**Title:** Determinants of increased central excess pressure in dialysis: role of dialysis modality and arteriovenous fistula

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## ABSTRACT

**Background:** Arterial reservoir-wave analysis (RWA) - a new model of arterial hemodynamics - separates arterial wave into reservoir pressure (RP) and excess pressure (XSP). The XSP integral (XSPI) has been associated with increased risk of clinical outcomes. The objectives of the present study were to examine the determinants of XSPI in a mixed cohort of hemodialysis (HD) and peritoneal dialysis (PD) patients, to examine whether dialysis modality, and presence of an arteriovenous fistula (AVF) are associated with increased XSPI.

**Method:** In a cross-sectional study, 290 subjects (232 HD, and 130 with AVF) underwent carotid artery tonometry (calibrated with brachial diastolic and mean blood pressure). The XSPI was calculated through RWA using pressure-only algorithms. Logistic regression was used for determinants of XSPI above median. Through forward conditional linear regression, we examined whether treatment by HD or presence of AVF is associated with higher XSPI.

**Results:** Patients with XSPI> median were older, had a higher prevalence of diabetes and cardiovascular disease, had a higher body mass index and were more likely to be on HD. After adjustment for confounders, HD was associated with a higher risk of higher XSPI (OR=2.39, 95%CI:1.16-4.98). In a forward conditional linear regression analysis, HD was associated with higher XSPI (standardized coefficient: 0.126, P=0.012), but upon incorporation of AVF into the model, AVF was associated with higher XSPI (standardized coefficient: 0.130, P=0.008) and HD was excluded as a predictor.

**Conclusion:** This study suggests that higher XSPI in HD patients is related to the presence of AVF.

## INTRODUCTION

Patients with end-stage kidney disease are at increased risk of all-cause and cardiovascular mortality. [1,2] Among non-traditional cardiovascular risk factors, aortic stiffness and increased wave reflection have been proposed to contribute to this increased risk of cardiovascular and over-all mortality. [3,4] Indeed, it is proposed - by the wave propagation model - that aortic stiffness leads to increased augmentation index (enhanced and earlier wave reflection) in the ascending aorta, resulting in increased cardiac workload and reduced coronary perfusion pressure. However, in an elderly dialysis cohort, aortic stiffness and augmentation index (AIx) were not significantly associated with increased risk of death upon adjustment for age and comorbidities. [5,6] Given that the wave propagation model does not consider the reservoir function of the arterial tree, a reservoir-wave approach (RWA) has been proposed to circumvent this limitation. [7-11] The RWA approach hypothesizes that the measured arterial pressure is the sum of a reservoir pressure wave (RP), which accounts for the dynamic storage and release of blood by the compliant arteries (the Windkessel effect), and an excess pressure wave (XSP), which is responsible for local changes in the pulse waveform. Theoretically, the aortic reservoir pressure is the minimum left ventricular work required to generate blood flow into the aorta, whereas the excess pressure provides information about the surplus of work performed by left ventricle and is believed to be analogous to flow. [10-13]

The added value of RWA has been demonstrated in patients with hypertension, in high risk patients, in patients with heart failure and in dialysis population. [14-20] Indeed, we and others have previously shown that higher excess pressure is associated with increase cardiovascular and all-cause mortality in dialysis population. [19,20] As XSPI is analogous to flow, and creation of an arteriovenous fistula (AVF: either native or graft) has been shown to increase stroke volume and increased myocardial contractility, we hypothesized that excess pressure should increase after

creation of AVF. [21-23]. Therefore, the aim of the present study was 1) to identify the determinants of excess pressure in dialysis patients, 2) to examine whether the dialysis modality has an impact on excess pressure, and 3) to examine whether the presence of AVF is associated with a higher excess pressure.

