



Coronary artery calcium burden, carotid atherosclerotic plaque burden, and myocardial blood flow in patients with end-stage renal disease: A non-invasive imaging study combining PET/CT and 3D ultrasound

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Background. Imaging-based measures of atherosclerosis such as coronary artery calcium score (CACS) and coronary flow reserve (CFR) as well as carotid atherosclerotic plaque burden (cPB) are predictors of cardiovascular events in the general population. The objective of this study was to correlate CACS, cPB, myocardial blood flow (MBF), and CFR in patients with end-stage renal disease (ESRD).

Methods and results. 39 patients (mean age 53 ± 12 years) with ESRD prior to kidney transplantation were enrolled. MBF and CFR were quantified at baseline and under hyperemia by $^{13}\text{N-NH}_3$ -PET/CT. CACS was calculated from low-dose CT scans acquired for PET attenuation correction. cPB was assessed by 3D ultrasound. Uni- and multivariate regression analyses between these and clinical parameters were performed. Median follow-up time for clinical events was 4.4 years. Kaplan–Meier survival estimates with log-rank test were performed with regards to cardiovascular (CV) events and death of any cause. CACS and cPB were associated in ESRD patients ($r = 0.48$; $p \leq 0.01$). While cPB correlated with age ($r = 0.43$; $p < 0.01$), CACS did not. $\text{MBF}_{\text{stress}}$ was negatively associated with age ($r = 0.44$; $p < 0.01$) and time on dialysis ($r = 0.42$; $p < 0.01$). There were negative correlations between $\text{MBF}_{\text{stress}}$ and CACS ($r = -0.62$; $p < 0.001$) and between $\text{MBF}_{\text{stress}}$ and cPB ($r = -0.43$; $p < 0.01$). Age and CACS were the strongest predictors for $\text{MBF}_{\text{stress}}$. CFR was impaired (< 2.0) in eight patients who also presented with higher cPB and higher CACS compared to those with a $\text{CFR} > 2.0$ ($p = 0.06$ and $p = 0.4$). In contrast to $\text{MBF}_{\text{stress}}$, there was neither a significant correlation

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between CFR and CACS ($r = -0.2$; $p = 0.91$) nor between CFR and cPB ($r = -0.1$; $p = 0.55$). CV event-free survival was associated with reduced CFR and MBF_{stress} ($p = 0.001$ and $p < 0.001$) but not with cPB or CACS.

Conclusions. CACS, cPB, and MBF_{stress} are associated in patients with ESRD. Atherosclerosis is earlier detected by MBF_{stress} than by CFR. CV event-free survival is associated with impaired CFR and MBF_{stress}. (J Nucl Cardiol 2021;28:2660–70.)

Key Words: End-stage renal disease • atherosclerosis • plaque burden • calcium score • myocardial blood flow

Abbreviations

CKD	Chronic kidney disease
CAD	Coronary artery disease
ESRD	End-stage renal disease
MPI	Myocardial perfusion imaging
MBF	Myocardial blood flow
CFR	Coronary flow reserve
cPB	Carotid artery atherosclerotic plaque burden
CACS	Coronary artery calcium score
PD	Peritoneal dialysis
HD	Hemodialysis

See related editorial, pp. 2671–2675

INTRODUCTION

Chronic kidney disease (CKD) is a major risk factor for the development of atherosclerosis and coronary artery disease (CAD) and patients with CKD are at increased risk for myocardial infarction, heart failure, and cardiac death.^{1,2} The pathophysiological interaction between the kidneys and the heart is termed the cardiorenal syndrome (CRS), with especially high risk for cardiovascular events in end-stage renal disease (ESRD) patients.³ Besides CAD of the large coronary arteries which often remains asymptomatic, microvascular disease, i.e., coronary microvascular dysfunction, is a frequent finding in this high-risk group.⁴

However, questions remain of how to assess cardiovascular risk in individual ESRD patients and how to identify patients who may benefit from further testing or a coronary intervention prior to transplantation.^{5,6} In suspected or known CAD the role of non-invasive myocardial perfusion imaging (MPI) in preselecting patients for coronary angiography is well established. Single photon emission computed tomography (SPECT) is a widely used imaging method with good diagnostic accuracy for the detection of relevant epicardial coronary artery disease in CKD patients.⁷ However, microvascular alterations may be missed by SPECT. Thus, quantitative myocardial perfusion positron emission computed tomography (PET) is the method of choice for quantitative MPI, as it additionally quantifies absolute myocardial blood flow (MBF) and coronary

flow reserve (CFR) – increasing diagnostic accuracy and adding prognostic information.^{4,8,9} Recently, global CFR was proven to be an independent factor for risk stratification for all-cause and cardiovascular mortality in ESRD.⁴ Another imaging-derived parameter of atherosclerosis is the coronary artery calcium score (CACS), which also showed independent prognostic value in suspected CAD.^{11–13}

Atherosclerosis – as a systemic disease – also causes carotid artery stenosis and peripheral artery disease.¹⁰ Apart from the calculation of intima to media thickness,^{10,14} carotid ultrasound enables the quantitation of carotid artery atherosclerotic plaque burden (cPB).¹⁵ cPB was the strongest predictor of coronary artery calcium score (CACS) in asymptomatic, otherwise healthy individuals.¹⁶ In the general population, cPB and CACS can serve as imaging biomarkers of future cardiovascular events in asymptomatic adults.¹⁶ However, the relation between myocardial perfusion, CACS, and cPB has not yet been studied in ESRD patients. Therefore, the aim of this study was to correlate the results from myocardial perfusion PET with CACS and cPB in a cohort of ESRD patients prior to kidney transplantation and to evaluate if CFR or absolute MBF are better indicators for coronary artery pathology.

