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Potential determinants of the E/e′ ratio in non-dialysis compared with dialysis patients

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Abstract

Aim: We hypothesized that arterial function and N-terminal natriuretic peptide (NT-proBNP) levels as a marker of volume overload, relate differently to E/e′ as an index of diastolic function in dialysis compared with non-dialysis patients with chronic kidney disease. We further examined whether cardiovascular risk factors attenuated these relationships.

Methods: We assessed cardiovascular risk factors and determined arterial function indices by applanation tonometry using SphygmoCor software and E/e′ by echocardiography in 103 (62 non-dialysis and 41 dialysis) patients.

Results: In established confounder adjusted analysis, dialysis status impacted the pulse wave velocity-E/e′ relationship (interaction $p = .01$) but not the NT-proBNP level-E/e′ association (interaction $p = .1$). Upon entering arterial function measures and NT-proBNP levels simultaneously in regression models, arterial function measures were associated with E/e′ ($p = .008$ to .04) in non-dialysis patients whereas NT-proBNP levels were related to E/e′ in dialysis patients ($p = .009$ to .04). Bivariate associations were found between diabetes ($p < .0001$) and E/e′ in non-dialysis patients, and haemoglobin concentrations and E/e′ ($p = .02$) in those on dialysis. Upon adjustment for diabetes in non-dialysis patients, only central pulse pressure remained associated with E/e′ ($p = .02$); when haemoglobin concentrations were adjusted for in dialysis patients, NT-proBNP levels were no longer associated with E/e′ ($p = .2$). In separate models, haemoglobin levels were associated with E/e′ independent of left ventricular mass index and preload and afterload measures ($p = .02$ to .03).

Conclusion: The main determinants of E/e′ may differ in non-dialysis compared with dialysis patients. These include arterial function and diabetes in non-dialysis patients, and volume overload and anaemia in dialysis patients.

KEYWORDS
arterial function indices, chronic kidney disease, E/e′, haemoglobin, NT-proBNP levels

SUMMARY AT A GLANCE

Impaired diastolic function is prevalent and problematic in people with chronic kidney disease. Using the ratio of E to e′ as a measure of impaired diastolic function, the factors most strongly associated with this metric were different depending on whether participants had dialysis-dependent CKD or not.

1 | INTRODUCTION

Impaired diastolic function and consequent heart failure with preserved ejection fraction (HFpEF) are highly prevalent in patients with chronic kidney disease (CKD).[1,2] The frequency of diastolic dysfunction increases in relation to CKD severity.[2] Accordingly, up to 85% of dialysis patients have some degree of diastolic dysfunction.[2] The prevalence of HFpEF is larger than that of heart failure with reduced ejection fraction (HFrEF) in CKD.[1] Moreover, mortality rates associated with HFpEF are larger than those related to HFrEF in CKD patients.[3]

Hemodynamic factors that mediate impaired diastolic function in CKD comprise increased afterload and preload.[4] With regard to increased afterload, CKD is characterized by marked arteriosclerosis, which increases arterial stiffness as is mostly estimated by carotid-femoral pulse wave velocity.[5] Increased arterial stiffness results in a larger forward wave pressure, which enhances wave reflection. These changes translate into an increased pulse pressure and reduced coronary perfusion.

Increased preload in CKD is mostly due to volume overload and anaemia.[4] In this regard, anaemia may lead to diastolic dysfunction via three pathways: (a) hyperdynamic circulation and increased preload, (b) myocardial ischemia and (c) myocardial fibrosis.[4,6–8] Both increased afterload and preload in CKD are associated with left ventricular hypertrophy, which is the most frequently identified cardiovascular abnormality in CKD.[4] Left ventricular hypertrophy is traditionally considered to be involved in the development of diastolic dysfunction among patients with CKD.[4] However, in an experimental model of chronic kidney disease, diastolic dysfunction occurred prior to changes in left ventricular geometry.[9]

N-terminal proB-type natriuretic peptide (NT-proBNP) is secreted by cardiomyocytes in response to stretch caused by increased left ventricular volume and pressure as well as other factors including particularly hypoxia.[10,11] In CKD, increased NT-proBNP concentrations is a marker of fluid overload.[12] NT-pro-BNP levels predict cardiovascular events and all-cause mortality in haemodialysis patients.[13] Kim and colleagues recently reported an association of NT-proBNP concentrations with volume overload as well as diastolic dysfunction in non-dialysis CKD Stage 5 patients.[14]

The impact of fluid overload on cardiovascular and all-cause mortality is well documented in dialysis patients.[15,16] By contrast, increased afterload may be a more important cardiovascular risk determinant in non-dialysis patients. Indeed, whereas pulse wave velocity independently predicted incident heart failure and mortality in non-dialysis patients that participated in the Chronic Renal Insufficiency Cohort,[17,18] it did not meaningfully improve cardiovascular and all-cause mortality risk discrimination and reclassification beyond clinical risk scores in 2 large dialysis cohorts.[19] We therefore hypothesized that, in established confounder adjusted analysis, impaired arterial function indices are more strongly associated with E/e′ in non-dialysis compared with dialysis patients whereas NT-proBNP levels are more closely related to E/e′ in dialysis compared with non-dialysis persons. E/e′ is calculated as the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity. It represents left ventricular filling pressure and is one of the echocardiographic indices of diastolic function.[1,14] Importantly in the present context, diabetes is related to impaired arterial function in CKD[20] whereas haemoglobin concentrations are inversely associated with natriuretic peptides in patients with HFpEF.[21,22] In view of these reported findings, we further examined whether traditional and non-traditional or renal cardiovascular risk factors including diabetes and haemoglobin levels, could explain the associations of arterial function measures and NT-proBNP levels with E/e′ in CKD patients.

