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Daily monitoring of arterial stiffness in children with end-stage renal disease

DISSERTATION

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ABBREVIATIONS

AS	arterial stiffness
PWV	pulse wave velocity
PTT	pulse transit time
AIx	augmentation index
CKD	chronic kidney disease
ESRD	end-stage renal disease
Tx	transplantation
HD	hemodialysis
BP	blood pressure
Ca	calcium
P	phosphate
PTH	parathyroid hormone
ACE	angiotensin converting enzyme inhibitor
CI	confidence interval

1 INTRODUCTION

1.1 Hemodynamic factors affecting pulse pressure amplitude

Ejection of blood from the heart into the aorta produces a pressure wave that extends to other arteries throughout the body. This forward travelling (incident) pressure wave (P1) is reflected at the arterial tree, generating a reflected „echo“ wave (P2) travelling backward towards the ascending aorta. The incident and reflected waves are summed up to pressure wave (Figure 1) (Appendix) (**Zitt E 2008**). The amplitude of the incident pressure wave and the timing of its intersection with the reflected pressure wave depends on the elastic properties of the arterial wall (**London GM 1994, Weber T et al. 2008, Nürnberger J 2009**).

Arterial stiffness can be quantified by the measurement of several parameters such as pulse wave velocity (PWV), analysis of pulse wave contours, measurement of elastic modus (mainly augmentation index „AIx“), stress-strain relationships, etc. (**Benetos A, Lacolley P 2006**). PWV (in m/s) is derived by dividing the distance from jugulum to symphysis (in m) to the difference in time (in s) between the beginning of the first wave and the beginning of the second (reflected wave). AIx (in %) can be obtained by calculating the quotient of the pressure peak of the initial and the reflected wave (Figure 2) (Appendix) (**Zitt E 2008, Mitchell GF 2006, Baulmann J et al. 2008**). During the past years, among these approaches, PWV and AIx have become the most reliable for the evaluation of arterial stiffness in clinical and epidimiological studies (**Benetos A, Lacolley P 2006**).

The property of the wall is described by two terms, arterial compliance and distensibility (**Baulmann J et al. 2010**). Distensibility is a measure of the elastic properties of an artery, whereas compliance is a measure of the local vessel capacity to respond to changes in blood volume (**Urbina EM et al. 2009**).

Vascular stiffening develops from a complex interaction between stable and dynamic changes involving structural and cellular elements of the vessel wall. The stability, resistence, and compliance of the vascular wall are dependent on the relative contribution of its 2 prominent scaffolding proteins: collagen and elastin (Figure 3) (Appendix) (**Zieman SJ et al. 2005**). Histological examination of the intima of stiffened vessels reveals abnormal endotthelial cells, increased collagen, broken elastin molecules, infiltration of vascular smooth muscle cells, macrophages and mononuclear cells, and increased matrix metalloproteinases, transforming growth factor, intracellular cell adhesion molecules, and cytokines (**Lakatta EG, Levy D 2003**).

1.2 Cardiovascular complications in children with chronic kidney disease

The survival rate of children with chronic kidney disease **(**CKD) in the U.S. remains low: for children on dialysis the lifespan decreases by 40-60 years and also decreases by 20-25 years for transplant patients compared to a US population of similar age and race (**Mitsnefes MM 2008**). In a statement by the American Heart Association on cardiovascular risk reduction in high-risk pediatric patients, those with CKD were classified in the highest risk stratum, alongside individuals with homozygous familial hypercholesterolemia, diabetes mellitus type 1, heart transplants or coronary aneurysms due to Kawasaki disease (**Lilien MR, Groothoft JW 2009**). The traditional risk factors for cardiovascular disease such as hypertension, dyslipidemia, diabetes are highly prevalent in CKD populations. However, there are many other cardiovascular risk factors that are either „uremia specific", or at least much more common in patients with CKD than in the general population. These include anemia, hyperparathyroidism, hyperhomocysteinemia, malnutrition and chronic low grade inflammation (**Wright J, Hutchison A 2009**). The risk factors for cardiac and vascular injury in children are similar to those of adults (**Mitsnefes MM 2008**) (Table 1).

Arterial stiffening in renal disease involves several mechanisms. Intima-medial thickening occures in response to increased wall stress from hypertension. Increased extracellular matrix collagen content and vascular smooth muscle cell proliferation are promoted by activated systemic and local renin-angiotensin-aldosterone system. Furthermore, elasticity of collagen and other extracellular matrix proteins are reduced because of advanced glycation end products formation. Arterial stiffening in renal disease is also driven by diffuse calcifications in the arterial media without much inflammation, producing a histological picture quite different from calcifications in complex atherosclerotic plaque. Some data support a role of osteoblast-like cells that secrete bone matrix proteins (**London GM et al. 2005, Zieman SJ et al. 2005, Persy V 2008)**. There is evidence that arterial stiffness becomes progressively worse as CKD progresses (**Querfeld U 2004 , Toussaint ND, Kerr PG 2007**, **Fassett RG et al. 2009**).

In adults with ESRD, calcifications are found in both the intimal and medial layers of the arterial wall. Intimal calcification is the result of advanced atherosclerosis. In contrast, diffuse, nonocclusive, medial calcification is more dominant than intimal calcification in young patients with ESRD and is closely associated with calcium-phosphate disorders, hypertension, long-term dialysis. Medial calcification increases arterial stiffness. High serum phosphate levels can induce both intimal and medial calcification (**London GM et al. 2003**). The factors in serum that could be responsible for medial calcification and osteoblastic differentiation of vascular cells are parathyroid hormone (PTH) fragments, vitamin D and high extracellular phosphate (**Safar ME et al. 2004**).

In young subjects with distensible arteries and low PWV, the reflected waves impact on central arteries during diastole, after ventricular ejection. The earlier return means that the reflected wave impacts on the central arteries during systole rather than diastole, amplifying aortic and ventricular pressure during systole and reducing aortic pressure during diastole, a finding which is well-known in uraemic patients. This will increase myocardial oxygen consumption, tend to coronary blood supply, induce myocardial hypertrophy, impair ventricular filling and ejection (**London GM 1994**).

There are two parallel processes involved in the development of cardiovascular disease in CKD patients. The first is cardiac remodelling leading to hypertrophy of the left ventricle as a response to mechanical or hemodynamic overload. The second process involves vascular injury: atherosclerotic, artheriosclerotic and vascular calcification (**Mitsnefes MM 2008**)

Table 1
Cardiovascular risk factors of chronic kidney disease (**Mitsnefes MM 2008)**

Traditional risk factors	CKD-related risk factors
Higher age	Decreased GFR
	Proteinuria
Male gender	Periph. renin-angiotensin-aldosterone activity
Hypertension	White race
↑ LDL Cholesterol	Dyslipidemia
↓ HDL Cholesterol	Hypoalbuminemia
Diabetes mellitus	Hemodynamic overload
Tobacco use	Anemia
Physical inactivity	Thrombogenic factors
Psychosocial stress	Hyperhomocysteinemia
Family history of CVD	Oxidative stress
LVH	Chronic inflammation
Obesity	

1.3 Arterial stiffness in healthy and in end-stage renal disease children (ESRD)

There are only a few studies of arterial stiffness in healthy and in end-stage renal disease children.

A report was done about brachial-ankle PWV (ba PWV) measures in 205 normotensive, healthy adolescents. They found that baPWV was greater in male patients than in female patients, and higher in African-American than Caucasian volunteers between the ages of 12 and 21 years (**Alpert BS, Collins RT 2007)** (Table 2).

BaPWV was measured in 970 healthy Japanese children (500 boys and 470 girls), and set up the normal baPWV values of children on the basis of age and gender (Table 2). The values of baPWV in children were higher in boys than in girls, and baPWV increased with age in both genders. Age, blood pressure and heart rate were significant determinants of baPWV in both male and female subjects, while the obesity index had no correlation with baPWV (**Niboschi A et al. 2006)**.

The finding of sex differences in a group of 262 healthy Korean adolescents was confirmed. In that study, correlations with blood pressure and BMI were demonstrated (**Im JA et al. 2007)** (Table 2).

Carotid-femoral PWV was measured by applanation tonometry in 1008 healthy subjects (ages between 6 and 20 years, 495 males). It was found that PWV correlated positively with age, height, weight, and blood pressure while correlating negatively with heart rate (**Reusz GS et.al. 2010**).

A typical aortic PWV of 6 to 7 m/s and reflected wave transit time 120-150 ms suggests that the effective reflecting distance is 40-50 cm from the heart in healthy young women and men, respectively. AIx falls slightly with growth during childhood and increases rapidly between 20 and 40 years of age. In contrast, pulse pressure, aortic PWV and forward wave amplitude increase moderately before 40 years of age (**Mitchell GF 2006**).

With young subjects the aortic, a.iliaca and a. femoralis PWV are 4-5 m/s and 8-9 m/s respectively (**Baulmann J et al. 2010**).

Values of baPWV and blood pressure in all four limbs of 123 healthy children between the ages of 8-19 years were measured (Table 2). Patients were examined in supine position and pulse wave contours were recorded from the four extremities simultaneously by the volume plethysmographic machine. There was no statistically significant difference between baPWV in the two groups. On the other hand values of baPWV in prepubescent females were higher than those in males and then became lower after puberty. The body weight correlated positively with baPWV, but BMI did not (**Wang CF et al. 2008)**.

The normal values of PWV (188 healthy subjects ages 6-23 years) and in children with ESRD (n=11) and after transplantation (Tx) (n=25) were established. The aim of the study was to evaluate PWV in children who underwent Tx, to assess which form of PWV was most suitable in patients after Tx and to compare PWV of the Tx patients to similar data of patients with ESRD studied previously. Known cardiovascular risk factors such as blood pressure, calcium and phosphate and parathyroid hormone levels as well as cumulative doses of calcitriol were analysed. PWV was measured by applanation tonometry (**Cseprekal O et al. 2009)** (Table 3). Seventeen patients had hypertension and received antihypertensive treatment. The diagnosis of hypertension was based on 24-hour ambulatory blood pressure measurement.

In the healthy population, the PWV values did not differ significantly between male and female subjects at any given age. The mean PWV was 4.93 m/s (Table 2). There was a linear correlation of PWV with age, height, weight, systolic BP and diastolic BP and a negative correlation with the heart rate.

The PWV of transplant patients matched the PWV of the control subjects of the same age. Although within the normal range, the systolic BP of Tx was higher than that of the control group. Ca did not change after Tx; creatinin, P, Ca*P as well as PTH decreased significantly. The laboratory parameters at the evaluation one year after transplantation were similar to those at the last control (Table 3). PWV may be reduced after Tx suggesting that uremia-induced cardiovascular changes might be reversible. Ca*P and the cumulative dose of calcitriol are closely related to increased arterial stiffness (**Cseprekal O et al. 2009)**.

Furthermore, the renal Tx seems to reduce or even reverse certain abnormalities seen in dialyzed patients. Tx seems to correct metabolic abnormalities. Aortic PWV was evaluated before and 6 months after Tx in the same children (n=15). Central hemodynamic parameters were measured by applanation tonometry. Eight of the patients were on anti-hypertensive drugs in the period before Tx (**Aoun B et al. 2010)**.

There was no significant difference in PWV and augmentation index in children on chronic hemodialysis and after Tx (Table 3). A positive correlation was found between PWV pretransplant and age. No correlation was found between PWV and Ca*P product neither before or after Tx (**Aoun B et al. 2010)**.

In the study of **Kis E et al. 2008** PWV 133 healthy individuals (6-23 years of age) and 11 patients on dialysis were measured to establish the normal values of PWV and to compare them with those in ESRD. A control group with subjects of equal age, height and weight was used. PWV was measured by a small portable tonometer (PulsePen) that was able to assess carotid artery pressure and to measure pulse wave velocity (PWV) non-invasively (Salvi.P. et al., 2004). There was a significant linear correlation between PWV and age, height, weight, and systolic and diastolic blood pressure and a significant negative correlation to the heart rate.

The PWV of the patients with ESRD did not differ significantly from the age-matched group. On the contrary, patients with ESRD had significantly increased PWV compared with the control group with subjects of similar height and weight (Table 2 & 3). There was no difference between the blood pressure and heart rate parameters of the patients with ESRD and either of the control groups. Eight children were treated with an angiotensin-converting enzyme inhibitor, six with enalapril and calcium channel blocker amlodipin and three patients had normal blood pressure without antihypertensive treatment. This study demonstrated increased PWV as a sign of increased arterial stiffness in children with ESRD.

The influence of mineral and bone metabolism on arterial stiffness in dialyzed (n=11) and renal transplanted (n=17) children was assessed. Among the dialyzed patients, seven were on peritoneal dialysis and four were on hemodialysis. 8 children on dialysis and 11 transplant patients had hypertension and received single treatment (amlodipin, or enalapril, or ramipril) or a combined treatment of ACE inhibitor and ß-blocker and/or a1-receptor blocker. PWV was measured by applanation tonometry (PulsePen). All measurements were done twice to confirm reproducibility (Table 3). A database of 188 healthy subjects (ranging between 6-23 years of age) was used for the calculation (**Kis E et al. 2009)**.

Briese S et al. 2008 studied changes in arterial functions in children after renal transplantation. A total of 36 patients with ESRD ages 6-18 years participated in the study. All patients had a functioning kidney transplant and received immunosuppressants. On the morning of the study patients took their medication, including all antihypertensive agents and immunsuppressants. Measurements of blood pressure, PWV and AIx were performed with the SphygmoCor device with an applanation tonometer. 49 healthy children ages 8-19 served as a control group (Table 2 & 3). Transplant patients and control subjects were matched for age, height, weight and BMI. Significant differences were found in systolic and diastolic blood pressure and in PWV and AIx. Compared with the controls, transplant patients had a significantly higher PWV and AIx. An association was not found with the degree of transplant dysfunction, glomerular filtration rate loss, or dose of immunosuppressive medication. AIx was associated with a serum calcium-phosphorus product and PWV correlated with systolic blood pressure and age.

This cross-sectional study of **Dursun I et al. 2009** included 37 dialysis patients (12 hemodialysis and 25 on peritoneal dialysis), 33 pre-dialysis patients and 18 healthy controls (Table 2). The carotid artery intima–media thickness and PWV were measured by using high-resolution ultrasound. The main aortic PWV in the dialysis group was higher than that in the pre-dialysis and control groups. There was no difference in PWV between the pre-dialysis group and control group. The mean aortic PWV on hemodialysis was higher than that on the peritoneal dialysis patients (Table 3).

Sonography of the common carotid artery was performed at baseline and after 12 months in patients (mean age 13.8 +/- 4.2 years) with CKD stages 3-5. Intima-media thickness and cross-sectional areas of the vessel wall, and lumen were measured. While vascular lesion rapidly progresses in CKD and in dialysis patients, abolition of the uraemic state by transplantation leads to stabilization or partial regression of CKD-associated arteriopathy (**Litwin M et.al. 2008**).

