Flow-Mediated Vasodilation in End-Stage Renal Disease

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Summary

Background and objectives An intact endothelium is essential for adaptations between arterial vasomotor tone and shear stress (SS), *i.e.*, flow-mediated vasodilation (FMD). Endothelial dysfunction occurs in hypertension, cardiac insufficiency, diabetes, atherosclerosis, and in end-stage renal disease (ESRD) patients, whose renal failure is associated with many of those cardiovascular diseases (CVD).

Design, setting, participants, & measurements Using a progressive hand-warming protocol and repeated measures ANOVA, we analyzed SS-mediated increase of brachial artery diameter (ΔBA) in 22 healthy controls, 18 CVD-negative ESRD patients (ESRD-CVD$^-$), and 17 CVD-positive ESRD patients (ESRD-CVD$^+$) to analyze the role of uremia *versus* CVD on FMD.

Results Hand-warming increased SS ($P < 0.001$) and ΔBA ($P < 0.001$). Negative interactions were observed between ΔBA and ESRD ($P < 0.001$), and between ΔBA and CVD$^+$ ($P < 0.02$), but there was no interaction between ESRD and CVD$^+$ ($P = 0.69$). For low and mild SS increases, ESRD-CVD$^-$ patients were characterized by similar ΔBA as controls, but it was lower than controls at higher SS ($P < 0.01$). In ESRD-CVD$^+$ patients, brachial artery diameter did not respond to mild and moderate SS increases, and showed "paradoxical" vasoconstriction at higher SS ($P < 0.05$). In ESRD, a positive and independent interaction was observed between ΔBA and 25(OH) vitamin D_3 insufficiency (≤15 μg/L; $P < 0.02$).

Conclusions These observations indicate that, independently of each other, ESRD and CVD$^+$ history are associated with endothelial dysfunction. They also suggest the importance of considering the relationships between SS and endothelial function in different clinical conditions.

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Introduction

Physiologic laminar fluid shear stress (SS), the product of shear rate (SR) and whole blood viscosity (WBV), applied to endothelial cells is responsible for endothelial cell survival and quiescence (1,2). Under physiologic conditions, SS is the principal mechanostimulus modulating vascular tone, through releasing endothelial-derived relaxing factors (nitric oxide [NO], prostacyclin, hyperpolarizing factors) associated with flow-mediated dilation (FMD). Under certain conditions, endothelium can also release contracting factors (endoperoxide and thromboxane) that can elicit endothelium-dependent contraction, and healthy endothelium has an equilibrated production of these factors, with balance favoring relaxing factors (3).

An intact endothelium is essential to maintaining an adaptation between arterial vasomotor tone and SS. In healthy subjects, it was shown that, under conditions of similar blood flow, FMD was dependent on SS changes induced by hematocrit modifications, with decreased hematocrit (decreased WBV component of SS) associated with decreased FMD and *vice versa* (4). Despite very high blood viscosity, polyglobulic mice overexpressing human erythropoietin did not develop hypertension or thromboembolism, and showed markedly increased NO synthase (NOS) and circulating and vascular tissue-NO levels (5). Administration of the NOS inhibitor L-nitroarginine methyl ester (L-NAME) led to resistance-vessel vasoconstriction, hypertension, and death (5).

Endothelium dysfunction disturbs the balance between relaxing and contracting factors, favoring the latter (3). It was typically observed in humans with hypertension, cardiac insufficiency, aging, diabetes, and/or atherosclerosis, and in end-stage renal disease (ESRD) (6–9). In patients with coronary atherosclerosis, acetylcholine induced "paradoxical" vasoconstriction of coronary arteries (10,11). Endothelial dysfunction in ESRD patients might be associated with abnormal responses to SS changes. In hemodialysis patients with cardiovascular disease (CVD; congestive heart failure, myocardial infarction, atherosclerosis), Besarab *et al.* (12) showed that correcting anemia to normal hematocrit was not recommended, because

it would increase the likelihood of adverse effects or outcome.