## METHODS

### Patient population and study design

In a cross-sectional study we aimed to study the determinants of excess pressure in a cohort of end-stage renal disease patients treated by chronic hemodialysis or chronic peritoneal dialysis. From August 2006 to June 2014, 328 patients underwent at least one extensive evaluation for medical history, laboratory data, pharmacological treatment and hemodynamic parameters of arterial stiffness. This cohort of patients was composed of adult patients on chronic dialysis (>3 months), with single-pool KT/V >1.4 in hemodialysis patients and a weekly KT/V of >1.7 in patients on peritoneal dialysis, stable dry weight and blood pressure medication. Patients were excluded if they had an acute episode of illness (infection, recent cardiovascular events) or any clinical conditions that would hamper hemodynamic measurements (absence of femoral pulse, systolic blood pressure of <90 mmHg). Coronary artery disease was defined as myocardial infarction, coronary artery revascularization or ischemic heart disease as shown by either a treadmill, echocardiography or thallium stress tests. History of atherosclerotic cardiovascular disease was defined by a history of non-hemorrhagic stroke, coronary artery disease, lower extremity amputation or revascularization. Hypertension was defined as brachial blood pressure ≥140/90mm Hg or antihypertensive drug usage.

**Hemodynamic measurements**

All measurements were performed in the same visit after 15 minutes of rest in a supine position. In hemodialysis patients, all assessments were performed prior to their mid-week dialysis session. Brachial artery blood pressure (BP) was recorded 6 times, with a 2-minutes interval using an automatic oscillometric sphygmomanometer BPM- 100 (BP-Tru, Coquitlam, Canada) by an experienced operator who was present in the room. In case of an AVF, measurements were performed on the contralateral arm. Immediately after BP measurements, radial and carotid pulse wave profiles were sequentially recorded in the same order by applanation tonometry (SphygmoCor system®, AtCor Medical Pty. Ltd., Sydney, Australia). Three consecutive recordings were performed for each site. Central pressure parameters were obtained by radial artery tonometry through generalized transfer function from which central systolic pressure (SP), diastolic pressure (DP), pulse pressure (PP), and augmentation index adjusted for heart rate of 75 bpm (AIx@75) were derived after calibration for brachial systolic and diastolic BPs. Carotid pressure wave forms were obtained by tonometry after calibration using brachial diastolic and mean arterial pressure, which was obtained by integration of the arterial pressure waveform. [24] Immediately after pulse wave recordings, we determined carotid-femoral pulse wave velocity (cf-PWV) and carotid-radial pulse wave velocities (cr-PWV) in triplicate by Complior® SP (Artech Medical, Pantin - France), using the maximal upstroke algorithm and direct measurements as previously described. [25,26] We used the ratio of cf-PWV/cr-PWV as a measure of arterial stiffness gradient (PWV ratio).

Reservoir-wave parameters were obtained using the pressure wave approach as previously described.[14,27] Reservoir pressure (RP), its integrals (RPI), excess pressure (XSP) and its integral (XSPI), diastolic rate constant (DC) and systolic rate constant (SC) were acquired from carotid

pressure waveforms. Accordingly, SC is the rate of system filling which is inversely proportional to the product of characteristic impedance ($Z_0$) and compliance (C), whereas DC is the rate of system emptying, which is inversely proportional to the product of peripheral vascular resistance (R) and compliance (C). RP was derived based on pressure alone and XSP was defined as the difference between total measured pressure and RP. A reservoir pressure analysis was considered valid with RP>0, XSPI>0, a numerical SC and DC, DC>0 and $P_\infty$ >0. RP proportion and XSP proportion were respectively the ratio of RPI or XSPI to total pressure integral x 100. The XSP:RP is the ratio of XSP proportion to RP proportion. Figure 2 summarizes the key parameters of RWA of the carotid artery.

Wave separation analysis was conducted to derive central pressure forward (Pf), pressure backward (Pb), and reflection magnitude (RM = (100 x Pb)/Pf) and reflection index (RI=(Pb x 100)/(Pb+Pf)) were calculated. This was performed on the central pressure waveform after application of a generalized transfer function on the radial artery pressure waveform. [28,29]

**Biochemical analysis**

All routine laboratory tests were performed on the mid-week hemodialysis session for patients on hemodialysis and in the morning in patients on peritoneal dialysis. The PTH was measured with the PTH stat assay from Roche diagnostics using two antibodies reactive with epitopes in the amino acid regions 26-32 and 37-42 (normal: 15-90 ng/L), and C-reactive protein was measured by an immunoturbidimetric method (normal <10 mg/L) as previously described. [25]