Table 2
Published normal pediatric PWV and AIx values

Age, years	No. of subjects	Method	PWV, m/s	AIx, %	Reference
14.8 (12.9-16.1)	25 (15m/10f)	applanation tonometry	5.14 (4.69-5.58)		Cseprekal O., 2009
13.27±3.3	49 (22m/27f)	applanation tonometry	4.68±0.7	-26,3±13,5	Briese S., 2009
12.1±4.4	18 (11m/7f)	ultrasound	6.29±1.39		Dursun I., 2009
14.8±1.2 14.8±2.6	970 (500m/470f)	oscillometric cuff	9.97±1.3 9.47±1.2		Niboshi A., 2006
14.5±1.2 14.8±1.5	262 (178m/84f)	oscillometric cuff	10.3±0.9 9.6±1.7		Im J.A., 2007
6-23	133	applanation tonometry	5.02±0.89		Kis E., 2008
145	11 (8m/3f)	applanation tonometry	501		Kis E., 2009
8-19	123 (51m/72f)	plethysmographic	1011±159 979±159 (cm/s)		Wang C.F., 2008
15.8±2.4 15.9±2.5	205 (99m/106f)	oscillometric cuff	10.9±1.4 10.4±1.3		Alpert B.S., 2007

Table 3
Published pediatric PWV and AIx values in children with ESRD

Age, years	No. of subjects	Method	PWV, m/s	AIx, %	Reference
Tx 15.1 (13.5-16.7)	25 (15m/10f)	applanation tonometry	5.46 (5.12-5.8)		Cseprekal O., 2009
Tx 14.0±3.4	36 (21m/15f)	applanation tonometry	5.43±0.9	-14.3±15.2	Briese S., 2009
Dialysis 14.3	11 (8m/3f)	applanation tonometry	572		Kis E., 2008
Tx 15	17 (11m/6f)	applanation tonometry	503		Kis E., 2009
Dialysis 13.8	11 (7m/4f)	applanation tonometry	58		Kis E., 2009
Dialysis 10.0±3.8	15 (10m/5f)	applanation tonometry	6.1±1.3	6.93±11.4	Aoun B., 2010
Tx 11.1±4.8	15 (10m/5f)	applanation tonometry	6.5±1.4	-0.53±17.05	Aoun B., 2010

1.4 Arterial function in adults with end-stage renal disease

Arterial function in adults with end-stage renal disease was demonstrated in some studies.

The aim of the report by **Blacher J et al. 2003** was to study the relationships between PWV index and cardiovascular and overall mortality in a population of ESRD patients undergoing hemodialysis. Multiple regression analysis was performed to assess linear associations between PWV and determinants of clinical, biochemical, and cardiovascular parameters in the populations of 242 patients with ESRD, 469 patients without ESRD, and in the entire population. The present study has shown that increased PWV index was a strong predictor of cardiovascular and overall mortality.

The association of impaired renal function expressed as lower GFR (44-81 ml/min per 1.73 m^2) or greater urinary albumin excretion (2-30 mg/mmol) with arterial stiffness (compliance and distensibility of the carotid, brachial, femoral arteries, carotid-femoral transit time and aortic AIx) was studied in 806 individuals. In patients with mild renal insufficiency, both a low GRF and albumin excretion were independently associated with greater arterial stiffness. These findings may explain, in part, why GRF and microalbuminuria are associated with a greater risk for cardiovascular disease (**Hermans MMH et al. 2006)**.

In contrast, **Sengstock D et al. 2009** showed that carotid-femoral PWV has correlated inversely with GFR in the combined group (264 subjects with chronic kidney disease stages 3-5 and in 149 subjects without previously recognized CKD). The combined group had a mean age of 61.9 years, consisting of subjects who were 51% male, 28% diabetic and 79% hypertensive.

The aim of the study by **Verbeke F et al. 2007** was to assess arterial stiffening and wave reflection in renal transplant recipients and healthy controls and to evaluate which factors could explain potential differences. Carotid augmentation index (AIx) and carotid-femoral PWV were measured in 200 transplant recipients and 44 controls using applanation tonometry. The impact of traditional and nontraditional cardiovascular risk factors was assessed using linear regression analysis. AIx (31% vs. 4%) and PWV (8.6m/s vs. 6.6 m/s) were higher in transplant recipients than controls. The signs of arterial stiffness were independently related to GFR, C-reactive protein and transplant kidney function.

A group of 36 patients, ranging from 27 to 68 years of age who had cardiovascular risk assessment and measurement of carotid artery intima media thickness, aorto-femoral PWV, systemic arterial compliance and arterial wave reflection (AIx) was involved. The measurement was performed before patients went on dialysis and 12 months after renal transplantation. Carotid intima media thickness was determined by ultrasound measurement, PWV and AIx by applanation tonometry. After successful renal transplantation there was an overall improvement in cardiovascular risk factors. PWV

(9.6m/s vs. 8.8 m/s) and AIx (24.3% vs. 15.9%) returned to more normal levels, reflecting improvement in blood pressure control and reduced artery stiffness (**Zoungas S et al. 2004)**.

It was demonstrated that cardiovascular risk reduces after kidney transplantation. Diabetic kidney transplant patients (n=33) had comparable PWV, but significantly greater AIx than their non-diabetic counterparts (n=77). Two consecutive measurements within a 1 year interval demonstrated improvements in central PWV. These findings suggested a post-transplant improvement of ventricular function and large arterial stiffness shortly after transplantation, despite evidence of remained kidney-failure-induced small arterial remodelling (**Khoshdel AR et al. 2010)**.

The renal insufficiency (increasing proteinuria and decreasing glomerular filtration rate) appears to be a key cardiovascular risk factor in the general population. In renal transplant recipients the role of graft dysfunction in cardiovascular risk is controversial. Some studies have shown no correlation between graft dysfunction and congestive heart failure or ischaemic heart disease and some have suggested that increased post-transplant serum creatinine levels were strongly associated with cardiovascular risk (Marcen R 2006).

Fassett R et al. 2009 will record aortic PWV AIx, brachial and central blood pressure in 140 patients with acute kidney injury and 12 months after the onset of the acute kidney injury. The group has two hypotheses of study. They will confirm that patients with acute kidney injury will have increased arterial stiffness compared to matched controls and patients who recover kidney function following acute kidney injury will have a concomitant reduction in arterial stiffness.

1.5 Recommendation for Standard Assessment for Clinical Research: a Scientific Statement from the American Heart Association, 2009

Three groups of noninvasive methods are used in the assessment of arterial stiffness:

- analysis of the arterial pressure waveforms
- calculation of the change in diameter of an artery with respect to the distending pressure
- measurement of PWV, which appears to be emerging as the „gold standard“ in studies of adults.

Measurement of the change in arterial diameter as it relates to distending pressure provides a reciprocal of arterial stiffness, defined as arterial distensibility. The method for evaluating brachial artery distensibility by use of waveform analysis of the arterial pressure signals was obtained from a standard cuff sphygmomanometer. The advantages of this noninvasive device include ease of use (a non-sonographer can perform the measurement), lack of observer bias (no manual readings are performed) and ability to perform measurements in the field (the device is portable).

Available modalities for standard assessment of arterial stiffness:

- Doppler ultrasound
- Magnetic resonance imaging
- ECG-gated oscillometric cuff technology
- Pressure tonometers (**Urbina EM et al. 2009**)

The aim of the study of **Wassertheurer S et al. 2010** was to validate the novel method which determines AIx and aortic systolic blood pressure based on an oscillometric method using a common cuff (ARCSolver) against a validated tonometric system (SphygmoCor) in 302 subjects. There was no significant difference in reproductibility of AIx for both methods. The results agree with common accepted tonometric measurements. Its application is easy and for widespread use.

1.6 Monitoring of arterial stiffness in adults

Monitoring of arterial stiffness was done only in adults.

The circadian variation of arterial stiffness in 16 healthy individuals was investigated and the hypothesis that there was a circadian pattern in the arterial stiffness with the circadian variation in the cardiovascular susceptibility was tested. Additionally a nighttime and daytime comparison of arterial stiffness (aortic-brachial pulse transit time) was performed. The greater reduction in the arterial stiffness was temporally coincident with the morning increase in the arterial pressure, heart rate and the lesser arterial stiffness found during the daytime (could be considered as a physiological adaptation to maximal physical activity) (**Bia D et al. 2008)**.

The aim of the study by **Lluberas S et al. 2008** was to assess arterial stiffness (aortic-brachial pulse transit time) in 20 healthy subjects over a 24 hour period of time and to characterize any differences that occured between sleep and wakefulness. As well as in the study of Bia D. 2008, arterial stiffness was greater during sleep than wakefulness, increased during the transition from wakefulness to sleep, and decreased during the transition from sleep to wakefulness.

The dynamic relation between diastolic and systolic blood pressure over 24 hours provides insight into the stiffness of the arterial wall. (**Dolan E et al. 2006)**. The number of participants was 11,291 (mean age 54.6 years) and all patients were untreated. A 24-hour recording of arterial pressure and the regression slope of diastolic on systolic blood pressure for each participant was computed. Dolan E. et al. defined ambulatory arterial stiffness index (AASI) as 1 minus the regression slope. AASI was higher in women than in men (0.42 vs. 0.4). Dolan E. et al. proposed AASI as a novel measure of arterial stiffness, which can be readily determined from ambulatory blood pressure recording and which independently predicts cardiovascular mortality, even in normotensive subjects.

The team of Li (**Li Y et al. 2006)** compared AASI with established measures of arterial stiffness and studied its distribution in 348 recruited Chinese and 1,617 European subjects. Among normotensive subjects the normal values of AASI are probably from 0.5 to 0.7 in young and older subjects, respectively.

Leoncini G et al. 2006 The investigation of the relationship between AASI and microalbuminuria, left ventricular hypertrophy and carotid atherosclerosis in 188 untreated patients with primary hypertension was done (**Dolan E et al. 2006)**. The AASI was 0.33-0.67.

1.7 Therapeutic strategies

There are a number of strategies to reduce vascular stiffening. Several factors involve lifestyle issues, such as reducing body weight, exercise, lowering salt intake. Other strategies are: focusing on nitric oxide-dependent pathways, antioxidants, transforming growth factor inhibition, advancing glycation end products cross-link breakers, renin-angiotensin-aldosterone system inhibitors (**Zieman SJ et.al. 2005**).

The overall strategy in the prevention of cardiovascular complications in children with CKD is evidence of long-term dialysis. The goal is to prevent the development and delay the progression of cardiomyopathy and atherosclerosis. Kidney transplantation should be the ultimate goal to minimize cardiovascular morbidity and mortality in patients with advanced CKD (**Mitsnefes MM 2008, Shroff R et al. 2011**).

The therapeutic strategies aim to reduce the high cardiovascular burden in CKD. The potential therapeutic interventions are the use of certain anthypertensive drugs and the reduction of vascular calcification (**Gusbeth-Tatomir P, Covic A 2007**).

Some post-transplant drugs cause vascular damage and increase cardiovascular risk in the kidney recipients (**Khoshdel AR, Carney SL 2008**). Hypertension occurs in approximately 80% of patients on cyclosporine following renal transplantation. **Ferro CJ et al. 2002** found cyclosporine, but not tacrolimus - to be associated with a higher AIx. Immunosuppression with cyclosporine appeared to abrogate the improvement in AIx. **Zoungas S et al. 2004** showed an improvement in AIx in the tacrolimus-treated group when compared with the cyclosporine treated group and supports the theory that tacrolimus immunosuppression may be the better in the long term for cardiovascular outcome in renal transplant recipients. **Khoshdel AR, Carney SL 2008** reported that a conversion from cyclosporine to tacrolimus improves cardiovascular risk profile. Parallel to this report, the advantages of mycophenolate mofetil for arterial distensibility in comparison to the other immunosuppressant drugs were found.

A confounding factor influencing arterial stiffness and PWV might be the use of antihypertensive drugs. ACE inhibitors and vasodilators such as calcium-channel blockers are known to decrease arterial stiffness and PWV via delayed return of the reflected wave from the periphery to the heart while decreasing its amplitude and systolic duration (**Kis E et al. 2009**). ACE inhibitors and angiotensin receptor blockers can reduce endothelial damage and are cardioprotective in adults with CKD (**Lilien MR, Groothoff JW 2009**).

Mitsnefes MM 2008 recommended treatment for children with CKD. Target blood pressure in children should be lower than the 90th percentile for normal values adjusted for age, gender and height or less than 120/80 mm Hg. Ambulatory blood pressure monitoring is recommended to assess the circadian rhythm. ACE inhibitors or angiotensin receptor blockers may be the preferred antihypertensive agents to slow the progression of CKD in children and possibly for regression of LVH. Calcium and

phosphorus levels must be within the normal range and the Ca*P product <55 mg2/dl2 in children on chronic dialysis.

Table 4
Mechanisms of and possible therapeutic measures for cardiovascular risk factors in children with renal failure (**Lilien MR, Groothoff JW 2009**)

Risk factor	Pathophysiological mechanisms	Possible therapeutic strategies
Duration of CKD	Endothelial dysfunction, arterial intimal calcification, arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification	Prevent CKD
Time-averaged serum calcium-phosphate product	Arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification	Reduce phosphate levels, consider parathyroidectomy, avoid calcium-constaining phosphate binders, consider intensified (nocturnal) hemodialysis
Conventional dialysis vs transplantation	Endothelial dysfunction, arterial intimal calcification, arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification, cardiac valve calcification	Provide early transplantation, consider intensified (nocturnal) hemodialysis
Cumulative intake of calcium-based phosphate binders	Arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification	Administer calcium-free phosphate binders
Cumulative intake of calcitriol	Arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification	Avoid high calcium-phosphate product values
Current serum phosphate level	Endothelial dysfunction, arterial intimal calcification, arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification	Reduce dietary phosphorus intake, administer calcium-free phosphate binders
Time-averaged serum intact PTH level	Arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification	Consider parathyroidectomy in cases of high serum calcium and intact PTH levels
Systolic blood pressure	Endothelial dysfunction, arterial intimal calcification, arterial medial calcification, left ventricular hypertrophy and myocardial remodelling, cardiac valve calcification	Administer intensive antihypertensive treatment

2 RATIONALE AND THE AIM OF THE STUDY

Cardiovascular disease accounts for 40% of all deaths among pediatric patients with end-stage renal disease. End-stage renal disease has a particularly large influence on the cardiovascular system in children, as indicated by the more than 700-fold increased risk of cardiac death compared with healthy children of the same age (**Lilien MR et al. 2009**). Several factors play a role in cardiovascular complications, mainly hypertension, alterations in calcium and phosphate homeostasis, chronic inflammation and anemia (**Aoun B et al. 2010**).

The elastic properties of the arterial system can be assessed non-invasively and easily. The parameters measured (pulse wave velocity, central blood pressure, augmentation index) are important from a pathophysiological point of view and share independent prognostic value. Consequently, their assessment in clinical practice has been recommended in the 2007 ESC/ESH Guidelines for the Management of Arterial Hypertension (**Weber T et al. 2008**).

Central pulse pressure, augmentation index and aortic pulse wave velocity are all predictors of morbidity and mortality in patients with chronic kidney disease (**Fassett RG et al. 2009**).

The current evidence shows the mortality rate of transplant patients is 6 to 8 times less than that of dialysis patients (**Khoshdel AR, Carney SL 2008**).

After successful renal transplantation there is overall improvement in cardiovascular risk factors and pulse wave velocity; and augmentation index returns to more normal levels, reflecting a reduction in arterial stiffness (**Zoungas S et al. 2004**).

A new, ambulatory arterial stiffness index, which is derived from 24-hour ambulatory blood pressure recordings in adults, is proposed (**Leoncini G et al. 2006, Li Y et al. 2006**). **Bia D et al. 2006** investigated the circadian variation of arterial stiffness in healthy adults using ambulatory recording of arterial pressure and pulse transit time. The arterial stiffness shows a circadian pattern with the highest and lowest levels. The greater reductions in the arterial stiffness were temporarily considered with the morning increase in the arterial pressure, heart rate, and myocardial oxygen consumption.

The 24-hour monitoring of arterial stiffness in children has never been investigated.

The aim of the study was:

1. to prove the hypothesis that the circadian profile of arterial stiffness exists
2. to determine and compare the daily rhythm of arterial stiffness in the controls and in the patients
3. to evaluate the daily arterial stiffness values in healthy children and in patients with ESRD, on hemodialysis, after transplantation (and with different times after transplantation)
4. to compare the impact of cyclosporine-A and tacrolimus medication on blood pressure and arterial stiffness in Tx children
5. to show the advantages of daily monitoring of augmentation index

3 PATIENTS AND METHODS

3.1 Patients

There were three groups of patients in the study:

- patients with ESRD stages 2-4 (n=14)
- patients on chronic hemodialysis (n=8)
- patients after Tx (n=40)

All patients underwent regular monitoring in KfH-Nierenzentrum UK-Eppendorf, Hamburg.

On the morning of the study:

- all patients took their medication, including all antihypertensive agents and immunosuppressants
- weight and height were measured
- blood was taken

Blood was tested with routine laboratory techniques for calcium, phosphorus, serum creatinine, cystatin C, parathyriod hormone.