2 | METHODS

2.1 | Patients

One hundred and three patients including 62 non-dialysis and 41 dialysis participants were enrolled at the Milpark Hospital in Johannesburg, South Africa. Patients with previously diagnosed heart failure, infection or/and active cancer were excluded. Only one male non-dialysis patient had paroxysmal atrial fibrillation and he experienced sinus rhythm at the time he was investigated. Non-dialysis patients had a chronic kidney disease epidemiology collaboration estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73m^2 upon enrolment. The mean (*SD*) eGFR in non-dialysis patients was 33.4 (17.9) ml/min/1.73m^2; 34 (54.8%), 16 (25.8%) and 12 (19.4%) of them had Stage 3, Stage 4 and Stage 5 CKD, respectively. Dialysis was performed thrice weekly for 4 h per session at the haemodialysis unit at Milpark Hospital. The study was carried out in accordance with the Helsinki Declaration as revised in 2013. Study approval was obtained from the University of the Witwatersrand Human (Medical) research Ethics Committee (protocol number: M15-08-43) in Johannesburg, South Africa. Each patient provided written informed consent prior to participation.

2.2 | Methods

Patient characteristics that were recorded included demographic variables, lifestyle factors, anthropometric features, traditional and non-traditional cardiovascular risk factors, established cardiovascular disease, arterial function indices, echocardiographic features and systemic vascular resistance. All investigations were performed on a single day. In dialysis patients, the data were recorded on the day prior to undergoing the respective procedure.

Traditional and non-traditional or renal cardiovascular risk factors were recorded as previously reported and provided in the online Supporting Information (Methods). For the present study, high phosphate was considered present when the phosphate concentration was >1.42 mmol/L or/and phosphate lowering drugs including calcium carbonate or sevelamer therapy in 41 and 1 patients, respectively, was used. Mean arterial blood pressure for the peripheral waveform was determined electronically by the SphygmoCor device (see below) and using the formula

$$MP = \frac{\sum_{i=T_0}^{T_F} P_i}{n}$$

where T_0 = start of the waveform; T_F = end of waveform; P_i = pressure points and n = number of pressure points. The mean blood pressure was recorded during eight consecutive heartbeats once the pulse waveform was consistent with less than 5% variation in pulse height and diastolic pressure.

Established cardiovascular disease comprised ischemic heart disease and cerebrovascular and peripheral arterial disease, the presence of which was confirmed by a cardiologist, neurologist and vascular surgeon, respectively.

Applanation tonometry and SphygmoCor software were used to determine central haemodynamic features as previously reported and provided in the online Supporting Information (Methods). We determined aortic pulse wave velocity, augmentation index, reflected wave pressure and reflection magnitude, central systolic and pulse pressure, peripheral pulse pressure and forward wave pressure.

NT-proBNP concentrations were determined by an electrochemiluminescence immunoassay on Cobas (Roche Diagnostics). The measurement range was 10 to 35 000 pg/ml. The intra-assay and inter-assay coefficients of variation were 3.0% and 4.8%, respectively.

Echocardiography was performed in accordance with recent recommendations[23,24] and using a Philips CX50 POC Compact Compact-Xtreme Ultrasound System (Philips Medical Systems [Pty] Ltd.) equipped with a 1.8–4.2 MHz probe that allowed for M-mode, 2D, pulsed and tissue Doppler measurements. We assessed left ventricular mass index by the linear method using 2D-guided M-mode echocardiography and indexed to body surface area, left ventricular end diastolic volume and diastolic function variables including the early (E)/late (atrial) diastolic wave (A) ratio, the peak mitral annulus motion during early diastole (averaged septal and lateral e′) and E/e′ ratio, as previously described and provided in the online Supporting Information (Methods).

Systemic vascular resistance was calculated from mean arterial pressure, right atrial pressure and cardiac output according to the equation: systemic vascular resistance = (mean arterial pressure−right atrial pressure)/cardiac output, assuming that right atrial pressure = 10 mmHg. Right atrial pressure was taken as a fixed value, as in previous studies among CKD patients.[25] Further details are given in the online Supporting Information.

2.3 | Data analysis

Results are given as mean (*SD*), median (interquartile range) or percentages as appropriate. Non-normally distributed variables were logarithmically transformed prior to entering them in linear multivariate regression models.

We compared the recorded characteristics between non-dialysis and dialysis patients in age, sex and race adjusted linear or logistic regression models as appropriate, with additional adjustment for waist-height ratio, mean blood pressure and heart rate upon comparing arterial function parameters and for left ventricular mass index upon comparing diastolic function markers.

The subsequent analyses aimed at identifying factors that were associated with E/e′. For this, potential established confounders were considered when they were related to E/e′ with a p value of <.2. These included age ($p = .03$), waist-height ratio ($p = .13$), mean blood pressure ($p = .17$) and heart rate ($p = .1$). In this regard, sex ($p = .6$), race ($p = .9$), body mass index ($p = .47$) and waist-hip ratio ($p = .6$) did not show a tendency to relate to E/e′. Sex was nevertheless forced into the models.