METHODS

Study Population

39 patients (14 female; 36%), mean age 53 ± 12 years (range 26–69) with ESRD on dialysis [12 peritoneal dialysis (PD); 27 hemodialysis (HD)], were prospectively enrolled in the study prior to kidney transplantation. Exclusion criteria were renal failure in a pre-dialysis state, prior kidney transplantation, or known CAD in patients individual history. All patients were asymptomatic at the time of imaging. Detailed patient characteristics are provided in Table 1.

PET Acquisition

A 128-slice PET/CT scanner (Biograph mCT, Siemens Healthcare) was used for PET imaging. Patients fasted for > 4 hour and refrained from caffeine or theophylline for 24 hour before imaging. A low-dose CT scan of the heart (100 kV, 60 mA with CARE Dose, 0.5 second per rotation,

Table 1. Patients characteristics

variable	all patients (N = 39)	PD (N = 12)	HD (N = 27)	p value
Demographics				
Age (years)	53 (26-69)	52 (26-69)	54 (27-69)	0.59
Women	14 (36%)	6 (50%)	8 (30%)	0.29
Duration of dialysis				
< 1 year	14 (36%)	6 (50%)	8 (30%)	0.65
1-3 years	15 (38%)	3 (25%)	12 (44%)	0.41
> 3 years	10 (26%)	3 (25%)	7 (26%)	0.28
Cardiovascular risk factors				
Hypertension	39 (100%)	12 (100%)	27 (100%)	
Diabetes	9 (23%)	4 (33%)	5 (18.5%)	0.24
Hypercholesterolemia	18 (46%)	8 (67%)	10 (37%)	0.11
Family history of CAD	6 (15%)	1 (8%)	5 (18.5%)	0.44
BMI (kg/m ²)	27.2 (18.5-37.1)	26.8 (19.3-32.4)	27.4 (18.5-37.1)	0.69
Medication				
Calcium channel blockers	24 (62%)	6 (50%)	18 (67%)	0.32
β-blockers	30 (77%)	10 (83%)	20 (74%)	0.53
Statins	11 (28%)	5 (42%)	6 (22%)	0.21
ACE inhibitors	7 (18%)	3 (25%)	4 (15%)	0.44
Angiotensin receptor blockers	18 (46%)	6 (50%)	12 (44%)	0.75
Diuretics	23 (59%)	7 (58%)	16 (59%)	0.96
Serum laboratories				
Total cholesterol	193 (128-370)	240 (164-370)	179 (128-236)	0.01
LDL	117 (64-246)	159 (92-246)	103 (64-133)	0.01
Triglycerides	193 (85-224)	212 (122-376)	187 (85-424)	0.59
Hb	11.2 (8.3-13.7)	11.9 (10.0-13.7)	10.9 (8.3-13.4)	0.02
Uric acid	5.9 (1.9-10.5)	5.9 (3.0-9.3)	6.0 (1.9-10.5)	0.81
Imaging parameters				
LVEF rest	54 (29-73)	55 (42-69)	54 (29-73)	0.86
LVEF stress	53 (33-70)	54 (42-69)	52 (33-64)	0.58
Ischemia (% myocardium)	0.7 (0-9)	1.2 (0-9)	0.4 (0-6)	0.36
Scar (% myocardium)	0.1 (0-3)	0 (0)	0.1 (0-3)	0.51
CFR	2.5 (1.4-4.7)	2.6 (1.5-4.7)	2.5 (1.4-3.9)	0.87
MBF stress (ml/g per minute)	2.8 (1.6-4.6)	2.9 (1.8-4.6)	2.7 (1.6-3.9)	0.44
MBF rest (ml/g per minute)	1.2 (0.7-2.2)	1.3 (0.7-2.2)	1.1 (0.7-1.6)	0.35
cPB	277 (0-801)	180 (0-396)	320 (0-801)	0.04
CACS	440 (0-3957)	340 (0-2243)	484 (0-3957)	0.65

CAD, coronary artery disease; BMI, body mass index; ACE, angiotensin converting enzyme; LDL, low density lipoprotein; Hb, hemoglobin; LVEF, left ventricular ejection fraction; CFR, coronary flow reserve; MBF, myocardial blood flow; cPB, carotid plaque burden; CACS; coronary artery calcium score

Pitch 1.2; 3 mm reconstructed slice thickness) for attenuation correction of PET data was acquired during shallow breathing. For the rest study ¹³N-NH₃ (352 ± 38 MBq) was given in an intravenous bolus. List-mode 3-dimensional PET images were acquired for 14 minutes. Infusion of adenosine was started through a separate intravenous line (0.14 µg/kg, 6 minutes) and a second dose of ¹³N-NH₃ (354 ± 39 MBq) was infused at the half time of adenosine infusion, followed by a 14 minutes.

list-mode acquisition. Quality control of PET and CT for attenuation correction was performed. List-mode data were resampled to attenuation-corrected static, electrocardiographically gated, and dynamic images (17 frames; 12 × 10 seconds; 3 × 20 seconds and 2 × 30 seconds). Emission data were corrected for randoms, dead time, scatter, and attenuation. All images were reconstructed iteratively by a 3D attenuation-weighted ordered-subsets expectation

maximization iterative reconstruction algorithm and time-of-flight (OSEM 3D; 2i21s, Gaussian smoothing at 8 mm full-width at half-maximum; zoom of 1).