3.1.1 Patients with ESRD stages 2-4

The group of patients with ESRD, stages 2-4, has 14 patients, ages 8.2-16.2 years (mean 11.5 years) (Table 5). The diagnoses leading to ESRD were (number of patients in parentheses) focal segmental glomerulosclerosis (2), polycystic kidney disease (1), renal hypo-dysplasia (3), vesicoureteric reflux and renal scarring (3), cystinosis (2), HUS (1), and ANCA-positive vasculitis (1). Three patients with the diagnoses of focal segmental glomerulosclerosis and ANCA-positive vasculitis were on immunosuppressive medication (Table 6). Ten patients received antihypertensive treatment (Table 7).

Table 5

Clinical and biochemical characteristics of patients with ESRD stages 2-4 (n=14)

Characteristics	Patients n=14 (mean±SD)	Patients n=14 (median)
Gender (male/female)	10/4	
Age (years)	11.5±3.3 (8.2-16.2)	11.7
Height (cm)	142±18.9 (119.2-173.3)	141.5
Weight (kg)	37.6±15.7 (21-67)	30.9
Serum creatinine (mg/dl)	2.4±1.4 (1-5.7)	1.8
GFR (ml/min/1,75m^2)	40.4±23.1 (22-132)	35.6
Cystatin C	1.2±1.4 (0.7-3.6)	0.9
GFR (cystatin C)	36.5±4.7 (31.4-42.1)	34.2
PTH (pg/ml)	113.2±131.4 (543-48)	88.2
Calcium (mmol/l)	2.3±0.3 (1.3-2.5)	2.4
Phosphorus (mmol/l)	1.3±0.2 (1.1-1.6)	1.3
Calcium-phosphorus product (mmol^2/l^2)	2.9±0.1 (1.4-4)	2.8

Table 6
Immunosuppressive medication in patients with ESRD stages 2-4 (n=14)

Patient	**Age (years)**	**Diagnosis, leading to ESRD**	**Azathioprine**	**Prednisone**	**Cyclosporine**	**Tacrolimus**	**MPA**
1	8.5	cystinosis					
2	14.7	vesicoureteric reflux und renal scarring					
3	12.9	cystinosis					
4	14.8	polycystic kidney disease					
5	8.3	HUS					
6	12.9	focal segmental glomerulosclerosis			200mg/d		1500mg/d
7	10.2	vesicoureteric reflux und renal scarring					
8	16.2	focal segmental glomerulosclerosis			270mg/d		
9	13.7	renal dysplasia					
10	8.5	vesicoureteric reflux und renal scarring					
11	11	renal dysplasia					
12	8.3	ANCA-positive vasculitis	12.5mg/d				500mg/d
13	8.2	acute kidney failure					
14	13.8	renal dysplasia					
All	mean 11.5±2.7		mean 12.5mg/d		mean 235 mg/d		mean 1000 mg/d

Table 7
Antihypertensive treatment in patients with ESRD stages 2-4 (n=14)

Patient	**Age (years)**	**Diagnosis, leading to ESRD**	**ACEI**	**ß-blocker**	**Calcium channel blocker**	**Diuretic**	**α-blocker**
1	8.5	cystinosis	x				
2	14.7	vesicoureteric reflux und renal scarring	x		x		
3	12.9	cystinosis	x				
4	14.8	polycystic kidney disease	x	x	x	x	
5	8.3	HUS	x				
6	12.9	focal segmental glomerulosclerosis	x		x	x	
7	10.2	vesicoureteric reflux und renal scarring	x		x		
8	16.2	focal segmental glomerulosclerosis	x				
9	13.7	renal dysplasia	x		x		
10	8.5	vesicoureteric reflux und renal scarring					
11	11	renal dysplasia					
12	8.3	ANCA-positive vasculitis			x	x	
13	8.2	acute kidney failure					
14	13.8	renal dysplasia					
All	mean 11.5±2.7		8	1	6	3	

3.1.2 Patients on hemodialysis

Eight patients on hemodialysis participated in the study. The average age was 13.2 years (9.3-17.4 years) (Table 8). The diagnoses leading to the 5th stage of ESKD were (number of patents in parentheses) focal segmental glomerulosclerosis (1), renal hypo-dysplasia (3), Prune Belly syndrome (1), oxalosis (1), ANCA-positive vasculitis (1), and lupusnephritis (1). Two patients - patients with lupusnephritis and with ANCA-positive vasculitis were prescribed immunosuppressive medication. Two patients did not need any antihypertensive treatment. Six patients were on antihypertensive medication (Tables 9&10). All patients received treatment with vitamin D ($25(OH)D_3$ 1000U/d and $1.25(OH)_2D_3$ 0.25μg/d), seven patients received erythropoetin (mean 2.800 U/week).

Table 8
Clinical and biochemical characteristics of patients with ESRD stage 5 (n=8)

Characteristics	Patients n=8 (mean±SD)	Patients n=8 (median)
Gender (male/female)	4/4	
Age (years)	13.2±2.7 (9.3-17.4)	12.6
Height (cm)	140.3±23.8 (108-171)	140.5
Weight (kg)	37.2±15.8 (18-61)	35.6
Serum creatinine (mg/dl)	4.4±2.3 (0.6-5.7)	4.2
PTH (pg/ml)	186.3±104.7 (24-360)	141
Calcium (mmol/l)	2.4±0.3 (2-2.9)	2.3
Phosphorus (mmol/l)	1.8±0.7 (1.1-3.5)	1.6
Calcium-phosphorus product ($mmol^2/l^2$)	4.3±0.2 (2.2-10.1)	3.9

Table 9

Immunosuppressive medication in patients with ESRD stage 5 (n=8)

Patient	**Age (years)**	**Diagnosis, leading to ESRD**	**Azathioprine**	**Prednisone**
1	12.2	oxalosis		
2	10.4	focal segmental glomerulosclerosis		
3	16.1	renal dysplasia		
4	17.4	lupusnephritis	50mg/d	2mg/d
5	12.2	renal dysplasia		
6	13.6	Prune Belly syndrom		
7	11.5	renal hypo-dysplasia		
8	9.3	ANCA-positive vasculitis	37.2 mg/d	
All	mean 12.8±2.7		mean 43.6mg/d	mean 2mg/d

Table 10
Antihypertensive medication in patients with ESRD stage 5 (n=8)

Patient	**Age (years)**	**Diagnosis, leading to ESRD**	**ACEI**	**ß-blocker**	**Calcium channel blocker**	**Diuretic**	**α-blocker**
1	12.2	oxalosis	x		x		
2	10.4	focal segmental glomerulosclerosis	x		x		
3	16.1	renal dysplasia					
4	17.4	lupusnephritis	x				
5	12.2	renal dysplasia		x	x		x
6	13.6	Prune Belly syndrom					
7	11.5	renal hypo-dysplasia	x	x	x	x	x
8	9.3	ANCA-positive vasculitis	x	x		x	
All	mean 12.8±2.7		5	3	4	2	2

3.1.3 Patients with ESRD stages 2-5

We mixed two groups of patients:

- the group of patients on hemodialysis (n=8)
- the group of patients with ESRD (2-4) (n=14).

The subgroup of children with ESRD (2-5) had 22 patients ages 12.1 ± 2.9 years. The characteristics of this group are presented in Table 11.

Table 11
Clinical and biochemical characteristics of patients with ESRD (n=22)

Characteristics	Patients n=22 (mean±SD)	Patients n=22 (median)
Gender (male/female)	14/8	
Age (years)	12.1±2.9 (9.2-17.7)	12.6
Height (cm)	141.4±20 (108.1-173.3)	140.5
Weight (kg)	37.5±15.4 (19-68)	31.2
Serum creatinine (mg/dl)	3.1±2 (0.5-5.7)	2.7
GFR (ml/min/1,75m^2)	43.3±22.9 (22-138.2)	25.3
PTH (pg/ml)	139.8±125 (296-543)	101.2
Calcium (mmol/l)	2.3±0.3 (1.3-2.6)	2.3
Phosphorus (mmol/l)	1.5±0.5 (0.7-1.6)	1.4
Calcium-phosphorus product (mmol^2/l^2)	3.4±0.1 (0.9-4.1)	3.2

3.1.4 Patients after transplantation

A total of 40 patients with a functioning kidney transplant, ages 8.2-17.7 years (mean 12.7 years), participated in the study. Transplantation had been performed 3.2 years (range 0.5-7.8 years) prior to the examination. The maximum number of transplants was 2 (4 patients) (Table 11). All patients received immunosuppressants. The cumulative intake of immunosuppressive medication is given in Table 13. Standard antihypertensive treatment consisted of an angiotensin converting enzyme inhibitor (Ramipril) and/or a beta-blocker (Metoprolol). A calcium channel blocker, an alpha-blocker, and a diuretic were added if the result was not satisfactory. Only three patients had not received antihypertensive treatment (Table 14). The diagnoses leading to ESRD and transplantation were (number of patents in parentheses) focal segmental glomerulosclerosis (3), polycystic kidney disease (4), renal hypo-dysplasia (17), vesicoureteric reflux and renal scarring (3), HUS (2), ANCA-positive vasculitis (1), chronic glomerulonephritis (1), Alport syndrome (1), Prune Belly syndrom (1), acute kidney failure (4), chronic tubulointerstitial nephritis (1), and Fanconi anemia (1).

Table 12
Clinical and biochemical characteristics of patients after Tx (n=40)

Characteristics	Patients n=40 (mean±SD)	Patients n=40 (median)
Gender (male/female)	25/15	
Age (years)	12.7±3.3 (8.2-17.7)	13.2
Height (cm)	141.6±17.3 (107-167.9)	140.7
Weight (kg)	40.5±13.6 (19-68)	39
Time since transplantation (years)	3.2±3 (0.5-7.8)	3.1
Serum creatinine (mg/dl)	1.2±0.6 (0.5-2.8)	0.9
GFR (ml/min/1,75m^2)	82.3±29.3 (30-138.2)	88.1
Cystatin C	1±0.8 (0.8-2.8)	0.8
GFR (cystatin C)	53.3±38 (29-120)	59.2
PTH (pg/ml)	182.2±132.7 (29.6-370)	82.7
Calcium (mmol/l)	2.3±0.5 (1.3-2.6)	2.4
Phosphorus (mmol/l)	1.2±0.3 (0.7-1.6)	1.3
Calcium-phosphorus product (mmol^2/l^2)	2.9±0.1 (0.9-4,1)	3.1

Table 13
Immunosuppressive medication in patients after Tx (n=40)

Patient	Age (years)	Diagnosis, leading to ESRD	Azathioprine	Prednisone	Cyclosporine	Tacrolimus	MPA
1	11.3	renal hypo-dysplasia		6 mg/d		5 mg/d	500 mg/d
2	17.1	polycystic kidney disease	50 mg/d		100 mg/d		
3	17.6	acute kidney failure		5 mg/d		2 mg/d	1000 mg/d
4	13.6	chronic glomeruloneohritis			120 mg/d		1500 mg/d
5	9.8	focal segmental glomerulosclerosis	25 mg/d	5 mg/d	220 mg/d		360 mg/d
6	16.7	renal hypo-dysplasia				4 mg/d	1000 mg/d
7	15	renal hypo-dysplasia	100 mg/d	3 mg/d		4 mg/d	
8	11.3	renal hypo-dysplasia	25 mg/d	1 mg/d		2 mg/d	
9	13.8	focal segmental glomerulosclerosis					750 mg/d
10	8.2	Prune Belly syndrom	25 mg/d	1 mg/d	120 mg/d		
11	17	renal hypo-dysplasia		5 mg/d		5 mg/d	500 mg/d
12	14.3	renal hypo-dysplasia		5 mg/d		3 mg/d	600 mg/d
13	17.1	Alport syndrome		5 mg/d	300 mg/d		1750 mg/d
14	8.5	HUS		1 mg/d	500 mg/d		
15	17.7	renal hypo-dysplasia		5 mg/d		4 mg/d	720 mg/d
16	13	HUS		5 mg/d		3 mg/d	750 mg/d
17	13.4	vesicoureteric reflux and renal scarring		2,5 mg/d	260 mg/d		
18	15.1	Fanconi anemia		2 mg/d	130 mg/d		180 mg/d
19	8.5	polycystic kidney disease	50 mg/d	5 mg/d	160 mg/d		400 mg/d
20	15.7	acute kidney failure				3 mg/d	1500 mg/d
21	14	acute kidney failure		1 mg/d	190 mg/d		1260 mg/d
22	16.9	renal hypo-dysplasia		1 mg/d		2 mg/d	200 mg/d

Patient	Age (years)	Diagnosis, leading to ESRD	Azathioprine	Prednisone	Cyclosporine	Tacrolimus	MPA
23	8.4	renal hypo-dysplasia		5 mg/d		3 mg/d	1000 mg/d
24	13.2	polycystic kidney disease		3 mg/d		3 mg/d	1000 mg/d
25	11	renal hypo-dysplasia		5 mg/d		3 mg/d	1000 mg/d
26	14	focal segmental glomerulosclerosis		5 mg/d	220 mg/d		1500 mg/d
27	10	renal hypo-dysplasia			120 mg/d		800 mg/d
28	12.2	renal hypo-dysplasia		1 mg/d	150 mg/d		1500 mg/d
29	14.6	renal hypo-dysplasia			160 mg/d		500 mg/d
30	10.5	renal hypo-dysplasia		5 mg/d		2 mg/d	540 mg/d
31	13.7	polycystic kidney disease			300 mg/d		1000 mg/d
32	13.3	polycystic kidney disease		1 mg/d	200 mg/d		1250 mg/d
33	10.1	vesicoureteric reflux and renal scarring			360 mg/d		
34	13.7	vesicoureteric reflux and renal scarring			150 mg/d		1000 mg/d
35	12	acute kidney failure				3 mg/d	1000 mg/d
36	10.6	renal hypo-dysplasia				2 mg/d	500 mg/d
37	9.3	ANCA-positive vasculitis		4 mg/d	500 mg/d		1000 mg/d
38	11	renal hypo-dysplasia		2 mg/d	360 mg/d		
39	9.4	chronic tubulointerstitial nephritis		2 mg/d	100 mg/d		1000 mg/d
40	15.1	renal hypo-dysplasia		1 mg/d	360 mg/d		
All	mean 12.7±3.3		mean 45 mg/d	mean 3.3 mg/d	mean 231 mg/d	mean 3,7 mg/d	mean 744 mg/d

Table 14
Antihypertensive treatment in patients after Tx (n=40)

Patient	**Age (years)**	**Diagnosis, leading to ESRD**	**ACEI**	**ß-blocker**	**Calcium channel blocker**	**Diuretic**	**α-blocker**
1	11.3	renal hypo-dysplasia	x	x	x		
2	17.1	polycystic kidney disease	x				
3	17.6	acute kidney failure	x	x			
4	13.6	chronic glomeruloneohritis	x	x			
5	9.8	focal segmental glomerulosclerosis	x	x			
6	16.7	renal hypo-dysplasia	x	x	x	x	
7	15	renal hypo-dysplasia	x				
8	11.3	renal hypo-dysplasia	x				
9	13.8	focal segmental glomerulosclerosis	x	x	x		x
10	8.2	Prune Belly syndrom					
11	17	renal hypo-dysplasia		x			
12	14.3	renal hypo-dysplasia	x	x			
13	17.1	Alport syndrome		x	x		
14	8.5	HUS					
15	17.7	renal hypo-dysplasia	x				
16	13	HUS		x			
17	13.4	vesicoureteric reflux and renal scarrin	x				
18	15.1	Fanconi anemia	x				
19	8.5	polycystic kidney disease					

Patient	Age (years)	Diagnosis, leading to ESRD	ACEI	ß-blocker	Calcium channel blocker	Diuretic	α-blocker
20	15.7	acute kidney failure	x	x		x	
21	14	acute kidney failure		x	x		
22	16.9	renal hypo-dysplasia	x	x	x		x
23	8.4	renal hypo-dysplasia	x	x	x		
24	13.2	polycystic kidney disease			x		
25	11	renal hypo-dysplasia		x	x		
26	14	focal segmental glomerulosclerosis	x	x	x		
27	10	renal hypo-dysplasia	x	x			
28	12.2	renal hypo-dysplasia	x				
29	14.6	renal hypo-dysplasia	x				
30	10.5	renal hypo-dysplasia	x				
31	13.7	polycystic kidney disease		x	x		
32	13.3	polycystic kidney disease	x				
33	10.1	vesicoureteric reflux and renal scarrin	x				
34	13.7	vesicoureteric reflux and renal scarrin	x	x	x	x	
35	12	acute kidney failure		x			
36	10.6	renal hypo-dysplasia		x			
37	9.3	ANCA-positive vasculitis	x	x			x
38	11	renal hypo-dysplasia	x	x			
39	9.4	chronic tubulointerstitial nephritis	x				
40	15.1	renal hypo-dysplasia			x		
All	mean 12.7±3.3		27	23	13	3	3

3.1.5 Controls

Seventeen healthy children and teenagers participated in the study. They were monitored for more than 24 hours for blood pressure and arterial stiffness; single measurements of height and weight were taken. Blood pressure was measured before the daily pressure monitoring. All teenagers had single blood pressure results within the 50-95th percentile for the corresponding age, gender, and height. The common characteristics of controls are shown in Table 15.

