Aortic Pulse Wave Velocity as a Biomarker in Chronic Dialysis Patients

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Contents

Abstract

Cardiovascular mortality is considered the main cause of death in patients receiving dialysis and is 10–20 times higher in such patients than in the general population. A high percentage of all cardiovascular mortality diseases are

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associated with stiffening of the arteries, a direct consequence of atherosclerosis. Increased central arterial stiffening is a hallmark of the aging process and consequence of many disease states, such as diabetes, atherosclerosis, and chronic renal compromise. Accelerated arteriosclerosis is a major risk to long-term survivors on maintenance hemodialysis.

Measuring of the pulse wave velocity provides useful information regarding the mechanical properties of the arterial tree and can be used to assess the stiffness and endothelial function. From all the different methods to assess arterial stiffness, carotid to femoral pulse wave velocity has emerged as the gold standard method. Two Doppler waves are recorded transcutaneously at the base of the neck for the right common carotid artery and over the right common femoral artery. After that, the Doppler waves are identified and their time delay diversity is measured simultaneously with electrocardiography. Time delay (transition time, ΔT) is the time from the R wave to the foot of the carotid or femoral Doppler waveform.

There is a high prevalence of increased pulse wave velocity in a relatively young hemodialysis patient population. Vascular stiffening likely begins much earlier and progresses more rapidly in hemodialysis patients. Accelerated arteriosclerosis is a major risk to long-term survivors on maintenance hemodialysis. The pulse wave velocity measured at baseline was markedly higher in chronic hemodialysis patients than in general population patients, with a greater than twofold higher annual increase. In the general population group, only factors associated with the progression of arterial stiffness in the elderly were evident (traditional risk factors), but in chronic kidney disease patients, arterial stiffness (i.e. pulse wave velocity) is accelerated due to synergism between age and traditional risk factors plus factors related to renal comorbidity (nontraditional risk factors). Patients with end stage renal disease face a particularly high risk of cardiovascular disease and total mortality. It is now known that pulse wave velocity, C-reactive protein and serum albumin are strongly and independently predictive of outcome in chronic hemodialysis patients. Whether enhanced arterial stiffness is a risk factor contributing to the development of cardiovascular disease or a marker of established cardiovascular disease is a matter of debate. The pulse wave velocity is a strong independent predictor of over-all and cardiovascular mortality with high-level performance values, assessed by simple, indirect, reproducible and noninvasive evaluation of regional arterial stiffness.

Keywords

Pulse wave velocity • Stiffness • Clinical biomarker • Chronic dialysis • Doppler • Cardiovascular mortality • Traditional risks factors • Nontraditional risk factors

Abbreviations

C	Incisura
CCA	Common carotid artery
CFA	Common femoral artery
CHP	Chronic dialysis patients

CKD	Chronic kidney disease
CRP	C-reactive protein
CV	Cardiovascular
D	Dicrotic wave
DD	Dialysis duration
ECG	Electrocardiogram
ESRD	End-stage renal disease
GPP	General population patients
P	Percussion wave
PWV	Pulse wave velocity
S	Starting point
T	Tidal wave
TT	Transit time
ΔD	Relative change in vascular diameter
ΔS	Vascular cross sectional surface area
ΔT	Time delay, time diversity

Key Facts of Arteriosclerosis

- Increased arterial stiffness is the result of atherosclerosis, vascular calcification and changes in collagen/elastin ratio content in the vessel wall.
- Stiffening and thickening of the arterial walls are two important components of atherosclerosis.
- Arterial stiffness is a cause of premature return of reflected waves in late systole, increasing central pulse pressure and the load on the ventricle.
- Accelerated atherosclerosis 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.
- Accelerated arteriosclerosis is a major risk to long-term survivors on maintenance hemodialysis and the most frequent cause of cardiovascular morbidity in patients with end stage renal disease.

Key Facts of Doppler Effect

- The Doppler ultrasound, measuring the changes in ultrasound waves, can actually measure how fast or slow blood is moving, which can indicate a circulatory problem.
- Doppler ultrasound imaging can also be used to identify atherosclerotic plaque buildup in the blood vessels, narrowed or blocked arteries.
- The most widely used method of evaluating arterial stiffness is Doppler ultrasound that measures aortic pulse wave velocity in the area running from the common carotid artery to the common femoral artery.

Key Facts of Aortic Pulse Wave Velocity

- Pulse wave velocity is a measure of arterial stiffness, or the rate at which pressure wave (not blood) moves down the vessel.
- In aging and arteriosclerosis, central elastic arteries become stiffer, diastolic pressure decreases while systolic and pulse pressures are augmented due to increased pulse wave velocity.
- By measuring the pulse wave velocity it is possible to noninvasively assess stiffness and age of the arteries and thus the risk of cardiovascular events with fatal ending.

Key Facts of Hemodialysis

- Hemodialysis is the default therapy for patients in end stage renal disease.
- Hemodialysis is a method that is used to achieve the extracorporeal removal of waste products such as urea, creatinine and free water from the blood when the kidneys are in end stage renal disease.
- In chronic hemodialysis patients, increased arterial stiffness has recently become intensively investigated as a major novel cardiovascular risk factor.
- Dialysis patients have rigid blood vessels in which stiffening starts earlier and are more pronounced by accelerated aging of blood vessels compared with patients from the general population.

Summary Points

- This chapter focuses on arterial stiffness, which describes the reduced capability of an artery to expand and contract in response to pressure changes.
- Increased central arterial stiffening is a hallmark of the aging process and the consequence of many disease states, such diabetes, atherosclerosis, and chronic renal compromise.
- The pulse wave velocity is a physiological phenomenon that is used to assess the stiffness of large vessels, measuring the speed of pressure wave propagation, not the displacement of the blood.
- While traditional risk factors predominated in the general population, nontraditional risk factors (uremia, infection, biocompatibility of dialysis membranes, acidosis, etc…) play an increasingly important role, being perhaps dominant in end-stage renal disease patients.
- The larger stiffness of the blood vessels in patients on hemodialysis, which occurs earlier and progresses rapidly, increases the speed of the pulse wave and the number of cardiovascular events.
- Aortic pulse wave velocity may represent a surrogate end point, which may in fact indicate in which patients the traditional cardiovascular risk factors translate into real risk.

- The salient finding of this chapter is that the pulse wave velocity was a strong independent predictor of cardiovascular mortality with high-level performance values, assessed by simple, indirect, reproducible, and noninvasive evaluation of regional arterial stiffness in chronic dialysis patients.

