Research article

Disparate information provided by pulse wave velocity versus other measures of aortic compliance in end-stage renal disease

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Abstract

Introduction: Unfavorable changes in cardiac and arterial function are related to poor prognosis in chronic kidney disease (CKD). We compared hemodynamic profiles between subjects with end stage renal disease and two control groups with corresponding pulse wave velocities (PWV).

Methods: Non-invasive hemodynamics were recorded during passive head-up tilt in CKD stage 5 patients (n=35), patients with primary hypertension (n=35, n=30 with antihypertensive medications), and in subjects without cardiovascular or renal diseases and cardiovascular medications (n=70). The groups were selected to have corresponding age, sex, body mass index and PWV. Hemodynamic data was captured using whole-body impedance cardiography and radial tonometric pulse wave analysis.

Results: Supine blood pressure did not differ between the groups, but upright diastolic blood pressure was lower in CKD patients than in the two control groups ($p \leq 0.001$ for both, RANOVA). Despite similar PWV, supine aortic pulse pressure was higher in CKD patients versus non-medicated subjects ($p=0.029$). Two additional measures indicated reduced aortic compliance in CKD patients versus both control groups: lower ratio of stroke index to aortic pulse pressure ($p \leq 0.023$) and higher aortic characteristic impedance ($p \leq 0.003$). Subendocardial viability ratio was lower in the CKD group than in both control groups ($p \leq 0.039$).

Conclusion: In the absence of differences in PWV, higher aortic pulse pressure and characteristic impedance, and lower ratio of stroke index to aortic pulse pressure, suggest reduced aortic compliance and impaired left ventricular function in CKD patients. Lower subendocardial viability ratio predisposes the CKD patients to impaired cardiac oxygen supply versus hypertensive patients and non-medicated controls.

Introduction

Arterial stiffness evaluated by measuring pulse wave velocity (PWV) is associated with mortality in subjects with mild to severe chronic kidney disease (CKD) [1,2]. However, in addition to traditional risk assessment, PWV has only minor prognostic value in end stage renal disease (ESRD) [3]. Cardiovascular (CV) mortality in ESRD is 10-20 times higher than in age-standardized controls [4,5]. Not only the traditional risk factors but also kidney disease related factors like uremic toxins increase the CV risk [4,6]. Large epidemiological studies include heterogenic patient populations with different causes of CKD like primary glomerulonephritis or diabetic kidney disease, which influence the CV risk and outcomes.

In 2564 patients with a mean estimated glomerular filtration rate (eGFR) of 40.68±15.92 ml/min/m^2, higher aortic PWV was associated with decreased eGFR [7]. In addition to decreased eGFR, higher urine albumin to creatinine ratio has also been related with increased PWV [8]. Although arterial stiffness associates with poor prognosis in CKD, conflicting results on the relation of declining renal function and PWV have been published [9–16], and decreasing renal function was not related with higher PWV in all studies [9–11,14]. As in the general population, also within CKD patients hypertension, diabetes and age are related with increased PWV [9,16]. Higher PWV has been associated with diabetic and hypertensive renal diseases, but not so clearly with chronic glomerulonephritis [17]. This is probably one of the causes for the contradictory results regarding the association of PWV with CKD [17].

Functional and structural cardiac changes have been related with CKD that contribute to the mortality of CKD subjects [18,19]. Aortic characteristic impedance, a noninvasive measure evaluating the influence of proximal aorta on left ventricular afterload, is inversely related with aortic compliance [20] and directly with left ventricular mass and geometry, independent of blood pressure (BP) level [21]. Cardiac circulatory status can also be evaluated by subendocardial viability ratio (SEVR; Buckberg index), a variable reflecting coronary perfusion related with cardiac workload [22]. Lower SEVR values impact cardiovascular morbidity and mortality in CKD [23,24].

Aortic pulse pressure (PP) (AoPP) and the ratio of stroke index to aortic PP (SI/AoPP) can also be used to evaluate large arterial compliance [25]. The ratio of SI to PP has been associated with CV morbidity in hypertensive patients independent of age and left ventricular mass [26]. To our knowledge, this variable has not been studied in CKD.

Hemodynamic alterations in CKD have been widely investigated but studies of functional hemodynamic measurements are scarce and many of these studies have focused on orthostatic hypotension or autonomic responses [27–29]. The supine to upright change in body posture is a CV stimulus that can be used to examine the regulation of hemodynamics [30–32]. The hemodynamic changes in ESRD are of

special interest because the associated increase in CV risk is not totally predictable by traditional risk factors.

The aim of the present study was evaluate the nontraditional hemodynamic CV risk factors in CKD stage 5 or 5D patients with treatment and medication-controlled hypertension in supine and upright positions, and compare the results with i) subjects without CV medications and ii) hypertensive patients so that these two control groups had corresponding age, sex distribution, body mass index (BMI), and PWV values when compared with the CKD group. In additional analyses, variables of aortic compliance were further compared between the 35 CKD patients, 253 medicated hypertensive patients, and 400 normotensive subjects.

Materials and methods

Study population

The present investigation is a part of an ongoing DYNAMIC-study focusing on non-invasive measurement of hemodynamics (Clinicaltrialsregister.eu 2006-002065-39; Clinicaltrials.gov NCT01742702). The study has been approved by the Ethics Committee of the Tampere University Hospital (study code R06086M) and all study subjects gave informed consent.

Here hemodynamics of 35 subjects with CKD stage 5 or 5D were measured. Their medical history was collected and physical examination was performed according to the study protocol [30–32]. Two control groups from the study population were selected to the CKD patients with the aim to reduce the confounding effect of the traditional risk factors sex, age, and body size on the results. 1) Subjects without known CV disorders, kidney diseases and medications with direct CV effects (from altogether 615 DYNAMIC-study subjects). Two sex, age, and BMI selected controls (n=70) were chosen for each CKD subject so that PWV was comparable between the participants. 2) Thirty-five subjects with hypertension but without CKD (eGFR ≥ 80 ml/min/1.73 m^2 and albuminuria 0 in dipstick test) presenting with comparable PWVs to the CKD study group were selected from 504 study subjects. The selection of the controls to each CKD study subject was performed as follows: subjects with similar sex, corresponding age (range ±6 years with two exceptions that were -14 and -10 years), BMI (range ±4 kg/m^2), and pulse wave velocity (range ±3.6 m/s with three exceptions that were -10, +11 and +10 m/s). Successive selections were performed so that possible deviations in the values of the previous selections were counterbalanced.

