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Forearm reactive hyperemia and mortality in end-stage renal disease

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Forearm reactive hyperemia and mortality in end-stage renal disease.

Background. Reports on the general population indicated that decreased endothelial-mediated vasodilation has a prognostic impact on cardiovascular (CV) morbidity and mortality. Flow-dependent vasodilation of conduit arteries and ischemia-induced forearm reactive hyperemia are impaired in end-stage renal disease (ESRD). Whether deterioration of vasodilator function in ESRD patients has a prognostic impact has not been documented. The aim of this study was to determine whether the impaired forearm postischemic vasodilation is an independent predictor of mortality in ESRD patients, independently from CV end-organ damages, which are usually associated with decreased vasodilatory response.

Methods. Common carotid artery intima-media thickness (CCA-IMT), aortic stiffness (pulse wave velocity - PWV), and LV mass (LVM) were determined for 78 stable ESRD patients on hemodialysis. Forearm postischemic vasodilation [flow debt repayment (FDR)] was measured by venous plethysmography. All-cause mortality served as the outcome variable over a median follow-up of 60 ± 27 months.

Results. Twenty-four deaths occured (16 of CV origin). According to Cox regression adjusted for age, CCA-IMT, LVM, and PWV, all-cause mortality was independently associated with decreased FDR (RR 0.69 for every 10% increase; 95% CI 0.56–0.85; $P = 0.0006$) and increased aortic PWV (RR 1.16 for 1 m/s increase; 95% CI 1.04–1.29; $P = 0.0091$).

Conclusion. Our data indicate that lower postischemic forearm reactive hyperemia is associated with all-cause mortality of ESRD patients, independently of the presence of end-organ damage such as LVH or arteriosclerosis.

Several reports on the general population have indicated that decreased endothelial-mediated vasodilation of conduit arteries has a prognostic impact on cardiovascular (CV) morbidity and mortality [1–5], and is associated with CV end-organ damage such as left ventricular hypertrophy (LVH) and carotid artery wall thickening [6–8]. Flow-dependent vasodilation of peripheral conduit arteries and ischemia-induced forearm reactive hyperemia are impaired in ESRD patients, and are also associated with CV end-organ damage such as LVH, highly calcified atherosclerosis, arterial stiffening, and increased carotid artery intima-media thickness (IMT) [9, 10]. All of the above-mentioned end-organ damages are associated with mortality in these patients [11–14]. The present study was designed to determine whether the alterations in ischemia-induced hyperemic response evaluated noninvasively by forearm postichemic vasodilation has an end-organ damage-independent impact on mortality in ESRD patients.

Key words: vasodilation, endothelium, kidney, mortality.

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METHODS

Subjects

Patients followed in a single unit were included in the study between the September 1, 1994 and May 31, 1996, and were followed-up until September 30, 2002, the reference date for analysis of survival time. Patients were eligible for inclusion when: (*1*) they had been on hemodialysis (HD) at least for 3 months (58 ± 21 months; mean ± SD; range 10–84); (*2*) they had no clinically evident cardiovascular disease (CVD); and (*3*) they agreed to participate in the study which was approved by our Institutional Review Board. In all, 78 (54 males and 24 females) patients fulfilled the entry criteria. Patients who underwent renal transplantation ($N = 5$) and patients who moved away ($N = 1$) were censored on the day of transplantation or departure. All but 6 patients were Caucasian, and 7 patients had diabetes mellitus. The follow-up was 60 ± 27 months (range 10–96 months). Data on mortality were obtained for the entire cohort. The age off the cohort at inclusion was 54 ± 15 years (range 23–81 years). During follow-up, all patients were dialyzed using the same techniques, as previously reported in detail [15]. Patients received epoietin when necessary to maintain predialysis

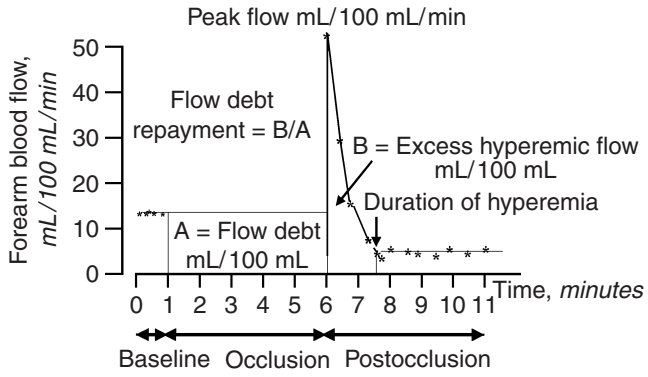

Fig. 1. Schematic representation of a reactive hyperemic response in the human forearm blood flow after 5 minutes of ischemia. See **Methods** for definitions.

hemoglobin level between 10–12 g/dL, and 60 patients received antihypertensive therapy [angiotensin-converting enzyme (ACE) inhibitor, calcium channel blocker, or β-blocker alone or in combination].