**Statistical analysis**

Results were reported as mean ± standard deviation or median [$25^{th}$-$75^{th}$ percentiles] where appropriate. To identify the determinants of XSPI, we separated the population according to the median value of XSPI. Differences in characteristics parameters between groups were evaluated using Fischer's exact test, Mann-Whitney U or independent Student t tests. To examine if dialysis modality was associated with increased risk of high XSPI, we used multivariable logistic regression analysis and adjusted for age, diabetes status, cardiovascular disease, mean arterial pressure, BMI, heart rate and cf-PWV. After log transformation of XSPI, we used a multiple linear regression analysis in a forward conditional manner by using the following parameters as independent: age, CVD, diabetes status, BMI, cr-PWV, cf-PWV, PWV ratio, heart rate, mean blood pressure. To examine whether any effect of hemodialysis is related to the presence of an AVF, we conducted the same regression analysis by adding this information into the list of independent parameters. As part of sensitivity analysis MBP was replaced by brachial diastolic and then systolic BP, and again with forced entrance of age and CVD into the model. Finally, we conducted an additional forward conditional multivariable analysis by restricting our population to hemodialysis patients only. We also conducted adjusted model by including clinically important parameters into the model (age, CVD, diabetes, dialysis vintage, heart rate, BMI and mean blood pressure). All statistical analyses were performed using IBM SPSS version 25.0 (SPPS Inc., Chicago, ILL, USA).

## RESULTS

From the 328 subjects that were eligible, 38 subjects (12%) were excluded because of unavailable or unreliable measurements of carotid pulse waveforms, leaving 290 subjects in the study (Figure 1). There were 58 (20%) patients on PD and 232 (80%) on HD. Among patients on HD, 130 (56%) had an AVF. Table 1 shows the clinical, biochemical and pharmacological characteristics of the subjects.

### Determinants of higher excess pressure integral

Patients with XSPI above median were older and had a higher body mass index, had a higher prevalence of diabetes and cardiovascular disease, were treated more frequently by hemodialysis, and had a higher rate of aspirin, beta-blockers and calcium channel blockers use (Table 2). As expected, patients with higher XSPI had a higher cf-PWV, systolic and pulse pressures, with a slightly lower heart rate. Table 2 also shows the detailed hemodynamic parameters obtained through wave separation analysis of central pressure waveform after application of generalized transfer function of the radial pressure waveform.

### Dialysis modality and excess pressure integral

In multivariable logistic regression analysis (enter mode) adjusted for age, diabetes status, cardiovascular disease, mean arterial pressure, BMI, heart rate and cf-PWV, patients on hemodialysis had a higher risk of having an XSPI above median (OR= 2.39, 95%CI:1.16-4.98).

In a forward conditional regression analysis using age, diabetes, CVD, mean arterial pressure, heart rate, cf-PWV, cr-PWV, PWV ratio, type of dialysis and BMI, treatment by hemodialysis

was independently associated with a higher XSPI (Table 3: Model 1). Figure 3A shows that XSPI is higher in HD patients after adjustment for PWV ratio, heart rate, diabetes status, MBP and BMI. As part of sensitivity analysis, we used diastolic blood pressure instead of mean blood pressure (Table 3: Model 2), which still showed that hemodialysis was associated with increased excess pressure. In further sensitivity analysis, where MBP was replaced by brachial systolic blood pressure, hemodialysis was not independently associated with increased excess pressure (Table 3: Model 3).

**Arteriovenous fistula and excess pressure integral**

Since excess pressure integral was higher in hemodialysis patients (even after adjustment for potential confounders), we examined to see whether this difference was due to presence of an AVF. Indeed, by means of a forward conditional regression analysis we added presence of an AVF to the same model (i.e. a model which included age, diabetes, CVD, mean arterial pressure, heart rate, cf-PWV, cr-PWV, PWV ratio, type of dialysis, and BMI). As shown in Table 3, the addition of AVF into the analysis, resulted in a model where AVF was associated with a higher excess pressure and the dialysis modality was no longer statistically significant (Table 3: Model 4). Figure 3B shows that XSPI is higher in patients with AVF after adjustment for PWV ratio, heart rate, diabetes status, MBP and BMI. Further sensitivity analysis was performed by replacing MBP by brachial diastolic and systolic blood pressure (Table 3: Model 5 and 6 respectively), and both consistently showed that AVF was independently associated with higher excess pressure. In addition, we forced entered age and CVD (enter mode), variables which were eliminated from the final forward conditional model, and the results pertaining to the association of AVF and excess pressure remained similar (Standardized coefficient: 0.126; P=0.011).