Given the above, the associations of arterial function markers and NT-proBNP with E/e′ were first assessed in age and sex and subsequently in established confounder (age, sex, waist-height ratio, mean blood pressure and heart rate) adjusted models; additional adjustment for left ventricular mass index and left ventricular end diastolic volume was made when deemed indicated. To assess the impact of CKD status (non-dialysis versus dialysis) on arterial function-diastolic function and NT-pro-BNP-diastolic function relationships, we added interaction terms together with their components to the models. This was followed by stratified analysis, that is, analysis in non-dialysis and dialysis patients separately. Subsequently, we re-assessed the arterial function-diastolic function and NT-pro-BNP-diastolic function relationships after additional adjustment for patient characteristics that were associated with diastolic function in bivariate analysis.

Statistical analysis was performed on IBM SPSS statistics program (version 23.0 IBM). Significance was set at $p < .05$.

3 | RESULTS

3.1 | Recorded characteristics in non-dialysis and dialysis patients

The recorded characteristics in non-dialysis and dialysis patients are given in Table 1. Black patients were more often on dialysis whereas the reverse applied to white participants. In age, sex and race adjusted analysis, systolic and mean blood pressure were significantly larger in dialysis compared with non-dialysis patients.

With regard to non-traditional/renal cardiovascular risk factors, dialysis patients experienced significantly more frequent high phosphate concentrations, larger intact parathyroid hormone and ferritin concentrations and smaller haemoglobin and uric acid levels and were more often treated with intravenous iron and erythropoietin stimulating agents compared with non-dialysis participants.

NT-proBNP concentrations were larger in dialysis compared with non-dialysis patients. As given in Table 2, among arterial function parameters, central systolic blood pressure was significantly larger in dialysis compared with non-dialysis patients.

As also shown in Table 2, on echocardiography, the left ventricular mass index tended to be larger in dialysis compared with

TABLE 1 Baseline recorded characteristics in non-dialysis and dialysis patients

Characteristic	Chronic kidney disease patients		
	Non-dialysis ($n = 62$)	Dialysis ($n = 41$)	p
Demographics			
Age (years)	58.6 (14.1)	55.3 (15.1)	.4
Female sex (%)	20 (32.2)	18 (43.9)	.1
Black (%)	**18 (29.0)**	**24 (58.5)**	**.004**
Asian (%)	21 (33.9)	9 (21.9)	.1
White (%)	**21 (33.9)**	**3 (7.3)**	**.006**
Mixed (%)	2 (3.2)	5 (12.2)	.2
Anthropometry			
Body mass index (kg/m^2)	27.8 (5.6)	27.2 (5.9)	.5
Waist-hip ratio	0.96 (0.12)	0.98 (0.09)	.09
Waist-height ratio	0.59 (0.09)	060 (0.11)	.5
Major traditional risk factors			
Hypertension (%)	53 (85.5)	39 (95.1)	.1
Systolic blood pressure (mmHg)	**138 (20)**	**146 (21)**	**.02**
Diastolic blood pressure (mmHg)	81 (9)	85 (15)	.1
Mean blood pressure (mmHg)	**100 (11)**	**105 (14)**	**.02**
Heart rate (beats/min)	74 (15)	76 (12)	.4
Dyslipidemia (%)	49 (86.0)	25 (69.4)	.06
Diabetes (%)	21 (33.9)	14 (34.2)	.9
Non-traditional/renal risk factors			
Dialysis duration, months	-	36 (12–48)	-
Estimated GFR	33.4 (17.9)	-	-
Phosphate (mmol/L)	1.2 (0.9–1.4)	1.4 (0.9–1.7)	.1
Calcium (mmol/L)	2.3 (2.2–2.4)	2.3 (2.1–2.4)	.2
High phosphate	**12 (19.7)**	**30 (81.1)**	**<.0001**
Intact PTH (pg/ml)	**83.0 (56.0–195.6)**	**520.3 (193.0–790.0)**	**<.0001**
Haemoglobin (g/dl)	**12.9 (10.2–15.1)**	**10.8 (9.8–12.0)**	**<.0001**
Transferrin saturation (%)	20.5 (16.7–27.2)	22.6 (18.0–26.1)	.4
Ferritin (ng/ml)	**124 (49–247)**	**360 (146–603)**	**<.0001**
Uric acid (mmol/L)	**0.42 (0.12)**	**0.25 (0.09)**	**<.0001**
Intravenous iron therapy (%)	**9 (14.5)**	**34 (82.9)**	**<.0001**
ESA therapy (%)	**10 (16.1)**	**38 (92.7)**	**<.0001**
Cardiovascular disease	13 (20.9)	7 (17.1)	.8
NT-proBNP (pg/ml)	**527 (78–1901)**	**4060 (1100–13 022)**	**<.0001**
SVR (mmHg/l/min)	21.1 (15.9–27.1)	20.4 (16.1–24.1)	.6

Note: Data are expressed as mean (*SD*) or median (interquartile range) unless indicated otherwise, and were analyzed in age, sex and race adjusted linear or logistic regression models as appropriate. Significant differences are shown in bold. High phosphate was considered present when the phosphate concentration was >1.42 mmol/L or/and phosphate lowering drugs including calcium carbonate or sevelamer therapy in 41 and 1 patients, respectively, was used.
Abbreviations: ESA, erythropoietin stimulating agent; GFR, glomerular filtration rate; NT-proBNP, N-terminal B-type natriuretic peptide; PTH, intact parathyroid hormone; SVR, systemic vascular resistance.

non-dialysis patients ($p = .07$). E′ was significantly smaller and E/e′ significantly larger in dialysis compared with non-dialysis patients; upon additional adjustment for left ventricular mass index, e′ remained significantly smaller in dialysis patients whereas E/e′ no longer differed between dialysis and non-dialysis participants.