Introduction

The pulse wave is a physiological phenomenon that propagates through the arteries due to the reciprocal transformation between the kinetic energy of a segment of the expelled blood volume and the potential energy of a stretched segment of the resilient vascular wall. The pulse wave analysis provides useful information regarding the mechanical properties of the arterial tree and can be used to assess the stiffness and endothelial function. Arterial stiffness is a general term that collectively describes distensiblility, compliance, and elastic modulus of the arterial vascular system. These properties are not homogeneous along the arterial tree, muscular and elastic vessels differ. The elastic properties of arteries vary along the arterial tree, with more elastic proximal arteries and stiffer distal arteries. The velocity of propagation of the pulse wave increases with decreased arterial distensibility. Moreover, wave reflections, which amplify the pressure wave, are generated at the level of peripheral arterial bifurcations and smaller muscular arteries (Laurent et al. 2006).

In recent years, great emphasis has been placed on the role of arterial stiffness in the development of CV diseases. Indeed, the assessment of arterial stiffness is increasingly used in the clinical assessment of patients. Increased central arterial stiffening is a hallmark of the aging process and the consequence of many disease states, such as diabetes, atherosclerosis, and chronic renal compromise. The most consistent and well-reported changes are luminal enlargement with wall thickening (remodeling) and reduction of elastic properties (stiffening) at the level of large elastic arteries, namely arteriosclerosis (Izzo and Shykoff 2001). Arteriosclerosis refers to reduced arterial compliance due to increased fibrosis, loss of elasticity, and vessel wall calcification affecting the media of large and middle-sized arteries. In dialysis patients, both atherosclerosis (affecting mainly the intima of the arteries) and arteriosclerosis (affecting predominantly the media of large and middle-sized arteries diffusely) is prominent (Kanbay 2010).

Arterial stiffness describes the reduced capability of an artery to expand and contract in response to pressure changes. Parameters that describe vessel stiffness include compliance and distensibility. The consequence of reduced compliance/distensibility is an increased propagation velocity of the pressure pulse along the arterial tree, called pulse wave velocity (PWV). PWV inversely correlates with arterial distensibility and relative arterial compliance (Cecelja and Chowienczyk 2012).

Mechanical behaviour of large arteries is extremely complex and provides serious difficulties, both on the theoretical and technical aspects. Indeed, arteries have marked anisotropy, exhibit non-linear visco-elastic properties, and have powerful adaptive mechanisms (Nichols and O'Rourke 2005). An understanding of the basic

principles of haemodynamics and generating pulse wave, require integrated knowledge of physicists, physiologists, biologists and medical doctors. Earlier physicists such as Young (1808), Poiseuille (1840), and Korteweg (1878) established hydraulic and elastic theory. Important contributions to the analysis of the pressure wave and PWV were made by physiologist Marey (1860) and Mackenzie (1902) by developing and experimenting with various types of sphygmographs. It is impossible to extrapolate segmental arterial stiffness to the whole arterial tree, because no single arterial segment has identical viscoelastic properties. Despite these obstacles, simple parameters derived either from the Windkessel model or based on the arterial wave propagation that have been developed. Otto Frank (1899) originally used the principle of conservation of mass to quantify the Windkessel model of the arterial system. According to this description, the large conductance arteries distend to accommodate blood ejected from the heart during systole and recoil to propel blood through the small resistance vessels in diastole (Sagawa K et al. 1990).

Total arterial compliance (C_{tot}), the sum of all arterial compliances in the system, determines the ability of the arterial system to store blood, whereas the total peripheral resistance (R_{tot}), the average input pressure divided by the average flow, determines the ability of the arterial system to resist blood flow. According to this description, C_{tot} is higher in young subjects, allowing the arterial system to accommodate an entire stroke volume without generating much pulse pressure (i.e., difference between systolic and diastolic pressures). However, with an increase in arterial stiffness with age, C_{tot} decreases and ejection creates a larger pulse pressure (Quick et al. 2006).

Arterial stiffening increases in patients with chronic renal insufficiency, and aortic PWV, a marker of stiffening, is a strong independent predictor of mortality in this population.

In uremic patients, elasticity and digestibility of collagen and other extracellular matrix proteins are reduced because of reactions with methylglyoxal and other reactive carbonyl compounds, which are increased. Intima-medial thickening occurs in response to increased wall stress from hypertension. 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 (Goldsmith et al. 2004).

Document Map

While we mention three ways for PWV measuring, attention is kept on the stiffness measuring using Doppler ultrasound. Foot-to-foot Doppler estimating method is explained by time delay of the signal acquired by the carotid and femoral arteries with synchronous ECG monitoring. It is a method of PWV calculating based on the carotid to femoral signals time delay using a standard equation of speed. In the following text, an associative correlation between hemodialysis duration and arterial stiffness expressed by PWV through coefficient of determination and scatter diagram

is presented. We emphasize the associated interaction of traditional and dialysis-specific factors in the impact of increasing stiffness of the arteries in patients on dialysis.

Estimation of PWV progression have concluded that dialysis patients have rigid blood vessels with more pronounced stiffening by accelerated aging of blood vessels compared with GPPs. To distinguish the patients who survived and who did not survived, we used discrimination ability of a model, by assessing cut-off point of PWV.

Both groups (survived or not survived) formed by the PWV cut-off point value present statistically significant difference regarding survival. A plot of the Kaplan-Meier estimate of the survival function indicates significantly higher CV mortality observed in patients with PWV $\geq$11.8 m/s. PWV as an independent predictor for CV outcome is assessed by Cox-regression model analysis.

Pulse Wave Velocity Estimation

Arterial stiffness, estimated by aortic PWV, is an independent predictor of CV mortality and morbidity. However, the clinical applicability of these measurements and the elaboration of PWV reference values are difficult due to differences between the various devices used Salvi et al. (2008)). Arterial stiffness is assessed noninvasively by PWV measurement, that is, the velocity of the pulse wave to travel a given distance between two sites of the arterial system.

There are three different non-invasive techniques to measure arterial stiffness:

1. Measuring of PWV expressed through time delay ΔT [ms].
2. Measuring of the relative change in vascular diameter $\Delta D = D_1/D_2$, or relative change in vascular cross sectional surface area $\Delta S = S_1/S_2$ during PWV pressure propagation.
3. Registration and analysis of different segments from arterial pressure waveforms (S, P, T, C and D) and calculating indexes: ejection elastic index, dicrotic dilatation index and dicrotic elastic index (Fig. 1).