Finally, as part of sensitivity analysis, we excluded patients with peritoneal dialysis and conducted the analysis only on HD patients with and without fistula. In patients on HD without AVF the median number of antihypertensive drugs was higher (2 [1-3]) compared to HD patients with AVF (1 [0 -1], P=0.005). Using a similar forward conditional approach, there was a signal that an AVF was associated with a higher XSPI (standardized coefficient = 0.096, P=0.091), but it failed to reach a statistical level of significance (Figure 3C).

**Dialysis modality, AVF and wave reflection**

Based on wave-propagation model, as part of sensitivity analysis, we examined the impact of dialysis modality and AVF on heart rate adjusted augmentation index using the same variables as for excess pressure. In this model, only age, cardiovascular disease and mean arterial pressure were associated with higher AIx@75, but dialysis modality and AVF were excluded as important predictors of AIx@75.

In a similar manner, we examined the impact of dialysis modality and AVF on reflection magnitude and reflection index. In these models, only age, heart rate, cardiovascular disease and mean arterial pressure were associated with reflection magnitude and reflection index, but dialysis modality and AVF were excluded as significant predictors.

## DISCUSSION

In this cross-sectional analysis of prevalent dialysis population, we showed that comorbid conditions were associated with increased excess pressure. Moreover, hemodialysis patients had a higher excess pressure after adjustment for comorbid conditions, but this increase in excess pressure was mostly related to the presence of an arteriovenous fistula after adjustment for confounding factors.

RWA is a new model of arterial pressure that incorporates the reservoir function with wave-propagation. The RWA approach is based on the assumption that the measured arterial pressure is the sum of a reservoir pressure wave, which results from the dynamic storage and release of blood by the compliant vessel, and an excess pressure wave, which is responsible for local changes in the pulse waveform. Theoretically, the aortic reservoir pressure is the minimum left ventricular work required to generate blood flow into the aorta, whereas the excess pressure - analogous to flow - provides information about the surplus of work performed by left ventricle. [10-13] Given that previous studies have shown increased stroke volume and increased myocardial contractility after a creation of AVF, it is reasonable to expect that excess pressure should increase after creation of AVF. [21-23]

AVF is the vascular access of choice for hemodialysis. [30] In a recent meta-analysis, it was shown that creation of dialysis AVF reduced SBP, DBP and MBP by estimated average of 8.7, 5.9 and 6.6-mm Hg respectively. [31] This observation is also in line with the use of ROX arteriovenous coupler, which is used to create an AVF between distal external iliac vein and artery, and which has been shown to reduce the ambulatory SBP by an average of 13.5 mm Hg in a group of patients with resistant hypertension [32]. Indeed, epidemiological observational studies using administrative databases show that hemodialysis with an AVF gives a better survival advantage

over the use of central venous catheters. [33-36] However, this view has recently been challenged as the survival advantage of native AVF is more likely related to general better health of patients referred for AVF creation and who develop a functioning AVF. [37-39] While it could be proposed that AVF may have potential protective effects through reduction in blood pressure, AVF also bypasses part of the blood flow that is destined to organ perfusion, increases heart rate, myocardial contractility and stroke volume and cardiac output. [21-23,40-42] Given the association between increased XSPI and clinical outcomes, this reduction in blood pressure by AVF may potentially have adverse effects through disturbances in flow dynamics. [18-20] In our study, restricting the analysis to HD patients, after adjustment for other determinants of XSPI, subjects with AVF had a numerically higher XSPI. While this difference failed to reach the statistical level of significance (P=0.091), one would have expected a lower XSPI in patients with AVF because of a better general state of vascular health in this population. Indeed, patients with AVF may have a strong selection bias because not all subjects develop a functioning AVF due to cumulative stress of co-morbidities on peripheral arteries and veins. These cumulative co-morbidities lead to both arterial disease (stenosis and calcification) and scarcity of veins that results from multiple venous punctures required over the life course of chronic disease. We know from our previous study that high XSPI is associated with increased risk of both cardiovascular and overall mortality. Accordingly, one would have expected to have a higher XSPI in patients without AVF, who are generally sicker. Therefore, the association of high XSPI with AVF are more likely related to changes in flow dynamics due to AVF.