3.2 | Established confounder adjusted associations of arterial function and NT-proBNP concentrations with diastolic function in all, non-dialysis and dialysis patients

In all patients, central systolic blood pressure [β (*SE*) = .133 (0.050), $p = .009$, model $R^2 = .172$], central pulse pressure [β (*SE*) = .110 (0.035), $p = .002$, model $R^2 = .194$], peripheral pulse pressure [β (*SE*) = .062 (0.025), $p = .01$, model $R^2 = .160$], forward wave pressure [β (*SE*) = .108 (0.046), $p = .02$, model $R^2 = .184$] and NT-proBNP [β (*SE*) = 1.870 (0.540), $p = .001$, model $R^2 = .220$] were associated with E/e′. Arterial function parameters and NT-proBNP concentrations were not associated with e′ and E/A (data not shown).

As shown in Table S1, CKD status (non-dialysis vs. dialysis) impacted the pulse wave velocity-E/e′ relationship significantly (interaction $p = .01$). As given in Table S2, CKD stage did not influence the NT-proBNP-E/e′ association (interaction $p = .1$).

Table 3 shows the age and sex adjusted and established confounder adjusted associations of arterial function and NT-proBNP levels with E/e′ in stratified analysis. In non-dialysis but not dialysis patients, pulse wave velocity, reflected wave pressure, central systolic and pulse pressure, peripheral pulse pressure and forward wave pressure were each significantly associated with E/e′. NT-proBNP was significantly associated with E/e′ in both non-dialysis and dialysis patients. Further adjustment for left ventricular mass or left ventricular end diastolic volume did not materially alter any of the significant relationships as also given in Table 3.

Arterial function parameters and NT-pro-BNP levels were not associated with E/A and e′ in stratified analysis (data not shown).

Among non-dialysis patients, the estimated glomerular filtration rate was not associated with E/e′ [β (*SE*) = −.031 (0.034); partial $R = -.123$; $p = .4$].

3.3 | Independent established confounder adjusted associations of arterial function and NT-proBNP concentrations with diastolic function in non-dialysis and dialysis patients

Table 4 gives the established confounder adjusted associations of arterial function measures and NT-proBNP concentrations with E/e′ in non-dialysis and dialysis patients when both potential determinants of E/e′ were entered simultaneously in the models. In non-dialysis patients, pulse wave velocity, central systolic and pulse pressure and peripheral pulse pressure but not NT-proBNP were significantly associated with E/e′. In dialysis patients, NT-proBNP was significantly

TABLE 2 Arterial function indices and echocardiographic characteristics in non-dialysis and dialysis patients

Characteristic	Expected values	Chronic kidney disease patients Non-dialysis ($n = 62$)	Dialysis ($n = 41$)	*p*
Arterial function				
Pulse wave velocity (mm/sec)		11.1 (2.3)	11.4 (4.3)	.5/.6[a]
Augmentation index (%)		66.9 (16.9)	66.3 (16.7)	.9/.9[a]
Reflected wave pressure (mmHg)		20.8 (14.3–25.0)	25.0 (15.0–29.0)	.1/.1[a]
Reflection magnitude (%)		67.5 (17.1)	66.9 (16.7)	.9/.9[a]
Central systolic BP (mmHg)		127 (17.2)	135 (20.9)	**.01/.02**[a]
Central pulse pressure (mmHg)		47 (15)	48 (16)	.09/.1[a]
Peripheral pulse pressure (mmHg)		57 (18)	61 (21)	.1/.2[a]
Forward wave pressure (mmHg)		31 (10.4)	35 (11)	.1/.1[a]
Echocardiographic characteristics				
Left ventricular mass index (g/m^2)	Men: 49–115; women: 43–95	88.7 (37.3)	101.9 (54.1)	.07
Left ventricular EDV (ml)	Men: 62–150; women: 46–106	125 (59)	140 (70)	.2
Ejection fraction (%)	Men: 52–72; women: 54–74	65.3 (13.9)	62.3 (13.9)	.1
E/A	>0.8 to <2.0	1.05 (0.38)	0.97 (0.35)	.1/.1[b]
E′ (cm/s)	≥8.5	**9.0 (2.6)**	**8.1 (2.8)**	**.01/.02**[b]
E/e′	≤14	**9.3 (4.3)**	**11.0 (4.6)**	**.02**/.05[b]

Note: Data are expressed as mean (SD) or median (interquartile range) and were analyzed in age, sex and race adjusted linear regression models as appropriate. Significant differences are shown in bold.

Abbreviations: BP, blood pressure; EDV, end diastolic volume.

[a]Additionally adjusted for waist-height ratio, mean blood pressure and heart rate.

[b]Additionally adjusted for left ventricular mass index.