Using the first technique, PWV is estimated from foot-to-foot transit time in the aorta and path length measurement. This technique offers a simple, reproducible, cheap, and noninvasive evaluation of segmental aortic stiffness.

Transit times are assessed as the time difference between two characteristic points on carotid and femoral waveforms. The characteristic points chosen are dependent on the type of waveform (flow, pressure, or diameter distension) and the algorithm used for its detection. The two most popular algorithms are: (I) the intersecting tangent algorithm (Sphygmocor® system and for manual identification) and (II) the point of maximal upstroke during systole (as used in the Complior® system). Different algorithms applied on the same waveforms can lead to differences in measured PWV values of 5–15 % (Millasseau et al. 2005).

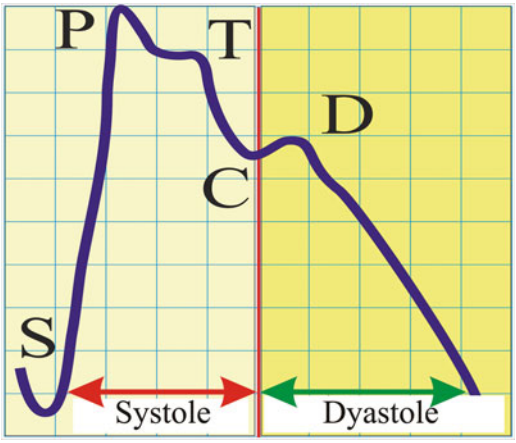

Fig. 1 Arterial pressure waveforms in systole and diastole. Graphic variation of pressure changes throughout one full heart cycle. This diagram can be used for classification of the arterial elasticity. There are several specific points on the pressure diagram that reflect appropriate hemodynamic events in the specific phases of the cardiac cycle: S (starting point) – blood discharging after aortic valve is open; P (percussion wave) – linearly increasing of arterial wall by left ventricular (*LV*) ejection; T (tidal wave) – reflected wave from the distal small arteries; C (Incisura) – end-point of systolic phase, aortic valve is closed now and D (dicrotic wave) – reflective blood pressure of aorta that crash into aortic valve

PWV Measured by Doppler

Carotid and femoral waves are analyzed by a General Electric Logiq pro 5 Doppler ultrasound machine. Although it is not possible to analyze the carotid and femoral waves simultaneously, they can be normalized separately with the electrocardiogram (ECG) (gatting).

Three parameters needed for foot-to-foot PWV calculating are obtained by Doppler ultrasound with a linear array (10 MHZ) probe synchronized with ECG during 2-s minimum sliding window: T_1 – time delay from "R – wave" of ECG to foot of the Common Carotid Artery (CCA) wave, T_2 – time delay from "R – wave" of ECG to foot of the Common Femoral Artery (CFA) wave and distance D measured from sternal notch (CCA) to the groin (CFA). The foot of the wave is defined at the end of diastole, when the steep rise of the systolic waveform begins. Path length (distance D) was defined by direct anthropometric measurement of the distance between suprasternal notch (fossa jugularis sternalis) and groin. Each of the three consequent recordings involved two or three cardiac cycles. To find the transit time (TT) we measured the time from the R wave of ECG to the foot of the waveform using digital calipers (Fig. 2).

It is now known that the measurement of carotid-femoral PWV is calculated by dividing the distance D by the ΔT, so-called TT (Transit Time). Time diversity ΔT is calculated by the time differences T_1 and T_2 yielding the time delay: $\Delta T = T_2 - T_1$. The speed of pulse wave (V) is calculated by standard equation for the speed: V (m/s) = S (m)/ΔT (s). Hence, PWV = D/Δt (m/s).

Fig. 2 Doppler of carotid artery – time delay measurement by CCA Doppler synchronized with ECG. Picture shows the basic principle of time delay estimation from heart beat to the emergence of carotid flow wave. Doppler of right common carotid artery obtains grey spectral wave and the *green curve* below it is obtained by synchronous recording of electrocardiography. The distance determined by two calipers mark, presented by two "red cross" is calculated as 50.0 ms time delay (TM). This time delay period is needed for the pulse wave to arrive from the heart to the carotid artery

Arterial Stiffness and Hemodialysis Duration

While traditional risk factors predominated in the general population, in chronic dialysis patients (CHP), nontraditional risk factors play an increasingly important role, being perhaps dominant in end-stage renal disease (ESRD) patients. Recently, many studies have focused on newly discovered nontraditional risk factors, such as vitamin D deficiency, CRP, fibrinogen, hyperhomocysteinemia, high plasma norepinefrin, accumulation of the endogenous inhibitor of the nitric oxide synthase asymmetric dimethylarginine, extracellular volume overload, hyperphosphatemia, and oxidant stress as a link between traditional and other nontraditional risk factors in CHPs. Nontraditional risk factors are more prevalent in ESRD patients compared to the general population (Zoccali et al. 2005). These include specific factors like uremia, infection, biocompatibility of dialysis membranes, hyperhomocysteinemia, acidosis, and hyperphosphatemia. Parallel testing and comparing the two groups (the hemodialysis and the general population) are providing an important data for the

influence of traditional risk factors for atherosclerosis in the general population and the combined impact of traditional and dialysis-specific risk factors in patients undergoing dialysis (Avramovski et al. 2013).

Coefficient of determination R^2 (0.3723) is showing that 37.23 % from the total variability is explained with the linear relation between PWV and dialysis duration (DD) or that 37.23 % from PWV is dependent on the DD. Only 37.23 % from the changes in PWV are a result of the DD value changes and the rest 62.77 % from the total variability between them are not explained (62.77 % of aortic PWV are dependent on other factors, which are not covered with the regression model). This model is used as criterion for best regression equation choice, so the greater its value is, the better the model of approximation will be (Table 1).

The regression parameter $b_o = 9.7797$ is showing the expected theoretical value of aortic PWV in case if DD would have a value equal to zero. This parameter also shows the point of the y-axis (dependent variable axis, aortic PWV) through which the regression line passes across. The regression parameter $b_1 = 0.2914$ signifies that at each increase of one unit (year) in DD, aortic PWV score increases for 0.2914 m/s. The equation of simple linear regression $\mathbf{y = 9.7797 + 0.2914 \cdot X}$ shows the average coordination of aortic PWV and DD variations. With this equation, we get the evaluated (theoretical) aortic PWV values in opposition to its empirical values.