The study has several strengths as it provides detailed analysis of a large sample size using RWA, wave separation analysis, vascular stiffness, and the use of various comorbidities and statistical procedures to perform various sensitivity analysis, which consistently show that AVF is associated with increased XSPI. There are also limitations that need to be mentioned. First,

while physiologically appealing and various sensitivity analyses support the robustness of our findings, the study only shows an association between AVF and XSPI and the causality is not demonstrated by this study. Second, we do not have any information regarding the extent of access blood flow at time of vascular assessment. Third, the pressure-only approach for calculation of reservoir-pressure waves assumes that the resultant excess pressure is proportional to the volume flow rate out of the left ventricle. However, the validation of this assumption in humans has recently been performed by Michail and colleagues. [43]

In conclusion, our study shows that patients on HD have higher excess pressure that is mainly related to the presence of an AVF. These observations need to be confirmed in dialysis patients by directly examining excess pressure before and after creation of an AVF, as the potential benefits of an AVF may be outweighed by increase in excess pressure.

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## CONFLICT OF INTEREST / DISCLOSURES

None

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## FIGURE LEGENDS

**Figure 1: Study flow chart.** Study flowchart shows the number of patients excluded for lack of carotid pressure waveform and unreliable reservoir-wave analysis (RWA), the number of patients on hemodialysis (HD), peritoneal dialysis (PD), with and without arteriovenous fistula (AVF).

**Figure 2: Reservoir-wave parameters.** The panel shows artery pressure waveform (□○□) decomposed into reservoir pressure (□) and excess pressure waveforms (□●□), systolic and diastolic constant rates.

**Figure 3: Adjusted excess pressure integral according to dialysis modality and arteriovenous fistula.** Panel A shows a higher level of adjusted excess pressure integral (XSPI) in patients on hemodialysis (HD) compared to patients on peritoneal dialysis (PD). Panel B shows a higher adjusted XSPI in patients with arteriovenous fistula (AVF) compared to dialysis patients without AVF. Panel C shows the adjusted XSPI in HD patients with or without AVF using a forward conditional approach. Bars represent 95% confidence intervals.

**Table 1: Demographic, biochemical and pharmacological characteristics**

| **Parameter** | N=290 |
|---|---|
| **Age (y)** | 64.8 ± 14.9 |
| **Male** | 173 (60) |
| **Diabetes** | 124 (43) |
| **CVD** | 151 (52) |
| **Smoking** | 115 (40) |
| **BMI (Kg/m$^2$)** | 27.2 ± 5.5 |
| **Weight (Kg)** | 74.0 ± 16.6 |
| **Peritoneal dialysis** | 58 (20) |
| **Hemodialysis access** | |
| Arteriovenous fistula* | 130 (56) |
| Catheter* | 102 (44) |
| **Dialysis vintage (y)** | 1.5 [0.5-3.3] |
| **stdKt/v** | 2.28 ± 0.26 |
| **Biochemical** | |
| Hb (g/l) | 113.0 ± 11.6 |
| Albumin (g/l) | 37.6 ± 3.5 |
| Calcium (mmo/l) | 2.20 ± 0.17 |
| Phosphate (mmol/) | 1.51 ± 0.38 |
| PTH (ng/l) | 285 [187-450] |
| Cholesterol (mmol/) | 3.85 ± 0.98 |
| TG (mmol/) | 1.94 ± 1.08 |
| CRP (mg/L) | 6.2 [2.5-14.4] |
| **Medication** | |
| ASA | 185 (64) |
| Warfarin | 54 (19) |
| Statin | 182 (63) |
| ACEi/ARB | 131 (45) |
| B-blockers | 167 (58) |
| Calcium channel blockers | 103 (36) |
| Diuretics | 132 (46) |
| Nitrates | 49 (17) |