Most of the CKD subjects were treated with antihypertensive agents (n=32), phosphorus binders (including calcium carbonate; n=28), erythropoietin (n=21), and statins (n=20). Thirty of the 35 controls with

hypertension used antihypertensive medications (most more than one), 5 patients were diagnosed to have hypertension during the recordings. The medications are presented in the Supplemental Table 1.

Additionally, the results of the 35 CKD stage 5 or 5D patients were further compared with those of 400 normotensive subjects (BP <135/85 mmHg) and 253 medicated hypertensive patients from the R06086M study database.

Laboratory tests

Laboratory tests performed after overnight fasting. In the hemodialysis patients these were taken in the beginning of the mid-week dialysis session. Laboratory analyses were performed using Cobas Integra 700/800, or Cobas 6000, module c501 (F. Hoffmann-LaRoche Ltd, Basel, Switzerland), or by ADVIA 120 or 2120 (Bayer Health Care, Tarrytown, NY, USA) analyzers. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI method [34].

Hemodynamic measurements

Hemodynamics were recorded by a research nurse in a quiet temperature-controlled laboratory. The subjects were to avoid caffeine products, smoking and heavy meals for 4 hours before the investigation. Beat-to-beat hemodynamics were captured for 5 min supine and for 5 min during passive head-up tilt using radial tonometric sensor and whole-body impedance cardiography [30–32]. The BP sensor was calibrated by contralateral brachial BP measurements. For the whole-body impedance cardiography measurement the CircMon^{R}-device (JR Medical Ltd., Tallinn, Estonia), and for the pulse wave analysis the tonometric pulse wave monitoring system (SpygmoCor PWMx, AtCor medical, Australia) were used. The protocol has been previously described to be repeatable and reproducible, and the correlation between stroke volume recordings using impedance cardiography and 3D-echocardiography has been good [30–32].

Statistical analyses

For statistical analyses IBM SPSS Statistics software (version 26, Armonk, New York, USA) was used and p-values <0.05 were considered significant. Continuous data was reported as means and 95% confidence intervals (95% CI) if normally distributed, and as medians and interquartile ranges if asymmetrically distributed. Mean values of the hemodynamic variables were calculated from the last three minutes during supine and upright positions because the CV system was most stabile during this period.

Differences in demographics, supine mean hemodynamic variables and laboratory values between the CKD and control groups were examined using analysis of variances (ANOVA) with the Bonferroni correction in the post-hoc tests. For normalizing the skewed distributions of C-reactive protein and triglyceride

concentrations natural logarithms of the values were calculated. The smoking habits (never, previous, current smokers) were compared using the χ^2 test.

Differences of hemodynamics in the CKD group versus control groups were tested by repeated measures analysis of variances (RANOVA) separately for the 5 minutes supine and upright recordings. As the groups were selected so that mean age, sex, BMI were corresponding, adjustments were not needed. PWV measurement results were only performed in the supine position. Because BMI, sex, age, kidney function, central BP and presence of diabetes influence arterial stiffness, differences of PWV between the groups were also tested using RANOVA with adjustments for age, cystatin C, mean aortic BP, and diabetes (yes/no). Differences in PWV between subgroups due to CKD etiologies were tested by ANOVA. The Bonferroni correction was applied in all post-hoc analyses.

The additional analyses comparing 35 CKD stage 5 or 5D patients with 400 normotensive subjects and 253 medicated hypertensive patients were adjusted for differences in sex distribution, presence of diabetes, age, BMI, low-density lipoprotein cholesterol, and atherogenic index of plasma ($\log_{10}$ of plasma triglycerides to HDL cholesterol ratio, which has been related with arterial stiffness [33]); PWV was additionally adjusted for mean aortic pressure.

Results

Descriptives

From the 35 CKD subjects 16 were on dialysis (12 on hemodialysis and 4 on peritoneal dialysis) and 19 were in the predialysis stage. Four subjects had a transplanted kidney with impaired function. Mean time in dialysis (n=15, one with missing information) was 2.3 years (95% CI 0.1, 4.4) and mean time from CKD diagnosis was 15.8 years (95% CI 12.1, 19.6). The diagnoses of the kidney diseases were diabetic (n=5, type 1; n=3, type 2), glomerulonephritis (n=7), polycystic kidney disease (n=8), ischemic (n=4), obstructive nephropathy (n=3), and other or unknown reason (n=5). Within the CKD group mean age was 56 years (range 26-77) and 22 (63%) subjects were men. The selection process of the groups was successful, as sex distribution, age, BMI, height, and body surface area were well corresponding in the study groups (Table 1).

Blood pressure and its components between the study groups

Mean supine radial BP in the CKD group was 144/78 mmHg, in controls without CV medications 139/80 mmHg, and in the hypertension group 142/82 mmHg (Fig. 1A-1B). Neither supine nor upright systolic BPs were different between the groups ($p > 0.206$ for all comparisons, Fig. 1A). Supine diastolic BP was similar in the groups, but during upright position the CKD group presented with lower diastolic BP (74 (71,77)

mmHg) than the no-CV-medication (83 (80,86) mmHg, p=0.001) and hypertension groups (85 (81,89) mmHg, p<0.001, Fig. 1B).

Heart rate did not differ between study groups (p>0.174 for all comparisons, Figure 2A). Stroke index (stroke volume related to body surface area) was lower in the CKD group than in the other groups with the exception that supine stroke index was not significantly lower in the CKD group versus the hypertension group (p=0.081, Fig. 2B). Cardiac index (cardiac output related to body surface area) was lower in CKD versus no-CV medication controls both supine and upright (p=0.040 and 0.025, respectively), but no significant differences were observed between the CKD and hypertension groups (Fig. 2C). Supine systemic vascular resistance index was higher in the CKD group than in the no-CV medication group (p=0.031), but upright systemic vascular resistance index was similar in all groups (p>0.404 for all comparisons, Fig. 2D).