In the present study, we analyzed the SS-mediated vasodilation, comparing healthy controls to two groups of hemodialyzed ESRD patients: patients without any prior CVD (ESRD-CVD$^-$) and those with a documented history of CVD (ESRD-CVD$^+$).

Materials and Methods

Thirty-five ESRD patients on hemodialysis for at least 3 months (median, 45 months; range, 3 to 364 m) were included. Eighteen patients were ESRD-CVD$^-$: 10 with chronic glomerulonephritis, four with interstitial nephritis, three with adult polycystic kidney disease, and one with diabetes. Seventeen were ESRD-CVD$^+$: myocardial infarction, angina pectoris requiring medications, coronary artery bypass, percutaneous coronary angioplasty, congestive heart failure, peripheral artery bypass or percutaneous angioplasty, including seven hypertensive and atherosclerotic renal disease, four chronic glomerulonephritis, four diabetes mellitus, and two adult polycystic kidney disease. ESRD-CVD$^+$ patients were eligible if they had been clinically stable for at least 3 months before the study, and they agreed to participate in the study, which was approved by our Institutional Review Board. Patients were dialyzed for 4 to 6 hours, thrice weekly, to control body fluids and blood chemistries. Blood chemistries were determined before hemodynamic study. Twenty-two gender, age-, and body-surface area-matched healthy controls were evaluated for comparison.

Brachial Artery Hemodynamic Measurements

All subjects were advised to refrain from smoking and caffeine ingestion for >12 hours before testing. All subjects were fasting when FMD determinations were obtained in the morning. For ESRD patients, measurements were done before the first hemodialysis of the week.

After resting 30 minutes in a supine position, measurements were obtained in a temperature-controlled (23 ± 1°C) room. BP was measured with a mercury sphygmomanometer after 15 minutes of recumbency, using phases I and V of the Korotkoff sounds, respectively, as the systolic and diastolic BP.

On the arm opposite to the arteriovenous shunt, brachial artery (BA) internal diameter, stroke diameter changes, BA wall-intima-media thickness (IMT), and SR were independently measured with a high-resolution B-mode (7.5-MHz transducer) echotracking system (Wall-Track System, PIE Medical, Maastricht, the Netherlands), as described previously in detail (13–16). Briefly, vessel walls are identified automatically and their displacement is tracked throughout the cardiac cycle. According to phase and amplitude, the radiofrequency signal over six cardiac cycles is digitized and stored until analysis. The accuracy of the system is 30 μm for diastolic diameter (Dd) and less than 1 μm for stroke-diameter change. Radiofrequency matrices were acquired over 2 to 4 seconds, and acquisitions were repeated every 10 seconds. One patient-period corresponded to 450 radiofrequency acquisitions (500 to 700 megabytes). The entire procedure was videotaped on S-VHS tapes for image analysis. BA distensibility was determined from pulse pressure (PP) change and from BA diameter changes (ΔBA), Dd = Ds – Dd, where Ds is the systolic and Dd the diastolic BA diameter, according to following formula: BA distensibility ($kPa^{-1} \times 10^{-3}$) = 2[(Ds – Dd)/Dd]/PP (17). The BA incremental elastic modulus (Einc) was determined according to the previously reported formula (16,17): Einc = [(BA lumen cross-sectional area/BA-wall cross-sectional area + 1)×3)]/BA distensibility.

SR was measured with the same device but with different settings, as previously reported (13–16). The echo system is shifted to pulsed Doppler mode and a 30° oblique radiofrequency line is digitized at high frequency (24 MHz). The Doppler shift is determined in two successive wavelength windows; blood velocities are measured in coadjacent windows until the wall is reached, taking into account systolic distension. Vessel wall motion is filtered out by an autoadapting high-pass filter set at 20 Hz for BA measurement (low velocities and small distension). Therefore, blood velocities in the range of 10 mm/s to 2 m/s could be measured, and flow velocity profiles across the lumen and during the cardiac cycle could be constructed. Wall SR was then calculated by spatial derivation of blood velocities along the diameter, as a function of depth and time; the lower threshold was 7 $seconds^{-1}$. BA diameter and mean SR were the average of 10 to 15 cardiac cycles for each hand-warming step. SS was then calculated using the WBV measured, at each incremental SR value, by a cone-plate viscometer (EX100CTB Brookfield, MA) at 37°C.

