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CLINICAL INVESTIGATION

Studies of the vessel wall properties in hemodialysis patients

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Studies of the vessel wall properties in hemodialysis patients. Compliance is an important property of the arterial system and abnormalities in compliance can greatly affect cardiovascular function. The elastic properties of the common carotid artery were therefore studied in 24 normotensive hemodialysis patients and 24 healthy normotensives using a noninvasive technique. The hemodialysis patients and the control subjects were matched for blood pressure. Arterial distension was measured by Doppler analysis of the vessel wall movements and blood pressure was recorded by finger-phlethysmography (Finapres^{R}). The vessel wall distensibility (DC: 2.49 ± 0.23 10^{-3}/mm Hg; mean ± SEM) was significantly reduced and the end diastolic diameter (d: 7.3 ± 0.3 mm) was significantly increased in younger hemodialysis patients (36.3 ± 2.0 years) when compared with age-related controls (DC: 3.44 ± 0.24 10^{-3}/mm Hg; d: 6.3 ± 0.3 mm; mean ± SEM). In older hemodialysis patients (60.2 ± 2.3 years), there was no significant difference in vessel wall distensibility (DC: 1.55 ± 0.15 10^{-3}/mm Hg) and vessel diameter (d: 7.8 ± 0.3 mm) as compared with age-matched controls (DC: 1.77 ± 0.14 10^{-3}/mm Hg; d: 7.2 ± 0.3 mm). The results show that vessel wall distensibility of the common carotid artery is decreased in younger hemodialysis patients as compared with age-matched healthy subjects. The volume expanded state in hemodialysis patients cannot account for the decreased arterial distensibility, since volume depletion by hemodialysis was not associated with a significant change of arterial distensibility (DC 2.14 ± 0.44 10^{-3}/mm Hg before, DC 2.26 ± 0.45 10^{-3}/mm Hg after ultrafiltration, NS). The enhanced stiffness of the arteries could contribute to the higher incidence of cardiovascular disease in hemodialysis patients.

Cardiovascular disease is a major cause of morbidity and mortality in patients maintained by chronic hemodialysis. Death due to myocardial infarction and to stroke is more frequent in hemodialysis patients than in the total population [1, 2]. The risk factors for cardiovascular disease in patients with end-stage renal failure are still under discussion. There is controversy whether hemodialysis itself leads to accelerated arteriosclerosis. Pre-existing coronary artery disease seems to be significantly accelerated after the onset of hemodialysis [2].

Hypertension also increases cardiovascular morbidity and mortality. High blood pressure is very common in patients with end-stage renal failure. On the other hand, after starting chronic hemodialysis blood pressure often decreases to normal or hypotensive values.

Vessel wall elasticity is reduced independent of blood pressure levels in patients with essential hypertension [3, 4]. In patients treated by chronic hemodialysis, elastic properties of the vessel wall remain to be evaluated. London et al studied the aortal pulse wave velocity in normotensive and hypertensive hemodialysis patients at different ages and in a control group [5]. The aortal pulse wave velocity, indicative for arterial stiffness, was significantly increased in the hemodialysis group in comparison to the controls. However, the hemodialysis patients had higher systolic and lower diastolic blood pressure levels as well as a considerably higher pulse pressure than the control subjects. In renal allograft recipients studied two to three months after transplantation, arterial distensibility of the common carotid artery was reduced [6]. These patients had undergone long-term hemodialysis prior to renal transplantation. At the time of the study, they received immunosuppressive therapy including cyclosporin. This treatment could have influenced the vessel wall properties.

The present study was, therefore, designed to compare the vessel wall properties in patients from the chronic hemodialysis program and in normal subjects. Care was taken that both hemodialysis patients and normal subjects did not differ in blood pressure levels at the time of the measurements.