PET data were analyzed using commercially available software (syngo.PET Myocardial Blood Flow and MI Cardiology; syngo.via; Siemens Healthcare, Germany).

Analysis of Regional Perfusion

Static perfusion images were reangulated to short, horizontal, and vertical long axis slices for visual analysis. Each of the 17 myocardial segments was scored on a scale of 0–4 (normal, mildly, moderately, severely decreased, or absent perfusion) by two independent and experienced readers blinded to other data. Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were calculated. Abnormal perfusion was defined as a $SSS \geq 4$. Significant ischemia was defined as a $SDS \geq 3$. Coronary angiography was performed in these selected cases.

Quantification of MBF, CFR, and Left Ventricular Function

Absolute MBF (ml·g⁻¹·min⁻¹) was calculated from the dynamic stress and rest scans corrected for motion. Automated factor analysis was used to generate arterial input function and myocardial tissue time-activity curves. Hyperemic MBF (MBF_{stress}) was corrected for myocardial ¹³N-NH₃ activity (from the rest study). MBF_{stress} and resting MBF (MBF_{rest}) were calculated by fitting the time-activity curves to a 2-compartment kinetic model as described elsewhere.¹⁷ MBF_{rest} was normalized for cardiac work by dividing by the rate-pressure product and multiplying the result by 10,000.¹⁸ CFR was determined as the ratio of MBF_{stress} to corrected MBF_{rest} . Stress and resting left ventricular ejection fraction ($LVEF_{stress}$ and $LVEF_{rest}$) were calculated from the ECG-triggered PET data using the Corridor 4DM software (Invia, Ann Arbor, USA).

Coronary Artery Calcium Scoring

CACS assessment was performed using the low-dose, non-contrast multidetector CT scans for attenuation correction without prospective electrocardiography-gated acquisition. CACS was calculated by the Agatston method accounting for the area of coronary artery calcification in CT (> 130 Hounsfield units, preset value by the calcium scoring software, Siemens Healthcare, Germany) and expressed as Agatston score¹⁹ into the following categories: ≤ 100 ; 101–400, 401–1000 and > 1000.²⁰

3D Carotid Ultrasound

The Philips iU22 ultrasound system (Philips Healthcare, Bothell, Washington) with a dedicated 3D transducer was used. All scans were performed by physicians with advanced experience in head and neck ultrasound imaging. The protocol

included 3D imaging of the left and right common carotid artery and its bifurcation as far as assessable. All 3D-ultrasound recordings were analyzed using dedicated software for semiautomatic plaque quantification (Philips QLAB-VPQ). Carotid plaque burden (cPB) was expressed in mm³.¹⁶ cPB patients were stratified in the following tertiles: ≤ 154 mm³, 155–344 mm³, and ≥ 345 mm³ (13 patients each).

Follow-Up

Clinical follow-up was performed every 6 months. This included clinical patient interview, laboratory data, and recording of clinical events. End-points were major cardiovascular (CV) events and death from any cause.

Statistical Analysis

Analysis of discrete variables was performed using the Chi squared test. Continuous variables were compared either by a two-sided Student's *t* test for unpaired samples or by one-way analysis of variance (ANOVA) with a Bonferroni/Tamhane correction. Univariate and multivariate logistic regression analyses were performed to test for associations between continuous variables. Pearson's correlation or Spearman-Rho tests were used for the comparison of parametric normally or not normally distributed variables. Variables significantly correlated in the univariate analysis were included in a multivariate stepwise regression model. Two-sided *p* values < 0.05 were considered significant. Kaplan–Meier survival curves with log-rank test were performed for the analysis of patients survival. Analyses were performed with SPSS software package (IBM SPSS Statistics, Version 22.0. Armonk, NY).

All procedures performed were in accordance with the ethical standards of the institutional and research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments. The study was approved by the institutional review board of the Medical Association of Westfalen-Lippe and the Faculty of Medicine, University of Münster. Informed consent was given by all patients.

RESULTS

Detailed characteristics of the patient cohort are provided in Table 1.

CACS and cPB

22 (56%) individuals had a CACS < 100, eight patients (21%) had a CACS between 101 and 400 and nine patients (23%) had a CACS > 401 (six of which > 1000). CACS was not correlated with age ($r = 0.27$; $p = 0.97$; Figure 1A) or with the time on dialysis ($r = 0.28$; $p = 0.08$; Figure 1B). CACS did not differ between the PD and HD subgroups (Table 1).

cPB correlated with age ($r = 0.43$; $p = 0.007$; Figure 2A) but not with the time on dialysis