Hand-Warming Protocol

Because recommended hemoglobin levels should be maintained within 100 to 120 g/L, the progressive ΔSS was obtained by modifying SR. After 10 minutes, the glove-protected hand was introduced into a water-filled thermocontrolled device (Polystat 1, Bioblock Scientific, Illkirch, France) (14,16,18). The arm was positioned and immobilized in an inflatable splint. The echotracking probe was placed over the BA, 1 to 2 cm above the elbow, and carefully positioned with a stereotactic arm parallel to the main BA axis. Image quality was maintained throughout the study by minor adjustments in the *XYZ* axes. The skin was gel-coated to avoid any direct contact with the probe. After 15 minutes of rest, the measurements were obtained at a water temperature of 35°C (neutrality). The water temperature was then increased in successive 5-minute increments from 35°C to 38°C to 41°C to 44°C; each level was maintained for 5 minutes. BA diameter measurements were repeated 10 to 15 times per cardiac cycle during each step and averaged. Changes in BA diameter (ΔBA) and SS (ΔSS) were expressed in % from baseline. Flow-mediated dilation (FMD) was normalized and expressed as FMD = ΔBA diameter (% from baseline)/ΔSS (% from baseline/100). After a 15-minute recovery period, the BA diameter was measured before and after sublingual administration of 150 μg of glyceryl trinitrate (GTN).

Statistical Analyses

Data are expressed as means ± SD or as medians (95% confidence interval[CI]), according to the distribution. Baseline between-group comparisons of quantitative variables used ANOVA, with a Bonferroni correction for mul-

tiple comparisons. ANOVA for repeated measures, with Geisser Greenhouse F-test adjustments, was used to evaluate the effects of hand-warming on BA diameter and SS (both expressed as % changes from baseline), and to analyze the interactions of these changes with the presence of ESRD (1, no; 2, yes), CVD history (1, no; 2, yes), and age (1, <50 years; 2, ≥50 years), vitamin D status (1, serum 25(OH) ≤15; 2, serum 25(OH) >15 μg/L). Spearman correlation coefficients were determined to assess relationships between BA and SS changes at different heating steps. Analyses were performed using NCSS 2000 (G. Hintze, Kaysville, UT).

Results

Clinical data and BA characteristics for control subjects and the two groups of ESRD patients are summarized in Tables 1 and 2. Not surprisingly ESRD-CVD$^+$ patients were older and had higher systolic BP and PP. Moreover, their CVD$^+$ status was associated with significantly progressive increases of baseline BA diameter, wall thickness, and elastic modulus, and decreases of SR and SS that were significantly lower. Furthermore, ESRD-CVD$^+$ patients had significantly higher von Willebrand factor and plasminogen-activator inhibitor values but similar circulating endothelin-1. The most significant differences between ESRD-CVD$^+$ and ESRD-CVD$^-$ were the former's significantly lower serum concentrations of both 25(OH) and 1,25(OH)$_2$ vitamin D$_3$ forms.