Data collection and hemodynamic measurements

Brachial blood pressure (BP) was measured with a mercury sphygmomanometer after 15 minutes of recumbency. Phases I and V of the Korotkoff sounds were taken as the systolic (SBP) and diastolic BP (DBP), respectively. Five measurements taken at 2-minute intervals were averaged. Common carotid artery intima-media thickness (CCA-IMT) was measured on the far wall with a high-resolution B-mode 7.5-MHz transducer (Wall-Track System; Pie Medical, Maastricht, The Netherlands) with computer-assisted acquisition, storage, and processing with specific software (Eurequa; TSA, Meudon, France) [16]. Aortic pulse wave velocity (PWV) was determined using transcutaneous Doppler flow recordings with a nondirectional Doppler unit (10 MHz; SEGA M842, Paris, France) and the foot-to-foot method from the CCA and the femoral artery in the groin [15]. Echocardiographic determination of LV mass according to the Penn convention [17] was performed using a Hewlett-Packard (Palo Alto, CA, USA) Sonos 100 device equipped with a 2.25-MHz probe.

Forearm blood flow (FBF in mL/100 mL/min) was measured by venous occlusion plethysmography (Perivein; Janssens, Belgium), as previously described [10](Fig. 1). A mercury strain gauge was placed on the largest part of the arm distal to the humeral epicondyle. A venous occlusion cuff was placed around the upper arm and connected to an automatic inflator. An arterial occlusion cuff was placed proximal to the venous cuff and the gauge. After control flow measurements, the arterial cuff was inflated to 300 mm Hg for 5 minutes. Ten seconds before deflating the arterial cuff, the venous cuff was inflated to 50 mm Hg. At time "zero," the arterial cuff was deflated and the FBF was immediately measured, with repetition of measurements every 15 seconds until resting flow levels were reached, then every minute until 5 minutes. The following parameters were determined (Fig. 1): the flow debt (A, area under the curve between the start and end of ischemia period), the postischemic peak flow, the duration of the hyperemia, the excess hyperemic flow (B, area under the curve between the release of ischemia and duration of hyperemia), and the flow-debt repayment (FDR = B/A). All measurements were made with a wrist cuff inflated at 20 mm Hg above the SBP. Forearm hemodynamic parameters and response to reactive hyperemia in age and blood pressure matched nonuremic subjects were previously published [10].

Laboratory methods

Blood was obtained before hemodynamic investigations after an overnight fast. The plasma was separated without delay at 4°C in a refrigerated centrifuge and stored at −20°C until determinations were performed. Routine biochemical parameters were determined using standard methods, and serum albumin, plasma fibrinogen, and C-reactive protein (CRP) were measured nephelometrically. Total plasma homocysteine was assessed with fluorometric high-performance liquid chromatography.

Statistical analysis

Data are expressed as mean ± SD. Information compiled from the questionnaire filled out at entry into the study included personal and family histories. Causes of death (WHO International Classification of Disease, 9th edition) were obtained from death certificates, hospital records forms, and autopsy data reviewed by the authors. During the follow-up period, we recorded 24 deaths, including 16 fatal CV events.

Univariate and multivariate correlations studies were done using least-squares method. The outcome event studied was all-cause mortality. The primary analyses concerned the survival curves and Cox proportional hazards model. Survival was estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. Factors prognostic of survival were identified with the use of the univariable Cox proportional hazards regression model. The assumption of proportional hazards over the time and assumption of linearity was verified before the analyses and was met by all covariates. Due to high colinearity between several variables, data reduction procedure was used to determine the final Cox model. The number of variables in the model was reduced using automatic forward stepwise selection algorithm. The variable with the strongest association with the outcome was entered first, followed by the next strongest, until all variables that are related to the outcome ($P < 0.05$) are entered into the model. Any variable that has been entered but is no longer significant after other variables have been added to the model is sequentially