Table 15
Clinical characteristics of controls (n=17)

Characteristics	Patients n=17 (mean±SD)	Patients n=17 (median)
Gender (male/female)	10/7	
Age (years)	13.3±2 (11-17.3)	13.5
Height (cm)	160.9±11.8 (143-175)	160.5
Weight (kg)	47.4±6.9 (38-56)	46.5

3.2 Method of arterial stiffness measurement

Arterial stiffness was analysed with BPLab/Vasotens Arteriograph (OOO Petr Telegin).

http://www.bplab.com: „...OOO Petr Telegin offers an opportunity of analyzing main artery stiffness by 24-hour ambulatory blood pressure monitoring. In contrast with other available devices on the market with the function of arterial stiffness analyze, which can be used only for office research, arteriograph BPLab provides an opportunity of making daily trends of various hemodynamic indexes. Arteriograph BPLab is an instrument, which combines monitoring of basic parameters of blood pressure and heart rate with the analysis of main artery stiffness, using BPLab/ Vasotens software. The use of this software allows mathematical processing of pressure oscillograms records to be performed. As a result, the following parameters can be measured by BPLab arteriograf:

- Blood pressure parameters (systolic BP, diastolic BP, mean blood pressure, heart rate, pulse arterial pressure, central aortic pressure),
- arterial stiffness parameters (pulse wave velocity in aorta (PWVao), augmentation index (AIx), pulse transit time (PTT), reflected wave transit time (RWTT), maximum rate of arterial pressure rise (dp/dt) stroke systolic area index (Ssys) and et.)

24 hour trends of hemodynamics rates and a table of measuring results allows PTT, AIx and other parameters to be evaluated, describing arterial stiffness during a 24-hour

monitoring period, and thus receiving not only 24-hour BP and heart rate profiles, but also stiffness parameters...“

Standard sequence of 24-hour monitoring includes the following main stages:

- instructing the patient
- working out the test schedule and programming the monitor
- attaching the monitor to the patient
- checking measurements
- monitoring
- transmitting monitor readings to the computer
- processing and analysis of monitor readings

Patients were informed that any quick, sudden or unnecessary movements, such as walking around, etc, would hinder the ability of the device to record accurate measurements. In addition, patients were also informed that the shifting of the device (any slight change in the position of the cuff once affixed) could also result in inaccurate readings.

The monitor was connected to the PC by a communication cable and programme data was recorded to the monitor using the BPLab software. Data was recorded by use of the following:

- registration data
- test schedule (it contains intervals between measurements during daytime, nighttime, and limits of daytime and nighttime). The interval between readings was 15 minutes during the day/30 minutes at night. Daytime was defined as the hours between 06.00-22.00.

Pneumo-cuff was applied to the left arm, of the patients. In cases of contraindications, the cuff could be applied on the right arm. The cuff was applied over the patient`s clothes. The monitor was put into a casing and placed on the patient´s side, opposite the cuff. After that, the cuff was connected to a pneumoplug by means of a flexible tube. The width of the cuff had to be 40 % of the shoulder´s length. The length of the cuff had to be 80-100% of the shoulder´s circumference.

The monitoring was usually carried out over a period of 24 hours (sometimes 22-26 hours). The monitor automatically measured blood pressure, pulse rates and arterial stiffness parameters. The patient´s diary was completed during the monitoring.

After the monitor had been removed from the patient, it was connected by a cable to the PC. The following data was transferred from the monitor to the computer: pre-set

parameters of test schedule and registration data, table of readings, and the records of native curves.

3.3 Statistical analysis

For statistical analysis we used SPSS software, version 18.0. Data is presented as mean and 95% confidence intervals (CI).

4 RESULTS

4.1 Patients with ESRD

The blood pressure results of these patients are also within normal limits for the corresponding age (mean), gender, height (mean) as also seen in the controls and transplant patients. PTT (24-hours) is 138.9-174.7ms, AIx (24-hours) is -57.7 - -29.7% (Table 16).

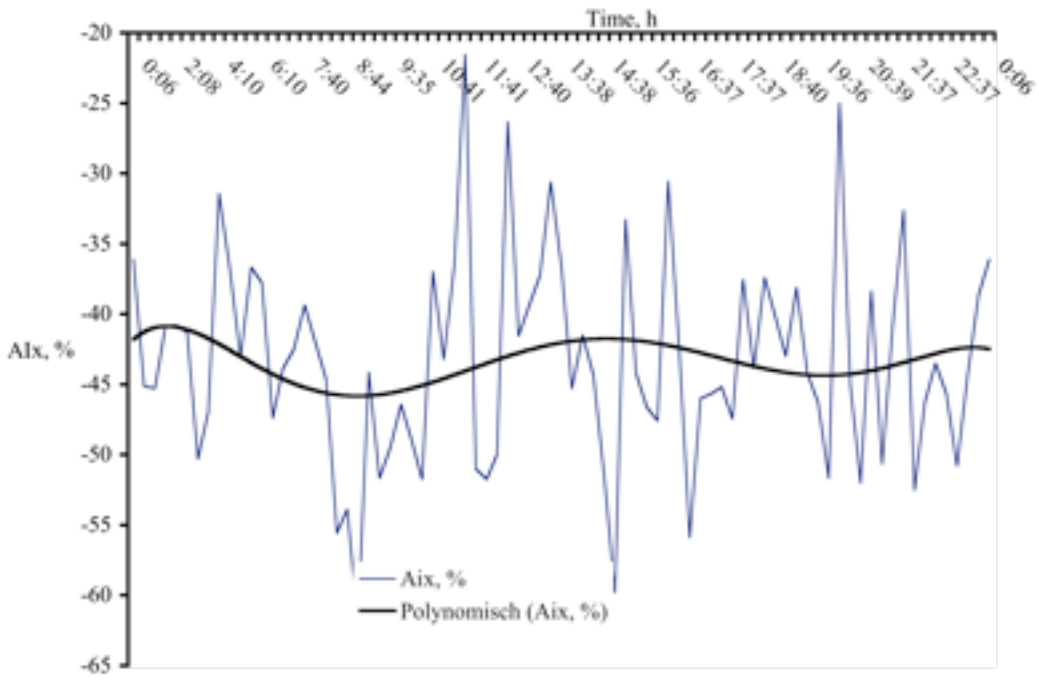
The curve of the AIx profile is almost flat. Two small peaks are at about 1.00 and 14.00 hours (Figure 4).

Table 16

Characteristics of blood pressure and arterial stiffness monitorings in patients with ESRD stages 2-4 (n=14)

Characteristics	Mean±SD	Median
Systolic BP (mmHg)-24-h	113.6±12.2 (92.2-124.3)	115
Diastolic BP (mmHg)-24-h	65.9±10.9 (46.2-77.7)	67.1
Mean BP (mmHg)-24-h	81.6±11.7 (61.8-92.6)	82.3
Pulse pressure (mmHg)-24-h	47.7±8.7 (39.6-56.6)	46.4
PTT, ms-24-h	156.8±17.9 (131-190)	156
AIx, %-24-h	-43.7±14 (-63--23)	-44.5
Systolic BP (mmHg)-day	115.7±11.8 (96.3-125.1)	117.6
Diastolic BP (mmHg)-day	67.5±10.3 (48.8-79.4)	68.5
Mean BP (mmHg)-day	83.3±11.2 (63.9-94)	85
Pulse pressure (mmHg)-day	48.1±8.9 (39.1-57.8)	47.7
PTT, ms-day	157.5±16.5 (132-189)	156
AIx, %-day	-43.6±13.7 (-62--25)	-45.5
Systolic BP (mmHg)-night	99±8.4 (85.1-129)	105
Diastolic BP (mmHg)-night	55.6±8 (41.9-76)	59.9
Mean BP (mmHg)-night	70.3±8.7 (58.4-93.1)	76.6
Pulse pressure (mmHg)-night	43.4±6.6 (38.6-57.3)	46.3
PTT, ms-night	144.1±14.3 (113-190)	151.5
AIx, %-night	-41.3±11.2 (-81--13)	-43.5

Figure 4
Daily profile of AIx in patients with ESRD 2-4 (n=14)



4.2 Patients on hemodialysis

The blood pressure results of these patients are normal for the corresponding age (mean), gender, and height (mean). PTT (24-hours) is ms, AIx (24-hours) is -57.7 - -29.7% (Table 17).

The circadian profile of AIx has the max peak at night at about 3.30. The values of AIx are greater during the night than during the day (Figure 5).

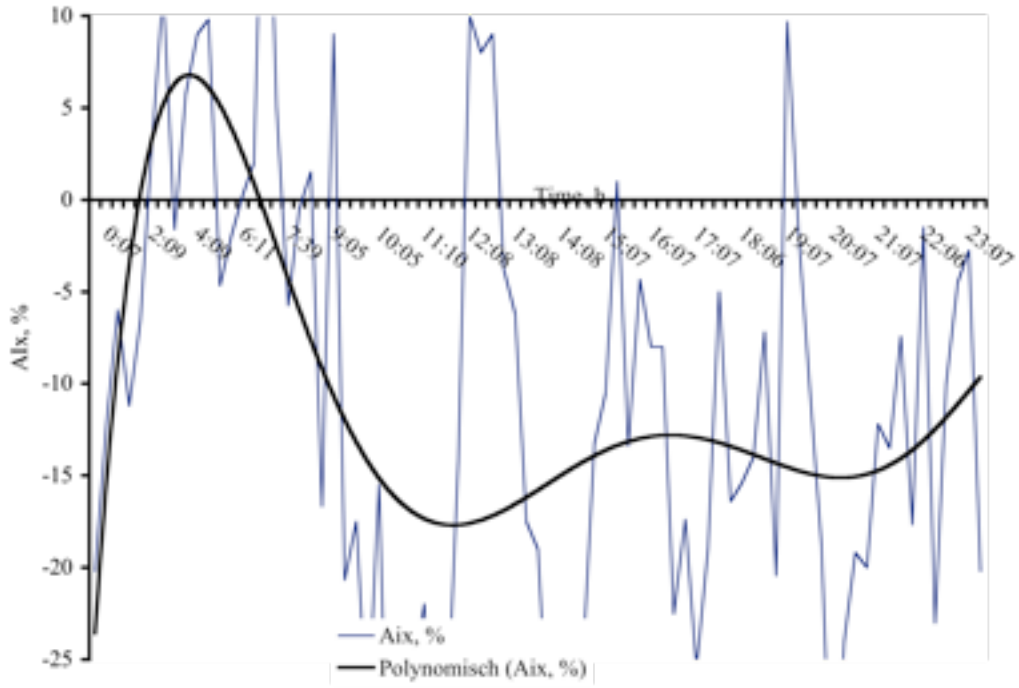
Table 17

Characteristics of the group on hemodialysis (n=8)

Characteristics	Mean±SD	Median
Systolic BP (mmHg)-24-h	114.8±10.5 (105.4-129.8)	111.7
Diastolic BP (mmHg)-24-h	74.2±11.5 (61.9-82.8)	77.3
Mean BP (mmHg)-24-h	88±11.2 (77.7-99.8)	90.2
Pulse pressure (mmHg)-24-h	40.5±7 (28.8-47.2)	41.2
PTT, ms-24-h	129.3±13.6 (96-146)	134
AIx, %-24-h	-16.1±14.7 (-55--4)	-14
Systolic BP (mmHg)-day	115.4±10.4 (107.5-130.4)	112.7
Diastolic BP (mmHg)-day	76.1±10.5 (65.2-83.2)	77.4
Mean BP (mmHg)-day	89.5±10.4 (80.1-100.6)	88.3
Pulse pressure (mmHg)-day	39.3±7 (28.6-47.5)	40.1
PTT, ms-day	133.5±13.7 (124-146)	132
AIx, %-day	-17.3±15.7 (-55--4)	-12.5
Systolic BP (mmHg)-night	107.7±8.8 (96.9-128.3)	104
Diastolic BP (mmHg)-night	67±9.2 (46.1-81.9)	70.8
Mean BP (mmHg)-night	82±8.6 (66.3-97.7)	83.2
Pulse pressure (mmHg)-night	40.7±5.5 (29.4-51.3)	41.3
PTT, ms-night	140.3±11.8 (133-146)	141
AIx, %-night	-20±12.2 (-55--10)	-15.5

Figure 5

Circadian variation of AIx in patients on hemodialysis (n=8)



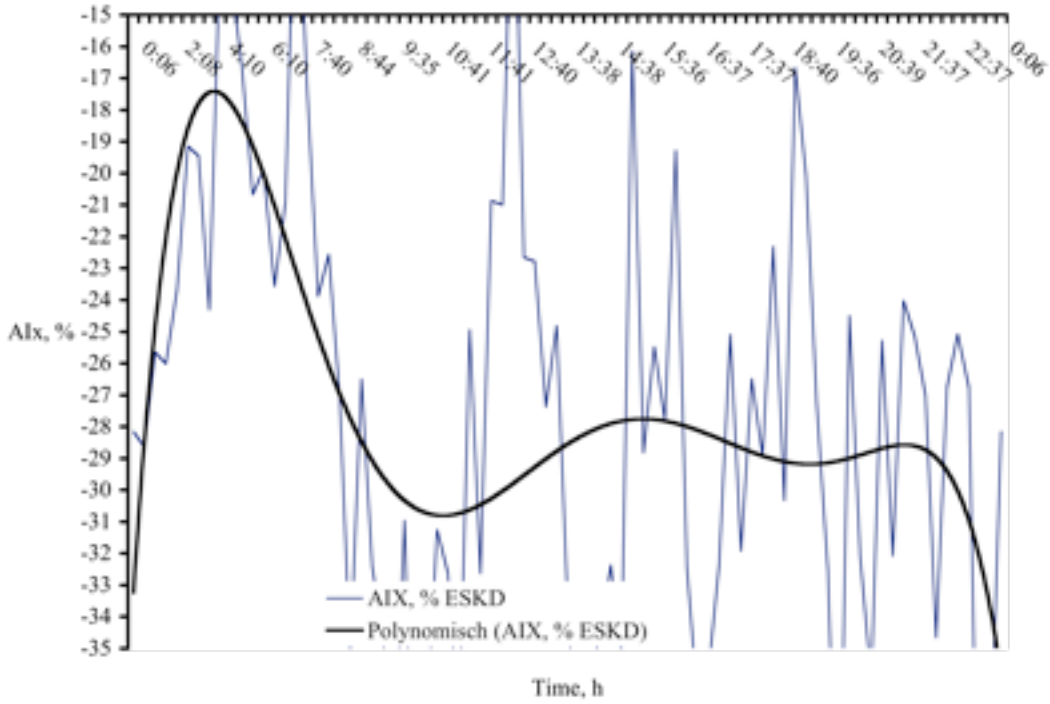
4.3 All patients with ESRD (n=22)

Table 18
Characteristics of the group with ESRD (n=22)

Characteristics	Mean±SD	Median
Systolic BP (mmHg)-24-h	114±11.6 (92.2-129.8)	114.6
Diastolic BP (mmHg)-24-h	68.7±11.1 (46.2-82.8)	68.9
Mean BP (mmHg)-24-h	83.7±11.5 (61.8-99.8)	83.6
Pulse pressure (mmHg)-24-h	45.3±8.2 (28.8-56.6)	45.6
PTT, ms-24-h	147.6±16.5 (96-190)	146
AIx, %-24-h	-34.5±14.3 (-63--4)	-38
Systolic BP (mmHg)-day	115.6±11.4 (96.3-130.4)	116.4
Diastolic BP (mmHg)-day	70.1±10.3 (48.8-83.2)	71.4
Mean BP (mmHg)-day	85.1±10.9 (63.9-100.6)	86.8
Pulse pressure (mmHg)-day	45.5±8.4 (28.6-57.8)	44.2
PTT, ms-day	150.3±15.6 (124-189)	147
AIx, %-day	-35.7±14.3 (-62-4)	-39
Systolic BP (mmHg)-night	101.6±8.5 (85.5-129)	105
Diastolic BP (mmHg)-night	59±8.4 (41.9-81.9)	62
Mean BP (mmHg)-night	73.8±8.7 (59.8-97.7)	76.6
Pulse pressure (mmHg)-night	42.6±6.2 (37.3-57.3)	44.4
PTT, ms-night	143±13.6 (106-190)	148.5
AIx, %-night	-34.9±11.5 (-81--10)	-39.5

Similar to the patients on hemodialysis, the circadian profile of AIx in this group also has the max peak at night at about 3.00. The values of AIx are greater at night than during the day (Figure 6).