Effect of Hand-Warming on BA Hemodynamics

Hand-warming significantly increased the BA diameter ($P < 0.001$), exhibiting a significant negative interaction with ESRD ($P < 0.001$), CVD$^+$ ($P < 0.02$), but no interaction with age ($P = 0.64$), and lack of interaction between ESRD and CVD$^+$ ($P = 0.69$; Table 3A). In ESRD, the BA diameter did not respond to mild and moderate SS increases in ESRD-CVD$^+$ (correlation between ΔSS and ΔBA diameter vas negative but nonsignificant). At higher SS, a negative significant correlation was observed between ΔSS and ΔBA diameter ($P < 0.05$). In ESRD-CVD$^-$ patients, mild and moderate SS increases induced similar ΔBA diameter to those in controls, but, at maximal (44°C) stimulation, the slope (β-coefficient) of the ΔSS-ΔBA-diameter curve was significantly lower for ESRD-CVD$^-$ compared with controls (table 4). GNT-induced BA dilation in ESRD-CVD$^+$ was significantly lower, with a significantly higher GTN-to-FMD ratio (Table 1).

Hand-warming significantly increased SS ($P < 0.001$), not interacting with ESRD ($P = 0.09$) or age ($P = 0.20$). In ESRD patients, a significant interaction was observed between changes in SS and documented CVD$^+$ ($P < 0.001$), and between age and CVD$^+$ ($P < 0.01$; Table 3B).

In ESRD patients, significant interactions were observed between ΔBA diameter and serum 25(OH) vitamin D$_3$ status ($P = 0.01$) and CVD$^+$ ($P < 0.01$), but with no direct interaction between vitamin D$_3$ status and CVD$^+$ ($P = 0.52$; Table 3C).

Discussion

As physiologically expected, SS changes were accompanied with flow-mediated dilation (FMD), as evaluated by BA dilation (ΔBA). The significant interaction between ESRD and ΔBA indicates that FMD was lower in ESRD patients, but, independently of ESRD status, FMD was also significantly influenced by documented history of CVD complications. This ESRD-CVD$^+$ population was charac-

Table 1. Brachial artery characteristics

Variable	Controls (1) $n = 22$	ESRD-CVD$^-$ (2) $n = 18$	ESRD-CVD$^+$(3) $n = 17$	P-ANOVA
Age (years)	50.1 ± 15.6	48.2 ± 10.5	63.5 ± 10.6	<0.01[a]
Gender (male/female)	13/9	11/7	11/6	0.44
Body mass index (kg/m^2)	24.5 ± 2.9	24.6 ± 4.4	25.9 ± 3.6	0.22
Systolic blood pressure (mmHg)	126 ± 17.5	136 ± 19.5	155 ± 23.8	<0.001[a]
Diastolic blood pressure (mmHg)	77 ± 11.1	75.5 ± 12.6	74 ± 9.2	0.78
Mean blood pressure (mmHg)	93 ± 11.2	96 ± 14.2	101 ± 11.4	0.21
Pulse pressure (mmHg)	49 ± 17	61 ± 12.3	80 ± 23	<0.001[a]
BA intima-media thickness (μm)	427 ± 60	450 ± 55	479 ± 50	<0.05[e]
Baseline BA diameter (mm)	4.10 ± 0.65	4.40 ± 0.70	4.90 ± 0.95	<0.01[d]
Baseline BA Einc (kPa x 10^3)	3.06 ± 1.15	3.95 ± 2.1	6.28 ± 3.15	<0.001[a]
Baseline BA blood velocity (cm/s)	4.15 ± 1.9	3.95 ± 1.85	2.35 ± 1.9	<0.01[a]
Baseline BA blood flow (ml/s)	35.0 ± 23	36.0 ± 20.1	22.8 ± 17	<0.05[a]
Baseline BA shear rate (s^{-1})	49 ± 11.4	45.5 ± 21.1	35.4 ± 20.1	<0.01[a]
Whole blood viscosity (cPoise)	3.58 ± 0.36	2.70 ± 0.35[b]	2.78 ± 0.34	<0.001[b;c]
Baseline BA shear stress (dynes/cm^2)	17.6 ± 4.7	12.6 ± 5.8	8.3 ± 6.2	<0.001[a]
ΔBA diameter (% from baseline at 44°C)	7.5 ± 3.62	4.7 ± 2.72[f]	1.5 ± 1.65	<0.001[a;f]
Δ Shear stress (% from baseline at 44°C)	234 ± 125	289 ± 169	395 ± 295	<0.05
FMD (ΔBA diameter/Δshear stress)	3.6 ± 1.7	1.85 ± 1.2[b]	1.05 ± 0.85	<0.001[a;b]
GTN-induced dilation (GTN %)	20.7 ± 5.65	19.0 ± 4.3	11.20 ± 4.6	<0.001[a]
GTN/FMD (ratio)	3.50 ± 2.9	5.7 ± 2.8	8.1 ± 4.1	<0.05[c]