A Fig. 3 shows a scatter plot of aortic PWV and DD. There is a positive association between these variables. The data from each one of 80 examined patients is displayed as a collection of colored points (blue circles) determining the cross-sectional point of "x" axis – DD value, with "y" axis – PWV value. Each point has the value of one variable determining the position on the horizontal axis and the value of the other variable determining the position on the vertical axis. Linear regression lines computed by data acquired from different aortic PWV patient's status dependent on aortic stiffness are plotted and shown by different colors and line styles (light blue solid line, red dashed line and dark blue solid line). Linear regression line plotted with dark blue solid line shows a positive correlation between aortic PWV and DD. The 95 % confidence interval is presented by red dashed line and prediction interval is presented by light blue solid line.

The high CV mortality rate in dialysis population has become a major issue and it's not simply related to the increased acceptance of elderly subjects. A recent cross-sectional haemodialysis study found that while traditional coronary risk factors may apply to this population, other factors including the uraemic milieu and the haemodialysis procedure itself were probably contributory (Cheung et al. 2000). Haemodialysis causes numerous changes including abnormal complement activation with disordered leukocyte-endothelial interactions, the release of plasma factors including tumour necrosis factor-alpha and reactive oxygen species (Himmelfarb et al. 2002; Schroder et al. 2001). These processes cause vascular oxidative stress and consecutive elevation of PWV in latter period as result of the vascular stiffness increase. Because of this, the impact of nontraditional risk factors and the above-mentioned factors, nontraditional and specific dialysis factors are conditioning progressive yearly increase of artery stiffness in dialysis patients or PWV increase of average 0,291 m/s in every single year spent in dialysis.

Table 1 Linear regression analysis of aortic PWV and dialysis duration. This table shows the results of relationship between a scalar dependent variable (*PWV*) and explanatory variable (*DD*) obtained by linear regression. The high value of the coefficient of determination ($R^2 = 0.3723$) and the low value of the coefficient of statistical significance ($p < 0.0001$) shows that there is a strong positive correlation between PWV and DD. This means that 37.23 % from the total variability is explained with the linear relation between PWV and DD or that 37.23 % from PWV is dependent of the DD

Regression						
Dependent Y		Pulse wave velocity, m/s				
Independent X		Dialysis duration, years				
Sample size		80				
Coefficient of determination R^2		0.3723				
Residual standard deviation		1.9666				
Regression equation						
$\mathbf{y = 9.7797 + 0.2914 \cdot X}$						
Parameter		**Coefficient**	**Std. error**	**95 % CI**	**t**	**P**
Intercept	$\mathbf{b_0}$	**9.7797**	0.3216	9.1395–10.4199	30.4118	**<0.0001**
Slope	$\mathbf{b_1}$	**0.2914**	0.04285	0.2061–0.3767	6.901	**<0.0001**

PWV pulse wave velocity, *DD* dialysis duration, *Std. Error* standard error, *CI* confidence interval

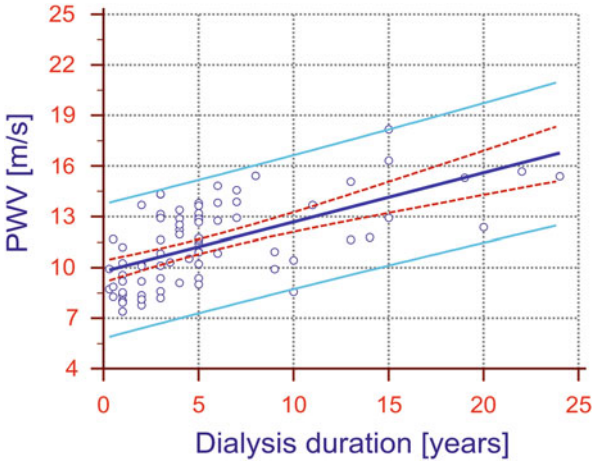

Fig. 3 Linear regression scatter plot of aortic PWV and dialysis duration. A Fig. 3 shows the results from linear regression analysis between pulse wave velocity (*PWV*) and dialysis duration (*DD*) presented as scatter plot, a graph of plotted points that shows the relationship between two sets of data. Linear regression line plotted with *dark blue solid line* shows a positive correlation between aortic PWV and DD, the 95 % confidence interval is presented by *red dashed line* and prediction interval is presented by *light blue solid line*. Abbreviations: *PWV* pulse wave velocity, *DD* dialysis duration

Progression of Arterial Stiffness

Aortic stiffness is associated with increased CV mortality in patients with chronic kidney disease (CKD). Traditional CV risk factors may play some role in the progression of aortic stiffness before development of advanced CKD, and that the enhanced rates of progression of aortic stiffness in CKD patients on dialysis are probably determined by more specific CKD-related risk factors such as advanced-glycation end products (AGEs) (Utescu et al. 2013). Modification of vascular extracellular matrix by advanced AGEs may result in progression of vascular stiffness. Because of higher exposure to glucose and uremic toxins, patients on dialysis have higher tissue levels of AGEs, increased vascular stiffness, and enhanced central augmentation pressure compared to general population patients (GPP). However, the rate of progression of arterial stiffness and the role of CV risk factors in the progression of arterial stiffness are not enough established in longitudinal prospective studies. Although age is one of the most important determinants of CV risk, large artery stiffness is also a key independent predictor of CV mortality (London et al. 2001).

It is now known that progression of arterial stiffness in CHPs compared to the GPPs is pronounced. It was evaluated in longitudinal prospective study in 3 years period (Avramovski et al. 2013). The progression of PWV in CHP during the 36-month period (mean difference 0.6395 ± 0.18373 m/s, $p < 0.001$) compared to