Figure 6
Circadian variation of AIx in patients with ESRD (n=22)



4.4 Patients after transplantation

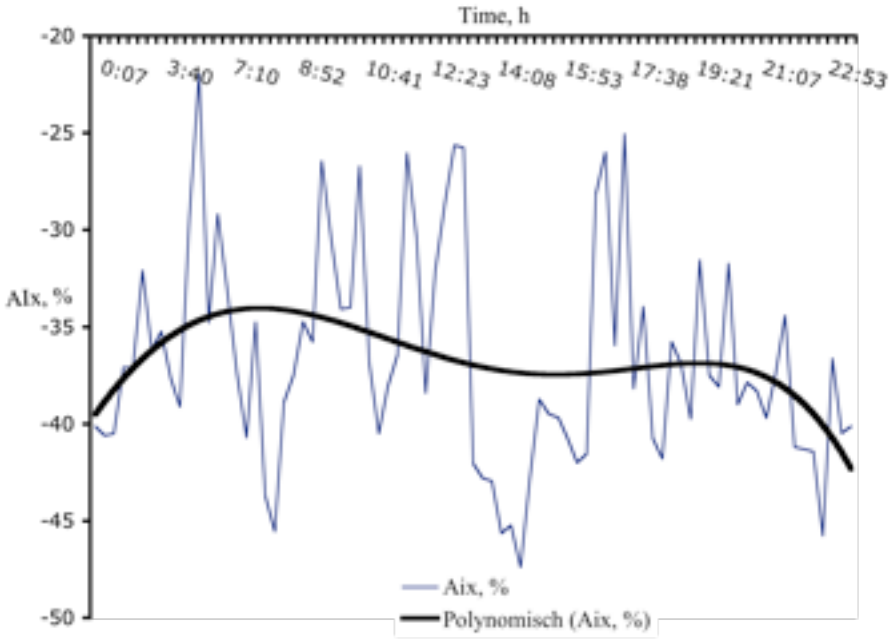
The patients' blood pressure results were within the 50-95th percentile for the corresponding age (mean), gender, and height (mean). PTT (24-hours) is 132.5-165.5ms, AIx (24-hours) is -57.6 - -24.2% (Table 19).

There is a circadian pattern in arterial stiffness (AIx) in the patients after Tx. AIx is greater during wakefulness (Figure 7).

Table 19
Characteristics of blood pressure and arterial stiffness in patients after Tx (n=40)

Characteristics	Mean±SD	Median
Systolic BP (mmHg)-24-h	118.7±12.6 (100.6-141)	119.3
Diastolic BP (mmHg)-24-h	70.4±11.3 (51.2-94.3)	69.2
Mean BP (mmHg)-24-h	85.9±11.7 (67.9-108.1)	86.4
Pulse pressure (mmHg)-24-h	48.3±8.5 (39.5-62.7)	47.6
PTT, ms-24-h	149±16.5 (95-187)	150
AIx, %-24-h	-40.9±16.7 (-74--23)	-46
Systolic BP (mmHg)-day	120.6±11.9 (102.8-144.1)	121.4
Diastolic BP (mmHg)-day	74.8±10.8 (51.1-129.5)	72.8
Mean BP (mmHg)-day	87.2±11.3 (67.5-109.8)	88.3
Pulse pressure (mmHg)-day	48.9±8.9 (40-63.2)	48.4
PTT, ms-day	148.9±15.3 (93-192)	149
AIx, %-day	-42.3±16.5 (-77--24)	-47
Systolic BP (mmHg)-night	110.6±8.6 (92.7-133.6)	108.9
Diastolic BP (mmHg)-night	63.2±7.9 (47.7-87.9)	61
Mean BP (mmHg)-night	78.7±8.5 (59.8-101.3)	77
Pulse pressure (mmHg)-night	47±7 (37.3-60.8)	45.8
PTT, ms-night	143.7±14.4 (106-188)	146
AIx, %-night	-41±13.3 (-68--20)	-48

Figure 7
Circadian variation of AIx in patients after Tx (n=40)



We divided the group of transplant patients into two subgroups:

• patients with a post-transplant time 0-1 years (n=19)

• patients with a post-transplant time 1-8 years (n=17).

The characteristics of blood pressure and arterial stiffness are given in Table 20, the AIx variations in these groups are presented in Figure 8 and Figure 9.

The group of patients with a time after transplantation of more than 8 years is too small (n=4) for additional analysis.

There is a tendency: the time after Tx increases blood pressure and increases AIx (Table 20).

Table 20
Characteristics of blood pressure and arterial stiffness in patients after Tx with various times after Tx

Characteristics	Time after Tx 1-8 years n=17 (mean±SD)	Median	Time after Tx 0-1 years n=19 (mean ±SD)	Median
Systolic BP (mmHg)-24-h	121.6±12.5 (138-108)	119.8	115.4±12.6 (141-96.1)	116.9
Diastolic BP (mmHg)-24-h	74.1±11.9 [CI 0.3/13.2]*(87.9-60.2)	70.8	67.3±10.9 (94.3-51.2)	68.5
Mean BP (mmHg)-24-h	89.6±11.8 [CI 0.7/13.2]*(102.6-76.4)	87.5	82.6±11.4 (108.1-67.4)	84.6
Pulse pressure (mmHg)-24	47.5±8.3 (56.6-39.5)	47.8	48.1±8.3 (62.7-40.5)	47.1
PTT, ms-24-h	149.6±15.3 (171-116)	155	148±17 (187-95)	150
AIx, %-24-h	-37.4±14.6 (-60--23)	-34.5	-42.3±17.6 (-74--4)	-46

∗-significant differences of results in both groups [p<0,05]

The AIx profile for the patients in the group with a post-transplant time 0-1 years has the maximum values at night and a peak at about 19.30 hours and the minimum value at about 13.00 (Figure 8).

In the group of the patients with a post-transplant time 1-8 years the maximum value of AIx is at about 8.00 hours (Figure 9).

Figure 8

Daily variation of AIx in patients after Tx with the post-transplant time 0-1 years (n=19)

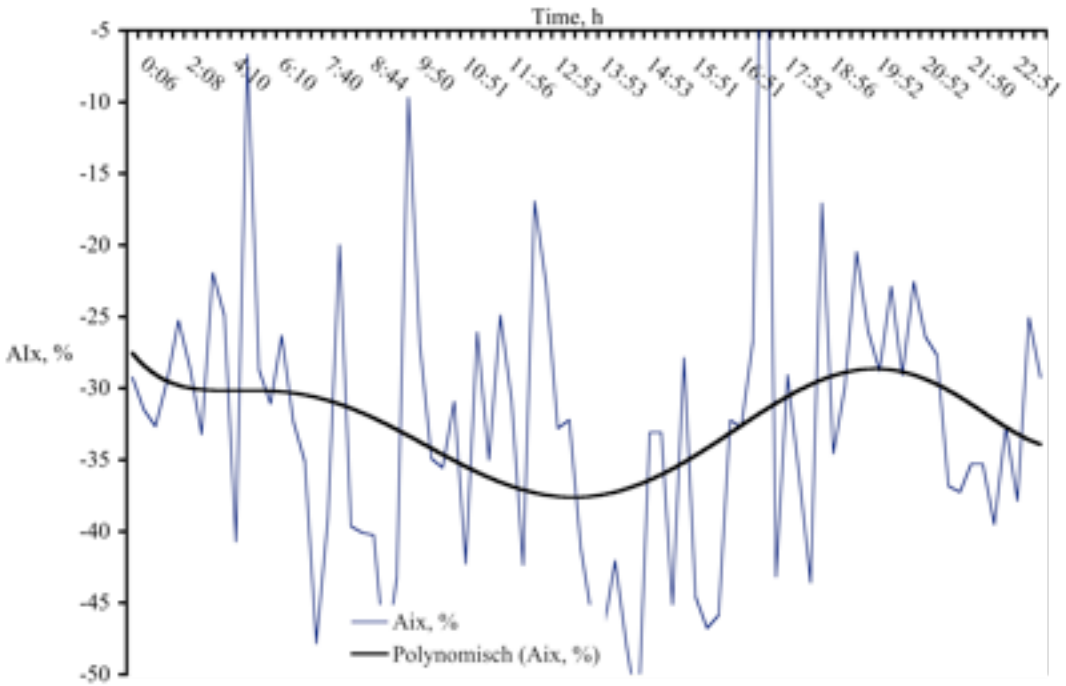
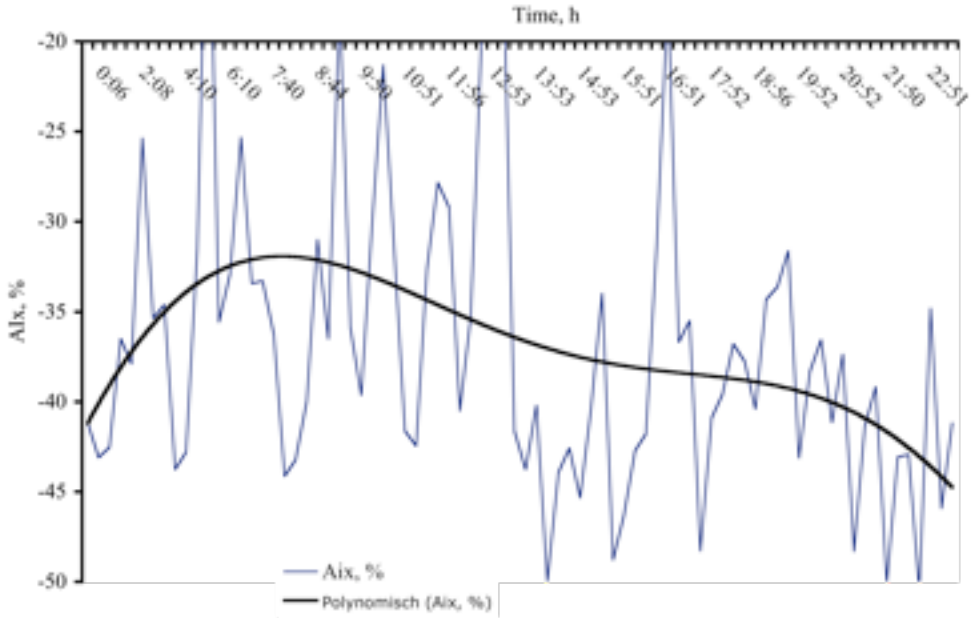


Figure 9

Daily variation of AIx in patients after Tx with the post-transplant time 1-8 years (n=17)



We divided our transplant group into two subgroups:

- patients on CSA (n=22)
- patients on Tacrolimus (n=14).

The characteristics of blood pressure and arterial stiffness in both these groups are in Table 21. The Tx patients on CSA has a significantly higher level of serum creatinine [CI 0.03/0.8] and the CFR is also significantly less than in the Tx patients on Tacrolimus [CI 0.07/1.3].

There were no differences in the blood pressure level, AIx, and PTT ranges between the groups.

Table 21
Characteristics of blood pressure and arterial stiffness in transplant patients on CSA and Tacrolimus

Characteristics	CSA n=22 (mean±SD)	Median	Tacrolimus n=14 (mean±SD;)	Median
Serum creatinene (mg/dl)	1.2±0.6(2.8-0.6) [CI 0.03/0.8] [p<0.05]	1.1	0.8±0.4 (2.3-0.5)	0.74
GFR (ml/min/1,75m2)	73.9±24.2(113.7-24.2) [CI 0.07/1.3] [p<0.05]	73	100.4±27.7 (138.2-30)	101.9
PTH (pg/ml)	101.6±85.4 (370-63.6)	78.9	118.5±79.4 (	102.8
Calcium (mmol/l)	2.4±0.6 (4.1-2.3)	2.4	2.4±0.3	2.4
Phosphorus (mmol/l)	1.3±0.3 (1.6-1.1)	1.3	1.3±0.2	1.2
Calcium-phosphorus product (mmol2/l2)	3.12±0.18	3.1	3.12±0.06	2.8
Systolic BP (mmHg)-24-h	120.3±12.5 (141-102)	119.4	116.2±12.2 (138-96.1)	118
Diastolic BP (mmHg)-24-h	71.5±11.2 (94.3-54.5)	69.3	68.7±10.8 (87.9-51.2)	68.2
Mean BP (mmHg)-24-h	87.4±11.8 (108.1-72.3)	86.7	83.6±11.2 (102.6-67.4)	84.6
Pulse pressure (mmHg)-24-h	48.8±8.7 (62.7-39.5)	47.7	47.4±8.3 (55.5-40.5)	48.9
PTT, ms-24-h	148±16.9 (187-95)	151	147.8±16 (162-116)	150
AIx, %-24-h	-40.6±17.8 (-74--4)	-46.5	-39±15.6 (-60--23)	-39
Systolic BP (mmHg)-day	121.2±11.8 (144.1-74.3)	122.1	119±11.6 (141.5-101.2)	120.4
Diastolic BP (mmHg)-day	77.4±10.7 (129.5-53.8)	75.1	71±10.6 (90.3-51.1)	70.5
Mean BP (mmHg)-day	87.9±11.5 (109.8-47.4)	88.3	85.9±10.7 (104.6-67.5)	87.2
Pulse pressure (mmHg)-day	49.6±8.7 (63.2-40)	48.9	47.9±8.6 (54.6-40.8)	49
PTT, ms-day	147.6±15.1 (192-112)	138	148±15.4 (167-119)	151
AIx, %-day	-41.8±18.5 (-77--4)	-47	-40.5±13.9 (-69--24)	-43
Systolic BP (mmHg)-night	111.5±8 (133.6-92.7)	109.9	108.9±9.3 (126.9-89.3)	108
Diastolic BP (mmHg)-night	64.4±7.5 (87.9-47.7)	61.7	61.8±7.9 (81.5-50.4)	57.3
Mean BP (mmHg)-night	79.9±7.9 (101.3-59.8)	77.9	76.8±9.2 (96.2-64.1)	74
Pulse pressure (mmHg)-night	47±6.8 (60.8-38.8)	45.5	46.4±6.9 (58.8-36.1)	47
PTT, ms-night	144.5±14.9 (188-109)	145.5	143.2±14.5 (179-100)	145.5
AIx, %-night	-40.9±13.4 (-68--12)	-45	-38.5±13.8 (-62--20)	-41.5

4.5 Follow-up patients

We compared the same biochemical characteristics and the characteristics of blood pressure and arterial stiffness in both groups (transplant patients and the same follow-up patients in about 12-15 months) (Table 22). In 12-15 months after the first monitoring there is a tendency of reduction of AIx.