Values are means ± SDs. FMD, flow-mediated dilation; BA, brachial artery; GTN, glyceryl trinitrate; ESRD, end stage renal disease; CVD, cardiovascular disease.
[a]$P < 0.01$: 3 vs 1 or vs 2; [b]2 vs 1; [c]3 vs 1; [d]$P < 0.05$: 3 vs 1 or vs 2, [e]3 vs 1, [f]1 vs 2.

Table 2. Blood chemistries and treatments characteristics

Variable	ESRD-CV$^-$ n = 18	ESRD-CV$^+$ n = 17	*t*-test, *P*
Hemoglobin (g/L)	10.6 ± 1.45	10.9 ± 1.50	0.46
HsCRP (mg/L)	1.8 (1 to 7.5)	5.2 (1 to 15)	0.13
Serum albumin (g/L)	35.3 ± 4.1	35.8 ± 2.4	0.38
Fibrinogen (g/L)	4.02 ± 0.75	4.06 ± 0.95	0.46
Total cholesterol (mmol/L)	4.51 ± 1.10	4.54 ± 1.35	0.61
LDL cholesterol (mmol/L)	3.15 ± 1.05	3.16 ± 1.20	0.98
Serum calcium (mmol/L)	2.24 ± 0.22	2.37 ± 0.17	0.06
Serum phosphates (mmol/L)	1.71 ± 0.45	1.76 ± 0.42	0.39
Parathormone (pg/ml)	476 ± 338	535 ± 393	0.42
25(OH)-vitamin D_3 (μg/L)	17.0 ± 6.7	10.3 ± 4.1	<0.01
1,25$(OH)_2$-vitamin D_3 (pg/L)*	18.9 ± 5.7	13.8 ± 4.8	<0.01
Blood urea (mmol/L)	29.1 ± 4.8	27.3 ± 4.3	0.09
Kt/V	1.31 ± 0.20	1.28 ± 0.16	0.29
Homocysteine (μmol/L)	34.3 ± 8.3	41.7 ± 14.4	0.19
Von Willebrand factor(%)	157 ± 34	213 ± 64	<0.01
Plasminogen-activator inhibitor (μg/L)	3.5 (2.5 to 10)	7 (6–18)	<0.05
Endothelin-1 (pg/ml)	3.6 (2.6–8.2)	1.9 (1.1 to 2.8)	0.07
Erythropoietin (units/wk)	3500 (2170 to 6160)	5000 (3630 to 7370)	0.84
ACE inhibitors (*n* patients)	7	9	0.40
Beta blockers (*n* patients)	6	5	0.48
Calcium channel blockers (*n* patients)	4	7	0.29
Statins (n patients)	2	8	<0.05
Antiplatelet therapy (*n* patients)	0	9	<0.05

Values are means ± SD or Median (95% CI); n, number of patients.

terized by the absence of a ΔBA response to mild and moderate ΔSS and "paradoxical" BA diameter decrease in response to higher SS shear stress.

