KIDNEY DYSFUNCTION UNDERLIES LEFT VENTRICULAR HYPERTROPHY IN TREATED HYPERTENSION

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Introduction

- Arterial stiffness is recognized as a strong cardiovascular (CV) risk factor.
- Pulse wave velocity (PWV) and augmentation index (AI) are well-known markers for arterial stiffness.
- PWV is faster as CKD is advanced.
- The presence of CKD is by itself CV risk.
- The relation between AI and CKD stages remains unclear.

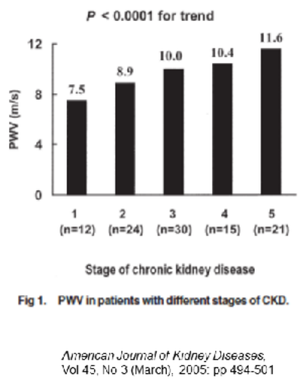

Fig 1. PWV in patients with different stages of CKD.

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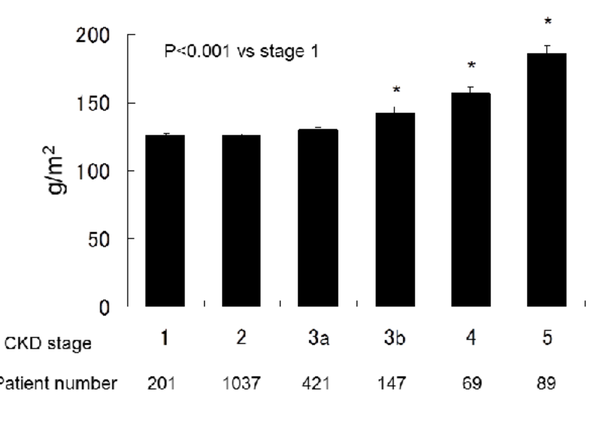
LVMI



Multiple regression to LVMI

R=0.37, F=54, df(6,1957), p<0.0001

	β	t	p
Sex	11.0	6.3	<0.0001
eGFR	-0.445	-12.2	<0.0001
SBP	-1.89	-0.30	0.76
PP	2.54	0.41	0.68
SBP2	2.00	0.32	0.74
PP2	-2.11	-0.37	0.73

Stepwise regression to LVMI

R=0.39, F=35, df(14,1949), p<0.0001

eGFR: β=-0.492, t=-13, p<0.0001

Method 1

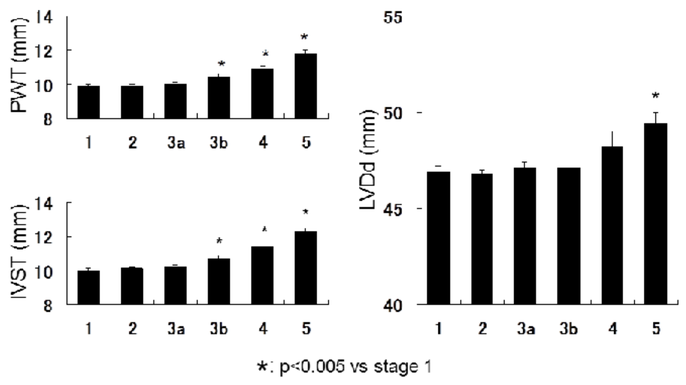
Among the data from a cross-sectional study for treated hypertensive patients (ABC-J study: UMIN 000002966), 3887 patients were selected because their serum creatinine was measured. Using MDRD equation for Japanese, estimated glomerular filtration rate (eGFR) was calculated, and the patients were divided into 6 groups according to a revised CKD classification (http://www.jsn.or.jp/guideline/pdf/CKD_evidence2013/all.pdf).

Table 4 | Multiple regression models of ΔSBP2 in treated hypertensives

N	1,727			
Adjusted R^2	0.379			
Independent variables	β	95% CI.	β	P
Physical variables				
Gender	−2.358	−3.256 to −1.480	−0.148	<0.001
Age	−0.004	−0.034 to 0.027	−0.005	0.813
Height	−0.185	−0.235 to −0.134	−0.215	<0.001
BMI	−0.200	−0.290 to −0.109	−0.085	<0.001
Hemodynamic variables				
PR	−0.335	−0.362 to −0.310	−0.508	<0.001
DBP	0.140	0.113 to 0.167	0.207	<0.001
Classes of drugs				
ARB	−1.012	−1.682 to −0.343	−0.062	0.003
ACEI	−0.516	−1.512 to 0.479	−0.021	0.309
CCB	−0.837	−1.619 to −0.056	−0.049	0.035
αBL	−2.122	−3.158 to −1.087	−0.077	<0.001
Diur	1.890	0.690 to 3.090	0.102	0.002
βBL	0.537	−0.218 to 1.292	0.028	0.163
Nitro	−3.675	−4.882 to −2.468	−0.118	<0.001
Interactive term				
CCB × Diur	−1.953	−3.414 to −0.493	−0.089	0.009