Variables representing arterial stiffness and myocardial perfusion

Due to the selection procedure of the participants, there were no significant differences in PWV between the CKD group (9.7 (8.8,10.6) m/s) versus the two control groups (mean PWV within no-CV-medication 9.5 (9.0,10.0) m/s, within hypertension 9.6 (9.1,10.0) m/s, p=0.358, Fig. 3A). When adjusted for age, cystatin C, mean aortic BP, and diabetes, PWV did not differ between the CKD and control groups, either (p=0.082, Fig. 3B). The etiology of CKD related with PWV (p=0.002, ANOVA), but because of the small sample size there were no differences in post hoc analyses between groups. The absolute PWVs were: CKD due to diabetes (n=8) 10.4 (8.9,11.9) m/s; ischemic nephropathy (n=4) 13.9 (8.0,19.9) m/s; glomerulonephritis, tubulointerstitial disease or polycystic kidney disease (n=18) 8.9 (7.8,10.0) m/s; and unknown reason (n=5) 8.6 (6.4,10.7) m/s. Neither CKD stage (5 or 5D) associated with PWV in the ESRD subjects (p=0.371, T-test).

Regardless of PWV, supine AoPP was higher in the CKD group when compared with the no-CV-medication group (p=0.029) and was numerically but not significantly higher in CKD patients versus subjects with hypertension (p=0.074, Fig. 3C). No significant differences in AoPP were detected in the upright position.

Aortic characteristic impedance was higher in the CKD group than in both control groups regardless of body position (Fig. 3D). The SI/AoPP ratio, a variable representing aortic compliance, was lower in the CKD subjects when compared with the no-CV medication and hypertension groups (p<0.010 supine and p<0.024 upright, for both control groups, Fig. 3E).

Myocardial oxygen supply and perfusion, as evaluated by means of SEVR, was lower in the CKD group when compared with the no-CV-medication (p<0.001 supine; p=0.039 upright) and hypertension groups (p<0.001 supine, p=0.001 upright, Fig. 3F).

Pulse wave analysis showed no significant differences in the times to first or second central systolic peaks, time to the return of the reflected wave, or supine augmentation indexes. Extracellular water balance was also corresponding in the CKD and the two control groups (Table 2). However, supine ejection duration was

longer in the CKD group versus both control groups, a finding predisposing to lower SEVR and lower measures reflecting aortic compliance in CKD.

Additional comparisons of CKD patients with 400 normotensive and 253 medicated hypertensive subjects

In this analysis, the proportions of male subjects and diabetics were higher in CKD patients and hypertensive patients than in normotensive controls, whilst the percentages of present and previous smokers did differ between the groups (Supplemental Table 2). Mean age, systolic and diastolic BP, unadjusted pulse wave velocity, and plasma triglycerides and atherogenic index were higher, and HDL cholesterol was lower in CKD patients and hypertensive patients than in normotensive controls. Diastolic blood pressure was lower in CKD patients than in hypertensive patients, while LDL cholesterol was lowest in CKD patients. BMI and LDL cholesterol were highest in medicated hypertensive patients (Supplemental Table 2).

After adjustments for the above confounding differences, PWV was no longer different between the study groups (Supplemental Fig. 1A). Moreover, in the adjusted analysis aortic characteristic impedance was higher in the CKD group than in normotensive subjects and medicated hypertensive patients ($p<0.001$ and $p=0.040$, respectively, Supplemental Fig. 1B), and subendocardial viability ratio was lower in CKD patients than in medicated hypertensive patients ($p=0.016$, Supplemental Fig. 1B).

Discussion

In the present cross-sectional study ESRD was related with lower measures of aortic compliance and reduced myocardial perfusion and oxygen supply capacity when compared with subjects without cardiovascular or renal diseases, and with hypertensive subjects.

Arterial stiffness evaluated by means of PWV has been related with mortality at different CKD stages [1,2,7], but the association of PWV with declining renal function remains unresolved [11–13,19]. The etiology of kidney disease associates with arterial stiffness so that patients with ESRD originated from hypertension or diabetes present with higher PWV when compared with ESRD due to chronic glomerulonephritis [17]. Variable CKD etiology might be a confounding factor between different studies.

The present CKD group consisted of a wide range of etiologies, which diminishes the effects of single diseases on hemodynamic variables. The hemodynamic changes related with ESRD were studied by comparing subjects with CKD stages 5 and 5D to subjects without diagnosed CV diseases and subjects with hypertension. PWV, which is the gold standard for measuring arterial stiffness, was corresponding in all study groups due to the selection protocol. Similar time to the return of the reflected wave in the study groups supports the view of similar propagation of arterial pressure waves (Table 2). The CKD group and

the two control groups (Table 1) represent rather well the average Finnish adult population that has a mean BMI of 27.8 kg/m^2 and BP of 135/80 mmHg and contains approximately 11-16 % of smokers [35]. Already a small increase in BP is a risk factor for arterial stiffening, while hypertension is the leading pathophysiological risk factor linked with CKD [36]. In this study, supine BP did not differ between the groups, which supports the view that hypertension in the CKD patients was well managed. Medications with direct CV effects naturally influence the hemodynamic variables. However, the number and type of antihypertensive medications between the CKD and hypertension groups were rather similar with the exceptions of furosemide and beta blocker use (Supplemental Table 1).

Higher PWV links ESRD patients with poor prognosis, but arterial stiffening is not the only harmful CV change in CKD patients. Cardiac structural and functional changes like left ventricular hypertrophy and myocardial insufficiency also relate CKD with increased CV morbidity [37,38]. In the current study, CKD subjects presented with changes reflecting impaired cardiac perfusion and oxygen supply. In addition, the change of body position from supine to upright resulted in lower diastolic BP in the CKD group versus the other groups (Fig. 1B), which predisposes the CKD patients to lower coronary perfusion in the upright position. The SEVR is a noninvasive estimate of myocardial workload, oxygen supply and perfusion [22], and lower SEVR has been associated with higher CV mortality in CKD patients [24]. The CKD group also presented with increased left ventricular ejection duration (Table 2). Due to increased ejection duration the reflected wave arrives earlier during the cardiac cycle, and this increases the central systolic pressure. Subsequently, the left ventricle works against greater pressure, while there is a parallel decrease in coronary perfusion pressure during diastole [39].