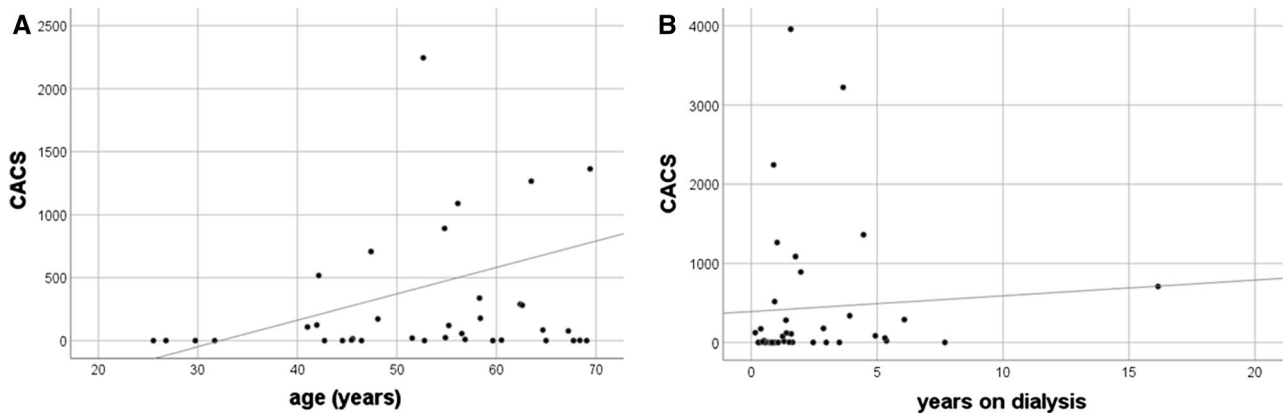


Figure 1. Scatterplot diagrams of CACS in correlation to age (A) and time on dialysis (B).

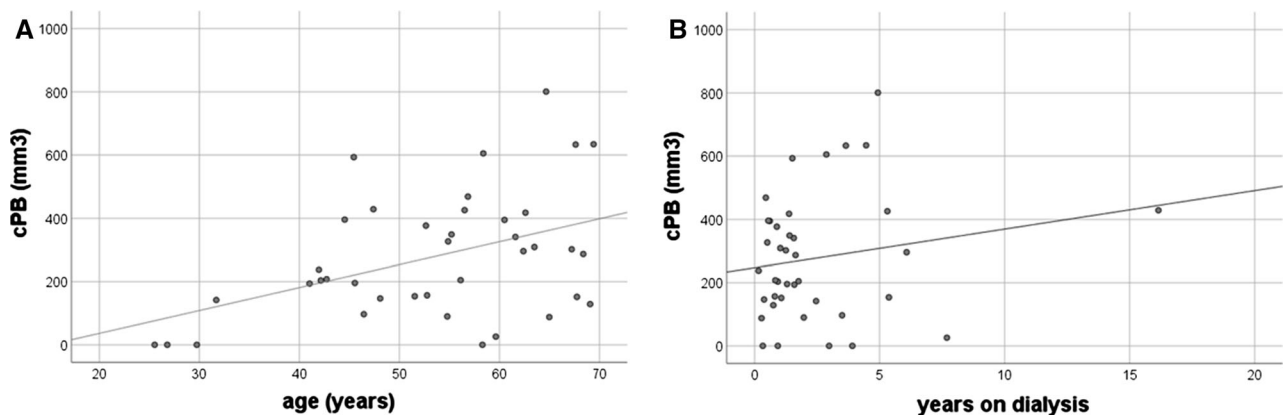


Figure 2. Scatterplot diagrams of cPB in correlation to age (A) and time on dialysis (B).

($r = 0.18$; $p = 0.28$; Figure 2B). cPB was significantly higher in the HD as compared to the PD subgroup (Table 1). cPB showed a moderate association with CACS ($r = 0.48$; $p = 0.002$).

MBF, CFR, and Left Ventricular Function

MBF_{rest} ranged from 0.7 to 2.2 ml·g·min and MBF_{stress} ranged from 1.6 - 4.6 ml·g·min. Individuals with MBF_{stress} < 2 ml·g·min (N = 3) presented with higher cPB (393 ± 219 vs 268 ± 197 mm³) and higher CACS (2136 ± 1583 vs. 299 ± 671) compared to those with MBF_{stress} > 2 ml/g/min. Mean MBF_{stress} did not differ between patients on PD or HD (Table 1). There was a negative correlation between MBF_{stress} and CACS ($r = -0.62$; $p < 0.0001$; Figure 3A) and between MBF_{stress} and cPB ($r = -0.43$; $p = 0.007$; Figure 3B). MBF_{stress} impaired with increasing CACS and cPB, respectively. In contrast, CFR remained stable with increasing CACS and cPB (Table 2), since MBF_{rest}

decreased. Moreover, there was a moderate correlation between MBF_{stress} and LVEF_{rest} ($r = 0.32$; $p = 0.05$) but there was no correlation between CFR and LVEF_{rest} ($r = 0.14$; $p = 0.94$).

MBF_{stress} was negatively associated with age ($r = 0.44$; $p < 0.01$) and the time on dialysis ($r = 0.42$; $p < 0.01$). MBF_{stress} decreased from 3.16 ± 0.58 ml·g·min. in patients < 1 year on dialysis to 2.46 ± 0.56 ml·g·min. in patients > 3 years on dialysis ($p < 0.05$; Figure 4A). In contrast, CFR did not change ($p = 1.0$; Figure 4B).