TABLE 3 Established confounder adjusted associations of arterial function and NT-proBNP levels with E/e′ in non-dialysis and dialysis patients

	Chronic kidney disease patients					
	Non-dialysis			Dialysis		
	β (*SE*)	*p*	Model R^2	β (*SE*)	*p*	Model R^2
Pulse wave velocity	**.599 (0.188)**	**.002**[a]	**.206**	−.113 (0.169)	.5[a]	.080
	.661 (0.203)	**.002**[b]	**.268**	−.098 (0.192)	.6[b]	.111
	.626 (0.206)	**.004**[c]	**.287**	−.127 (0.196)	.5[c]	.133
	.692 (0.201)	**.001**[d]	**.323**	−.045 (0.198)	.8[d]	.145
Augmentation index	.013 (0.032)	.7[a]	.160	−.038 (0.061)	.5[a]	.107
	.004 (0.037)	.9[b]	.220	−.074 (0.069)	.3[b]	.155
	.003 (0.037)	.9[c]	.230	−.075 (0.072)	.3[c]	.155
	−.008 (0.037)	.8[d]	.294	−.081 (0.065)	.2[d]	.187
Log reflected wave pressure	6.551 (3.280)	.05[a]	.222	4.100 (5.062)	.4[a]	.114
	8.568 (4.131)	**.04**[b]	**.289**	2.380 (6.202)	.7[b]	.126
	8.262 (4.296)	.06[c]	.291	2.569 (6.351)	.7[c]	.127
	9.694 (3.996)	**.02**[d]	**.382**	.129 (6.119)	.9[d]	.140
Reflection magnitude	.013 (0.031)	.7[a]	.160	−.044 (0.061)	.5[a]	.111
	.003 (0.036)	.9[b]	.220	−.079 (0.068)	.2[b]	.161
	.003 (0.036)	.9[c]	.230	−.081 (0.071)	.2[c]	.161
	−.009 (0.036)	.8[d]	.295	−.085 (0.064)	.2[d]	.193
Central systolic BP	.059 (0.033)	.08[a]	.125	.041 (0.037)	.3[a]	.129
	.229 (0.071)	**.002**[b]	**.264**	.058 (0.078)	.5[b]	.135
	.213 (0.073)	**.005**[c]	**.275**	.062 (0.080)	.5[c]	.137
	.261 (0.069)	**<.0001**[d]	**.349**	.016 (0.077)	.8[d]	.141
Central pulse pressure	**.122 (0.035)**	**.001**[a]	**.235**	.060 (0.051)	.2[a]	.133
	.158 (0.043)	**.001**[b]	**.295**	.051 (0.064)	.9[b]	.137
	.149 (0.044)	**.002**[c]	**.306**	.051 (0.065)	.5[c]	.138
	.176 (0.042)	**<.0001**[d]	**.379**	.026 (0.064)	.7[d]	.145
Peripheral pulse pressure	**.088 (0.029)**	**.004**[a]	**.203**	.033 (0.036)	.4[a]	.100
	.125 (0.036)	**.001**[b]	**.284**	.027 (0.039)	.5[b]	.131
	.118 (0.037)	**.002**[c]	**.296**	.027 (0.040)	.5[c]	.131
	.139 (0.035)	**<.0001**[d]	**.364**	.013 (0.038)	.7[d]	.147
Forward wave pressure	.085 (0.046)	.06[a]	.215	.108 (0.077)	.2[a]	.149
	.117 (0.054)	**.03**[b]	**.296**	.102 (0.088)	.2[b]	.160
	.113 (0.055)	**.04**[c]	**.300**	.101 (0.089)	.3[c]	.161
	.136 (0.051)	**.01**[d]	**.399**	.076 (0.087)	.4[d]	.163
Log NT-proBNP level	**1.495 (0.665)**	**.03**[a]	**.155**	**2.374 (1.056)**	**.03**[a]	**.202**
	1.650 (0.714)	**.03**[b]	**.206**	2.427 (1.215)	.05[b]	.229
	1.414 (0.770)	.07[c]	.211	2.476 (1.253)	.05[c]	.230
	1.638 (0.693)	**.02**[d]	**.291**	**3.106 (1.106)**	**.008**[d]	**.341**

Note: Significant associations are shown in bold.

Abbreviations: BP, blood pressure; Log, logarithmically transformed; NT-pro-BNP, N-terminal pro B-type natriuretic peptide; SE, standard error.

[a]Adjusted for age, sex.

[b]Adjusted for age, sex, waist-height ratio, mean blood pressure and heart rate.

[c]Adjusted for age, sex, waist-height ratio, mean blood pressure, heart rate and left ventricular mass index.

[d]Adjusted for age, sex, waist-height ratio, mean blood pressure, heart rate and left ventricular end diastolic volume.

associated (when entered together with pulse wave velocity or peripheral pulse pressure) or tended to be associated [when entered together with augmentation index ($p = .05$), reflected wave pressure ($p = .06$), reflection magnitude ($p = .05$), central systolic pressure ($p = .05$) or forward wave pressure ($p = .05$)] with E/e′ whereas arterial function parameters were not related to E/e′.

TABLE 4 Independent established confounder adjusted associations of arterial function measures and NT-proBNP levels with E/e′ in non-dialysis and dialysis patients

