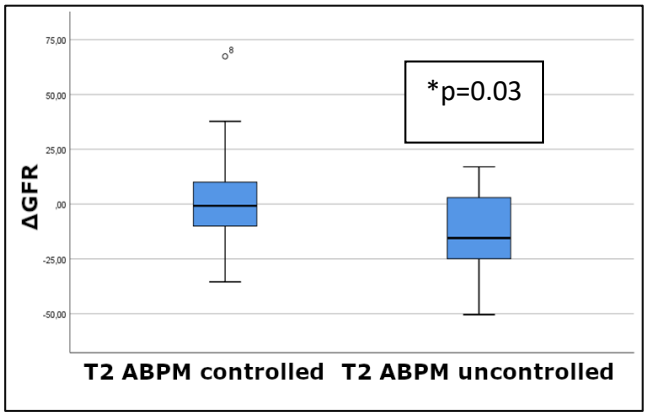


Figure 1b.: Correlation of 24h ABPM bloodpressure values and PWV-Z at the second follow-up.
PWV: pulse vawe velocity
SBP systolic blood pressure
DBP: diastolic blood pressure

Figure 2.



Comparison of changes in GFR between controlled and uncontrolled hypertensive patients at the second follow-up.
ΔGFR: GFR difference between T2 and T1 ($T2_{GFR}$ - $T1_{GFR}$)

Conclusion

Pediatric KTX patients harbor risk factors that may affect their cardiovascular health. While we were unable to predict the evolution of renal function based on PWV and ABPM at T_1, these risk factors correlated closely with GFR at follow-up suggesting that control of hypertension may have an impact on the evolution of GFR.

3. Subclinical cardiac dysfunction in pediatric kidney transplant recipients identified by speckle-tracking echocardiography

Renal transplantation (KTX) improves prognosis in children with end-stage kidney disease; still, these patients are prone to cardiovascular damage due to multiple risk factors. Our aim was to assess myocardial structure and function in pediatric KTX by conventional and speckle tracking echocardiography (STE) in association with established cardiovascular risk factors.

Methods

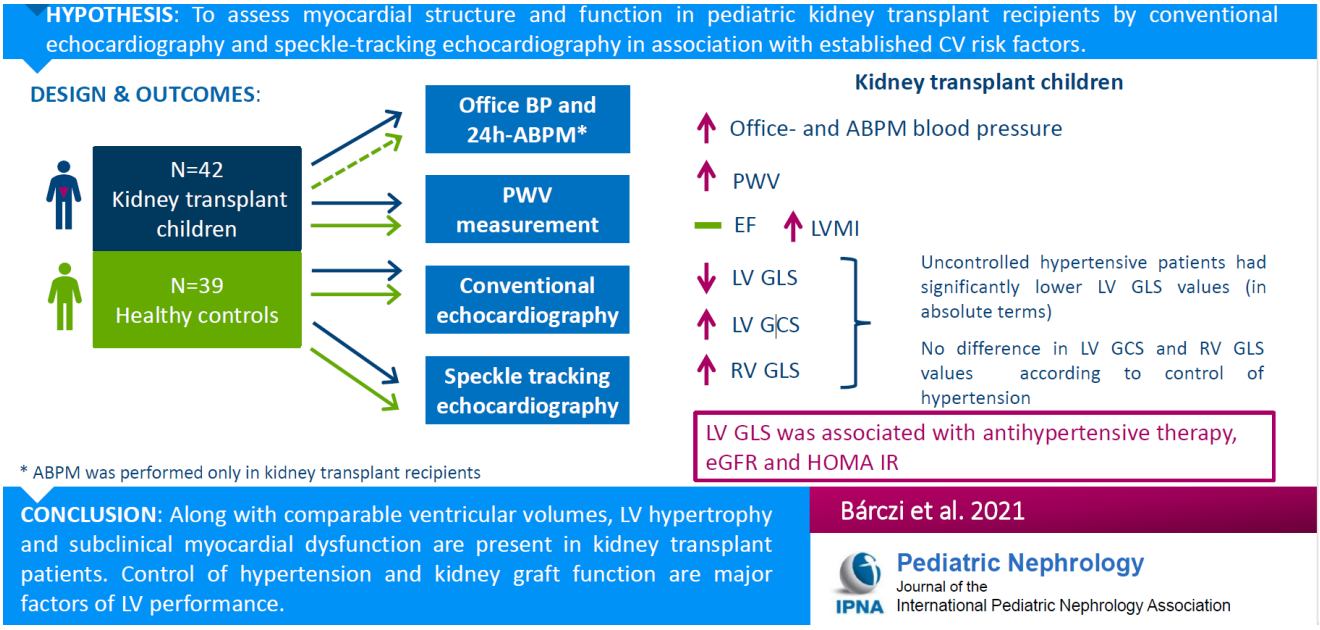
Forty-two KTX and 39 healthy age- and gender-matched children were evaluated. KTX recipients were further categorized according to the control of hypertension assessed by 24-hour ambulatory blood pressure monitoring (ABPM). Subjects underwent pulse wave velocity (PWV) measurement, conventional echocardiography and 2-dimensional STE. Left- and right ventricular (LV, RV) global longitudinal strain (GLS) and LV circumferential strain (GCS)

were measured. Glomerular filtration rate (eGFR) was calculated according to the Schwartz formula.

Results (Fig.1.)

KTX patients had increased blood pressure and arterial stiffness. LV ejection fraction (EF) was preserved along with elevated LV mass index (LVMi), while LVGLS was significantly lower whereas LVGCS and RVGLS were increased in KTX. Uncontrolled hypertensives had lower LVGLS compared to those with controlled hypertension. Using multiple forward stepwise regression analysis, 24-hour SBP and relative wall thickness (RWT) were independent determinants of LVMi, whereas antihypertensive therapy and eGFR were independent determinants of LVGLS.

Figure 1.



Conclusions

Cardiac morphology and function show distinct changes after KTX. Along with comparable ventricular volumes, LV concentric hypertrophy and subclinical myocardial dysfunction are present. Control of hypertension and renal graft function are major factors of LV performance. STE may be useful to reveal early myocardial dysfunction in pediatric KTX.

4. Difficulties during the study

Patient involvement and follow-up became difficult and at times impossible after the outbreak of the COVID-19 pandemic. That is why we asked for a one-year extension to carry out the investigations, by the end of which we were able to complete the tasks set. During the lockdown periods, we have published review articles and case reports related to the topic, as hypertension, renal insufficiency and transplantation, that, in addition to fulfilling the task set, also contributed to a broader national and international elucidation of the topic. These works are listed in the bibliography.