CFR ranged from 1.4 to 4.7 in the total cohort. There were also no significant differences between patients on PD or HD (Table 1). CFR was impaired (< 2.0) in eight patients (20%; $p = 0.47$). These individuals also presented with higher cPB (394 ± 169 vs 247 ± 197 mm³) and a higher CACS (679 ± 1119 vs 379 ± 833) compared to those with a CFR > 2.0 ($p = 0.06$ and $p = 0.4$, respectively). There was neither a significant correlation between CFR and CACS

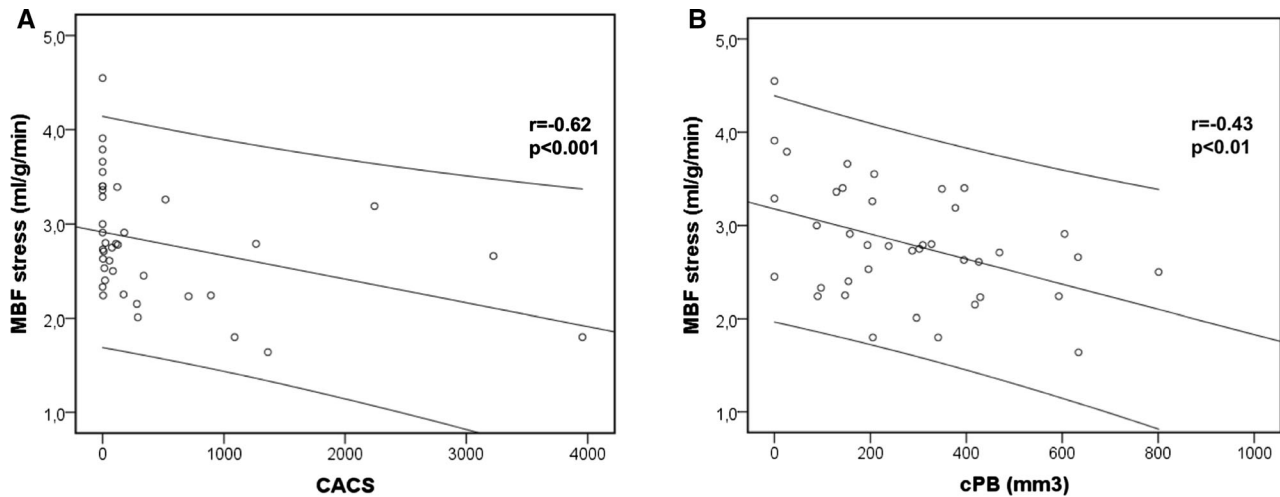


Figure 3. Correlation between absolute MBF_{stress} and CACS (A) and cPB (B), respectively.

Table 2. CFR, MBF (rest, stress), and Hb dependent on CACS and cPB

	Gender		Age Years	MBF _{rest} (ml/g/ min)		MBF _{stress} (ml/g/ min)		CFR global		Hemoglobin	
	Male (N)	Female (N)		Mean	SD	Mean	SD	Mean	SD	Mean	SD
CACS categories											
0–100	9	13	51.5 ± 13.9	1.3	0.3	3.0	0.6	2.5	0.7	11.2	1.1
101–400	7	1	53.5 ± 8.7	1.1	0.2	2.6	0.5	2.5	0.8	10.8	1.8
401–1000	3	0	48.1 ± 6.4	1.0	0.2	2.6	0.6	2.7	0.5	11.9	1.5
> 1000	6	0	61.8 ± 6.5	1.0	0.3	2.3	0.6	2.6	1.1	11.7	1.7
cPB tertiles											
First	5	8	48.8 ± 15.7	1.2	0.3	3.1	0.7	2.7	0.7	10.9	1.1
Second	8	5	53.9 ± 10.2	1.2	0.3	2.7	0.5	2.3	0.5	11.3	1.4
Third	12	1	57.1 ± 8.0	1.1	0.4	2.6	0.5	2.7	0.9	11.4	1.7

CFR, coronary flow reserve; MBF, myocardial blood flow; cPB, carotid plaque burden; CACS, coronary artery calcium score; SD, standard deviation

($r = -0.2$; $p = 0.91$) nor between CFR and cPB ($r = -0.1$; $p = 0.55$). There were inverse correlations between MBF_{rest} and hemoglobin ($r = -0.39$; $p = 0.015$) and between CFR and hemoglobin ($r = 0.32$; $p = 0.048$).

Significant correlations are summarized in Table 3. In a stepwise multivariate regression analysis hemoglobin proved as strongest predictor for MBF_{rest} . Age and CACS were the strongest predictors for MBF_{stress} whereas only age was predictive for cPB.

Ischemia

Reversible stress perfusion defects were observed in four patients (10%). In these cases ischemia ranged from 4 to 9%. Global CFR was ≥ 2.0 in all cases and MBF_{stress} was impaired (< 2.0 ml·g·min) in only one case. None of the patients had significant coronary artery stenoses $> 50\%$ in subsequent coronary angiography.