We calculated aortic characteristic impedance from the forward wave amplitude, ejection duration and stroke volume [40]. The estimation of left ventricular remodeling by aortic characteristic impedance using applanation tonometry has been reported to be reliable when compared with magnetic resonance imaging [41]. Furthermore, Payne et al. showed that pulse wave analysis transfer functions are reliable in patients with variable degrees of renal dysfunction [42]. Aortic characteristic impedance is related with left ventricular hypertrophy and geometry independent of the level of BP within hypertensive subjects [21]. Aortic characteristic impedance is indirectly proportional to aortic diameter, which could explain group differences, but in the present study the groups were standardized by sex and body size, which probably reduces differences in mean aortic diameter between the groups. The SI/AoPP ratio is also an estimate of aortic compliance [26]. In 294 hypertensive subjects SI/AoPP was shown to be a stronger predictor of CV events than PP or BP alone [26]. Decreased arterial compliance transfers pulsatile flow to the peripheral microcirculation e.g. in the kidneys [43]. The present subjects with CKD presented with increased supine PP, while supine and upright aortic characteristic impedance was higher and SI/AoPP was lower than in the hypertension group and the no-CV-medication group despite similar PWV. These findings support the view

that not only arterial stiffening but also changes in cardiac function predispose the CKD patients to higher CV risk. The additional results, where the 35 CKD patients were compared with 400 normotensive subjects and 253 medicated hypertensive patients, further support the view that measures of aortic compliance can be impaired in stage 5 CKD patients in the absence of changes in PWV.

In the general population several traditional CV risk factors are well identified, but CKD patients have been excluded from most clinical trials [44]. Contradictive results of BP and blood glucose targets, benefits of statins or aspirin use have been published in CKD patients, particularly in CKD stage 5D patients [45]. Detailed knowledge of CV pathophysiology in CKD patients is rather scarce, but in addition to the control of traditional risk factors, the importance of metabolic factors like inflammation and changes in calcium-phosphate-regulation should be considered [6]. The preventive interventions against CV events should probably be initiated much earlier and not only when PWV is increased. Moreover, more accurate risk stratification methods for CKD patients should be developed. The CKD patients would probably benefit from early and detailed hemodynamic characterization that would guide their treatment when attempting to avoid the CV complications that shorten their life-expectancy [46,47].

The present study is not without limitations. First, our study included CKD patients with several different kidney diseases with various traditional risk factor profiles. On the other hand, the present distribution of kidney diseases corresponds quite well to the average Finnish renal replacement therapy population [48]. The study protocol was rather demanding and patients in poor physical condition could not be included. Subsequently, the study population consisted of rather young CKD patients (mean age 55.9 years), whereas the prevalence of renal replacement therapy in Finland is highest in the age group 65-74 years [48]. Age is one of the most important factors affecting hemodynamics and the exclusion of elderly subjects from this study dismisses the effect of old age on the present results. The present study did not focus on uremic toxins or CKD-related mineral and bone disorder, the factors of which also have a significant influence on the prognosis and arterial calcification of CKD patients [49–51]. These medical conditions warrant further investigation in the future.

Conclusion

The functional hemodynamic changes in the phenotype of CKD stage 5 patients reflected reduced aortic compliance, lower left ventricular function, and impaired coronary perfusion despite corresponding PWV when compared with the control groups. Such findings predispose the CKD patients to adverse CV events. The progression of the CV deviations during chronic renal insufficiency warrants further study.

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Statement of ethics

This study was approved by the Ethics Committee of the Tampere University Hospital (study code R06086M). The study was conducted ethically in accordance with Declaration of Helsinki and all study subjects gave informed consent.

Conflict of interest statement

No conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract form.

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Author contributions

JKK participated in the study design and data collection, performed statistical analyses, and drafted the article. AMHT participated in data collection and revising manuscript. AJT participated in data collection, analyzing data, and revising manuscript. KV, SM and JM edited the article and participated in intellectual contributions. IP designed the study with JKK, supervised data collection and the research, participated in statistical analysis, and edited the article.

References

1 Baumann M, Wassertheurer S, Suttmann Y, Burkhardt K, Heemann U. Aortic pulse wave velocity predicts mortality in chronic kidney disease stages 2-4. J Hypertens. 2014 Apr;32(4):899–903.

2 Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999 May;99(18):2434–9.

3 Tripepi G, Agharazii M, Pannier B, D'Arrigo G, Mallamaci F, Zoccali C, et al. Pulse wave velocity and prognosis in end-stage kidney disease. Hypertension. 2018 Jun;71(6):1126–32.

4 Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998 Nov;32(5):S112–9.

5 de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LMJ, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA. 2009 Oct;302(16):1782–9.

6 Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant. 2018 Oct;33(Suppl 3):iii28–34.

7 Townsend RR, Wimmer NJ, Chirinos JA, Parsa A, Weir M, Perumal K, et al. Aortic PWV in chronic kidney disease: a CRIC ancillary study. Am J Hypertens. 2010 Mar;23(3):282–9.

8 Kim ED, Tanaka H, Ballew SH, Sang Y, Heiss G, Coresh J, et al. Associations between kidney disease measures and regional pulse wave velocity in a large community-based cohort: the atherosclerosis risk in communities (ARIC) study. Am J Kidney Dis. 2018 Jul DOI: 10.1053/j.ajkd.2018.04.018

9 Tholen S, Klofat K, Pan CR, Schmaderer C, Lutz J, Heemann U, et al. Progression of aortic pulse wave velocity in patients with chronic kidney disease. J Clin Hypertens. 2013;15(11):833–8.

10 Kong X, Ma X, Tang L, Wang Z, Li W, Cui M, et al. Arterial stiffness evaluated by carotid-femoral pulse wave velocity increases the risk of chronic kidney disease in a Chinese population-based cohort. Nephrology. 2017 Mar;22(3):205–12.

11 Chue CD, Edwards NC, Davis LJ, Steeds RP, Townend JN, Ferro CJ. Serum phosphate but not pulse wave velocity predicts decline in renal function in patients with early chronic kidney disease. Nephrol Dial Transplant. 2011 Aug;26(8):2576–82.

12 Sedaghat S, Mattace-Raso FUS, Hoorn EJ, Uitterlinden AG, Hofman A, Ikram MA, et al. Arterial stiffness and decline in kidney function. Clin J Am Soc Nephrol. 2015 Dec;10(12):2190–7.

13 Ford ML, Tomlinson LA, Chapman TPE, Rajkumar C, Holt SG. Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. Hypertension. 2010 May;55(5):1110–5.

14 Jia L, Zhang W, Ma J, Chen X, Chen L, Li Z, et al. Pulse pressure, instead of brachium-ankle pulse wave velocity, is associated with reduced kidney function in a Chinese Han population. Kidney Blood Press Res. 2017;42(1):43–51.