Methods

Patients

Twenty-four normotensive hemodialysis patients and 24 normotensive healthy controls were included into the study to compare the mechanical vessel wall properties of healthy subjects and the patients with end-stage renal failure. Hemodialysis patients had been in the hemodialysis program for periods ranging from 12 to 96 months (average 41 ± 3.6 months). Prior to hemodialysis, the hemodialysis patients had been hypertensive for at least one year (blood pressure > 140/90 mm Hg). In the two months preceding the study, the hemodialysis patients, however, had blood pressure < 140/90 mm Hg and were not on antihypertensive drugs. The hemodialysis patients underwent hemodialysis three times a week for three to five hours using an arteriovenous fistula. To take into account the influence of age on arterial compliance, the hemodialysis patients and the control persons were subdivided into two age groups (Table 1). The younger groups ranged from 25 to 50 years and the older groups ranged from 51 to 75 years. None of the control subjects had a disturbance of kidney or liver function, or diabetes mellitus or hyperlipidemia. Normal serum values for calcium (2.4 ± 0.2 mmol/liter) and glucose (109 ± 8 mg/dl) were measured in the hemodialysis patients. Pathological serum values, not differing between the younger and older hemodialysis patients, were found for creatinine (10.2 ± 0.5 mg/dl), potassium (5.8 ± 0.1 mmol/liter), phosphate (5.8 ± 0.1 mg/dl), triglycerides (177 ± 10

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Table 1. Age, systolic and diastolic blood pressure (BPs, BPd), body height (body ht), body mass index (BMI) in young and older hemodialysis patients (HD1, HD2) and age-matched healthy, young and older normotensive controls (C1, C2)

	C1	C2	HD1	HD2
N	12	12	12	12
Age *years*	36.8 ± 2.5	58.2 ± 1.6	36.3 ± 2.0	60.2 ± 2.3
BPs *mm Hg*	125 ± 4	125 ± 4	125 ± 4	122 ± 4
BPd *mm Hg*	66 ± 4	67 ± 3	66 ± 4	60 ± 5
Body ht *cm*	172 ± 4	171 ± 2	167 ± 3	168 ± 2
Body wt *kg*	67 ± 24	69 ± 2	61 ± 3	65 ± 3
BMI kg/m^2	22.6 ± 0.9	23.6 ± 0.6	21.9 ± 0.7	23.0 ± 0.7

Data represent mean ± SEM of 12 patients (*N*).

mg/dl) and hematocrit (31.4 ± 0.9%). Total serum cholesterol was higher in the older (255 ± 12 mg/dl) than in the younger hemodialysis patients (205 ± 9 mg/dl).

In each patient, the vessel wall properties of the left common carotid artery were studied noninvasively after a 10-minute supine rest using a multi-gate pulsed Doppler system [7, 8]. The method is based upon the processing of low frequency Doppler signals originating from the sample volumes coinciding with the anterior and posterior vessel walls. The positions of the sample volumes are continuously adjusted according to the displacement of the wall. Concomitantly, blood pressure was recorded by finger-plethysmography using the Finapres^R device [9, 10]. The shunt arm was never used for this measurement. The blood pressure curves and the pulse curves were synchronized by cross correlation analysis [8]. Using this noninvasive technique, the end diastolic diameter (d) and relative ($\Delta d \times d^{-1}$) systolic increase of vessel diameter were measured. From these data and from the systolic and diastolic blood pressure (BPs, BPd), the relative diameter change per mm Hg [distension = $\Delta d \times d^{-1} \times (BPs - BPd)^{-1}$ in $\% \cdot mm\ Hg^{-1}$; the cross sectional compliance ($CC = 0.5\pi \times \Delta d \times d \times (BPs - BPd)^{-1}$ ($10^{-3}\ mm^2 \times mm\ Hg^{-1}$)] and the arterial wall distensibility [$DC = 2\Delta d \times d^{-1} \times (BPs - BPd)^{-1}$ ($10^{-3} \times mm\ Hg^{-1}$)] can be determined [8, 11, 12]. The coefficients of variation were 3.4% for the end diastolic diameter, 7.4% for the relative systolic increase of vessel diameter, 12% for the relative diameter change per millimeter mercury pulse pressure, 12.2% for CC and 10.8% for DC (N = 15).