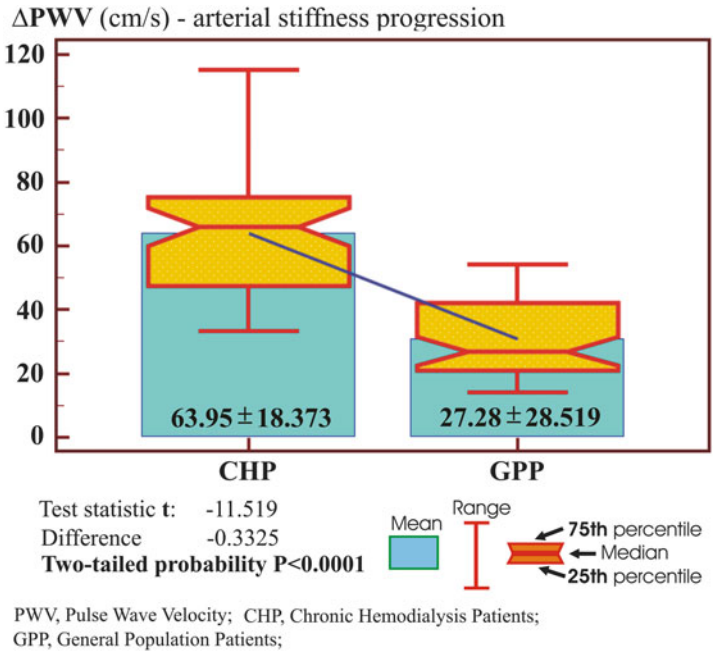

Fig. 4 Pronounced progression of arterial stiffness in chronic hemodialysis patient (*CHP*) compared to the general population patient (*GPP*) group. This *box whisker* diagram shows comparative results from PWV progression in 36-month follow-up period among CHPs and GPPs. ΔPWV in both groups is presented as a difference between PWV in the baseline and after 36 months. Its mean value and SD is 63.95 ± 18.373 cm/s for CHP and 27.28 ± 28.519 cm/s for GPP. It is obvious that there is a faster and pronounced progression of PWV in CHP than in the GPP group. The results of mean, range, 75th percentiles, median and 25th percentiles, test statistics, difference and two-tailed probability of P are presented in this figure, too (Figure courtesy of Korean Journal of Internal Medicine (KJIM 2013; 28: Fig. 4, p 469). The figure is published with permission from the KJIM and copyrights are reserved). Abbreviations: *PWV* pulse wave velocity, *CHP* chronic hemodialysis patients, *GPP* general population patients

the progression of PWV in GPP during the same period (mean difference 0.2728 ± 0.28519 m/s, $p < 0.001$) is pronounced (Fig. 4).

Estimated and compared patients from the control group did not include a young healthy population. The control group consisted of participants from the general population who were not spared from the normal process of atherosclerosis, aging, and osteoporosis. The patients in this group had functioning kidneys, to exclude the influence of renal comorbidity. There is a high prevalence of increased PWV in a relatively young hemodialysis patient population. Vascular stiffening likely begins much earlier and progresses more rapidly in hemodialysis patients ($p < 0.001$). The PWV value measured at baseline was markedly higher (24 %) in CHP than in GPP, with a greater than twofold higher annual increase. In the GPP group, only factors associated with the progression of arterial stiffness in the elderly were evident (traditional risk factors), but in CKD patients, arterial stiffness (i.e., PWV) is

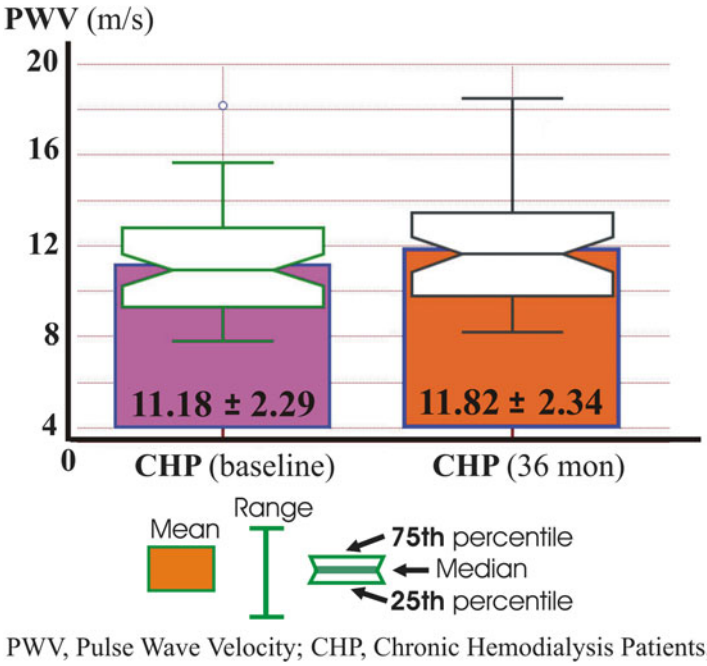

Fig. 5 Values of 3-year PWV follow-up period in CHP (baseline and after 36 months). The results from the PWV progression in CHPs during 36-months follow-up period are presented in Fig. 5. The mean value of 11.18 ± 2.29 m/s is compared with the mean value of 11.82 ± 2.34 m/s after 3-years. *Box plots*, *notched box plots and lines* are presenting results of mean, range, 75th percentiles, median and 25th percentiles of PWV in CHPs. Abbreviations: *PWV* pulse wave velocity, *CHP* chronic hemodialysis patients, *36 mon* 36-months follow-up period

accelerated due to synergism between age and traditional risk factors plus factors related to renal comorbidity (nontraditional risk factors).

The marked increase in aortic stiffness with aging and little change in peripheral arterial stiffness results in a reversal of the gradient of arterial stiffness from the youthful pattern of a compliant proximal aorta, which was evident in individuals aged <50 years, to a pattern of greater aortic stiffness in older participants (Fantin et al. 2007). The progression of blood vessel aging is significantly greater in dialysis patients. In this population, the chronological age is greater than biological age, expressed through the increased arterial stiffness (Fig. 5).

It is now known that progression of PWV over a 36-month period, and the significant difference between the CHP and GPP groups, suggest that arterial stiffening has progressed further in dialysis patients compared to the general population, which suggests a significant distinction in the aging and stiffness of their arteries, and so thus the biological age of both populations (despite almost identical chronological age: 59.3 ± 11.8 vs. 59.7 ± 11.9 years).

GPPs have an increased vascular stiffness; this is associated with traditional risk factors and urea, hemoglobin, albumin, CRP, and glucose levels. Nontraditional risk

factors, or uremia-related specific factorssuch as anemia (hemoglobin), inflammation (CRP), hypoalbuminemia, and abnormal lipoproteins-might play a role in the accelerated progression of arterial stiffness only in CHPs (Avramovski et al. 2013). Fortunately, arterial stiffening can be monitored by a simple noninvasive method, measuring the PWV, which enables evaluation of the risk of CVr events.