Values are mean±SD, n (%), or median [25$^{th}$-75$^{th}$ percentile]

CVD: cardiovascular disease, std Kt/V: standardized Kt/V, ACEi: angiotensin-converting-enzyme inhibitor, ARB: angiotensin receptor blockers, ASA: acetylsalicylic acid, CRP: C-reactive protein, Hb: hemoglobin, PTH: parathyroid hormone, TG: triglyceride.

*: percentage based on hemodialysis patients only.

**Table 2: Clinical and hemodynamic parameters according to excess pressure integral**

| | Excess pressure integral | | |
|---|---|---|---|
| | **Below median (n=145)** | **Above median (n=145)** | **P** |
| **Clinical characteristics** | | | |
| Age (y) | 60.7 ± 16.0 | 69.0 ± 12.4 | **<0.001** |
| Male | 85 (59) | 88 (61) | 0.811 |
| Cardiovascular disease | 53 (37) | 98 (68) | **<0.001** |
| Diabetes | 40 (28) | 88 (58) | **<0.001** |
| Smoking | 65 (45) | 50 (34) | 0.093 |
| Dialysis vintage (y) | 1.7 [0.5 – 3.7] | 1.2 [0.5-3.2] | 0.281 |
| Weight (kg) | 72.9 ± 15.6 | 75.1 ± 17.6 | 0.254 |
| BMI (kg/m$^2$) | 26.4 ± 4.9 | 28.0 ± 5.9 | **0.014** |
| Hemodialysis | 106 (73) | 126 (87) | **0.005** |
| Arteriovenous Fistula | 60 (41) | 70 (48) | 0.288 |
| **HR** | 71.2± 10.2 | 65.0± 10.0 | **<0.001** |
| **Brachial BP** | | | |
| SBP (mmHg) | 123.0 ± 20.0 | 142.1± 26.5 | **<0.001** |
| DBP (mmHg) | 73.9 ± 12.7 | 68.2 ± 12.8 | **<0.001** |
| MBP (mm Hg) | 90.9 ± 15.0 | 93.5 ±17.7 | 0.180 |
| **Carotid BP** | | | |
| SBP (mmHg) | 114.6 ± 20.7 | 135.3 ± 27.0 | **<0.001** |
| DBP (mmHg) | 73.6 ± 12.8 | 67.3 ± 13.0 | **<0.001** |
| PP (mmHg) | 41.0 ± 14.3 | 68.0 ± 20.5 | **<0.001** |
| **Carotid Reservoir-Wave** | | | |
| XSPI (kpa.s) | 0.26 [0.20-0.31] | 0.56 [0.45-0.74] | **<0.001** |
| XSP (mm Hg) | 13.8 ± 3.1 | 26.9 ± 9.0 | **<0.001** |
| Time at XSP (ms) | 41.0 ± 14.3 | 68.0 ± 20.5 | **<0.001** |
| RPI (kpa.s) | 1.38[1.16-1.85] | 2.29 [1.63-2.94] | **<0.001** |
| RP (mm Hg) | 33.3 ± 12.9 | 50.2 ± 19.0 | **<0.001** |
| Time at RP (ms) | 30.6 ± 3.6 | 33.0 ± 3.9 | **<0.001** |
| Proportion of XSPI (%) | 15.1 ± 4.8 | 22.4 ± 8.8 | **<0.001** |
| XSPI:RPI | 0.18 ± 0.07 | 0.31 ± 0.17 | **<0.001** |
| Systolic constant rate (x10$^{-2}$) | 19.8 [15.8-25.5] | 16.6 [10.8-21.4] | **<0.001** |
| Diastolic constant rate (x10$^{-2}$) | 2.9 [2.1-4.4] | 3.4 [2.8-4.2] | 0.041 |
| **Pulse wave velocity** | | | |
| cf-PWV (m/s) | 12.6 ± 3.9 | 14.8 ± 3.9 | **<0.001** |
| cr-PWV (m/s) | 9.1± 1.6 | 8.6 ± 1.8 | **0.031** |
| PWV ratio | 1.42 ± 0.49 | 1.76 ± 0.49 | **<0.001** |
| **Central wave separation (GTF)** | | | |
| AIx@75 (%) | 24.1 ± 11.6 | 28.7 ± 9.2 | **<0.001** |
| Forward wave (mmHg) | 28.0 ±8.3 | 42.9 ± 11.8 | **<0.001** |
| Backward wave (mmHg) | 14.0 ± 5.4 | 23.3 ± 8.0 | **<0.001** |
| Reflection Magnitude | 49.6 ± 9.2 | 53.7 ± 9.4 | **<0.001** |
| Reflection Index | 32.9 ± 4.2 | 34.7 ± 3.7 | **<0.001** |
| **Medication** | | | |
| ASA | 76 (52) | 109 (75) | **<0.001** |
| Warfarin | 23 (16) | 31 (21) | 0.291 |
| ACEi/ARB | 57 (39) | 74 (51) | 0.059 |
| Beta-Blockers | 73 (50) | 94 (65) | **0.017** |
| Calcium channel blockers | 37 (26) | 66 (46) | **0.001** |