Table 22

Biochemical characteristics and the characteristics of blood pressure and arterial stiffness in the follow-up patients (n=15)

Characteristics	Tx n=15 (mean±SD)	Median	Follow-up n=15 (mean±SD)	Median
Serum creatinine (mg/dl)	1.2±0.8 (3-0.6)	0.7	1.3±0.9 (2.8-0.5)	0.8
GFR (ml/min/1,75m2)	81.4±38.5 (132.2-30)	91.3	86.4±39 (138.2-30)	95.7
PTH (pg/ml)	81.7±54.5 (150-73.1)	67.8	91.8±45.6 (235-66.3)	93.2
Calcium (mmol/l)	2.3±0.7 (4.3-1.9)	2.4	2.6±0.6 (2.6-2.4)	2.4
Phosphorus (mmol/l)	1.2±0.4 (1.5-0.9)	1.4	1.3±0.2 (1.5-1)	1.3
Calcium-phosphorus product (mmol2/l2)	2.7±0.2	3.3	3.3±0.1	3.1
Systolic BP (mmHg)-24-h	118.4±12.3 (134.5-98.6)	118.4	116.6±11.5 (133.1-99.5)	119.5
Diastolic BP (mmHg)-24-h	69±10.8 (79.5-56.1)	68.7	69.9±11 (87.9-51.2)	71.1
Mean BP (mmHg)-24-h	84.8±11.5 (96.8-70.8)	85	84.7±11.5 (102.6-67.9)	86.9
Pulse pressure (mmHg)-24-h	49.3±8.3 (55.9-40)	48.7	47.5±7.2 (61.2-43.1)	47.3
PTT, ms-24-h	147.9±18 (206-126)	150	156.2±17.7 (167-125)	152
AIx, %-24-h	-42.4±18 (-59--23)	-42.5	-44±17 (-60--23)	-46

4.6 Controls

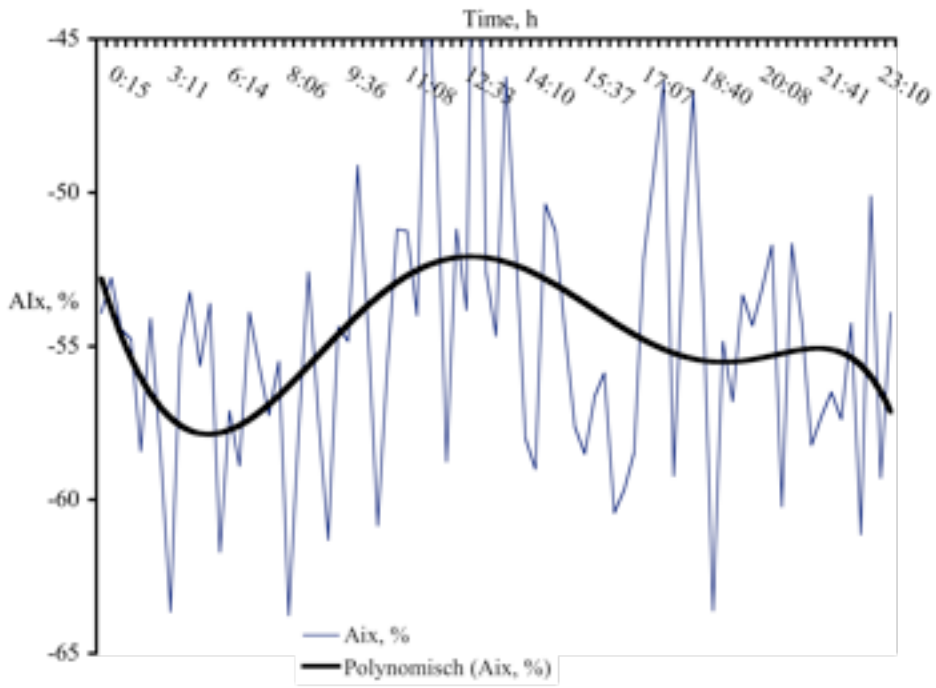
The daily monitoring of blood pressure and arterial stiffness results are presented in Table 23 and Figure 10. The blood pressure readings for the controls are within the 50-95th percentile for the corresponding age, gender, and height. PTT (24-hours) is 131.5-164.7ms, AIx (24-hours) is -66.9 - 37.9%.

There is a circadian pattern in the arterial stiffness (AIx) in the controls. AIx is greater during the day (6:00-22:00) than at night. The curve in the daily profile of AIx has two peaks at about 12.00 and 22.00 hours. The arterial stiffness increases especially during the transition from sleep to wakefulness and decreases during the transition to sleep (Figure 10).

Table 23
Characteristics of blood pressure and arterial stiffness in controls (n=17)

Characteristics	Mean±SD	Median
Systolic BP (mmHg)-24-h	114.9±12.3 (127.6-101.8)	114.9
Diastolic BP (mmHg)-24-h	66.6±11.6 (78-58.1)	66.5
Mean BP (mmHg)-24-h	81.6±12.3 (91.2-73.8)	81.8
Pulse pressure (mmHg)-24-h	45.8±7.9 (58.9-37.3)	48.2
PTT, ms-24-h	148.1±16.6 (187-103)	147
AIx, %-24-h	-52.4±14.5 (-67--35)	-54
Systolic BP (mmHg)-day	115.2±11.3 (126.7-103.6)	117.3
Diastolic BP (mmHg)-day	67.6±11 (79.5-53.6)	67.5
Mean BP (mmHg)-day	82.5±11.6 (93.5-71.1)	81.6
Pulse pressure (mmHg)-day	47.6±7.2 (57.3-36.4)	48.5
PTT, ms-day	145±15.9 (178-132)	143
AIx, %-day	-53.5±13.9 (-71--32)	-53
Systolic BP (mmHg)-night	106.8±9.9 (119.1-95.4)	104.4
Diastolic BP (mmHg)-night	58.9±10.5 (73.3-47.1)	56.9
Mean BP (mmHg)-night	73.5±10.8 (84.4-61.8)	71.5
Pulse pressure (mmHg)-night	47.7±6.2 (56.6-39.1)	47.3
PTT, ms-night	154.5±16.5 (186-125)	141
AIx, %-night	-55.3±9.9 (-76--31)	-57

Figure 10
Circadian variation of AIx in controls (n=17)



4.7 The common characteristics of blood pressure and arterial stiffness in all groups (controls, patients after Tx, ESRD patients, patients on hemodialysis) (Table 24, 25, 26, Figure 11)

Table 24

The common characteristics of blood pressure and arterial stiffness in all groups (controls (n=17), patients after Tx (n=40), ESRD patients (n=22), patients on hemodialysis (n=8))

Characteristics	Controls (n=17) (Mean±SD)	Median	ESRD (n=22) (Mean±SD)	Median	HD (n=8) (Mean ±SD)	Median	Tx (n=40) (Mean ±SD)	Median
Systolic BP (mmHg)-24-h	114.9±12.3	114.9	114±11.6	114.6	114.8±10.5	111.7	118.7±12.6	119.3
Diastolic BP (mmHg)-24-h	66.6±11.6	66.5	68.7±11.1	68.9	74.2±11.5	77.3	70.41±11.3	69.2
Mean BP (mmHg)-24-h	81.6±12.3	81.8	83.7±11.5	83.6	88±11.2	90.2	85.9±11.7	86.4
Pulse pressure (mmHg)-24-h	45.8±7.9	48.2	45.3±8.2	45.6	40.5±7	41.2	48.3±8.5	47.6
PTT, ms-24-h	148.1±16.6	147	147.6±16.5	146	129.3±13.6	134	149±16.5	150
AIx, %-24-h	-52.4±14.5	-54	-34.5±14.3	-38	-16.1±14.7	-14	-40.9±16.7	-46
Systolic BP (mmHg)-day	115.2±11.3	117.3	115.6±11.4	116.4	115.4±10.4	112.7	120.6±11.9	121.4
Diastolic BP (mmHg)-day	67.6±11	67.5	70.1±10.3	71.4	76.1±10.5	77.4	74.8±10.8	72.8
Mean BP (mmHg)-day	82.5±11.6	81.6	85.1±10.9	86.8	89.5±10.4	88.3	87.2±11.3	88.3
Pulse pressure (mmHg)-day	47.6±7.2	48.5	45.5±8.4	44.2	39.3±7	40.1	48.9±8.9	48.4
PTT, ms-day	145±15.9	143	150.3±15.6	147	133.5±13.7	132	148.9±15.3	149
AIx, %-day	-53.5±13.9	-53	-35.7±14.3	-39	-17.3±15.7	-12.5	-42.3±16.5	-47
Systolic BP (mmHg)-night	106.8±9.9	104.4	101.6±8.5	105	107.7±8.8	104	110.6±8.6	108.9
Diastolic BP (mmHg)-night	58.9±10.5	56.9	59±8.4	62	67±9.2	70.8	63.2±7.9	61
Mean BP (mmHg)-night	73.5±10.8	71.5	73.8±8.7	76.6	82±8.6	83.2	78.7±8.5	77
Pulse pressure (mmHg)-night	47.7±6.2	47.3	42.6±6.2	44.4	40.7±5.5	41.3	47±7	45.8
PTT, ms-night	154.5±16.5	141	143±13.6	148.5	140.3±11.8	141	143.7±14.4	146
AIx, %-night	-55.3±9.9	-57	-34.9±11.5	-39.5	-20±12.2	-13.5	-41±13.3	-48

Table 25

Significant differences of blood pressure and arterial stiffness results between groups

Characteristics	ESRD (n=22) (Mean±SD)	Median	HD (n=8) (Mean±SD)	Median	Tx (n=40) (Mean±SD)	Median
Systolic BP (mmHg)-24-h	114±11.6 (92.2-129.8)	114.6	114.8±10.5 (105.4-129.8)	111.7	118.7±12.6(100.6-141)[CI 0.1/18.8]* [p<0.05] [CI 2.9/32.7]** [p<0.05]	119.3
Diastolic BP (mmHg)-24-h	68.7±11.1 (46.2-82.8)	68.9	74.2±11.5 (61.9-82.8)	77.3	70.41±11.3 (51.2-94.3)	69.2
Mean BP (mmHg)-24-h	83.7±11.5 (61.8-99.8)	83.6	88±11.2 (77.7-99.8)	90.2	85.9±11.7 (67.9-108.1)	86.4
Pulse pressure (mmHg)-24-h	45.3±8.2 (28.8-56.6)	45.6	40.5±7 (28.8-47.2)	41.2	48.3±8.5(39.5-62.7) [CI 0.6/9.4]* [p<0.05]	47.6
PTT, ms-24-h	147.6±16.5 (96-190)	146	129.3±13.6(96-146)[CI -62.9/-7] [p<0.05]	134	149±16.5(95-187)[CI15.9/55.3]** [p<0.05]	150
AIx, %-24-h	-34.5±14.3(-63--4)[CI 8.1/30.8] [p<0.05]	-38	-16.1±14.7(-55--4)[CI 26.1/50.5] [p<0.05]	-14	-40.9±16.7(-74--23)[CI1.7/20.9] [CI -41.4/-12.6]** [p<0.05]	-46
Systolic BP (mmHg)-day	115.6±11.4 (96.3-130.4)	116.4	115.4±10.4 (107.5-130.4)	112.7	120.9±11.9 (102.8-144.1)	121.4
Diastolic BP (mmHg)-day	70.1±10.3 (48.8-83.2)	71.4	76.1±10.5 (65.2-83.2)	77.4	74.8±10.8(51.1-129.5) [CI 1.3/19.5] [p<0.05]	72.8
Mean BP (mmHg)-day	85.1±10.9 (63.9-100.6)	86.8	89.5±10.4 (80.1-100.6)	88.3	87.2±11.3 (67.5-109.8)	88.3
Pulse pressure (mmHg)-day	45.5±8.4 (28.6-57.8)	44.2	39.3±7 (28.6-47.5)	40.1	48.9±8.9 (40-63.2)	48.4
PTT, ms-day	150.3±15.6 (124-189)	147	133.5±13.7 (124-146)	132	148.9±15.3 (93-192)	149
AIx, %-day	-35.7±14.3(-62--4)[CI 3.1/29.2] [p<0.05]	-39	-17.3±15.7(-55--4)[CI 19.4/51.9] [p<0.05]	-12.5	-42.3±16.5(-77--24)[CI-44.8/-11.9]** [p<0.05]	-47
Systolic BP (mmHg)-night	101.6±8.5 (85.5-129)	105	107.7±8.8 (96.6-128.3)	104	110.6±8.6 (92.7-133.6)	108.9
Diastolic BP (mmHg)-night	59±8.4 (41.9-81.9)	62	67±9.2 (46.1-81.9)	70.8	63.2±7.9(47.7-87.9) [CI 1/15.4] [p<0.05]	61
Mean BP (mmHg)-night	73.8±8.7 (59.8-97.7)	76.6	82±8.6 (66.3-97.7)	83.2	78.7±8.5 (59.8-101.3)[CI 2.1/18] [p<0.05]	77
Pulse pressure (mmHg)-night	42.6±6.2 (37.3-57.3)	44.4	40.7±5.5 (29.4-51.3)	41.3	47±7 (37.3-60.8)	45.8
PTT, ms-night	143±13.6 (106-190)	148.5	140.3±11.8 (133-146)	141	143.7±14.4 (106-188)	146
AIx, %-night	-34.9±11.5(-81--10)[CI 0.1/34.7] [p<0.05]	-39.5	-20±12.2(-55--10)[CI 13.4/55] [p<0.05]	-13.5	-41±13.3(-68--20)[CI -42.4/-7.9]** [p<0.05]	-48

Red-significant differences of results as compared to control;

*-significant differences of results in the Tx group as compared to ESRD group; **-significant differences of results in the Tx group as compared to HD group.

With reference to Table 25: there are significant differences in blood pressure levels in the transplant group in comparison with the control group and with the other groups of patients. Despite this the results of the 24-hour pressure monitoring are normal. The AIx values are significantly higher in the groups of patients than in the control group. In the transplant patients the range of AIx is also significantly different from the results of AIx in ESRD and the dialysis patients.

Table 26

Significant differences of clinical and biochemical characteristics in patients

Characteristics	ESRD n=22 (Mean±SD)	Median	HDn=8 (Mean±SD)	Median	Tx n=40 (Mean±SD)	Median
Gender (male/female)	14/8		4/4		25/15	
Age (years)	12.1±2.9 (9.2-17.7)	12.6	13.2±2.7 (9.4-17.4)	12.6	12.7±3.3 (8.2-17.7)	13.2
Height (cm)	141.4±20 (108.1-173.3) [CI-44.9/-6.9] [p<0.05]	140.5	140.3±23.8 (108-171) [CI-67/-9.3] [p<0.05]	140.5	141.6±17.3 (107.1-167.9) [CI-28.5/-9.4] [p<0.05]	140.7
Weight (kg)	37.5±15.4 (19-68)[CI-18.2/-1.4] [p<0.05]	31.2	37.2±15.8(18-61)[CI-19.7/-0.7]	35.6	40.5±13.6 (19-68)	39
Serum creatinine (mg/dl)	3.1±2 (0.5-5.7)	2.7	4.4±2.3(1.7-8.4) [CI-4/-2.3]* [p<0.05]	4.2	3.2±3 (0.5-2.8)	0.9
PTH (pg/ml)	139.8±125 (296-543)	101.2	186.3±104.7 (24-360) [CI-147.6/-144]* [p<0.05]	187.5	182.2±132.7 (29.6-370)	82.7
Calcium (mmol/l)	2.3±0.3 (1.3-2.6)	2.3	2.4±0.3 (2-2.9)	2.3	2.37±0.5 (1.3-2.6)	2.4
Phosphorus (mmol/l)	1.52±0.5(0.7-1.6) [CI-5/-0.6]* [p<0.05]	1.4	1.8±0.7 (1.1-3.5)	1.6	1.23±0.3 (0.7-1.6)	1.3
Calcium-phosphorus product (mmol2/l2)	3.4±0.1	3.2	4.3±0.2 [CI-9.9/-2.3]* [p<0.05]	3.6	2.9±0.1	3.1

Red-significant differences of characteristics of patients as compared to control;

*-significant differences of characteristics in the groups of ESKD and HD patients as compared to Tx patients.