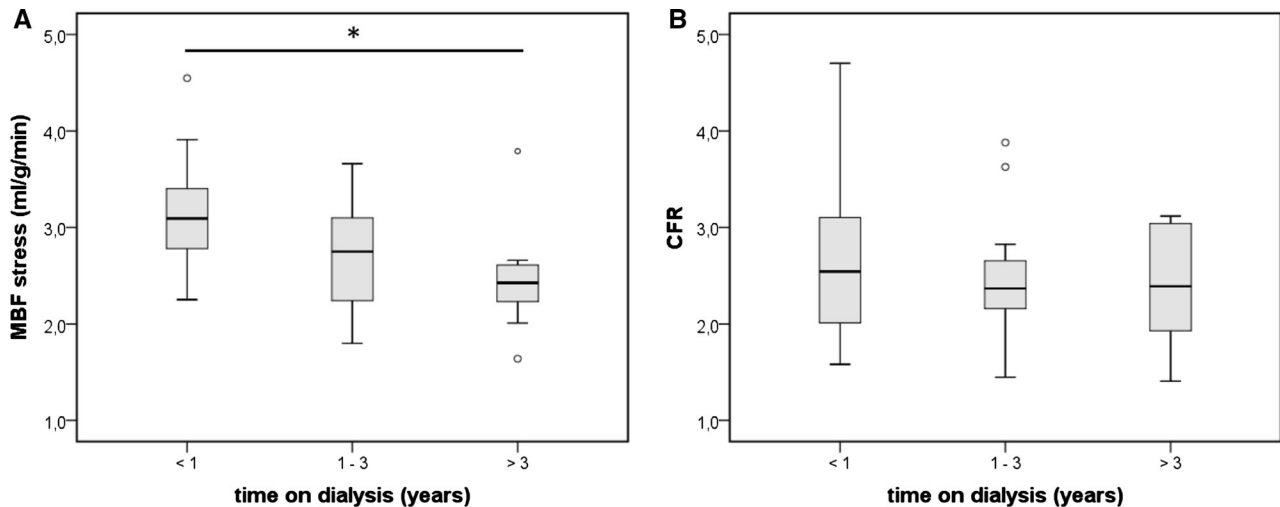


Figure 4. MBF_{stress} (A) and CFR (B) dependent from the time on dialysis. * indicates significant differences ($p < 0.05$).

Table 3. Summary of significant correlations

Parameter	Univariate	
	cc	p value
CFR _{global}		
Hb	0.318 ^b	0.048
MBF _{rest}		
Hb	- 0.386 ^b	0.015
CACS	- 0.424 ^b	0.007
MBF _{stress}		
Age	- 0.439 ^a	0.005
cPB	- 0.425 ^a	0.007
CACS	- 0.619 ^b	<0.0001
Time from first dialysis	- 0.419 ^b	0.008
Summed years of dialysis	- 0.413 ^b	0.009
cPB		
Age	- 0.425 ^a	0.007
CACS	0.476 ^b	0.002
CACS		
MB_{stress}	- 0.619 ^b	<0.0001
MB_{rest}	- 0.424 ^b	0.007
cPB	0.476 ^b	0.002

Variables independently correlated in a multivariate analysis are presented in bold type

Hb, hemoglobin; CACS, coronary artery calcium score; cPB, carotid plaque burden; MBF, myocardial blood flow; cc, correlation coefficient

^aPearson's r

^bSpearman's rho

Predictive Value

10 patients (26%; two men, eight women) presented with CACS < 100 and cPB < 154 mm³ (= lower tertile limit), whereas 29 patients (74%; 23 men, six women) presented with either CACS > 100 or cPB > 154 mm³ or both. None of the patients with low CACS and cPB presented with impaired CFR or MBF_{stress}. Among the patients with high CACS and/or cPB only eight patients (27.5%) showed impaired CFR and three (10%) impaired MBF_{stress}. Patients with low CACS and cPB were older by trend (55.3 ± 8.8 vs 47.3 ± 17.7 years; $p = 0.2$) but there were no differences regarding the time on dialysis (2.4 ± 3.1 vs 2.5 ± 2.4 years; $p = 0.91$).

Median follow-up time was 4.4 years (mean 3.6 ± 1.1 years). In the follow-up, there were four major cardiovascular events (MACE): 2 myocardial infarctions, 1 stroke, and 1 pulmonary embolism. There were six deaths, all by non-cardiovascular causes. CV event-free survival was associated by reduced CFR and MBF_{stress} ($p = 0.001$ and $p < 0.001$) but not with cPB or CACS (Figure 5). On the other hand overall survival could not be predicted by any of these variables (all $p > 0.25$).

DISCUSSION

We investigated the association between quantitative MBF, CACS and cPB in patients with ESRD assigned for kidney transplantation evaluation. Our main

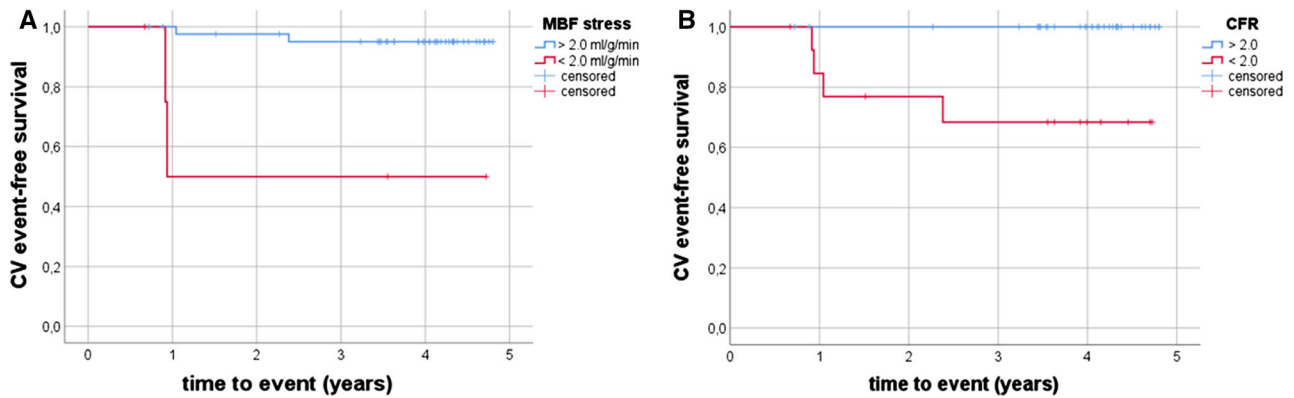


Figure 5. Kaplan-Meier plots showing CV event-free survival in order to MBF_{stress} (A) and CFR (B).

findings were: MBF_{stress} but not CFR was significantly correlated with CACS and cPB. The strongest predictors for MBF_{stress} were CACS and age, whereas cPB was best predicted by age. On the other hand the strongest predictor for CACS was MBF_{stress}. Particularly the combination of low CACS and low cPB resulted in a high negative predictive value for preserved MBF and CFR.