	Chronic kidney disease patients					
	Non-dialysis			Dialysis		
	β (*SE*)	*p*	Model R^2	β (*SE*)	*p*	Model R^2
Pulse wave velocity	**.533 (0.244)**	**.03**		−.045 (0.181)	.8	
Log NT-proBNP level	1.236 (0.750)	.1	**.300**	**3.180 (1.129)**	**.009**	**.314**
Augmentation index	−.010 (0.048)	.8		−.071 (0.069)	.3	
Log NT-proBNP level	.627 (0.732)	.4	.243	2.465 (1.248)	.05	.263
Log reflected wave pressure	7.677 (5.073)	.1		2.576 (5.997)	.7	
Log NT-proBNP level	.276 (0.710)	.7	.290	2.457 (1.267)	.06	.239
Reflection magnitude	−.011 (0.047)	.8		−.075 (0.068)	.3	
Log NT-proBNP level	.629 (0.733)	.4	.243	2.449 (1.244)	.05	.267
Central systolic BP	**.207 (0.082)**	**.01**		.064 (0.079)	.4	
Log NT-proBNP level	1.027 (0.704)	.1	**.311**	2.504 (1.241)	.05	.248
Central pulse pressure	**.136 (0.049)**	**.008**		.050 (0.062)	.4	
Log NT-proBNP level	1.061 (0.688)	.1	**.328**	2.430 (1.237)	.05	.247
Peripheral pulse pressure	**.107 (0.040)**	**.01**		.042 (0.045)	.4	
Log NT-proBNP level	1.141 (0.687)	.1	**.320**	**2.662 (1.243)**	**.04**	**.252**
Forward wave pressure	**.128 (0.061)**	**.04**		.100 (0.086)	.3	
Log NT-proBNP level	.533 (0.662)	0.4	**.329**	2.474 (1.241)	.05	.270

Note: Arterial function parameters and NT-pro-BNP levels were entered together in multivariable regression models adjusted for age, sex, race, waist-height ratio, mean arterial pressure and heart rate. Significant associations are shown in bold.
Abbreviations: BP, blood pressure; Log, logarithmically transformed; NT-pro-BNP, N-terminal pro B-type natriuretic peptide; SE, standard error.

TABLE 5 Arterial function-E/e′ relationships after additional adjustment for diabetes in non-dialysis patients and NT-proBNP levels-E/e′ relationship after additional adjustment for haemoglobin concentrations in dialysis patients

	Chronic kidney disease patients					
	Non-dialysis			Dialysis		
	β (*SE*)	*p*	Model R^2	β (*SE*)	*p*	Model R^2
Pulse wave velocity	.384 (0.202)	.06	.415			
Augmentation index	−.004 (0.032)	.9	.416			
Log reflected wave pressure	5.112 (3.854)	.2	.438			
Reflection magnitude	−.005 (0.031)	.9	.321			
Central systolic BP	.135 (0.067)	.05	.355			
Central pulse pressure	**.096 (0.042)**	**.02**	**.442**			
Peripheral pulse pressure	.068 (0.036)	.06	.425			
Forward wave pressure	.077 (0.050)	.1	.446			
Log NT-pro-BNP level				1.760 (1.257)	.2	.291

Associations were assessed in age, sex, waist-height ratio, mean blood pressure and heart rate adjusted models. Significant associations are shown in bold.
Abbreviations: BP, blood pressure; Log, logarithmically transformed; NT-pro-BNP, N-terminal pro B-type natriuretic peptide; SE, standard error.

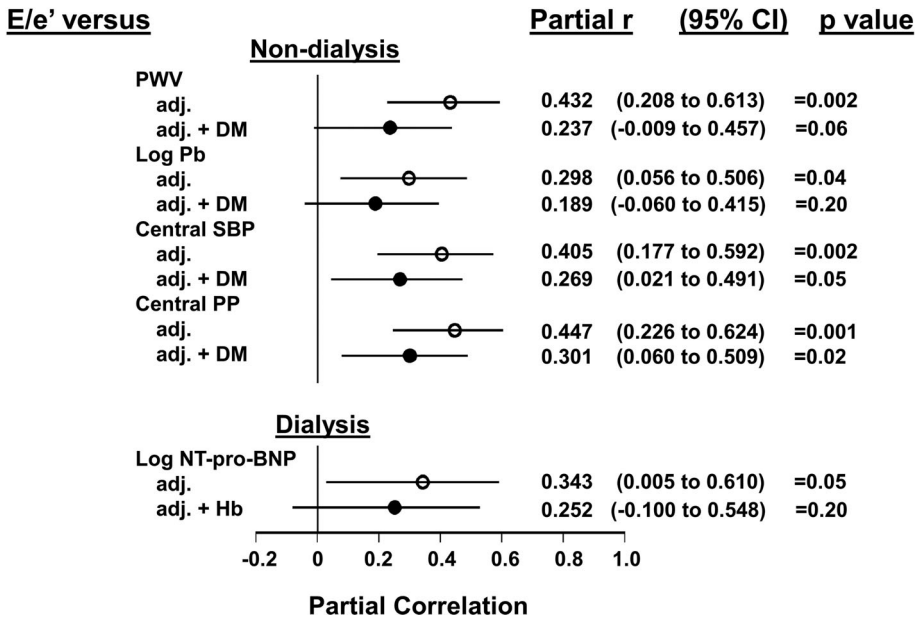

FIGURE 1 Partial correlations (95% CI) for the associations of arterial function measures with E/e′ before (open circles) and after (closed circles) additional adjustment for diabetes in non-dialysis patients and haemoglobin concentrations in dialysis patients. Age, sex, waist-height ratio, mean blood pressure and heart rate were adjusted for in all models. CI, confidence interval; PWV, pulse wave velocity; adj., adjusted; DM, diabetes mellitus; log, logarithmically transformed; Pb, backward pressure or reflected wave pressure; SBP, systolic blood pressure; PP, pulse pressure; NT-pro-BNP, N-terminal B-type natriuretic peptide

TABLE 6 Association of haemoglobin concentrations with E/e′ in dialysis patients

Haemoglobin concentration	β (*SE*)	*p*	Model R^2
	−.877 (0.401)	.03[a]	.233
	−.896 (−0.411)	.03[b]	.236
	−1.061(0.432)	.02[c]	.298
	−1.011 (0.441)	.03[d]	.312
	−.990 (0.454)	.03[e]	.241