Table 1. Clinical and hemodynamic characteristics of ESRD patients

Variable	ESRD
Body mass index *kg/m²*	24 ± 4
Systolic blood pressure *mm Hg*	148 ± 28
Diastolic blood pressure *mm Hg*	82 ± 14
Left ventricular mass index *g/m²*	181 ± 42
Carotid intima-media thickness *μm*	800 ± 98
Aortic pulse wave velocity *m/s*	11.2 ± 3.2
Baseline forearm blood flow *mL/100 mL/m*	4 ± 1.3[a]
Peak forearm blood flow *mL/100 mL/m*	28 ± 10[a]
Flow debt repayment %	87 ± 32[a]
Duration of hyperemia *seconds*	103 ± 40[a]
Tobacco *pack/year*	12 ± 18
Hemoglobin *g/L*	108 ± 21
Total cholesterol *mmol/L*	5.2 ± 1.2
Triglycerides *mmol/L*	2 ± 1
Serum albumin *g/L*	40 ± 2.2
Serum CRP *mg/L*	11.2 ± 12
Homocysteine *μmol/L*	36.7 ± 14.5

FBF is forearm blood flow. Duration of hyperemia 127 ± 36 (seconds). Baseline FBF 3.5 ± 1.3 (mL/100 mL/m); peak FBF 29.2 ± 9.1 (mL/100 mL/m); Flow debt repayment 116 ± 31(%).

[a]Normal values for age- and blood pressure-matched nonuremic subjects [10].

deleted. The following variables were tested (with duration of HD at inclusion as a time entry variable): aortic PWV, FDR, CRP, CCA-IMT, age, and LV mass index. Variables were considered to be significant for $P < 0.05$ in the final multivariable model.

All tests were performed using NCSS 2001 and SAS software (J. Hintz, Kaysville, Utah, USA).

RESULTS

The clinical and hemodynamic characteristics are shown in Table 1. Many of the studied parameters were correlated among themselves (Table 2).

Outcome and prognostic impact of FDR

During follow-up, 24 deaths occurred (16 of CV origin). RR and 95% CI for different variables with univariable Cox regression and after adjustment for confounding variables are shown in Table 3. After the adjustment aortic PWV and FDR emerged as being the only two variables independently associated with all-cause mortality. Figure 2 shows the probability of all-cause survival according to median value of FDR.

DISCUSSION

The salient result of this study is the demonstration that ESRD patients have significantly impaired vascular adaptation to ischemic stimuli and that lower postischemic forearm vasodilation is an independent predictor of all-cause mortality. The two independent prognostic factors for mortality are impairments of large artery function, characterized by increased aortic stiffness, and impairment of the microcirculation characterized by lower FDR. This association existed after adjustment for CV end-organ damage, including LVH and CCA-IMT.

In many studies analyzing the association between different vasodilatory responses and outcomes, the Cox proportional analyses were adjusted to conventional risk factors, such as age, sex, BP, blood lipids, diabetes, smoking, or the extent of vessel disease [1–5]. Nevertheless, in patients with hypertension and CVD, arterial dysfunction (including reactive vasodilation) is also associated with markers of end-organ damage such as CCA-IMT, LVH, and extent of intramural plaque [6–8]. Because all of these end-organ damages were considered to be risk factors independently associated with the prognosis, the exact relevance and independence of arterial vasodilatory responses still needs to be confirmed. This remark is especially relevant for ESRD patients, in whom it has been shown that (according to the variables introduced into the Cox models) the LVH, the CCA-IMT, aortic arteriosclerosis, or low-grade systemic inflammation were independent predictors of mortality [11–14]. As shown herein, all of these parameters were also associated with lower FDR (Table 2), and the proportional hazards model had to be adjusted not only to conventional risk factors but also to the extent of end-organ damage. Our data show that the relevance of impaired postischemic hyperemia as a prognostic factor was significant after the adjustment for end-organ damage such as LVH or CCA-IMT.

Several studies on general populations have shown that the decrease of coronary or forearm endothelium-mediated vasodilation is associated with the occurrence of CV events in follow-up studies. Using coronary angiography and determination of endothelium dependent flow reserve, Al Suwaidi et al [1] showed higher incidence of CV events in patients with severe endothelial dysfunction, assessed as microcirculatory response to acetylcholine. Similar results were obtained by studying coronary vasomotor response [2]. Additional information was provided by Halcox et al [5], who showed that epicardial and microvascular coronary endothelial dysfunction independently predict acute CV events in patients with and without coronary artery disease (CAD). The prognostic value of endothelial dysfunction was also demonstrated using less invasive methods, such as forearm endothelial dysfunction evaluated by strain-gauge plethysmography and intra-arterial infusions of acetylcholine in patients with stable CAD or uncomplicated hypertension [3, 4].