The BioImage Study investigated the relationship of several (imaging) biomarkers and cardiovascular outcome in a large population of asymptomatic adults without known cardiovascular or renal disease.¹⁶ Here, a distinct correlation between CACS and cPB was described. In another study cPB was shown to be predictive of mortality and to occur more frequently in patients on HD than on PD,²¹ the latter also observed in our study. In line with the BioImage Study, we found a significant correlation between CACS and cPB also in patients with ESRD. In a multivariate regression analysis the strongest predictors for CACS and cPB were MBF_{stress} and age. Thus, the results of our study are in line with the current understanding of atherosclerosis as a systemic and diffuse disease. Interestingly, cPB was only moderately associated with and not predictive of MBF_{stress} in the multivariate analysis. Instead, CACS turned out to be predictive for MBF_{stress}. This is not surprising since CACS reflects the extent of coronary artery atherosclerosis which directly influences myocardial perfusion and the degree of atherosclerosis in the carotid arteries does not necessarily preclude coronary atherosclerosis with a similar extent. Our findings indicate that none of the imaging parameters is able to predict the others with sufficient accuracy in patients with ESRD. Importantly, CACS is not limited to intimal calcification but also superposed by smooth muscle cell mediated, metabolic media calcification in patients with ESRD.²² This also could explain the only moderate

correlation between CACS and cPB, since cPB is rather a marker of ‘classical’ atherosclerosis resulting from subintimal plaque development. Due to this different pathophysiology, the clinical value of CACS in CKD patients still remains controversial.¹³ Interestingly, CACS did not correlate with age. This finding may be explained by the different pathophysiology of media calcification but also (at least partly) by the distinctly younger age of patients studied here as compared with a classical CAD population.

Another factor associated with MBF_{stress} was the time on dialysis. This finding supports the assumption that the duration of renal replacement therapy has a strong impact on myocardial perfusion, mainly due to rarefaction of small intramyocardial vessels.^{23–25} We found impaired CFR in 20% of our patients, which is less than reported in other studies³³ and most probably due to the relatively young study cohort. Prior investigations have suggested that CKD is associated with abnormal coronary vasodilator function,²⁶ which results from multiple mechanisms including decreased capillary density,²⁷ vascular remodeling,²⁸ and endothelial dysfunction.^{29,30} Early stage microvascular disease may be the reason for impaired MBF_{stress} in our patient cohort. This can be assumed since global CFR was still preserved and significant epicardial CAD could be excluded by angiography in selected cases with mild to moderate regional ischemia. Thus, we interpret the data in that way that regional ischemia is most probably related to regional microvascular dysfunction, since technical image artifacts could be excluded. This can be missed by the assessment of *global* CFR.

Although preliminary results based on a rather small patient cohort should always be interpreted with care, our results indicate that the combination of low cPB and low CACS may have a high negative predictive value with regards to the exclusion of CAD. On the