15 Xu T, Xie J, Zong X, Wang W, Ren H, Chen N. Pulse wave velocity: a valuable predictor for cardio-cerebrovascular disease and death in PD patients. Blood Purif. 2015;40(3):203–8.

16 Radzi AB, Kasim SS. Pulse wave velocity in assessing arterial stiffness in patients with mild-to-moderate renal impairment. J Hypertens. 2019 Jul;37:e285.

17 El Ghoul B, Daaboul Y, Korjian S, El Alam A, Mansour A, Hariri E, et al. Etiology of end-stage renal disease and arterial stiffness among hemodialysis patients. BioMed Res Int. 2017 Feb;2017:2543262.

18 Cerasola G, Nardi E, Palermo A, Mulè G, Cottone S. Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review. J Nephrol. 2011 Feb;24(1):1–10.

19 Bansal N, Roy J, Chen H-Y, Deo R, Dobre M, Fischer M, et al. Evolution of echocardiographic measures of cardiac disease from CKD to ESRD and risk of all-cause mortality: findings from the CRIC study. Am J Kidney Dis. 2018 Sep;72(3):390–9.

20 Mitchell GF, Lacourcière Y, Ouellet J-P, Izzo JL, Neutel Joel, Kerwin LJ, et al. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension. Circulation. 2003 Sep;108(13):1592–8.

21 Pucci G, Hametner B, Battista F, Wassertheurer S, Schillaci G. Pressure-independent relationship of aortic characteristic impedance with left ventricular mass and geometry in untreated hypertension: J Hypertens. 2015 Jan;33(1):153–60.

22 Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ Res. 1972 Jan;30(1):67–81.

23 Ekart R, Bevc S, Hojs N, Hojs R. Derived subendocardial viability ratio and cardiovascular events in patients with chronic kidney disease. Cardiorenal Med. 2019;9(1):41–50.

24 Di Micco L, Salvi P, Bellasi A, Sirico ML, Iorio BD. Subendocardial viability ratio predicts cardiovascular mortality in chronic kidney disease patients. Blood Purif. 2013;36(1):26–8.

25 Chemla D, Hébert J-L, Coirault C, Zamani K, Suard I, Colin P, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol-Heart Circ Physiol. 1998 Feb;274(2):H500–5.

26 de Simone G, Roman MJ, Koren MJ, Mensah GA, Ganau A, Devereux RB. Stroke volume/pulse pressure ratio and cardiovascular risk in arterial hypertension. Hypertension. 1999 Mar;33(3):800–5.

27 Zanotto T, Mercer TH, van der Linden ML, Traynor JP, Petrie CJ, Doyle A, et al. Baroreflex function, haemodynamic responses to an orthostatic challenge, and falls in haemodialysis patients. PloS One. 2018;13(12):e0208127.

28 Gallieni M, Butti A, Guazzi M, Galassi A, Cozzolino M, Brancaccio D. Impaired brachial artery endothelial flow-mediated dilation and orthostatic stress in hemodialysis patients. Int J Artif Organs. 2008 Jan;31(1):34–42.

29 Hathaway DK, Cashion AK, Wicks MN, Milstead EJ, Gaber AO. Cardiovascular dysautonomia of patients with end-stage renal disease and type I or type II diabetes. Nurs Res. 1998 Jun;47(3):171–9.

30 Tahvanainen A, Koskela J, Tikkakoski A, Lahtela J, Leskinen M, Kahonen M, et al. Analysis of cardiovascular responses to passive head-up tilt using continuous pulse wave analysis and impedance cardiography. Scand J Clin Lab Invest. 2009;69(1):128–37.

31 Tahvanainen AM, Tikkakoski AJ, Leskinen MH, Nordhausen K, Kahonen M, Koobi T, et al. Supine and upright haemodynamic effects of sublingual nitroglycerin and inhaled salbutamol: a double-blind, placebo-controlled, randomized study. J Hypertens. 2012 Feb;30(2):297–306.

32 Koskela JK, Tahvanainen A, Haring A, Tikkakoski AJ, Ilveskoski E, Viitala J, et al. Association of resting heart rate with cardiovascular function: a cross-sectional study in 522 Finnish subjects. BMC Cardiovasc Disord. 2013;13:102.

33 Choudhary MK, Eräranta A, Koskela J, Tikkakoski AJ, Nevalainen PI, Kähönen M, et al. Atherogenic index of plasma is related to arterial stiffness but not to blood pressure in normotensive and never-treated hypertensive subjects. Blood Press. 2019 May;28(3):157–67.

34 Levey AS, Stevens LA, Schmid CH, Zhang Y (Lucy), Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May;150(9):604–12.

35 Koponen P, Borodulin K, Lundqvist A, Sääksjärvi K, Koskinen S. Terveys, toimintakyky ja hyvinvointi Suomessa : FinTerveys 2017 -tutkimus [Internet]. http://www.terveytemme.fi/finterveys/. [cited 2019 Oct 2]. Available from: http://www.julkari.fi/bitstream/handle/10024/136223/Rap_4_2018_FinTerveys_verkko.pdf?sequence=1&isAllowed=y

36 Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: Core curriculum 2019. Am J Kidney Dis. 2019 Jul;74(1):120–31.

37 Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barré PE. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. J Am Soc Nephrol. 1995 Jun;5(12):2024–31.

38 Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Stancanelli B, et al. Left ventricular mass monitoring in the follow-up of dialysis patients: Prognostic value of left ventricular hypertrophy progression. Kidney Int. 2004 Apr;65(4):1492–8.

39 Vlachopoulos C, O'Rourke M. Genesis of the normal and abnormal arterial pulse. Curr Probl Cardiol. 2000 May;25(5):303–67.

40 Chemla D, Plamann K, Nitenberg A. Towards new indices of arterial stiffness using systolic pulse contour analysis: a theoretical point of view. J Cardiovasc Pharmacol. 2008 Feb;51(2):111–7.

41 Bargiotas I, Bollache E, Mousseaux E, Giron A, Cesare A de, Redheuil A, et al. MR and applanation tonometry derived aortic impedance: Association with aging and left ventricular remodeling. J Magn Reson Imaging. 2015 Feb;41(3):781–7.

42 Payne RA, Lilitkarntakul P, Dhaun N, Melville V, Asai T, Goddard J, et al. Renal dysfunction does not affect the peripheral-to-central arterial pressure transfer function. Hypertension. 2010 Dec;56(6):1083–8.