While the response of large conduit arteries to ischemia is mediated by endothelium-mediated increase in arterial diameter and/or flow velocity, whether decreased postischemic hyperemia observed in the present study reflects endothelial dysfunction in ESRD patients is less clear. Myogenic, neural, and accumulation of vasodilator substances, such as adenosine, prostaglandins, and/or ischemic metabolites, play critical roles in the reactive hyperemic response due to transient interruption of the blood supply. The adjustment of the microcirculation to ischemia is also mediated by recruitment of microvessels.

Table 2. Correlation matrix report: FDR as a dependent variable

	Age	SBP	Aix	PWV	SAlb	CCAIMT	LV mass	CRP	FDR
Age *years*	1.000								
SBP *mm Hg*	0.116	1.000							
Aix %	0.376[b]	0.439[c]	1.000						
PWV *m/s*	0.605[c]	0.411[c]	0.458[c]	1.000					
Salb *g/L*	−0.476[c]	−0.199	−0.379[b]	−0.423[c]	1.000				
CCAIMT μ*m*	0.587[c]	0.401[c]	0.412[c]	0.620[c]	−0.346[b]	1.000			
LVM g/m^2	0.178	0.379[c]	0.262[a]	0.347[b]	−0.120	0.565[c]	1.000		
CRP *mg/L*	0.543[c]	0.193	0.315[a]	0.557[c]	−0.639[c]	0.527[c]	0.228[a]	1.000	
FDR %	−0.489[c]	−0.300[b]	−0.492[c]	−0.544[c]	0.511[c]	−0.561[c]	−0.262[a]	−0.517[c]	1.000

Abbreviations are: SBP, systolic BP; Aix, augmentation index; PWV, pulse wave velocity; Salb, serum albumin; CCAIMT, common carotid artery intima-media thickness; LVM, left ventricular mass; T-Ch, total cholesterol; CRP, C-reactive protein; FDR, flow debt repayment.

[a] $P < 0.05$.

[b] $P < 0.01$.

[c] $P < 0.001$.

Table 3. Cox regression for all-cause mortality in ESRD patients

Variable	RR and 95% CI	*P* value	Wald Z-value
UNIVARIABLE			
Age *years*	1.05 (1.02–1.09)	0.0025	3.020
Gender *0-M, 1-F*	0.64 (0.24–1.75)	0.389	−0.980
Diabetes *0-no, 1-yes*	2.23 (0.65–7.60)	0.203	0.712
Body mass index kg/m^2	1.04 (0.93–1.16)	0.477	1.274
Duration HD *months*	1.0 (0.99–1.02)	0.919	1.056
Systolic BP (mmHg)	1.02 (1.0–1.03)	0.0321	2.128
Diastolic BP (mmHg)	0.97 (0.93–1.01)	0.081	−1.749
LV mass index (g/m^2)	1.02 (1.01–1.03)	0.0212	2.390
Carotid IMT μ*m*	1.02 (1.01–1.04)	0.0006	3.524
Aortic PWV *m/s*	1.29 (1.17–1.42)	0.00001	4.979
Flow debt repayment (10%)	0.59 (0.48–0.73)	0.00001	−4.786
Smoking *pack/years*	1.03 (1.01–1.05)	0.0004	3.519
Hemoglobin *g/L*	0.96 (0.87–1.05)	0.363	−0.938
Total cholesterol *mmol/L*	1.10 (0.75–1.62)	0.751	0.495
HDL-C *mmol/L*	3.13 (0.90–10.9)	0.0728	1.798
LDL-C *mmol/L*	1.01 (0.57–1.63)	0.959	0.052
Triglycerides *mmol/L*	1.18 (0.82–1.69)	0.368	0.903
Serum albumin *g/L*	0.79 (0.67–0.92)	0.0023	−3.055
Serum CRP *mg/L*	2.53 (1.60–4.00)	0.0001	3.963
Homocystein μ*mol/L*	1.00 (0.96–1.03)	0.509	−0.851
MULTIVARIABLE			
Flow debt repayment (10%)	0.69 (0.56–0.85)	0.0006	−3.417
Aortic PWV *m/s*	1.16 (1.04–1.29)	0.0091	2.608

Abbreviations are: HD, hemodialysis; BP, blood pressure; LV, left ventricular; IMT, intima-media thickness; PWV, pulse wave velocity; HDL, high-density lipoproteins; LDL, low-density lipoproteins; CRP, C-reactive protein.