Table 3. Repeated measures ANOVA report for hand-warming-induced changes of brachial artery diameter (ΔBA) and shear stress (ΔSS)

A. Measure: Changes in brachial artery diameter (ΔBA)

Analysis	F-ratio	*P*-value
ΔBA measure	22.75	<0.01
ΔBA x Age interaction	0.46	0.64
ΔBA x ESRD interaction	12.88	<0.01
ΔBA x CVD$^+$ interaction	4.90	<0.02
ESRD x CVD$^+$ interaction	0.16	0.69

B. Measure: Changes in brachial artery shear stress (ΔSS)

Analysis	F-ratio	*P*-value
ΔSS measure	89.34	<0.01
ΔSS x Age interaction	1.61	0.20
ΔSS x ESRD interaction	2.52	0.09
ΔSS x CVD$^+$ interaction	10.94	<0.01
Age x CVD$^+$ interaction	8.52	<0.01

C. Measure: ΔBA in ESRD patients (including vitamin D_3 status)

Analysis	F-ratio	*P*-value
ΔBA measure	29.80	<0.01
ΔBA x CVD$^+$ interaction	6.04	<0.01
ΔBA x vitamin D_3 status interaction	4.60	<0.02
CVD$^+$ x vitamin D_3 status interaction	0.42	0.52

The lower FMD observed herein in response to reactive hyperemia confirmed previously reported findings (8,11), but it also indicates that the arterial response to increased SS is heterogeneous and influenced by factors other than ESRD alone. A positive, physiologic correlation between locally increased SS and increased BA diameter was seen in controls and ESRD-CVD$^-$ patients. The ΔSS-ΔBA diameter relationship for those latter patients was similar for small (38°C) or mild (41°C) SS increases but was significantly lower at maximal (44°C) mechanostimulation (Figure 1 and Table 2). Factors known to contribute to endothelial dysfunction in ESRD include reduced bioactivity of NO pathway, with decreased endothelial NOS (eNOS) activity or inhibition *via* accumulation of endogenous inhibitors, such as asymetric-dimethyl-arginine (ADMA) (9–11,19). The FMD decline observed in ESRD-CVD$^-$ patients at higher SS could be interpreted as resulting from the time-limited NO-mediated response not compensated by synergic factors (prostacyclin and endothelium-derived hyperpolarizing factor, EDHF). Indeed, during more sustained hyperemia (like with the hand-warming protocol), EDHF plays an important role and can compensate for the lower NO response (18,20).

In ESRD-CVD$^+$ patients, the small and moderate SS increases did not induce FMD, while for high SS, we observed a significant and negative correlation between SS and FMD, with decreased BA diameter observed in five patients with the highest SS elevation (Figure 1C). This observation looks like the paradoxical acetylcholine-induced vasoconstriction seen in atherosclerotic coronary arteries in the general population (10,11), and suggests that, in the presence of endothelial dysfunction associated