43 O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005 Jul;46(1):200–4.

44 Goff David C., Lloyd-Jones Donald M., Bennett Glen, Coady Sean, D'Agostino Ralph B., Gibbons Raymond, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. Circulation. 2014 Jun;129(25_suppl_2):S49–73.

45 Gregg LP, Hedayati SS. Management of traditional cardiovascular risk factors in CKD: What are the data? Am J Kidney Dis. 2018 Feb;72(5):728–44.

46 Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. JAMA. 2019 Oct;322(13):1294–304.

47 Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, et al. The double challenge of resistant hypertension and chronic kidney disease. The Lancet. 2015 Oct;386(10003):1588–98.

48 Helve J, Finne P, Groop P-H. Finnish registry for kidney diseases report 2018 [Internet]. 2020 MayAvailable from: https://www.muma.fi/files/4770/Finnish_Registry_for_Kidney_Diseases_Report_2018.pdf

49 Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, et al. Cardiac calcification in adult hemodialysis patients: A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol. 2002 Feb;39(4):695–701.

50 London GM. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003 Sep;18(9):1731–40.

51 Lioufas NM, Pedagogos E, Hawley CM, Pascoe EM, Elder GJ, Badve SV, et al. Aortic calcification and arterial stiffness burden in a chronic kidney disease cohort with high cardiovascular risk: baseline characteristics of the impact of phosphate reduction on vascular end-points in chronic kidney disease trial. Am J Nephrol. 2020 Feb;51(3):201–15.

Figure legends

Fig. 1. Means (95 % confidence intervals) of supine and upright systolic (A) and diastolic (B) blood pressures in the group with chronic kidney disease (CKD, n=35), group with primary hypertension (n=35), and group without cardiovascular (CV) medications (n=70); repeated measures analysis of variances with the Bonferroni correction in post-hoc analyses, *p<0.05.

Fig. 2. Means (95 % confidence intervals) of supine and upright heart rate (A), stroke index (B), cardiac index (C), and systemic vascular resistance index (D) in the group with chronic kidney disease (CKD, n=35), group with primary hypertension (n=35), and group without cardiovascular (CV) medications (n=70); statistics as in Fig. 1, *p<0.05.

Fig. 3. Means (95 % confidence intervals) of supine pulse wave velocities without (A) and with adjustments for age, cystatin C, mean aortic blood pressure and diabetes (B), supine and upright aortic pulse pressure (C), aortic characteristic impedance (D), ratio of stroke index to aortic pulse pressure (D), and subendocardial viability ratio (F) in the group with chronic kidney disease (CKD, n=35), group with primary hypertension (n=35), and group without cardiovascular (CV) medications (n=70); statistics as in Fig. 1, *p<0.05.

Table 1. Descriptive statistics of the study groups as means and 95% confidence intervals of the mean, medians, and interquartile ranges (C-reactive protein and triglycerides), or numbers and percentages.

Variable		No-CV-medication (n=70)	Hypertension (n=35)	CKD 5 or 5D (n=35)
Male sex		44 (62.9%)	22 (62.9%)	22 (62.9%)
Smoking	Never	46 (65.7%)	17 (48.6%)	20 (57.1%)
	Present	9 (12.9%)	5 (14.3%)	6 (17.1%)
	Previous	15 (21.4%)	13 (37.1%)	8 (22.9%)
Alcohol amount (doses/week)		5.9 (3.9, 7.8)	4.4 (2.9, 5.9)	1.8 (0.3, 3.2)*
Diabetes		0 (0.0%)	3 (8.6%)	9 (25.7%)*
Coronary artery disease		0 (0.0%)	2 (5.7%)	4 (11.4%)*
Peripheral artery disease		0 (0.0%)	0 (0.0%)	1 (2.9%)
Age (years)		54.7 (51.9, 57.6)	55.0 (50.5, 59.5)	55.9 (51.3, 60.6)
Height (cm)		173.6 (171.6, 175.6)	173.7 (171.0, 176.5)	172.4 (169.7, 175.2)
Weight (kg)		80.3 (76.6, 84.1)	81.2 (76.4, 86.1)	79 (73.2, 84.8)
Boby mass index (kg/m^2)		26.5 (25.4, 27.5)	26.9 (25.4, 28.3)	26.4 (24.8, 27.9)
Body surface area (m^2)		1.94 (1.89, 1.99)	1.95 (1.89, 2.0)	1.92 (1.84, 2.00)
Leukocyte count (10^9/l)		5.7 (5.4, 6.0)	6.1 (5.4, 6.9)	6.3 (3.9, 6.3)
Hemoglobin (g/l)		145 (142, 148)	143 (140, 147)	113 (110, 116)*†
eGFR (ml/min/1.73m^2)		90 (87, 93)	90 (84, 96)	10.2 (8.0, 12.3)*†
QUICKI		0.353 (0.344, 0.360)	0.349 (0.337, 0.361)	0.335 (0.320, 0.350)
Fasting plasma				
C-reactive protein (mg/l)		0.6 (0, 2.1)	0.5 (0.5, 3.0)	2.1 (0, 4.6)*†
Creatinine (µmol/l)		76 (73, 79)	77 (71, 83)	657 (558, 755)*†
Cystatin C (mg/l)		0.87 (0.84, 0.91)	0.93 (0.85, 1.0)	4.42 (3.95, 4.88)*†
Urea (mmol/l)		NA	NA	25.7 (22.2, 29.0)
Potassium (mmol/l)		3.7 (3.7, 3.8)	3.6 (3.5, 3.8)	4.5 (4.3, 4.8)*†
Sodium (mmol/l)		140 (140, 141)	141 (140, 142)	139 (138, 140)*†
Uric acid (µmol/l)		302 (285, 320)	342 (310, 374)	408 (362, 454)*†
Phosphate (mmol/l)		0.9 (0.9, 1.0)	1.0 (0.9, 1.0)	1.7 (1.6, 1.8)*†
Calcium (mmol/l)		2.3 (2.3, 2.3)	2.3 (2.3, 2.4)	2.3 (2.3, 2.4)
PTH (pmol/l)		4.7 (4.2, 5.1)	5.7 (4.6, 6.7)	28.6 (19.0, 38.2)*†
Total cholesterol (mmol/l)		5.2 (5.0, 5.5)	4.6 (4.3, 5.0)	4.1 (3.7, 4.4)*†
LDL cholesterol (mmol/l)		3.1 (2.9, 3.4)	2.7 (2.4, 3.0)	2.3 (2.0, 2.6)*
HDL cholesterol (mmol/l)		1.6 (1.5, 1.7)	1.6 (1.4, 1.7)	1.2 (1.0, 1.4)*†
Triglycerides (mmol/l)		1.03 (0, 3.75)	0.92 (0.54, 1.9)	1.16 (0, 7.95)†
Glucose (mmol/l)		5.6 (5.4, 5.8)	5.9 (5.7, 6.2)	6.3 (5.3, 7.2)

