Differential Role of Fluid Overload versus Arterial Stiffness on the Development of High Blood Pressure in Patients at Risk of Cardiovascular Disease

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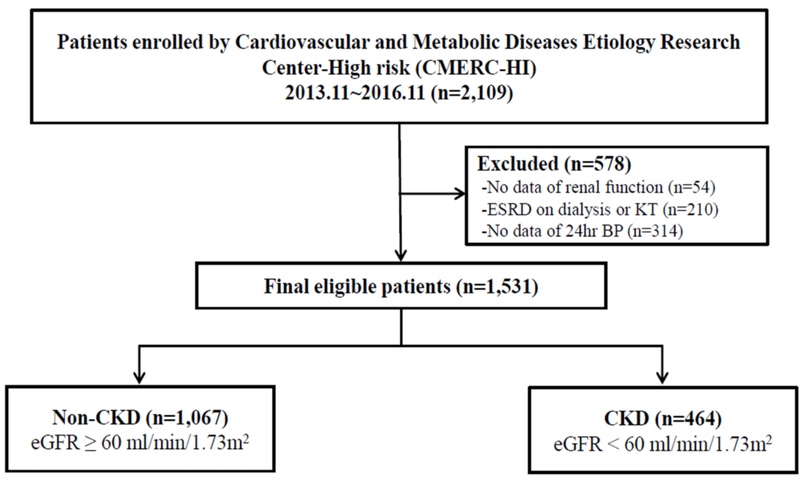
INTRODUCTION

Among many factors affecting blood pressure, it is uncertain whether fluid overload itself increases blood pressure. In this study, we aimed to clarify differential factors that determine blood pressure in patients with CKD and non-CKD and also explore the relative contribution of fluid overload to blood pressure in these patients.

METHODS



The CMERC-HI is a prospective observational cohort study in patients at high risk of cardiovascular disease. Between November 2013 and November 2016, a total of 1531 patients were included. Blood pressure and arterial stiffness were measured by ambulatory blood pressure monitoring and brachial artery pulse wave velocity (baPWV), respectively. Volume status were assessed by bioelectrical impedance analysis and presented as extracellular water/total body water (ECW/TBW). Estimated glomerular filtration rate (eGFR) was determined by CKD-EPI equation and CKD was defined as an eGFR of < 60 mL/min per 1.73 m^2 but not on dialysis.

RESULTS

Table 1. Baseline characteristics according to CKD status

Variable	Total (n=1,531)	non-CKD (n=1,067)	CKD (n=464)	P
Age (year)	60.4 ± 11.2	59.9 ± 10.9	61.5 ± 11.7	0.007
Male (%)	843 (55.1)	589 (55.2)	254 (54.7)	0.868
BMI (kg/m²)	25.3 ± 3.59	25.4 ± 3.5	25.0 ± 3.8	0.059
24hr systolic BP (mmHg)	129.1 ± 13.7	127.9 ± 12.7	131.7 ± 15.4	<0.001
24hr diastolic BP (mmHg)	77.5 ± 7.73	77.4 ± 7.7	77.6 ± 7.8	0.636
baPWV mean (cm/sec)	1504 ± 328	1474 ± 301	1572 ± 374	<0.001
ECW/TBW	0.384 (0.379 – 0.391)	0.383 (0.378 – 0.389)	0.389 (0.381 – 0.395)	<0.001
Overhydration (%)	93 (6.3)	34 (3.3)	59 (13.1)	<0.001
Hypertension (%)	1285 (84.3)	877 (82.7)	408 (87.9)	0.009
Diabetes (%)	597 (39.2)	372 (35.1)	225 (48.6)	<0.001
CVD (%)	301 (19.7)	246 (23.1)	55 (11.9)	<0.001
Laboratory finding				
Hemoglobin (g/dL)	13.5 ± 1.94	14.1 ± 1.5	12.2 ± 2.0	<0.001
Calcium (mg/dL)	9.1 ± 0.4	9.2 ± 0.4	9.0 ± 0.6	<0.001
Inorganic P (mg/dL)	3.6 ± 0.6	3.6 ± 0.5	3.8 ± 0.7	<0.001
HDL (mg/dL)	48.7 ± 13.0	50.1 ± 12.8	45.3 ± 13.1	<0.001
LDL (mg/dL)	95.6 ± 30.2	96.9 ± 30.5	92.5 ± 29.2	0.012
hs-CRP (mg/L)	0.8 (0.5 – 1.5)	0.8 (0.5 – 1.5)	0.9 (0.6 – 1.9)	0.003
eGFR (ml/min/1.73m2)	72.4 ± 28.9	88.8 ± 13.7	34.6 ± 16.3	<0.001
uACR (mg/g Cr)	5.06 (1.32 – 42.01)	2.19 (0.97 – 8.18)	39.59 (8.58 – 106.3)	<0.001

Note : [a] Mann-Whitney U-test, [b] both current and former smoking
Abbreviations: baPWV, brachial to ankle pulse-wave velocity; and ECW/TBW, extracellular water to total body water ratio

Table 2. Linear regression analyses between 24hr systolic blood pressure and clinical and biochemical variables