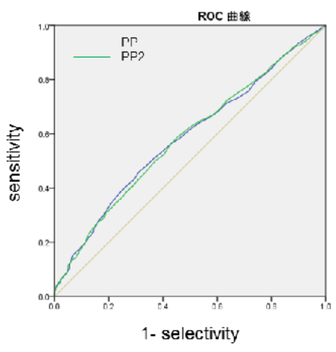
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; Diur, diuretics; Nitro, nitrates or nicorandil; PR, pulse rate; αBL, α-blockers; βBL, β-blockers.

Echocardiographic data



ROC analysis

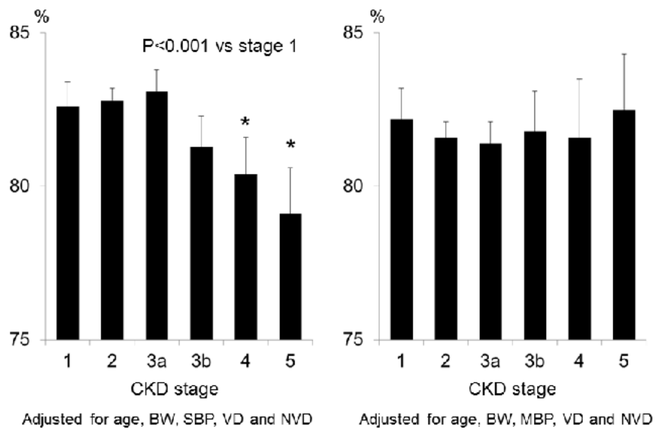
	AUC
Sex (male %)	0.503
Age (y/o)	0.540
Height (cm)	0.481
Weight (kg)	0.516
DM (%)	0.502
HL (%)	0.534
eGFR (ml/min)	0.419
SBP (mmHg)	0.559
DBP (mmHg)	0.478
PP (mmHg)	0.584
SBP2 (mmHg)	0.556
PP2 (mmHg)	0.583
AI (%)	0.534
PR (bpm)	0.435



Method 2

- Radial tonometry was performed for all patients to obtain pulse wave, assessing second peak of systolic blood pressure (SBP2).
- AI was defined as (SBP2-DBP)/(SBP-DBP).
- Body surface area (BSA) was assessed from body weight and height.
- Left ventricular mass index (LVMI) was calculated from echocardiographic data using a following equation:
- $[1.04 \times \{(LVDd+PWT+IVST)^3 - LVDd^3\} - 14] / BSA$
- LVDd: left ventricular diastolic diameter, PWT: posterior wall thickness, IVST: interventricular septal thickness
- Data were expressed as means±SEM. Statistical analyses were performed by ANOVA followed by Neumann-Keuls test, qui-square and regression analyses whenever appropriate. Statistical significance was considered as $p<0.05$.

Adjusted AI75



Summary

- DBP at stage 2 or later was lower than stage 1.
- PP and PP2 was started to elevate at stage 3a and 3b, respectively.
- Adjusted AI(75) was lowered or unaltered even though CKD stage was advanced.
- LVMI was increased in CKD stage 3b and after, suggesting reductions of arterial compliance.
- LVDd was considerably enlarged only at stage 5.
- LVMI was strongly related to sex and eGFR, rather than hemodynamic factors.
- LVH was expected when PP and PP2 were greater than 59 and 47 mmHg, respectively.

Patient background 1

CKD stage	1	2	3a	3b	4	5
Patient number	477	2295	697	223	89	106
Age (y/o)*	60	66*	70*	71*	67*	63
Sex (male, %)	46	51	52	51	60	58
DM (%)	28	26	28	28	30	33
HL (%)	41	48	52	54	37	37
Height (cm)	158	158	158	158	159	158
Weight (Kg)*	62	61	62	61	59*	58*
VD (class)*	1.53	1.53	1.61	1.86*	2.04*	2.19*
NVD (class)*	0.33	0.36	0.63*	0.82*	0.67*	0.72*

DM, HL, VD and NVD indicate diabetes mellitus, hyperlipidemia, vasodilator (calcium channel blocker, angiotensin receptor blocker, angiotensin converting enzyme inhibitor, and alpha blocker) and non vasodilator (diuretics and beta blocker) antihypertensive drugs, respectively. * indicates $p<0.05$ among 6 groups by ANOVA. Only average values were shown for clarity.