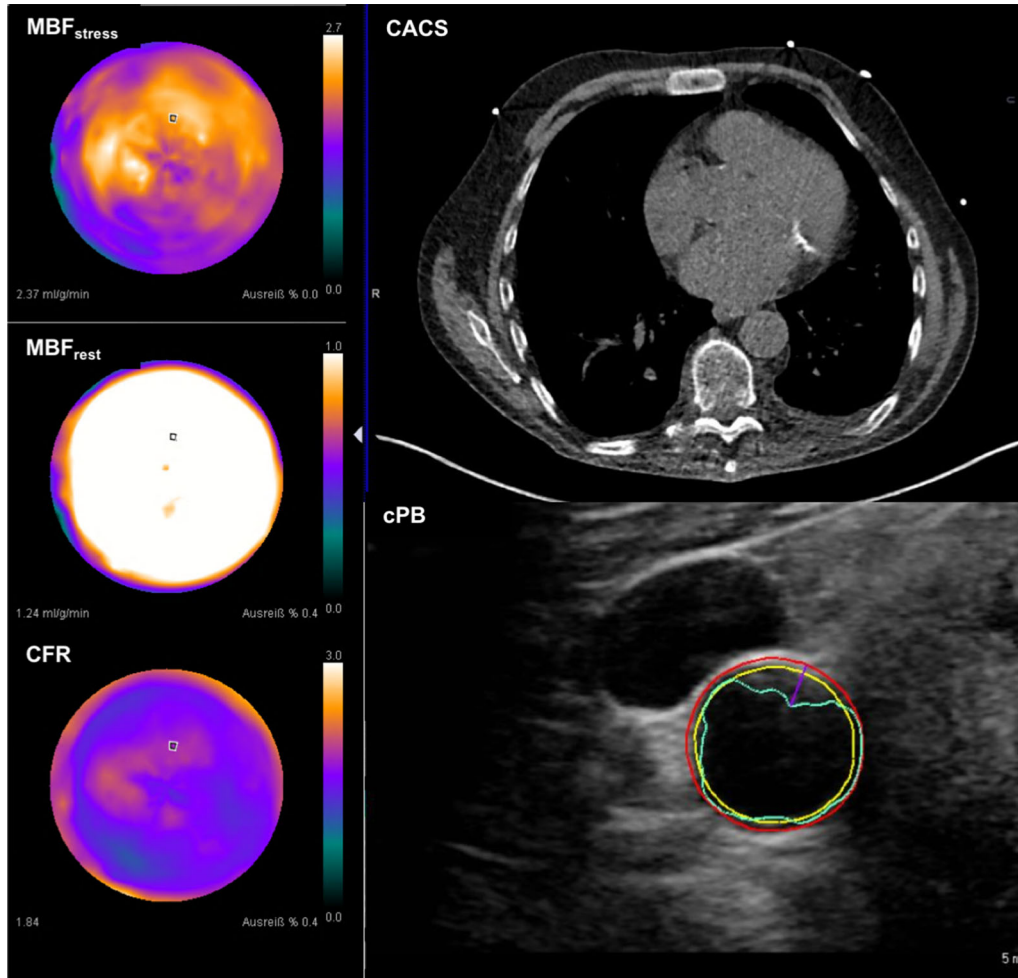


Figure 6. Example of a patient with globally impaired CFR (1.7) mostly due to an elevated MBF_{rest} (1.4 ml·g·min⁻¹). MBF_{stress} was 2.0 ml·g·min⁻¹, moderate CACS- and cPB values (Agatston score: 289; cPB: 296 mm³).

other hand the positive predictive value of CACS and cPB for CFR and MBF was low. Thus, it would be worth to evaluate in a larger study if the assessment of cPB and CACS may replace MPI in the evaluation prior to kidney transplantation listing in cases of normal findings. But on the other hand in this context importantly, our results indicate that cardiovascular event-free survival may be not predicted by cPB or CACS but only by CFR and MBF_{stress} . These findings are in line with previous study results in distinctly larger ESRD patient cohorts already showing the prognostic value of CFR in this particular patient group, although in these studies a lower cutoff value for CFR than in our study was used.^{4,31}

Notably striking was the observation that CFR was independently associated with the current Hb value and was neither correlated with CACS or cPB nor with age

or the time on dialysis. Increased MBF_{rest} has been already observed in mild CKD and was correlated with the degree of GFR.³² Anemia induces a compensatory increase in MBF_{rest} via increased nitric oxide release³³ which naturally also affects CFR. Although in former investigations impaired CFR was highly prevalent in patients with CKD (4, 35; example Figure 6), our results suggest that MBF_{stress} may be a better parameter for the early assessment of microvascular dysfunction. Variability of MBF_{rest} in the individual person is widely known and is probably related to differences in myocardial work load.³⁵ Although corrected for cardiac work increased MBF_{rest} due to other factors as metabolic oxygen demand or an enhanced activation of the sympathetic nervous and renin–angiotensin–aldosterone system³⁴ which is chronically activated in patients with ESRD cannot be ruled out. Therefore, when interpreting

CFR, changes in MBF_{rest} due to alterations in metabolic demand need to be considered.^{36–38} Altogether, the results of our study raise the question if absolute MBF_{stress} may be an earlier and more robust marker for CAD in patients with ESRD than CFR. This hypothesis is additionally supported by the finding that only MBF_{stress} was significantly correlated with $LVEF_{(rest)}$ but not CFR. In former studies absolute MBF_{stress} already shown to be more accurate than CFR in detecting CAD in non-CKD patients.^{35,37} Interestingly, MBF_{rest} was higher in patients without or minimal CACS and low cPB, a finding which is most probably caused by the higher frequency of females in these groups. Most studies report of higher MBF_{rest} in females, although the mechanisms of this phenomenon remain uncertain.³⁸

Study Limitations

The small size of the patient cohort is certainly a limitation of our study. Furthermore, the study population was young and time on dialysis was relatively short. These factors may explain the relatively low number of pathological findings. Another limitation is the use of a non-ECG-triggered, low-dose CT for CACS although CACS on that basis is feasible.^{39,40} Thus, a dedicated state-of-the-art CACS-CT was not performed additionally in order to avoid futile additional radiation exposure.

NEW KNOWLEDGE GAINED

Our results indicate that MBF_{stress} is a marker of subclinical atherosclerosis in patients with ESRD, whereas CFR may miss early stages of vascular dysfunction in this patient cohort. Nevertheless, impaired CFR and MBF_{stress} are predictors for CV event-free survival whereas cPB and CACS may be not.

CONCLUSIONS

Although CACS and cPB as parameters of coronary and systemic atherosclerosis are associated in patients with ESRD, only absolute MBF_{stress} but not CFR correlates with CACS and cPB. Furthermore, MBF_{stress} impairs with increasing time on renal replacement therapy. MBF_{rest} and CFR are regularly influenced by actual hemoglobin values. Thus, MBF_{stress} may serve as a robust parameter for the detection of microvascular disease in patients with ESRD than CFR.

Overall, our results indicate that quantitative MPI cannot be replaced by the assessment of CACS or cPB only. Nevertheless, there may be a good negative

predictive value. CV event-free survival is associated with impaired CFR and MBF_{stress} only.

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Disclosure

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