Variable	non-CKD (n=1,067)				CKD (n=464)			
	Univariate		Multivariate		Univariate		Multivariate	
	β	P	β	P	β	P	β	P
Age (per 1 year)	0.082	0.022	-0.097	0.042	0.186	0.002	0.040	0.594
Male	2.106	0.007	3.396	0.009	1.590	0.272	-0.784	0.745
BMI (per 1 kg/m²)	0.540	<0.001	0.540	<0.001	0.344	0.068	0.466	0.019
baPWV mean (per 100 cm/sec)	1.347	<0.001	1.511	<0.001	1.677	<0.001	1.526	<0.001
ECW/TBW (per 0.01)	0.020	0.911	0.025	0.905	3.508	<0.001	1.919	0.003
Hypertension	2.015	0.050	-0.195	0.863	0.057	0.980	-2.523	0.264
Diabetes	3.745	<0.001	2.197	0.014	7.859	<0.001	1.808	0.280
CVD	1.893	0.040	1.371	0.174	-0.189	0.933	2.885	0.244
Laboratory finding								
Hemoglobin (per 1 g/dL)	0.396	0.137			-1.676	<0.001	-0.572	0.292
Calcium (per 1 mg/dL)	-0.181	0.862			-5.127	<0.001	-0.682	0.677
Inorganic P (per 1 mg/dL)	-0.215	0.785			4.260	<0.001	1.864	0.172
HDL (per 1 mg/dL)	-0.089	0.004			-0.104	0.076		
LDL (per 1 mg/dL)	-0.009	0.487	0.020	0.137	0.034	0.193	0.037	0.154
hs-CRP (per 1 log) [a]	0.948	0.620			-1.018	0.632		
eGFR (per 1 mL/min/1.73 m²)	-0.048	0.091	0.024	0.480	-0.190	<0.001	-0.052	0.420
uACR (per 1 mg/g Cr)	0.004	0.314			0.043	<0.001	0.015	0.079

Note: [a] log transformed

Figure 1. ROC analysis for SBP > 140 mmHg in non-CKD and CKD patients

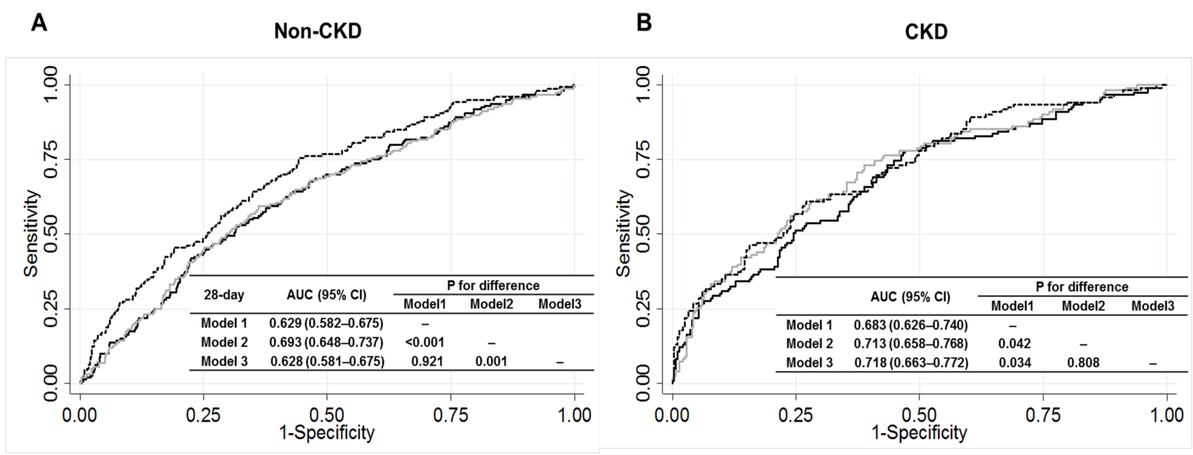


Table 3. NRI and IDI of clinical models with factors affecting blood pressure

	Non-CKD				CKD			
	NRI (SE)	P	IDI (SE)	P	NRI (SE)	P	IDI (SE)	P
Model 2 vs. Model 1	0.320 (0.213-0.427)	<0.001	0.111 (0.091-0.131)	<0.001	0.332 (0.210-0.454)	<0.001	0.099 (0.070-0.129)	<0.001
Model 3 vs. Model 1	0.018 (-0.037-0.072)	0.530	0.002 (0.001-0.005)	0.096	0.117 (0.036-0.197)	0.005	0.030 (0.013-0.046)	0.001

Model 1: Adjusted for age, sex, smoking, diabetes, diabetes, hypertension, cardiovascular disease, BMI, LDL, eGFR, diuretic use, and CKD status

Model 2: Model 1 + baPWV

Model 3: Model 1 + ECW/TBW

In CKD patients, multiple linear regression analysis after adjustment of confounders showed that both baPWV and ECW/TBW significantly associated with SBP. The area under the ROC for predicting SBP > 140 mmHg significantly increased after each of baPWV and ECW/TBW was added to a conventional model. This association was further confirmed by the net reclassification and integrated discriminant improvements (NRI/IRI). The predictability for high BP did not differ between baPWV and ECW/TBW in these patients.

CONCLUSION

We demonstrated that fluid overload come into play in the development of high blood pressure as kidney function declines. Arterial stiffness is more important in determining blood pressure in non-CKD patients. Our findings suggest that a stepwise approach is required in the management of hypertension depending on CKD stages.

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