With reference to Table 26: the controls are significantly taller and heavier than the patients. The patients with ESRD have significant hyperphosphatemia and hyperparathyroidism in comparison to the transplant group.

Table 27
The Pearson correlations between AIx and clinical and biochemical characteristics in controls and patients

Characteristic	Controls (n=17)		ESRD (n=22)		HD (n=8)		Tx (n=40)	
	Pearson correlation	(p)	Pearson correlation	(p)	Pearson correlation	(p)	Pearson correlation	(p)
Age (years)	-0.3	0.3	-0.09	0.6	-2	0.6	-0.2	0.07
Height (cm)	-0.4	0.1	-0.4	0.05	-0.3	0.5	-0.6	0.0001
Weight (kg)	-0.5	0.04	-0.1	0.5	-0.01	9	-0.5	0.002
Serum creatinine (mg/dl)			0.2	0.2	-0.02	0.9	-0.2	0.2
PTH (pg/ml)			0.08	0.7	-0.2	0.5	-0.01	0.9
Calcium (mmol/l)			0.04	0.8	0.01	9	0.1	0.4
Phosphorus (mmol/l)			0.38	0.1	-0.08	0.8	0.2	0.3
Systolic BP (mmHg)-24-h	-0.2	0.3	-0.2	0.3	-0.1	0.7	0.2	0.3
Diastolic BP (mmHg)-24-h	0.4	0.08	0.04	0.8	-0.5	0.9	0.1	0.3
Mean BP (mmHg)-24-h	0.2	0.4	-0.06	0.7	-0.09	0.8	0.2	0.3
Pulse pressure (mmHg)-24-h	-0.3	0.1	-0.6	0.003	-0.2	0.5	-0.2	0.1

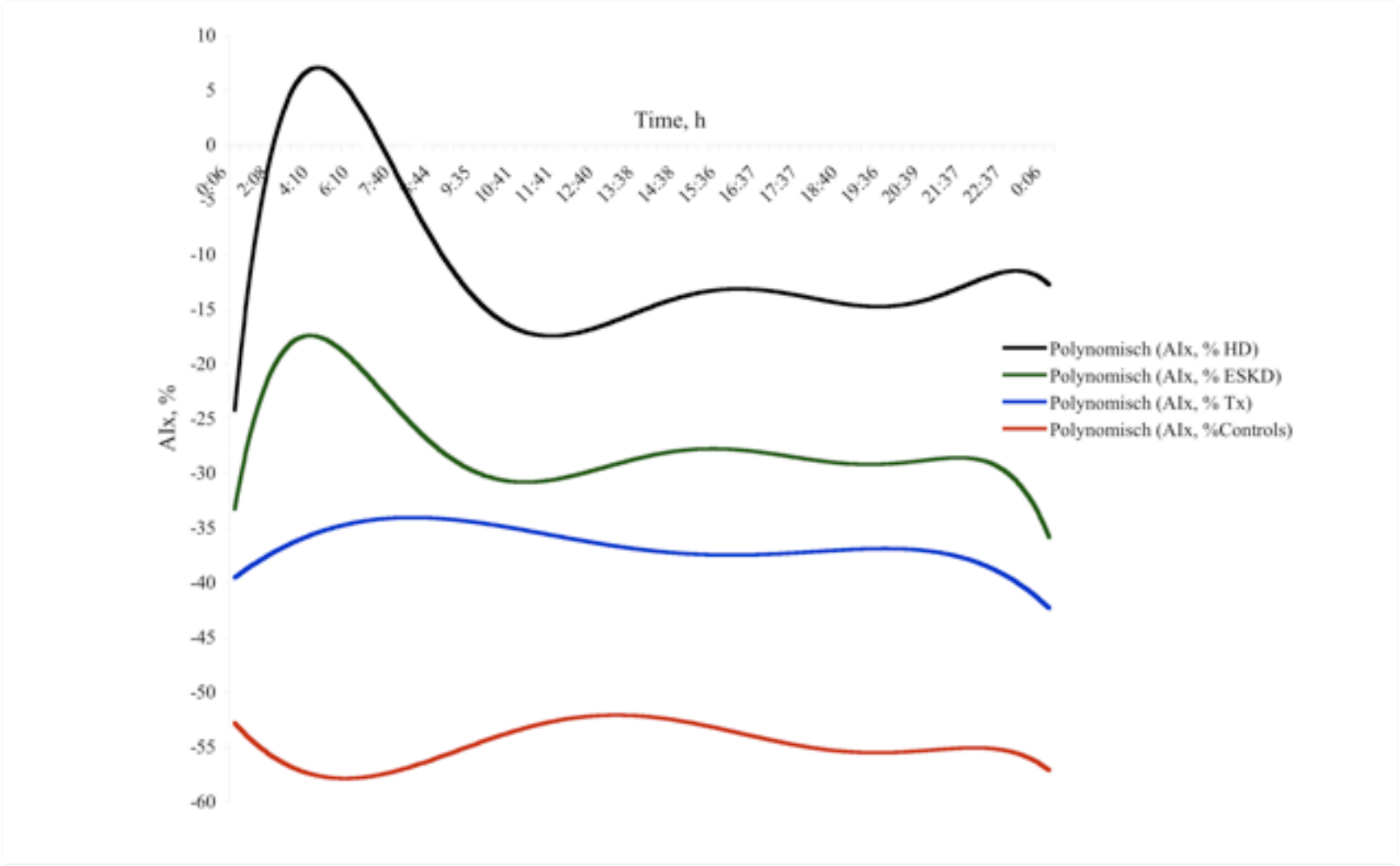
Red-significant correlation

There are significant negative correlations between AIx and

- weight in controls (p=0.04)
- height (p=0.05) and pulse pressure (p=0.003) in ESRD patients
- height and weight in Tx patients (p=0.0001 vs 0.002)

Figure 11

The common characteristics of AIx profile in all groups (controls (n=17), patients after Tx (n=40), ESRD patients (n=22), patients on hemodialysis (n=8))



With reference to Figure 11: there is the circadian profile of AIx in all groups:

- In the controls the curve rises during the day and falls at night
- In the transplant patients there is a similar trend in the AIx profile, but the peaks in the curve are earlier than in the controls (7.30 and 19.00 vs 12.00 and 22.00 hours)
- The patients with ESRD have the perverted daily rhythm of arterial stiffness. At night the range of AIx is higher than during the day.

4.8 Sample (patient F)

The blood pressure and the arterial stiffness were studied in patient F, male, 9.3 years, three times within a period of two years (Tab 28). The diagnose vasculitis led to ESRD, then to Tx. The patient received:

- during the time of ESRD stage 3: immunosuppressive medication (Azathioprine 12.5 mg/d, Cellcept 500mg/d), antihypertensive treatment (Calcium channel blocker, Diuretic)
- during the time on hemodialysis: immunosuppressive medication (Azathioprine 37.2 mg/d) antihypertensive treatment (ACEI, ß-blocker, Diuretic)
- after transplantation: immunosuppressive medication (Prednisone 4 mg/d, Cellcept 1000 mg/d, CSA 500 mg/d), and antihypertensive treatment (ACEI, ß-blocker, α-blocker)

Table 28
Characteristics of the blood pressure and the arterial stiffness in patient F

Characteristics	ESRD (Mean±SD)	HD (Mean±SD)	Tx (Mean±SD)
Systolic BP (mmHg)-24-h	115.5±11.7 (103.8-127.2	105.4±11.7 (93.7-117.1)	114.2±12.3 (101.9-126.5
Diastolic BP (mmHg)-24-	71.8±11.3 (60.5-83.1)	64.2±17.1 (64.4-98.6)	68.8±14.3 (54.5-83.1)
Mean BP (mmHg)-24-h	87.3±11.2 (76.1-98.5)	79.2±14.8 (64.4-94)	86.8±11.7 (75.1-98.5)
Pulse pressure(mmHg)24-	43.7±8.9 (34.8-52.6)	41.2±8.2 (33-49.4)	45.4±12.5 (32.9-57.9)
PTT, ms-24-h	165±17 (148-182)	126±22 (104-148)	136±15 (121-151)
AIx, %-24-h	-24±18 (-42--6)	-7±12 (-19-+5)	-24±13 (-37--11)

In the stages of ESRD and after transplantation the values of blood pressure and of AIx were similar. On the HD the value of AIx increases in comparison with the values before HD and after transplantation.

5 DISCUSSION

Our aims were not only to analyse the status of arterial stiffness in controls and in ESRD patients, but also to prove the hypothesis about the existence of a daily rhythm of arterial stiffness in children. We found that there is a circadian daily profile of arterial stiffness in children and teenagers.

It was shown in adults (20 volunteers) that the arterial stiffness (determined using the abPTT) was greater during sleep than wakefulness, increased during the transition from wakefulness to sleep, and decreased during the transition from sleep to wakefulness (**Lluberas S et al. 2008, Bia D et al. 2008**).

We ascertained also that there are circadian variations of AIx: 1) in controls the curve rises during the day, falls at night; 2) in transplant patients there is a similar trend of AIx profile, but the peaks of the curve are earlier than in controls (7.30 and 19.00 vs. 12.00 and 22.00 hours); 3)patients with ESRD have perverted daily rhythm of arterial stiffness. At night the range of AIx is higher than during the day.

We have studied two options of arterial stiffness: PTT and AIx. The daily value of augmentation index in the controls is -52.4±14.5 %.

In our patients AIx results are significantly higher than in the controls. In the group of HD patients AIx is especially high and significantly differs from the result in transplant patients. The practical value of the AIx is possibly the earliest diagnosis of vascular changes (**Baulmann J et al. 2009**).

There is contradictory literature and data about the arterial stiffness status in pretransplant and Tx children. **Cseprekal O et al. 2009. Briese S et al. 2008** wrote that PWV of 25 transplant children did not differ from controls. The PWV of 11 children on dialysis was not significantly different from the age-matched controls (**Kis E et al. 2008**). In contrary, **Dursun I et al. 2009** researched that the mean aortic PWV in the dialysis group (37 children) was higher than that in the predialysis (37 patients) and control groups (18 children). This study also proved that there was no difference in PWV between 33 predialysis children and the control group.

Following the recommendation from the American Heart Association for „Noninvasive Assessment of Subclinical Atherosclerosis in Children and Adolescents“ (2009) w used the oscillometric cuff technology (BPLab/Vasotens Arteriograph). **Niboshi A et al. 2006, Im JA et al. 2007, Alpert BS, Collins RT 2007** used oscillometric cuff technology in healthy children too. They reported pulse wave velocity results. We studied other parameters of arterial stiffness-pulse transit time and

augmentation index. Augmentation index like other parameters (PWV, central blood pressure) was recommended for assessment of elastic properties of the arterial system (ESC/ESH, 2007) and was proven to be a predictor of mortality and morbidity in patients with CKD (**Fasset RG et al. 2009**). Our control group has the AIx value (24-hours monitoring) -52.4±14.5 %. Unfortunately, we cannot compare this result with other literature data. We have not found any information about daily monitoring of arterial stiffness in children by using oscillometric cuff technology.

Our result of PTT (24-hour monitoring) in controls is 148.1±16.6 ms. **Mitchell GF 2006** suggested that reflected wave transit time was 120-150 ms in healthy adolescents. Mitchell GF did not describe the method of study for arterial stiffness.

There are traditional (such as hypertension, obesity) and „uremia specific“ risk factors (such as hyperparathyroidism, calcium-phosphate disorders) for cardiovascular disease in patients with CKD (**London GM et al. 2003, Mitsnefes MM 2008**). We have analysed the results of daily monitoring of blood pressure, the results of weight and calcium, phosphate and parathyroid hormone levels in all our patients.

All our patient groups are normotensive, in contrast to results of the study of **Briese S et al. 2008**. There are significant differences of blood pressure levels in the Tx group in comparison with the control group (diastolic BP-day range, diastolic and mean BP-night range) and in comparison with the other groups of patients (systolic and pulse pressure over 24-hour period). Despite this, the blood pressure levels in all patient groups were within the 50-95th percentile for the corresponding age, gender, and height. Similar results were described in the study of **Kis E et al. 2008**. Almost all of our patients received antihypertensive treatment.

All our patients were weighed. The weight of patients with ESRD significantly differs from the weight in controls. These patients weigh less than the controls. There is not any difference in weight between transplant patients and the controls.

The level of phosphate in transplant patients is normal. The patients with ESRD have reliable hyperphosphatemia in comparison with transplant group. Calcium-phosphate product in HD group is also higher than in transplant patients. All groups of patients have hyperparathyroidism. Our transplant patients, in contrast to transplant patients of Cseprekal O.,2009, have normal levels of calcium, phosphate, and calcium-phosphate product.

In our controls, only a negative correlation was found between AIx and body weight. **Cseprekal O et al. 2009** established a correlation of PWV with age, height, weight,

systolic BP, and diastolic BP in 188 healthy subjects. **Wang CF et al. 2008** wrote that body weight correlated positively with PWV in 123 healthy children.

We investigated the Pearson correlation between AIx and age, height, weight, blood pressure and mineral metabolism in the patients' groups. There were negative associations in ESRD patients: AIx-height and AIx-pulse pressure, in the group of transplant patients: AIx-height and AIx-weight. **Aoun B et al. 2010** found a positive correlation between PWV and age in fifteen pretransplant children. In 36 Tx children, **Briese S et al. 2008,** found an association between AIx with serum calcium-phosphorus product and PWV with systolic blood pressure and age.

Almost all our patients received antihypertensive medication. They took their medicine at about 08:00 and 20:00 hours. This medication impacts the results of arterial stiffness (**Asmar R 2001**, **Gusbeth-Tatomir P, Covic A 2007**). Despite this impact we can clain that the circadian rhythm in transplant patients differs from rhythm in predialysis and dialysis patients.

We compared the blood pressure levels and the arterial stiffness ranges in transplant children on CSA (n=22) and Tacrolimus (n=14). There are not any significant differences between these groups. The CSA medication does not seem to have any negative impact on the blood pressure and the arterial stiffness in transplant children. In the **Ferro CJ et al. 2002** study it was shown that cyclosporine, but not Tacrolimus, is associated with a higher AIx. Immunosuppression with cyclosporine appeared to abrogate the improvement in AIx in adults. **Zoungas S et al. 2004** wrote also about an improvement in AIx in the Tacrolimus-treated adult group as compared to the cyclosporine-treated group.

We compared the results of AIx between 20 transplant patients and the same patients about 1 year after the first monitoring and between transplant patients with different times after Tx. We saw that Tx leads initially to decreasing of AIx but the increasing of the time after Tx leads to decreasing of arterial stiffness.

We have proved that our ESRD children have a normal range of blood pressure, disturbance of calcium-phosphate metabolism, perverted daily rhythm of arterial stiffness, significantly higher level of AIx than in the controls and than in Tx patients.

We have proved that our transplant children have a normal range of blood pressure, normal levels of calcium, phosphate and calcium-phosphate product, the trend of AIx profile is similar to controls, significantly higher level of AIx than in the controls, the increasing of arterial stiffness with the increasing of the time after Tx.

Our results show that kidney transplantation in children reduces and corrects arterial stiffness and metabolic abnormalities seen in dialysis patients (**Aoun B et al. 2010**). Kidney transplantation should be the ultimate goal to minimize cardiovascular morbidity and mortality in patients with advanced CKD (**Mitsnefes MM 2008**). And we could say that normalization of blood pressure in children with CKD does not lead to satisfactory ranges of arterial stiffness. The „key point“ of arterial stiffness abnormalities is probably a disturbance of calcium-phosphate metabolism and secondary hyperparathyroidism (**Toussaint ND et al. 2007, Kis E et al. 2009**).

6 CONCLUSIONS

Our investigations showed that:

1. There is a circadian daily profile of arterial stiffness in children and teenagers.

2. The curve of augmentation index in healthy children rises during the day and falls at night. A similar trend of augmentation index profile is found in the transplant patients, but the peaks in the curve are earlier than in the controls. The patients with ESRD have a perverted daily rhythm of arterial stiffness: at night the range of augmentation index is higher than during the day.