Multiple regression to AI75

R:0.48, df(5,3881), p<0.0001. SBP was used as an independent variable

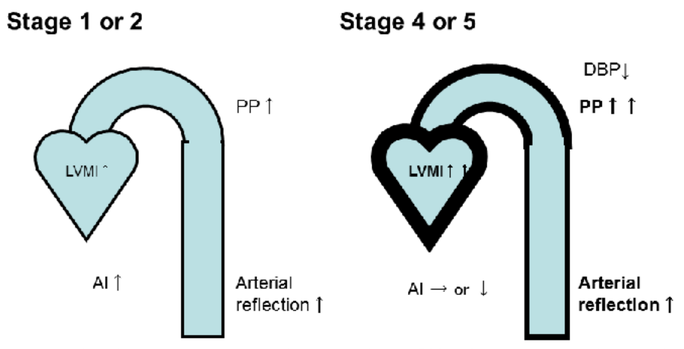
	β	t	p
Age	0.03	1.6	0.10
BW	-0.41	-24.4	<0.001
SBP	0.18	17.7	<0.001
VD	-1.37	-5.2	<0.001
NVD	1.81	5.9	<0.001

R:0.50, df(5,3881), p<0.0001. MBP was used as an independent variable

	β	t	p
Age	0.12	6.4	<0.001
BW	-0.43	-25.9	<0.001
MBP	0.29	20.2	<0.001
VD	-0.93	-3.5	<0.001
NVD	2.05	6.8	<0.001

BW, SBP, MBP, VD and NVD indicate body weight, systolic blood pressure, diastolic blood pressure, vasodilator and non-vasodilator antihypertensive drugs, respectively.

Ventriculo-vascular coupling and impedance mismatch



Physiologically, elastic artery temporally stores almost 50% of stroke volume in systolic period, which flows to periphery in diastolic phase. In advanced CKD, left ventricular hypertrophy was prominent partly because of increased aortic stiffness, especially elastic aorta. This would account for diastolic hypotension and low AI in advanced CKD.

Patient background 2

CKD stage	1	2	3a	3b	4	5
SBP (mmHg)*	140	138	137*	134*	136*	140
MBP (mmHg)*	101	98	96*	93*	94*	95*
DBP (mmHg)*	82	78*	75*	71*	73*	72*
PP (mmHg)*	57	60	61	62*	63*	68*
SBP2 (mmHg)*	129	128	127	124*	124*	127
PP2 (mmHg)*	47	50	51*	52*	52*	55*
PR (bpm)*	74	70*	68*	68*	68*	73
AI (%)	84	85	85	84	83	82
AI75 (%)	83	83	82	81	80	81

SBP, , MBP, DBP, PP, SBP2, PP2, AI and AI75 depict systolic blood pressure, diastolic blood pressure, mean blood pressure: DBP+(SBP-DBP/3), pulse pressure, second peak of systolic pressure, PP2=SBP2-DBP, augmentation index and AI adjusted for heart rate of 75. * indicates $p<0.05$ among 6 groups by ANOVA. Only average values were shown for clarity.

Simple regression to LVMI

	mean±SD	r	p
Sex (male %)	55	0.24	<0.0001
Age (y/o)	66±11	0.03	0.13
Height (cm)	159±9	0.06	<0.01
Weight (kg)	62±11	0.07	<0.01
DM (%)	27	0.06	<0.01
HL (%)	45	0.02	0.42
eGFR (ml/min)	64±23	0.29	<0.0001
SBP (mmHg)	135±16	0.16	<0.0001
DBP (mmHg)	76±12	0.05	<0.05
PP (mmHg)	60±14	0.22	<0.0001
SBP2 (mmHg)	125±18	0.10	<0.0001
PP2 (mmHg)	49±15	0.16	<0.0001
AI (%)	84±14	0.01	0.79
PR (bpm)	70±12	0.08	<0.001

Conclusions

- The present observations support that CV risk is increased in CKD stage 3b and later, and that significant fluid retention develops at stage 5.
- Our findings suggest that advanced CKD is a typical clinical example of arterial impedance mismatch.
- The present results propose that kidney function as well as PP and PP2 are suited to assess CV risk in treated hypertensive patients.

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