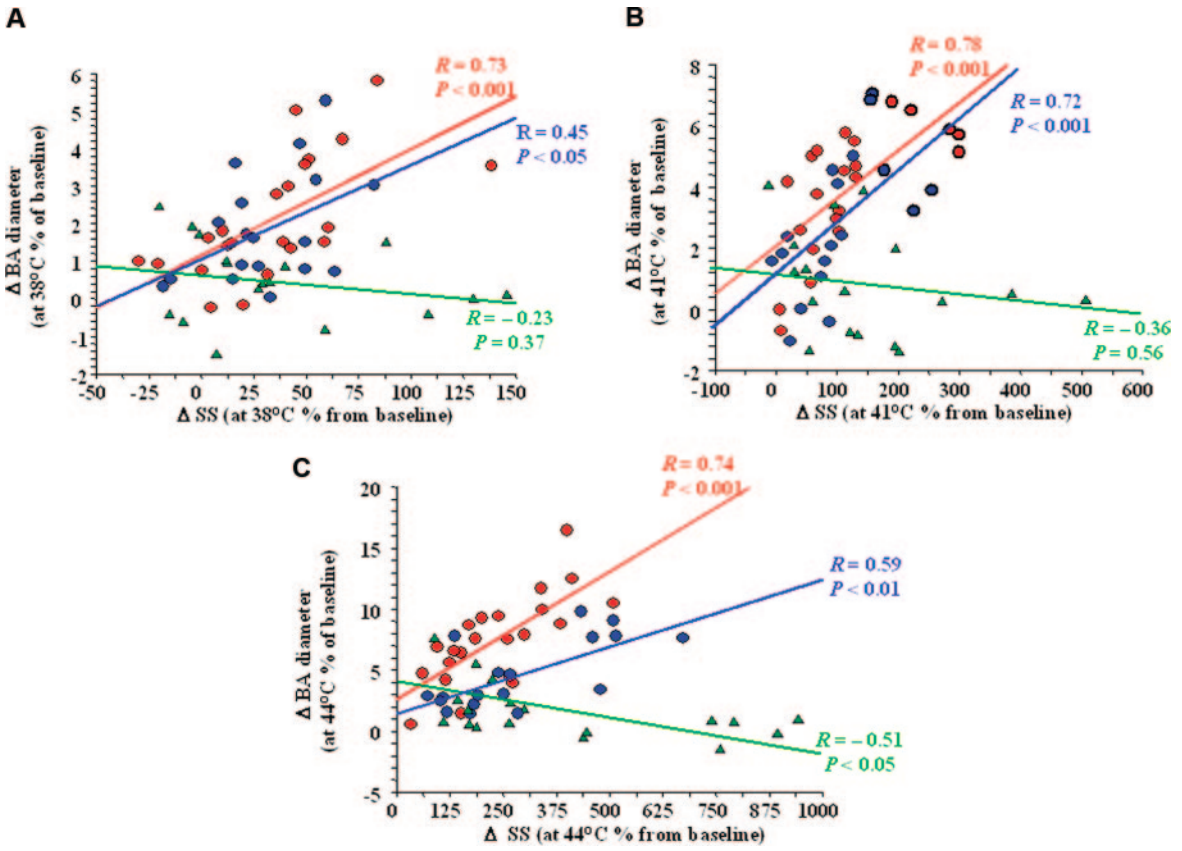

Figure 1. | **Relationships (adjusted for age and mean BP) between shear stress (ΔSS) and brachial artery (ΔBA) diameter changes at different hand-warming steps: (A) mild, (B) moderate, (C) high control subjects: red circles and regression lines; ESRD-CVD$^-$ patients: blue circles and regression lines; ESRD-CVD$^+$ patients: green triangles and regression lines.**

with atherosclerosis and CVD complications, in response to increased SS, the endothelium could release contracting factors that can elicit endothelium-dependent contraction. This has been demonstrated by experimental studies in polyglobulic mice (21,22). Polyglobulic mice overexpressing human erythropoietin did not develop hypertension or thromboembolism (5). Administration of the NOS inhibitor L-NAME led to resistance-vessel vasoconstriction, hypertension, and death (5). Three weeks' pretreatment of these mice with endothelin–1 receptor antagonist (ET_A) darusentan significantly prolonged their survival upon acute exposure to L-NAME (21). According to this experimental study, in the presence of endothelial dysfunction, endothelin-1 may be regarded as one factor contributing to flow-mediated vasoconstriction. In the present study, the ESRD-CVD$^+$ patients were older, and study in healthy population provided evidence that endothelial oxidative stress develops with aging and is associated with impaired endothelium-dependent dilation (23).

In ESRD patients, a significant positive interaction was observed between ΔBA diameter and serum 25(OH) vitamin D_3 status. This interaction was independent of CVD$^+$ status, suggesting an independent association between endothelial function and vitamin D status. Association between low or deficient 25-hydroxyvitamin D and impaired brachial artery FMD was demonstrated in a general population of middle-aged and older adults and in ESRD patients (22,24). It was shown experimentally that exposure to cholecalciferol improved the relaxation response of spontaneously hypertensive rat arteries to acetylcholine (25) and that vitamin D_3 stimulated prostacyclin production by vascular smooth muscle cells (26). Moreover, studies on aortic rings of spontaneously hypertensive rats have shown that Vitamin D derivatives acutely reduce endothelium-dependent contraction by reducing calcium influx into endothelial cells and decreasing production of endothelium-derived contracting factors (27). Vitamin D deficiency is modifiable, but whether its supplementation in humans could improve endothelial function should be evaluated by prospective randomized control trials.