Note: Significant associations are shown in bold.
Abbreviation: SE, standard error.
[a]Adjusted for age, sex, waist-height ratio, mean arterial pressure and heart rate.
[b]Adjusted for age, sex, waist-height ratio, mean arterial pressure, heart rate and left ventricular mass index.
[c]Adjusted for age, sex, waist-height ratio, mean arterial pressure, heart rate, left ventricular end diastolic volume and central systolic blood pressure.
[d]Adjusted for age, sex, waist-height ratio, heart rate, left ventricular end diastolic volume, central systolic blood pressure and log systemic vascular resistance.
[e]Adjusted for age, sex, waist-height ratio, heart rate, central systolic blood pressure and log systemic vascular resistance.

3.4 | Arterial function-E/e′ relationships after additional adjustment for diabetes in non-dialysis patients and the NT-proBNP levels-E/e′ relationship after additional adjustment for haemoglobin concentrations in dialysis patients

Among the baseline recorded patient characteristics as given in Table 1, bivariate associations were found between diabetes ($R = .530$, $p < .0001$), erythropoietin stimulating agent use ($R = .252$, $p = .04$) and high phosphate concentrations ($R = .246$, $p = .05$) with E/e′ in non-dialysis patients whereas haemoglobin ($R = -.359$, $p = .02$) concentrations were related to E/e′ in those on dialysis. Table 5 shows that upon additional adjustment for diabetes in established confounder adjusted models in non-dialysis patients, only the central pulse pressure-E/e′ relationship (partial $R = .301$, $p = .02$) remained significant; in each of the respective models, diabetes was independently associated with E/e′ (partial $R = .497$, $p = .002$, partial $R = .501$, $p < .0001$, partial $R = .458$, $p = .002$, partial $R = .501$, $p < .0001$, partial $R = .476$, $p < .0001$, partial $R = .457$, $p = .001$, partial $R = .444$, $p = .001$, and partial $R = .461$, $p = .0001$ for pulse wave velocity, augmentation index log reflected wave pressure, reflection magnitude, central systolic blood pressure, central pulse pressure and forward wave pressure, respectively). Upon additional adjustment for haemoglobin levels in dialysis patients, NT-proBNP was no longer associated with E/e′. The attenuation of arterial function indices-E/e′ relations upon additional adjustment for diabetes in non-dialysis patients and the NT-proBNP-E/e′ association upon additional adjustment for haemoglobin concentrations in dialysis patients is further illustrated in Figure 1.

As shown in the online Supporting Information (Table S1), additional adjustment for erythropoietin concentrations or high phosphate levels in non-dialysis patients did not materially alter the arterial function-E/e′ associations as were given above and in Table 3.

3.5 | Associations of haemoglobin concentrations with E/e′ in dialysis patients

Given the above-mentioned finding that haemoglobin concentrations weakened the NT-proBNP-E/e′ relationship in dialysis patients, we assessed the independent association of haemoglobin concentrations with E/e′. Table 6 shows that haemoglobin concentrations were associated with E/e′ when adjusted for age, sex, waist-height ratio, mean

blood pressure and heart rate (first model). The second model shows that the haemoglobin-E/e′ relationship was independent of left ventricular mass index. In the third model, left ventricular end diastolic volume and central systolic blood pressure were additionally adjusted for to account for preload and afterload, respectively. In the fourth model, mean blood pressure was replaced by systemic vascular resistance to account for arteriolar dilatation. In the fifth model, left ventricular end diastolic volume was omitted to avoid collinearity (Pearson $R = -.500$, $p < .0001$) between arteriolar dilatation and preload. Across the models, haemoglobin was similarly associated with E/e′.

4 | DISCUSSION

To our knowledge, this is the first study that compared the associations of arterial function indices and NT-proBNP concentrations as a reported marker of volume overload,[12] with diastolic function between non-dialysis and dialysis patients with CKD. Our main findings were as follows: (a) CKD status (dialysis vs. non-dialysis) influenced the relationship of pulse wave velocity with E/e′ independent of established confounders (interaction $p = .01$); accordingly, in stratified analysis, arterial stiffness, wave reflection and central pressures were significantly associated with E/e′ in non-dialysis but not dialysis patients; (b) although NT-pro-BNP concentrations were associated with E/e′ in both non-dialysis and dialysis patients, upon entering arterial function measures and NT-proBNP levels simultaneously in regression models, only arterial function indices were associated with E/e′ in non-dialysis patients and only NT-proBNP concentrations was related to E/e′ in dialysis participants; (c) diabetes attenuated the arterial function-E/e′ associations in non-dialysis patients whereas haemoglobin levels attenuated the NT-pro-BNP-E/e′ relations in dialysis patients; (d) in separate models, haemoglobin concentrations were associated with E/e′ independent of preload and afterload measures among dialysis patients. Taken together, these findings suggest that potential determinants of diastolic function may, at least to an extent, differ in non-dialysis compared with dialysis patients.

It is notable that diabetes prevalence and arterial function measures were overall similar among non-dialysis and dialysis patients in the present study. However, as expected, NT-proBNP concentrations were larger and haemoglobin concentrations were smaller in dialysis compared with non-dialysis participants. We believe that volume overload and anaemia may therefore, at least to some extent, override potential effects of impaired arterial function and diabetes on E/e′ in CKD patients once they require dialysis. By contrast, the effects of impaired arterial function and diabetes on E/e′ may outweigh those of volume overload and anaemia among those with milder CKD, that is, non-dialysis patients.