Arterial Stiffness and Cardiovascular Mortality

A high percentage of all CV diseases are associated with stiffening of the arteries, a direct consequence of atherosclerosis. Increased arterial stiffness is the result of many contributing factors, such as atherosclerosis, vascular calcification and changes in collagen/elastin ratio content in the vessel wall. The increase in artery wall stiffness is noticeable from the beginning of the arteriosclerosis process, before anatomical changes and clinical manifestations are observed. Atherosclerosis is the most frequent cause of CV morbidity in patients with ESRD. Patients with ESRD face a particularly high risk of CV disease and total mortality (Zaccali et al. 2003). Accelerated arteriosclerosis is a major risk to long-term survivors on maintenance hemodialysis (Safar et al. 2002). Myocardial infarction and cerebrovascular events occupy an important place in the mortality of these patients. The CV mortality rate of CHPs is approximately 20 times higher than that of the general population, and the cerebrovascular death rate is nearly 10 times higher.

The arterial system in ESRD patients undergoes structural remodeling very similar to changes with aging, and is characterized by diffuse dilation, hypertrophy and stiffening of the aorta and major arteries. In comparison with nonuremic patients, the intima-media thickness of major central arteries is increased in ESRD patients (London et al. 1997). There are large-scale cohort studies, which provide evidence that high PWV as a noninvasive marker for arterial stiffness is a useful predictive marker for CV events in subjects with CKD, hypertension and diabetes. Since epidemiological and clinical studies have shown that damage of large arteries is a major contributory factor to the high CV morbidity and mortality of patients with ESRD, such a population is particularly appropriate to analyze the impact of arterial stiffness on mortality (Blacher et al. 1999, 2003). PWV is a strong independent predictor of overall and CV mortality in a population of ESRD patients undergoing hemodialysis but (Guérin et al . 2001) have recently showed that arterial stiffness is not only a risk factor contributing to the development of CV disease but is also a marker of established more advanced, less reversible arterial changes.

Avramovski et al. (2014) in 36-month follow-up period, comparing the PWV results in survived (11.26 $\pm$ 2.37 m/s) and nonsurvived ESRD patients (13.13 $\pm$ 1.70 m/s) got significantly ($p < 0.001$) higher PWV in deceased patients. PWV in deceased patients from CV disease is more pronounced, it is equal to 13.7 $\pm$ 1.24 m/s ($p < 0.001$). At first sight, it is not very big difference, only about two and a half meters. But, if we know the fact, that an increase of aortic PWV by 1 m/s corresponds to an age, sex and risk factor adjusted, risk increases for 14 %, 15 % and 15 % in total CV events, CV mortality and all-cause mortality, respectively, the above mentioned

fact is not for underestimation. An increase in aortic PWV by 1 SD (standard deviation) was associated with respective increases of 47 %, 47 % and 42 % (Vlachopoulos et al. 2010b).

Estimation of Cut-Off Point

The most relevant way of structuring the comparison groups of ESRD, in order to obtain the statistical significance between them is grouping by cut-off PWV value. The PWV cut-off point value for ESRD patients where the sensitivity and specificity are highest (94.1 % and 61.4 %, respectively) is 11.8 m/s. Avramovski et al. found that the PWV cut-off point of 11.8 m/s is predictive of increased mortality in ESRD patients, especially for CV mortality. However, different studies have determined different cut-off points of PWV that is predictive of increased overall and CV mortality. The cut-off point of 12 m/s or greater was chosen based upon a study demonstrating this to be the level associated with clinically significant negative prognosis in patients with ESRD (Covic et al. 2005). Based on receiver operating characteristics (ROC) curve analysis mean PWV levels in CHPs show an optimal cut-off point at 12.0 m/s, while mean PWV levels in GPPs show an optimal cut-off point at 9.6 m/s/ (Boutouyrie 2010). The role of age in presenting normal, reference and cut-off point values needs careful consideration. As for blood pressure, it is not immediately clear whether normality should be defined according to age. It is now known that considering the PWV of 11.8 m/s as a relevant cut-off point speed, for all-cause and especially for CV mortality prediction generates two different subgroups of ESRD patients. There are statistically significant differences between those subgroups ($p < 0.001$) according to PWV value (13.65 ± 1.32 vs. 9.76 ± 1.29 for each one).

Predictors of Cardiovascular Survival

Vertical drop in a plot of the Kaplan-Meier indicates an event as series of horizontal steps of declining magnitude approaching the true survival function in CHPs (Fig. 6). Considering the fact that the mean value of PWV is 8.3 m/s (mean age 61.0 years) in the general population (Inoue et al. 2009) the majority of patients with ESRD could be considered to have increased arterial stiffness and elevated PWV equal to 12.50 m/s (mean age 59.3) as results of accelerated atherosclerosis (Avramovski et al. 2014). It is now known that there is a more than fourfold increased relative risk for lethal outcomes (all-causes mortality) in subgroups with more stiffened arteries (PWV $\geq$11.8 m/s, $P = 0.0037$). Relative risk for exposed groups according to CV lethal outcomes is a about 14-fold increased risk in subgroups with more stiffened arteries (PWV $\geq$11.8 m/s, $P < 0.0080$).

Avramovski hypothesized that there is no differences in survival in both subgroups of patients on dialysis just below and above the cut-off point (11.8 m/s). Comparative results of the two curves [(logrank), $x^2 = 13{,}1001$; degree of freedom (DF) = 1;

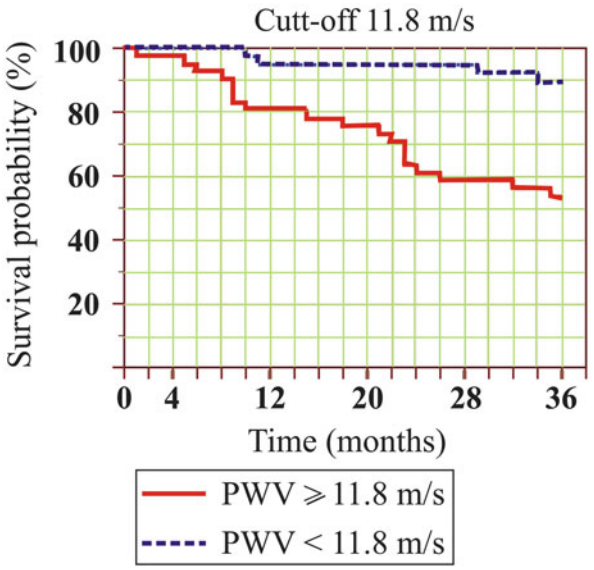

Fig. 6 Kaplan-Meier survival time according different cut-off value of PWV and CV events. This figure presents survival probability in CHPs according different PWV (above or below the cut-off velocity): PWV ≥11.8 m/s (*red staircase line*) and PWV <11.8 m/s (*blue staircase line*). Every vertical drop in a plot of the Kaplan-Meier indicates a CV event as series of horizontal steps of declining magnitude approaching the true survival function in CHPs during 36-months follow-up period. Abbreviations: *PWV* pulse wave velocity, *CV* cardiovascular, *CHP* chronic hemodialysis patients