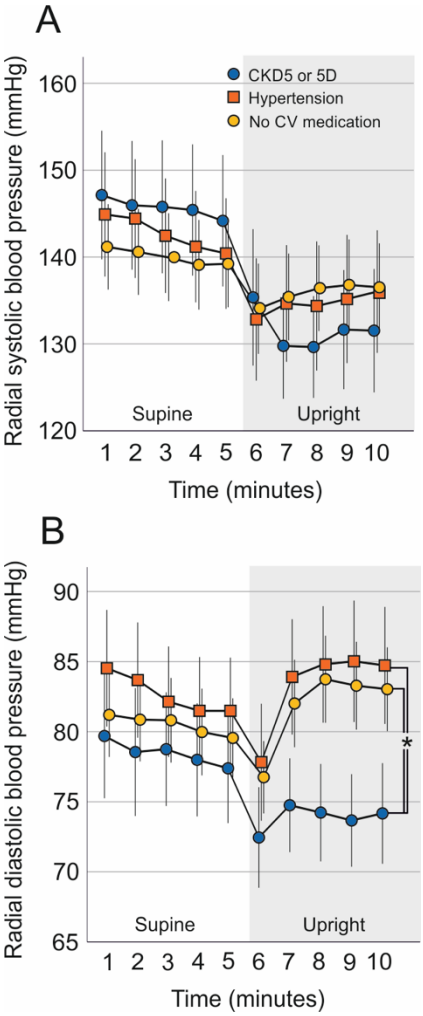
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate by CKD-EPI equation; PTH, parathyroid hormone; HDL, high density lipoprotein; LDL, low density lipoprotein; QUICKI, quantitative insulin sensitivity check index. Alcohol dose is presented as standard drinks (~12 grams alcohol) per week. Analysis of variances with the Bonferroni correction in the post-hoc test was performed for continuous variables and χ2-test for classified variables. Natural logarithms of CRP and triglycerides were calculated to normalize their distributions; *p<0.05 compared with no-CV-medication; †p<0.05 compared with hypertension. Within the CKD 5 or 5D group eGFR is only presented from subjects with CKD 5 (n=19).

Table 2. Means and 95% confidence intervals of supine pulse wave analysis values and extracellular fluid balance in the study groups.

	No-CV-medication (n=70)	Hypertension (n=35)	CKD 5 or 5D (n=35)
Aortic T1 (ms)	111 (108, 113)	110 (108, 113)	109 (106, 112)
Aortic T2 (ms)	230 (226, 235)	231 (223, 238)	232 (224, 241)
Aortic Tr (ms)	144 (141, 147)	144 (141, 146)	142 (139, 146)
Ejection duration (ms)	328 (323, 332)	325 (316, 334)	339 (328, 351)*†
Augmentation index (%)	27.2 (24.7, 27.8)	26.7 (23.1, 30.2)	29 (25.3, 32.8)
Augmentation index @75 (%)	22.1 (19.5, 24.7)	20.6 (21.2, 27.3)	24.2 (21.2, 27.3)
Extracellular water balance	1.00 (0.98, 1.02)	1.01 (0.95, 1.07)	1.03 (0.98, 1.09)

Abbreviations: CV, cardiovascular; @75, corrected to heart rate 75 beats per minute; T1, time to first systolic pressure peak; T2, time to second systolic pressure peak; Tr, time to reflected wave. Statistical analyses: Analysis of variances with the Bonferroni correction in the post-hoc test. *$p<0.05$ compared with no-CV-medication subjects; †$p<0.05$ compared with hypertensive subjects.

1 Fig. 1


A
Radial systolic blood pressure (mmHg)
160
150
140
130
120
CKD5 or 5D
Hypertension
No CV medication
Supine
Upright
1 2 3 4 5 6 7 8 9 10
Time (minutes)
B
Radial diastolic blood pressure (mmHg)
90
85
80
75
70
65
*
Supine
Upright
1 2 3 4 5 6 7 8 9 10
Time (minutes)