NT-proBNP levels are associated with diastolic function in the general population.[10,26] Increased NT-proBNP production in CKD is reportedly due to volume overload and left ventricular hypertrophy.[12] It is therefore of interest that in the present study, NT-proBNP concentrations were associated with E/e′ ratio independent of established confounders that included left ventricular mass index and end diastolic volume as a marker of cardiac preload,[27] in both non-dialysis and dialysis patients. Strikingly, haemoglobin concentrations that were associated with E/e′ among dialysis patients in bivariate analysis, weakened the NT-proBNP-E/e′ relationship in the respective group. In additional models among dialysis patients, haemoglobin concentrations were associated with E/e′ independent of not only left ventricular mass index but also arterial function, systemic vascular resistance and left ventricular end diastolic volume in dialysis patients.

NT-proBNP levels are most valuable in the management of heart failure patients.[10,27] Increased NT-proBNP production is generally considered to result from an increased ventricular mechanical load.[10,28] However, the mechanisms that regulate natriuretic peptide gene expression are not fully elucidated.[10] In this regard, systemic hypoxia and particularly hypoxia at the cardiomyocyte level comprise stimuli that can directly stimulate natriuretic peptide production.[10,11,28] With regard to haemoglobin concentrations, besides their effects on tissue hypoxia and myocardial fibrosis,[6–8] anaemia is associated with increased NT-pro-BNP concentrations in persons without heart failure and kidney disease.[29] Furthermore, in patients with HFpEF,[21] haemoglobin concentrations are associated with those of NT-pro-BNP and diastolic dysfunction severity. In another study,[22] haemoglobin levels were related to natriuretic peptide concentrations in patients with HFpEF but not those with HFrEF. Intravenous iron therapy reduces NT-proBNP levels in patients with heart failure and chronic kidney disease.[30] These reported data and our current findings suggest that low haemoglobin concentrations may mediate reduced diastolic function through impaired cardiomyocyte oxygenation rather than its haemodynamic effects[4] in dialysis patients.

In this study, diabetes was associated with E/e′ in bivariate analysis among non-dialysis patients. Upon additional adjustment for diabetes, we found that the arterial function-E/e′ relationships were consistently attenuated among non-dialysis patients and only the association between central pulse pressure and diastolic function remained significant ($p = .02$). In a previous study among non-dialysis patients, those with diabetic nephropathy experienced more impaired diastolic function compared with chronic glomerulonephritis participants.[31] Also, in the Chronic Renal Insufficiency Cohort study, carotid-femoral pulse wave velocity was 2 m/s faster in diabetic compared with non-diabetic participants, this within any decade.[20] Our current results suggest that diabetes can impact diastolic function directly as well as through its effects on central pulse pressure in non-dialysis CKD patients.

In non-CKD persons, pulse wave velocity and wave reflection mediate cardiac afterload in early and systole, respectively.[32,33] Both increased pulse wave velocity and wave reflection contribute to an enhanced central pulse pressure and thereby E/e′. [32,33] In line with these reported findings in the non-CKD population, in the present study, each of the respective arterial function measures was associated with E/e′ in non-dialysis patients. Furthermore, the central pulse pressure-E/e′ remained significantly associated with E/e′ even after additional adjustment for diabetes.

Although increased left ventricular mass is generally perceived as an essential intermediate step in the pathophysiology of CKD as well as hypertension induced diastolic dysfunction,[4] impaired diastolic function may antedate left ventricular hypertrophy.[4,9] We found that E/e′ was larger in dialysis compared with non-dialysis patients and this difference was no longer significant after adjustment for left ventricular mass index. Nevertheless, arterial function measure-E/e′, NT-pro-BNP-E/e′ and haemoglobin-E/e′ relationships were consistently unaltered upon adjustment for left ventricular mass index.

Arterial function and NT-proBNP concentrations were not associated with E/A in this study. This is not surprising as E/A cannot reliably distinguish between diastolic function and altered loading conditions.[34] E/e′ is strongly associated with incident cardiovascular events in both CKD and non-CKD patients.[1,35]

The present study has limitations. The study design was cross-sectional, which precludes determining cause-effect relationships. The number of enrolled patients was small, particularly in the dialysis group. Haemoglobin and NT-pro-BNP concentrations were assessed on one occasion only, that is, on the same day that other measurements were made. Conceptually, anaemia may need to be present for prolonged time periods in order for myocardial fibrosis to develop. We may therefore have underestimated the potential impact of low haemoglobin levels on diastolic function in dialysis patients. With regard to NT-pro-BNP concentrations, a single measurement at the time of arterial and cardiac function evaluation is likely most appropriate as CKD patients often experience major changes in volume status over time. All participants were enrolled at a single centre. We did not assess volume status by bioimpedance spectroscopy,[12,14] which may have been useful in the present context. We also did not consistently measure troponin concentrations, which reportedly comprise a useful biomarker of diastolic function in both non-CKD and CKD persons.[36,37] Finally, in non-dialysis patients, addressing proteinuria may have provided further insights. A strength of this investigation is that our conclusions originate in multivariable regression models in which we consistently adjusted for potential established confounders as well as those that were identified in bivariate analysis.

In conclusion, the main determinants of diastolic function may differ in non-dialysis compared with dialysis patients. These include arterial function and diabetes in non-dialysis patients and volume overload and anaemia in dialysis patients.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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