significance (P) = 0,0003; relative risk = 0.1744; 95 % CI = (0.0767–0.3965)] indicate significantly higher CV mortality in patients with PWV above cut-off point (PWV ≥11.8 m/s). With threshold of 0.95 or security risk error of 0.05, Avramovski rejected the null hypothesis and concluded that there is a statistically high significant difference (significance is very large) in both subgroups of dialysis patients with different PWV, regarding survival. Survival time according to different cut-off value of PWV dependent on CV events is presented in Fig. 6.

Are the traditional risks factors for atherosclerosis sufficient alone to describe high prevalence of CV disease in this condition? The traditional risk factors for atherosclerosis (age, elevated blood pressure, smoking status, low levels of HDL cholesterol, high levels of LDL cholesterol and triglycerides, obesities and diabetes) interacting to initiate atherosclerosis and promote the development of CV disease have enhanced our ability to assess risk in individual patients. In addition, understanding of new, so-called novel risk factors (CRP, homocysteine, plasma fibrinogen, interleukin-10, impaired glucose tolerance and metabolic syndrome) and when these are included along with the classic risk factors in assessing the global risk profile, may improve ability to predict future risk precisely. In uremic patients, traditional risk factors are added to specific, disease-related (inflammation and malnutrition)

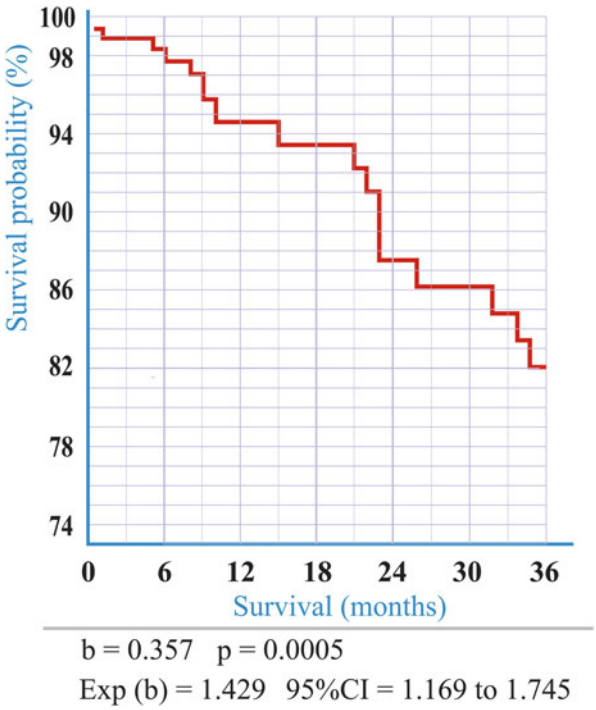

Fig. 7 Cox-regression survival analysis (predictors of CV outcome). The results from Cox-regression analysis of CV survival according to PWV as an independent predictor for the CV outcome in CHPs: regression coefficient $b = 0.357$, p value $= 0.0005$, hazard ratio coefficient Exp (b) $= 1.429$ and 95 % CI of Exp (b) $=$ 1.169–1.745 are presented in Fig. 7. *Red staircase line* indicates CV survival probability in CHPs in 36-months follow-up period. Every vertical drop in a plot means one fatal CV event. Abbreviations: *CV* cardiovascular, *CHPs* chronic hemodialysis patients, *PWV* pulse wave velocity, *CI* confidence interval

and treatment-related risk factors (incompatibility of dialysis membrane and dialysis adequacy) (Fruchart et al. 2004).

Using Mantel – Cox- regression analysis (proportional hazards regression) of CV survival in hemodialysis patients, the potential predictors of events ending with death we're analyzed. Assessments (regression coefficient [b], hazard ratio coefficient Exp [b], p value, and 95 % CI [confidence interval] of Exp [b]) of independent predictors for CV outcome after Cox-regression model analysis are presented in Fig. 7.

According to the Cox-regression analysis, the significant covariates retained by the model (backward stepwise) are only PWV, CRP and albumin. Covariates with positive regression coefficients (b), PWV (0.357) and CRP (0.083) are predictors of the CV events. They indicate decreased hazard and increased survival time. Albumin, as covariate with negative regression coefficient (b) (−0.1881), indicates decreased hazard and increased survival time. The predictor PWV has an Exp (b) hazard ratio coefficient of 1.429. The HR increases by 1.429 (42.9 %) with each unit increase in PWV. Foremost biomarker in predicting CV risk is PWV with more expressed statistical significance ($p < 0.0001$) than statistical significance of other covariates (CRP, $p < 0.001$; albumin, $p < 0.003$).

Aortic PWV may represent a surrogate end point, which may in fact indicate in which patients the traditional CV risk factors translate into real risk. Summary comparative results from meta-analysis of the predictive value of aortic stiffness

(carotid-femoral PWV) for all-cause and CV events are presented by Vlachopoulos et al.: HR: 1.63 for CV and 1.61 for all-cause mortality; HR: 1.44 for CV and 1.35 for all-cause mortality; HR: 1.20 for CV and 1.14 for all-cause mortality. Considering earlier before mentioned arguments, it remains to explain whether PWV as the main determinant of arterial stiffness, has some independent predictive value for the overall and CV – mortality. Several pathophysiological mechanisms may explain the association between increasing PWV and CV-mortality. Increased stiffness of the arteries is the cause of premature return of reflected waves in late systole, resulting in increased central pulse pressure and further ventricular overload. It reduces ejection fraction and increases the myocardial oxygenation demand.