| | | | |
|---|---|---|---|
| Nitrates | 19 (13) | 30 (21) | 0.116 |
| Diuretics | 63 (43) | 69 (48) | 0.556 |
| Statin | 88 (61) | 94 (65) | 0.544 |

Value are mean ± SD, n (%) or median [25th-75th percentile]. P value obtained by Fisher's exact test, Student t-test or Mann-Whitney U tests as appropriate.

RP, reservoir pressure; RPI, reservoir pressure integral; XSP, excess pressure; XSPI, excess pressure integral; cf-PWV, carotid-femoral pulse wave velocity; cr-PWV, carotid-radial pulse wave velocity; PWV ratio, ratio of cf-PWV-to-cr-PWV; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid,

**Table 3: Determinants of excess pressure integral according to dialysis modality and presence of arteriovenous fistula**

| Parameters | Without AVF in the model: Standardized coefficient | *P* | Adjusted R2 | Parameters | With AVF in the model: Standardized coefficient | P | Adjusted R2 |
|---|---|---|---|---|---|---|---|
| **Model 1** | | | 0.315 | **Model 4** | | | 0.316 |
| PWV ratio | 0.294 | <0.001 | | PWV ratio | 0.304 | <0.001 | |
| Heart rate | -0.282 | <0.001 | | Heart rate | -0.288 | <0.001 | |
| Diabetes | 0.203 | <0.001 | | Diabetes | 0.222 | <0.001 | |
| MBP | 0.176 | <0.001 | | MBP | 0.172 | 0.001 | |
| Hemodialysis | 0.126 | 0.012 | | Hemodialysis* | - | - | |
| BMI | 0.108 | 0.036 | | BMI | 0.101 | 0.050 | |
| | | | | AVF | 0.130 | 0.008 | |
| **Model 2** | | | 0.282 | **Model 5** | | | 0.285 |
| PWV ratio | 0.280 | <0.001 | | PWV ratio | 0.289 | <0.001 | |
| Heart rate | -0.264 | <0.001 | | Heart rate | -0.269 | <0.001 | |
| Diabetes | 0.247 | <0.001 | | Diabetes | 0.261 | <0.001 | |
| Hemodialysis | 0.100 | 0.050 | | Hemodialysis* | - | - | |
| DBP* | - | - | | DBP* | - | - | |
| | | | | AVF | 0.114 | 0.023 | |
| **Model 3** | | | 0.398 | **Model 6** | | | 0.407 |
| SBP | 0.409 | <0.001 | | SBP | 0.406 | <0.001 | |
| cr-PWV | -0.179 | 0.002 | | cr-PWV | -0.170 | 0.003 | |
| Heart rate | -0.235 | <0.001 | | Heart Rate | -0.239 | <0.001 | |
| Diabetes | 0.203 | <0.001 | | Diabetes | 0.201 | <0.001 | |
| PWV ratio | 0.142 | 0.014 | | PWV ratio | 0.155 | 0.007 | |
| Hemodialysis* | - | - | | Hemodialysis* | - | - | |
| | | | | AVF | 0.109 | 0.018 | |