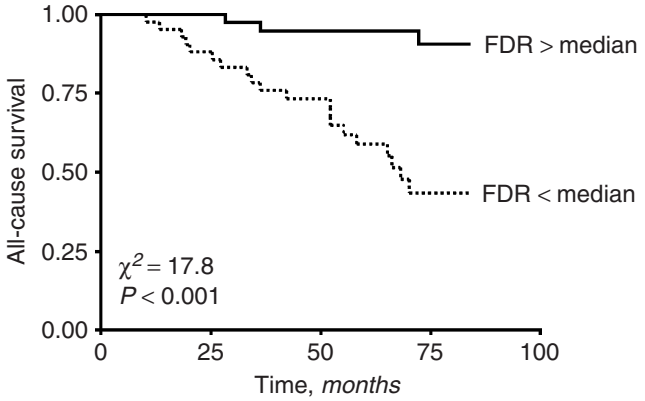

Fig. 2. Probability of all-cause survival between patients with flow debt repayment (FDR) > or < median value.

Structural changes in the microvasculature, including reduced capillary density, were described in ESRD patients [18], and alterations of FDR could be due to altered vasodilation, less microvascular density, and/or abnormal vessel recruitment. However, several arguments go against the latter. The principal one is that the baseline and peak FBF are similar in controls and ESRD patients [10], and the principal impairment observed is a shorter duration of hyperemia [10]. The peak reactive hyperemic response of FBF is not affected by L-NMMA, suggesting that nitric oxide (NO) plays minimal role in vasodilation at peak flow [19, 20]. On the contrary, the duration of the hyperemic response is reduced with L-NMMA, indicating that NO plays a modest but significant role in maintaining vasodilation after peak vasodilation [19, 21, 22]. The normal peak flow and rapid exhaustion of the hyperemic response observed in ESRD patients is more in line with possible alterations of NO-associated production or release [23–25].

The association of all-cause mortality with aortic PWV in ESRD patients reflects the advanced progression of athero-arteriosclerosis of large capacitive vessels [12, 26].

Vascular dysfunction was shown to be associated with low-grade systemic inflammation and associated with increased serum CRP and decreased serum albumin [27]. In ESRD patients, these latter two parameters are associated with end-organ damage, like FDR, CCA-IMT, the presence of atheromatous plaques, and poor prognosis [28–30]. In nonadjusted Cox proportional hazards models the lower serum albumin and higher CRP were significantly associated with increased hazard ratio for all-cause mortality, but also with abnormal forearm vasodilation and aortic PWV. However, upon introduction of the latter, this association was no longer retained after the adjustment for aortic PWV and FDR. The present study has several limitations. The principal limitation is the small sample size and the possibility that this population is not representative of larger HD patient populations. Indeed,

the mean age of the included patients was lower than that of those now being treated in HD units; the frequencies of comorbidities, including CVD, are lower, and that of diabetes lower than in North America and northern Europe. The cumulative all-cause mortality during the 5-year follow-up was 29.5%, and the studied population is at lower risk than usual HD patients populations. The limited sample size could have an impact on the modeling using Cox regression, and the lack of relationship of any of the other variables could be related to the sample size. Finally, another limitation could be the relationship between reactive forearm hyperemia and vasomotor alterations of coronary and systemic arteries. In a previous study a close relation of vasodilatory function in the human coronary and forearm circulations has been demonstrated, and the latter can be a useful surrogate in assessing the systemic endothelial function [31].

CONCLUSION

The results of this study demonstrated that forearm reactive hyperemia was impaired in ESRD patients due to the shorter duration of the hyperemic response. This altered hyperemic response was a strong and independent predictor of all-cause mortality, in association with arteriosclerosis of large capacitive arteries and increased aortic PWV. The exact mechanisms responsible for decreased reactive hyperemia, such as possibility of endothelial dysfunction, rarefaction of microcirculation, and decreased recruitment of vessels should be determined.

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