In the present study, the ΔSSs were obtained by SR modifications and could not be extrapolated to eventual ΔSSs in response to WBV or hemoglobin alterations. In that latter situation, where hemoglobin acts as an NO buffer and modulates NO bioavailability (28), the endothelium dysfunction could aggravate the arterial response to SS. In diabetics and diabetic patients with CKD, an inverse correlation was observed between hemoglobin and the vasodilatory response to acetylcholine or postischemic vasodilation (29–31). Physiologic studies in healthy humans have shown that, in the presence of intact endothelium, the hemoglobin variations alter arterial FMD only by changing the intensity of mechanostimulation (4). Indeed, decreased hematocrit/WBV was associated with lower FMD, while

Table 4. β-Coefficients (slope) of the relationships between changes of brachial artery diameter (FMD as % of baseline value) and shear stress (100% of baseline value) as shown in Figure 1

Subjects	β and *P* Baseline vs 38°C	β and *P* Baseline vs 41°C	β and *P* Baseline vs 44°C
Controls	0.026 ± 0.04; <0.001	0.017 ± 0.02; <0.001	0.020 ± 0.02; <0.001
ESRD-CVD$^-$	0.025 ± 0.05; <0.05	0.018 ± 0.03; <0.001	0.010 ± 0.01; <0.01
ESRD-CVD$^+$	−0.002 ± 0.02; 0.37	−0.004 ± 0.01; 0.56	−0.005 ± 0.004; <0.05

β-coefficient ± SD. At 44°C the slope for ESRD-CVD$^-$ is significantly lower than that of control subjects ($P < 0.01$). In ESRD-CVD$^+$ β-coefficient differed significantly from the other groups at each temperature step.

elevated hematocrit was associated with higher FMD. Under conditions of similar blood flow changes, hematocrit-induced SS variations changed the intensity of endothelial mechanostimulation and the corresponding response (4). Controlled randomized studies on ESRD patients showed that, in older subjects or diabetics and those with CVD complications, normalization of hemoglobin levels was associated with a trend toward worse outcomes (12). Our findings showed that ESRD-CVD$^+$ patients did not respond to increased SS by arterial vasodilatation but instead, paradoxically, by a tendency to progressive decrease ΔBA diameter in response to increased SS. SS changes were obtained by altering SR or flow, and they cannot be totally extrapolated to eventual changes in SS due to WBV or hemoglobin changes. Because of current anemia correction recommendations and their limitations, we could not modify the hemoglobin level and test vasomotor changes, which could be associated with WBV-related SS rise (blood transfusion or erythropoietin treatment).

By sensing the SS changes, endothelium plays a crucial role in controlling arterial remodeling. The creation of the arteriovenous fistula increases arterial SS and leds to long-term structural remodeling characterized by diameter increase and wall hypertrophy (32). The presence of endothelial dysfunction, as observed in ESRD patients with CVD, could be the factor associated with fistula nonmaturation (33).

The present study has several limitations. The arterial system is heterogeneous, and observations made on the brachial artery cannot be systematically extrapolated to other arterial territories. As already mentioned, the ΔSS were obtained by SR modifications and could not be extrapolated to eventual ΔSS in response to WBV or hemoglobin alterations. In addition, we studied the acute effects of SS modifications, which could be different from long-term changes, like those potentially induced by progressive WBV and/or hemoglobin changes.

In conclusion, our present observations indicate that, independently of each other, ESRD and CVD$^+$ history are associated with endothelial dysfunction. They also suggest the importance of considering the relationships between SS and endothelial function in different clinical conditions. Only prospective controlled randomized studies can evaluate whether the improvement of endothelial dysfunction might have an impact on ESRD patients' clinical outcomes.

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Disclosures

None.

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