Parameters presented in the table are those that were included in the final model.
* no value for standardized coefficient provided as the parameters was not included in the final model.
Model 1 was built using forward conditional regression analysis by using age, diabetes status, cardiovascular disease, body mass index (BMI), heart rate, mean blood pressure (MBP), Dialysis modality, carotid-femoral pulse wave velocity (PWV), carotid-radial PWV, the ratio of cf-PWV to cr-PWV (PWV ratio).
Model 2: Same as model 1 except MBP was replaced by brachial Diastolic Blood Pressure
Model 3: Same as model 1 except MBP was replaced by brachial Systolic Blood Pressure
Model 4: Same as in Model 1 + presence of arteriovenous fistulae (AVF)
Model 5: Same as in Model 2 + presence of arteriovenous fistulae (AVF)
Model 6: Same as in Model 2 + presence of arteriovenous fistulae (AVF)

**Figure 1**

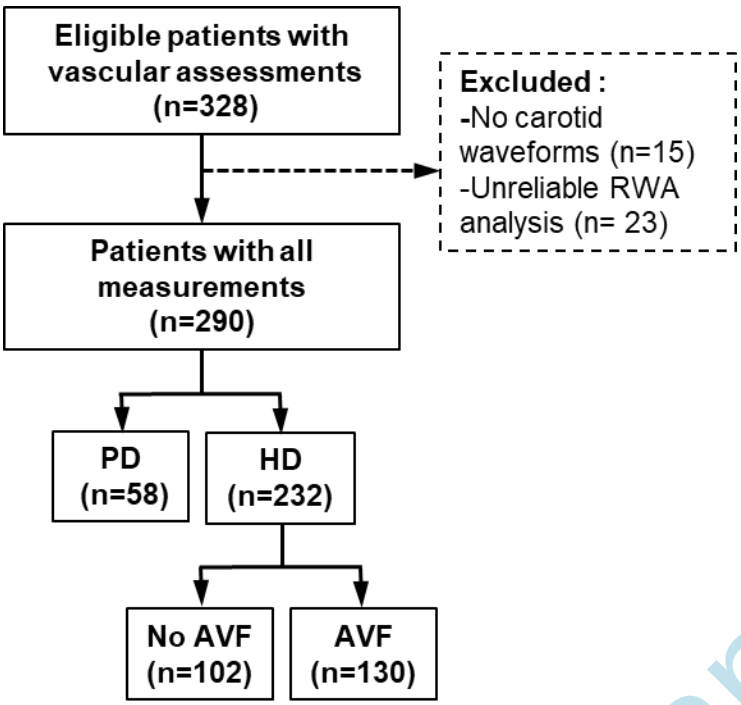

**Figure 2**

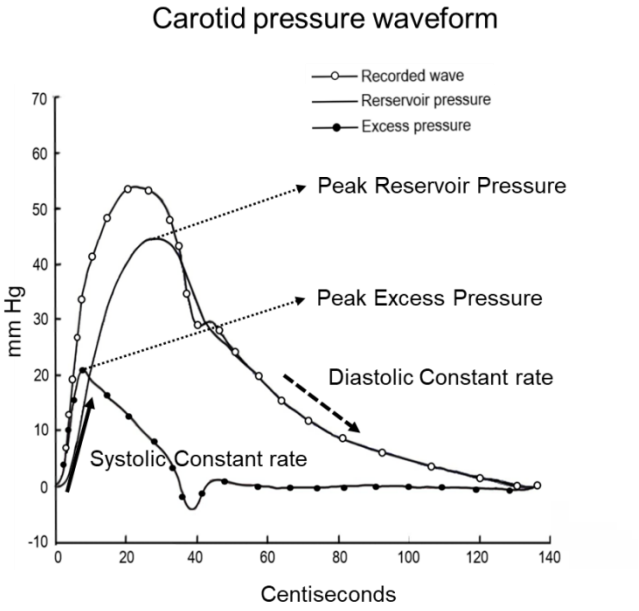

**Figure 3**