Potential Applications to Prognosis, Other Diseases or Conditions

The estimation of PWV as an indicator of artery stiffness has never been ascertained as a CV risk marker. Recently, many studies have confirmed its importance that aortic PWV is strongly associated with the presence and extent of atherosclerosis and constitutes a forceful marker and predictor of CV risk in *hypertensive patients*, *diabetes*, *chronic kidney disease*, *rheumatoid arthritis*, *degenerative disease* and many other diseases. PWV as a biomarker of disease is a predictor of coronary heart disease and stroke in a population-based study among apparently healthy subjects (Mattace-Raso et al. 2006), and provides additional predictive value above CV risk factors, measures of atherosclerosis, stiffness and pulse pressure. Viscoelastic properties of large arteries play an essential role in CV hemodynamics, especially in systolic blood pressure determination.

Large artery damage is a major contributing factor to the elevated CV morbidity and mortality observed in CV risk factors such as **hypertension**. Rich qualitative and quantitative information about the large arteries (stiffness, distensibility, pulsatility, compliance) is easily obtained by Doppler determination of PWV. Reduced arterial distensibility contributes to a disproportionate increase in systolic pressure and an increase in arterial pulsatility that is associated with an increase in CV morbidity and mortality. A number of longitudinal studies among hypertensive patients report the effects of elevated PWV as an independent predictor of cerebrovascular diseases and all-cause mortality. The relative risk of stroke mortality is 1.7 for PWV elevation of 4 m/s and that of all-cause mortality is 2.1 for PWV elevation of 5 m/s (Laurent et al. 2003).

Patients with **type 2 diabetes** have increased stiffness of central elastic arteries. However, whether peripheral muscular artery stiffness is equally affected by the disease remains sparsely examined. Diabetes is a predictor of central artery stiffness, and glucose is a determinant of peripheral artery stiffness (Zhang et al. 2011). Hyperhomocystinaemia is associated with macro and microangiopathic diabetic complications. Vitamin B_{12} is significantly associated with homocystein concentrations and is identified as a marginally independent correlate of PWV in diabetic patients in the absence of folate deficiency. Elevated homocystein and reduced vitamin B_{12} have a key role in the development of atherogenesis in diabetic patients

(Shargorodsky et al. 2009). Mortality risk doubled in subjects with diabetes (hazard ratio 2.34, 95 % CI 1.5–3.74) and in those with glucose intolerance (2.12, 95 % CI 1.11–4.0) compared with controls (Cruickshank et al. 2002).

Rheumatoid arthritis (**RA**) is a chronic, systemic, inflammatory disease, which is associated with increased CV risk that is not explained by traditional CV risk factors but may be due in part to increased aortic stiffness, an independent predictor of CV mortality (Mäki-Petäjä et al. 2006). The involvement of the CV system in the course of inflammatory lesion and connective tissue diseases may result in serious morbidity and mortality. PWV as an indicator of arterial distensibility predicts CV risk in RA patients. Decreased dilatation capacity leads to a reduction in arterial blood pressure and flow dynamics and impairment in coronary perfusion. Aortic PWV increases by only +6 % per decade in healthy individuals, which suggests that subjects with RA have arteries 20 years older than chronological control subjects. Contrary to findings by Klocke et al. (2003), there is not a significant difference in PWV between the RA and control groups.

Systemic inflammation may contribute to the increased incidence of CV disease in RA, because inflammation is known to play a pivotal role in the pathogenesis of CV disease (Libby 2002). All these changes in the CV system are in line with increased CV morbidity and mortality in RA patients. The CV mortality risk in patients with RA is approximately equal to the CV risk in patients with diabetes. In a prospective study, the 3-year incidence rate of fatal and nonfatal CV events was 9.0 % in RA patients and 4.3 % in the general population. Compared with the non-diabetic population, non-diabetic patients with RA and those with type 2 diabetes had comparable hazard ratios, 2.16 and 2.04 respectively (Peters et al. 2009). It is very likely that the use of common risk calculators (e.g., Framingham, SCORE) will underestimate the CV risk in RA patients.

Effective control of inflammation reduces the CV risk in patients with RA as it improves arterial stiffness and endothelial function. The measurement of PWV gives data values about the current state of blood vessels inflammation and assesses to the risk of CV disease in RA patients. This diagnostic method for assessment of arterial stiffness is useful not only to assess vascular features of blood vessels (rigidity, elastance, compliance, distensibility) but can assess the effectiveness of certain drugs in the course of therapy in certain diseases.

Conventional and noninvasive tools for evaluating atherosclerosis have been recently developed and are currently in use. The use of PWV has received increasing attention as a non-invasive method to measure vascular injury (Khoshdel et al. 2007). The first use of PWV was reported in 1922 in a study examining an association between age and arterial stiffness (Bramwell and Hill 1922). During the 1960s, as new techniques were developed to assess pulse wave and pressure, reports on PWV increased. At the time, PWV measurement procedures were complicated and not suitable for diagnostic purposes. The development of ultrasound Doppler technique made a big step forward, so now measuring the PWV has become a relatively simple method for fast, inexpensive, accurate and routine assessment of arterial stiffness. Following its commercialization in 1999, many reports on PWV have been published.

Here, we have indicated the potential value of using PWV, which is a convenient, inexpensive, and noninvasive test to identify vascular injury and predict vascular disease. The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) have added PWV measurement as an early index of large artery stiffening in the "2007 Guideline for the Management of Arterial Hypertension" (Mancia et al. 2007).

Definitions

Arterial stiffness Arterial stiffness is a term that describes rigidity of the arterial walls and the reduced capability of arteries to expand and contract according pressure changes.

Arteriosclerosis It is a broad term that describes hardening and elasticity loss of the inner and middle layers of the artery wall.

Atherosclerosis This is a condition where the arteries become stiffer and narrowed due to progressive thickening and hardening of their walls from waxy plaques on the inner lining.

Chronic Renal Insufficiency It is a stage based on reduced filtering capacity of the kidneys so that they are no longer capable to remove fluids and wastes from the body or of maintaining the adequate level of certain kidney-regulated chemical in the bloodstream.

Doppler ultrasound This is a noninvasive ultrasound test that is used to estimate blood flow through blood vessels based of series of generated pulses that is transmitted and then reflected from blood cells to detect movement of blood.

Foot of the wave This is the terminal point of diastolic spectral waveform that occurs at the beginning of the first ascent after diastole.

Hemodialysis Hemodialysis is a renal replacement therapy method in renal failure disease that is used to achieve the extracorporeal removal of waste products and free water from the blood.

Pulse Wave Velocity Measures the rate of pressure wave propagation across the vessel. Pressure wave is generated during blood flows through the vessels of circulatory system.

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