3. The daily value of augmentation index in the controls is -52.4±14.5 %.

- The patients with ESKD and the transplant patients have significantly higher levels of augmentation index than in the controls (-34.5±14.3 vs -40.9±16.7 [$p<0.05$]) and similar levels of pulse transit time as in the control group (147.6±16.5 vs 149±16.5). It proves that AIx is the earliest and the most sensitive test for arterial stiffness.

- Increasing of time after transplantation leads to increasing of arterial stiffness.

4. The cyclosporine-A medication, in comparison with the tacrolimus treatment, does not seem to have a negative impact on blood pressure and arterial stiffness in Tx children.

5. The daily monitoring of augmentation index:

- is non-invasive

- is exact (we got an average result, which is calculated from 50-70 measurements)

- is made within daily monitoring of blood pressure (it does not require any additional equipment)

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SUMMARY

Cardiovascular disease accounts for 40% of all deaths among pediatric patients with end-stage renal disease. End-stage renal disease indicated by the more than 700-fold increased risk of cardiac death compared with healthy children of the same age. The elastic properties of the arterial system can be assessed non-invasively and easily. The parameters measured (pulse wave velocity, central blood pressure, augmentation index) are important from a pathophysiological point of view and share independent prognostic value. Central pulse pressure, augmentation index and aortic pulse wave velocity are all predictors of morbidity and mortality in patients with chronic kidney disease. The 24-hour monitoring of arterial stiffness in children has never been investigated.

PATIENTS AND METHODS. We investigated and compared the blood pressure levels and the arterial stiffness ranges between controls (n=17), CKD patients stages 2-5 (n=22), and transplant children (n=40); between 20 transplant patients and the same patients about 1 year after the first monitoring; and between transplant patients with different times after Tx (the first year and 1-8 years); in transplant children on CSA (n=22) and tacrolimus (n=14). All patients underwent regular monitoring in KfH-Nierenzentrum UK-Eppendorf, Hamburg. Main artery stiffness was analysed with BPLab/Vasotens Arteriograph (OOO Petr Telegin).

CONCLUSIONS. We have proved that there is a circadian daily profile of arterial stiffness in children and teenagers. The curve of augmentation index in healthy children rises during the day and falls at night. A similar trend of augmentation index profile is found in the transplant patients, but the peaks in the curve are earlier than in the controls. The patients with ESRD have a perverted daily rhythm of arterial stiffness: at night the range of augmentation index is higher than during the day. The patients with ESKD and the transplant patients have significantly higher levels of augmentation index than in the controls (-34.5±14.3 [$p<0.05$] and -40.9±16.7 [$p<0.05$] vs -52.4±14.5 %) and similar levels of pulse transit time as in the control group. It proves that AIx is the earliest and the most sensitive test for arterial stiffness. Increasing of time after transplantation leads to increasing of arterial stiffness. Cyclosporine-A, in comparison with tacrolimus, does not seem to have a negative impact on blood pressure and arterial stiffness in Tx children.

In our study we represented a method of daily monitoring of augmentation index, which can be applied in every day practice. This investigation can help in stratification of the risk for cardiovascular events and is more suitable for therapeutic intervention in children with ESRD.

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2.**Моисеева С, Мюллер-Виефель ДЕ** (2010) Состояние сосудистого тонуса (индекс аугментации) у подростков с хронической почечной недостаточностью и после трансплантации почки. Педиатрия, журнал имени Г.Н. Сперанского 6: 17-20 (Russisch)

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APPENDIX

Fig 1, Fig 2, Fig 3

With reference to Fig 1&2:
P1 - forward travelling (incident) pressure wave (Fw);
P2 - backward travelling, reflected „echo“ wave (Rw);
P2-P1=Augmentation;
Aix=P2/P1

With reference to Fig 3:
AGE - advanced glycation end products;
VSMC - vascular smooth muscle cell;
MMP - matrix metalloprotease;
I-CAM - intercellular adhesion molecule;
TGF-β - transforming growth factor.

PULSWELLENKONTUR und PULSWELLENREFLEXION

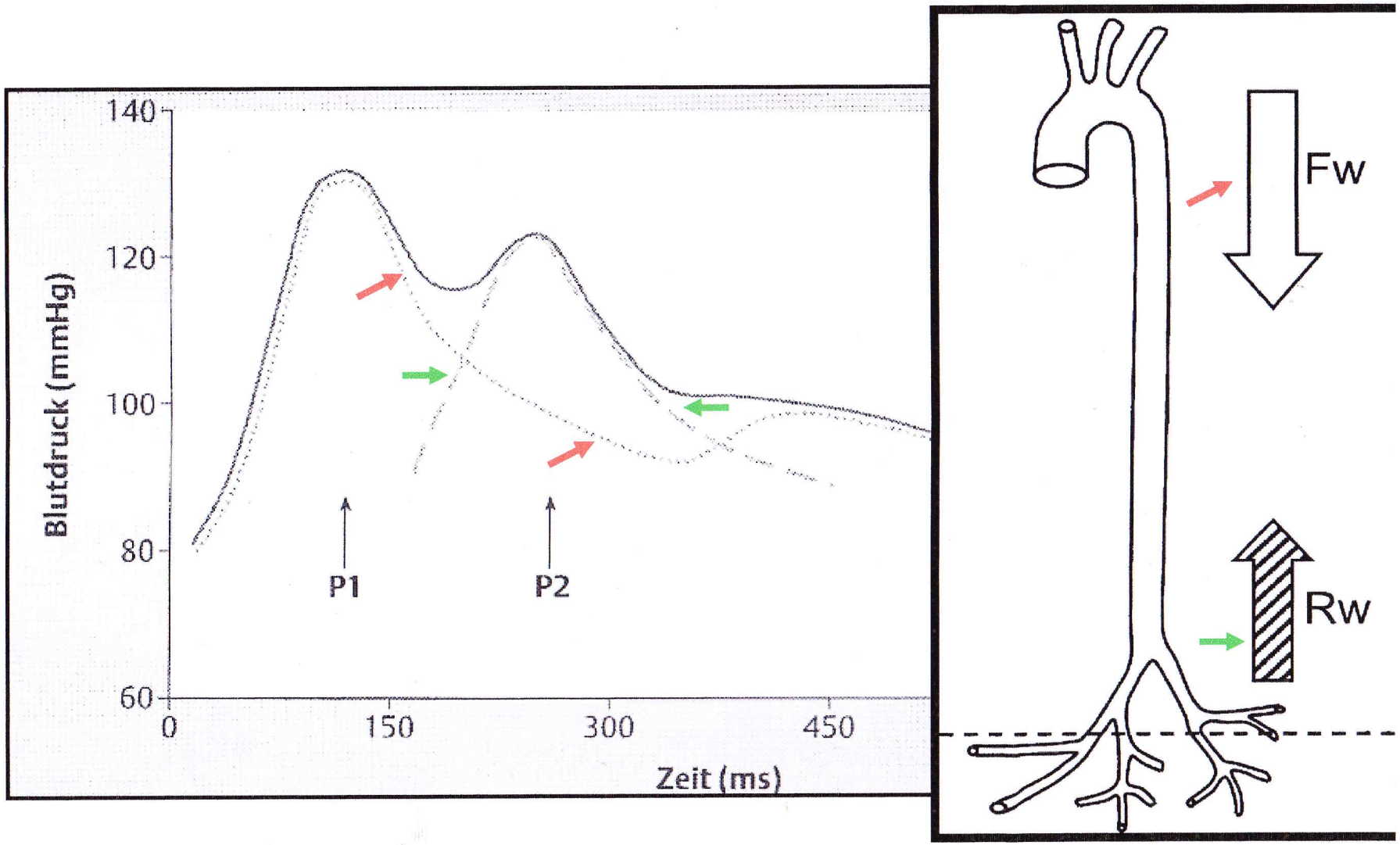
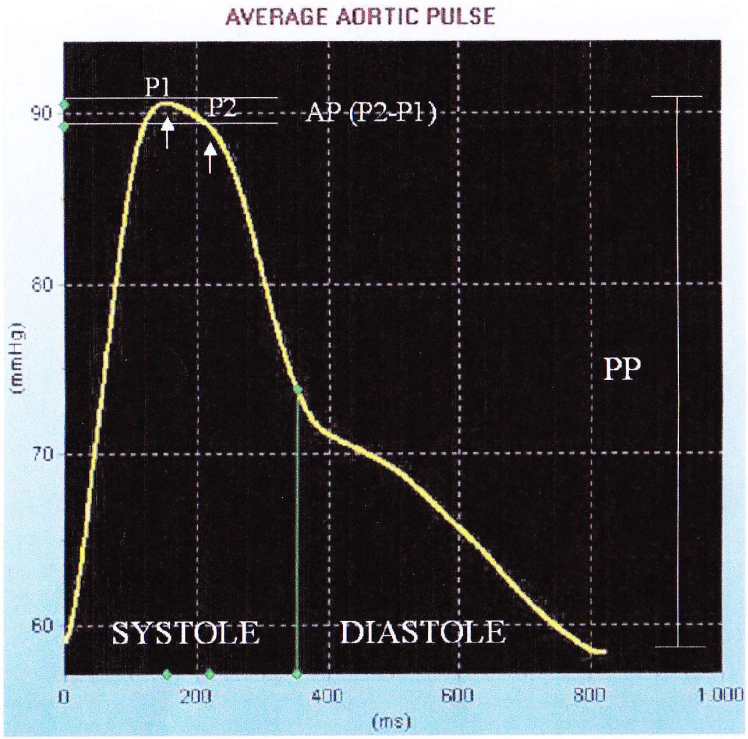


Figure 1

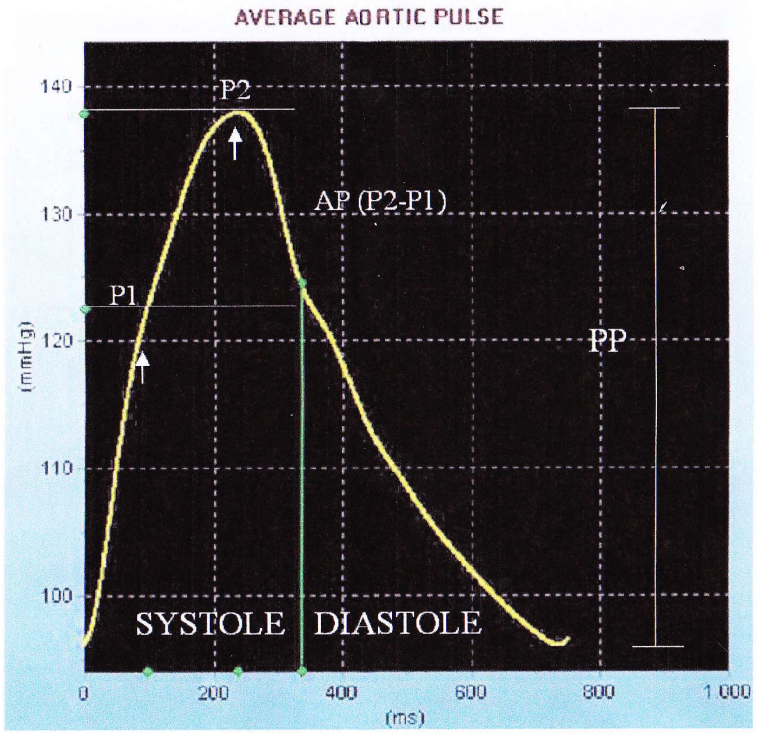
Nürnberger et al, DMW 2003; Millasseau, Clin Sci 2002

Aortale Pulswelle ermittelt aus tonometrisch aufgezeichneter Radialspulskurve

SphygmoCor®



Adoleszenz



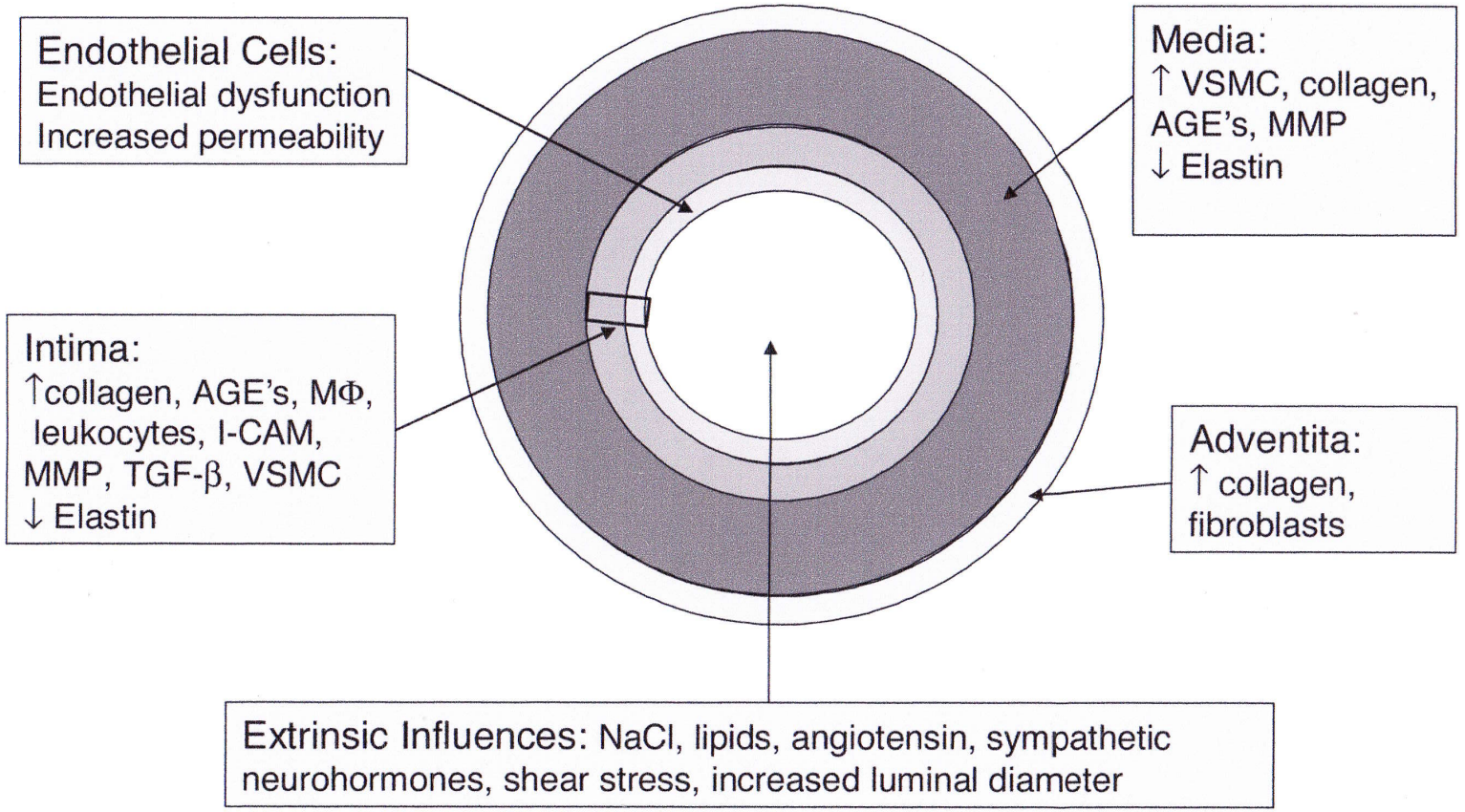
Greisenalter

- **P1**: Gipfel der primären Pulswelle (LV-Auswurf)
- **P2**: 2. Gipfel durch Überlagerung der primären mit reflektierter Pulswelle
- P2-P1 = **Augmentation** (**AG**) (-druck, **AP**)
- **Augmentationsindex** (**AIx**) = AG/PP oder P2/P1

EZ 07

Figure 2

Figure 1. Summary of the multiple causes and locations of arterial stiffness.



Zieman S J et al. Arterioscler Thromb Vasc Biol 2005;25:932-943

Figure 3