2

3

Fig. 2

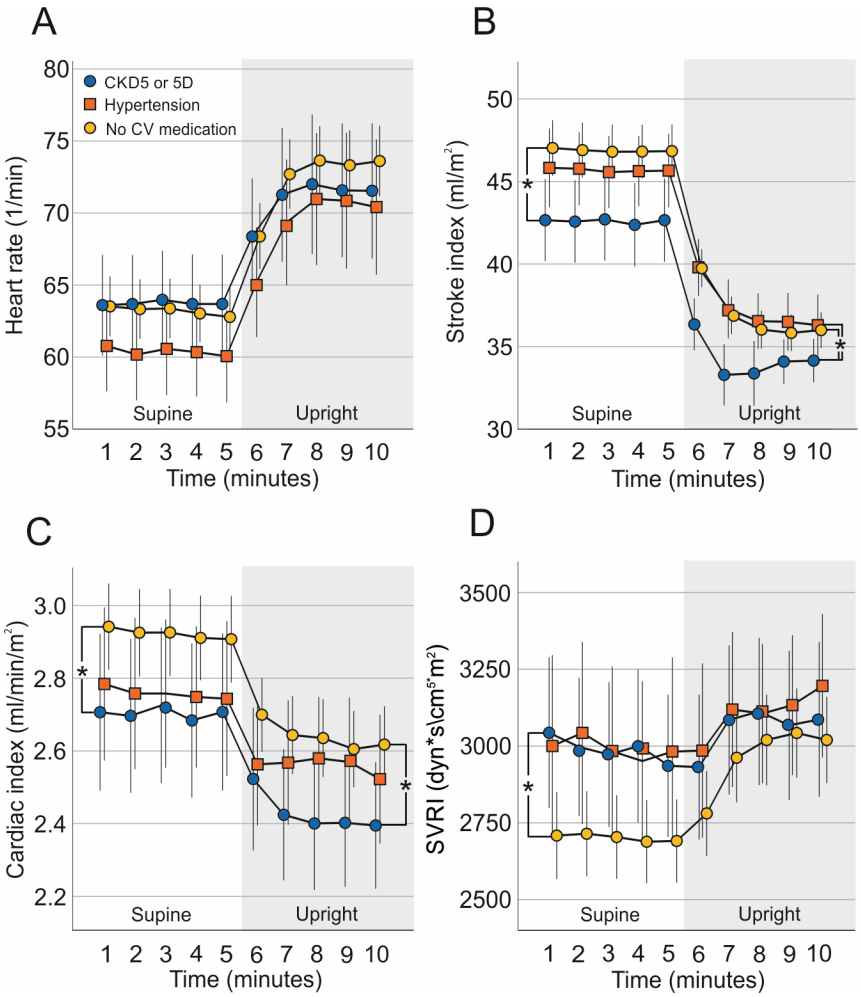
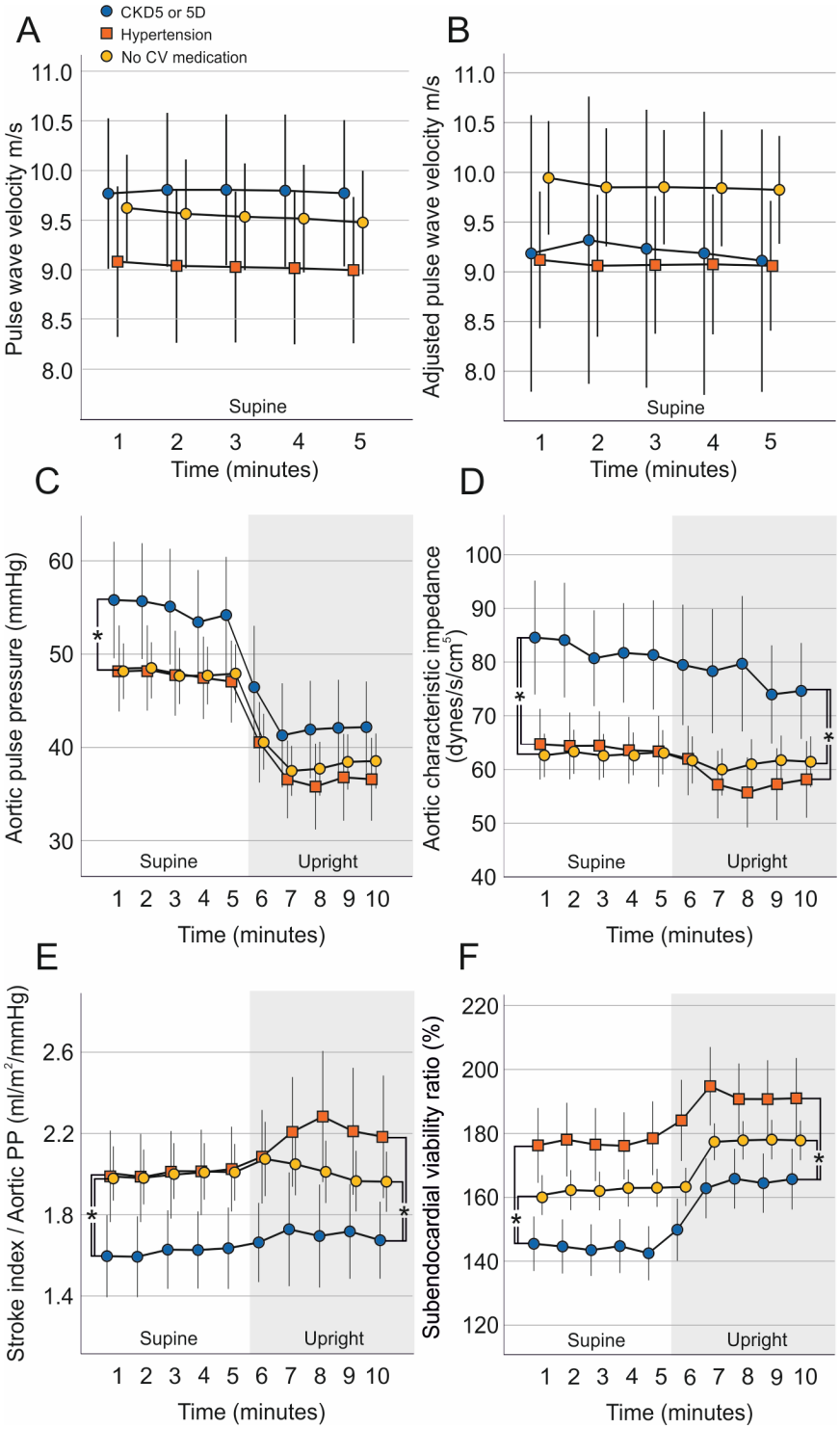

A
B
C
D
CKD5 or 5D
Hypertension
No CV medication
Heart rate (1/min)
Stroke index (ml/m²)
Cardiac index (ml/min/m²)
SVRI (dyn*s\cm⁵m²)
Supine
Upright
Time (minutes)
1 2 3 4 5 6 7 8 9 10
*

Fig. 3


A
CKD5 or 5D
Hypertension
No CV medication
Pulse wave velocity m/s
11.0
10.5
10.0
9.5
9.0
8.5
8.0
Supine
1 2 3 4 5
Time (minutes)
B
Adjusted pulse wave velocity m/s
11.0
10.5
10.0
9.5
9.0
8.5
8.0
Supine
1 2 3 4 5
Time (minutes)
C
Aortic pulse pressure (mmHg)
60
50
40
30
Supine
Upright
1 2 3 4 5 6 7 8 9 10
Time (minutes)
D
Aortic characteristic impedance (dynes/s/cm5)
100
90
80
70
60
50
40
Supine
Upright
1 2 3 4 5 6 7 8 9 10
Time (minutes)
E
Stroke index / Aortic PP (ml/m2/mmHg)
2.6
2.2
1.8
1.4
Supine
Upright
1 2 3 4 5 6 7 8 9 10
Time (minutes)
F
Subendocardial viability ratio (%)
220
200
180
160
140
120
Supine
Upright
1 2 3 4 5 6 7 8 9 10
Time (minutes)