Because of an inverse correlation between body weight and arterial compliance [13], we measured the body weight and height of the patients and the body mass index (BMI) was calculated [BMI = weight (kg) × height^{-2} (m^{-2})].

Routine biochemical parameters such as serum cholesterol and triglycerides were determined by standard methods.

Statistical significance was calculated using Student's t-test. All data are expressed as mean ± the standard error of the mean (SEM).

Results

The hemodialysis groups and the age-matched control groups did not significantly differ in body mass index as well as in systolic and diastolic blood pressure (Table 1).

The relative diameter change per mm Hg pulse pressure, the cross sectional compliance and the distensibility coefficient were significantly reduced in the old control group as compared with the young controls (Table 2). In addition, a significant increase of end diastolic diameter of the common carotid artery with age was observed in the healthy controls (Table 2).

Table 2. End diastolic diameter (d), relative diameter increase during the cardiac cycle (dist1), systolic increase in common carotid artery diameter per mm Hg pulse pressure (dist2), cross sectional compliance (CC) and distensibility coefficient (DC) in young and older hemodialysis patients (HD1, HD2), and in age-matched young and older normotensive controls (C1, C2)

	C1	C2	HD1	HD2
d *mm*	6.3 ± 0.3	7.2 ± 0.3[a]	7.3 ± 0.3	7.8 ± 0.3
dist1 %	8.7 ± 0.9	4.5 ± 0.2[b]	7.5 ± 0.6	4.4 ± 0.4[b]
dist2 *%/mm Hg*	0.15 ± 0.015	0.08 ± 0.003[b]	0.13 ± 0.01	0.07 ± 0.01[b]
CC 10^{-3} mm^2/ *mm Hg*	115 ± 11	66 ± 6.4[b]	99 ± 7.5	66 ± 5.3[b]
DC 10^{-3}/ *mm Hg*	3.44 ± 0.24	1.77 ± 0.14[b]	2.49 ± 0.23	1.55 ± 0.15[b]

Data represent mean ± SEM of 12 patients.
[a] $P < 0.05$, [b] $P < 0.01$

In the hemodialysis patients, there was an age-dependent reduction of the relative diameter change per mm Hg pulse pressure, of the cross-sectional compliance and of the distensibility coefficient (Table 2). In contrast to the normal subjects, there was no significant increase of the end diastolic diameter of the common carotid artery with age (Table 2).

The distensibility coefficient was significantly decreased and the end diastolic diameter of the common carotid artery was significantly increased in the young hemodialysis patients as compared with the young control group ($P < 0.05$, Fig. 1). In the old hemodialysis patients, the distensibility coefficient was slightly lower than in the age-matched control group. The difference was, however, not statistically different. This is also true for the end diastolic diameter (Fig. 1).

It was considered that the decreased distensibility coefficient in the younger hemodialysis patients as compared to the younger controls was due to differences in the end diastolic diameter. To test this possibility, arterial distensibility was compared in hemodialysis and in control patients matched for similar end diastolic vessel diameters. Five of the 12 younger hemodialysis patients and 5 of the 12 younger control subjects with an end diastolic vessel diameter between 6.3 and 6.9 mm were selected. In the hemodialysis group (N = 5, age 32.6 ± 1.9 years) the end diastolic diameter was 6.6 ± 0.1 mm; in the control group (N = 5, age 37.8 ± 3.8 years) the end diastolic diameter was 6.5 ± 0.1 mm (NS). Blood pressure was similar between both groups (118 ± 10/66 ± 4 mm Hg in the hemodialysis, 120 ± 5/66 ± 4 mm Hg in the control group, NS). In the hemodialysis group the distensibility coefficient was 2.82 ± 0.21 10^{-3}/mm Hg, and in the control group it was 3.81 ± 0.37 10^{-3}/mm Hg ($P < 0.05$). Thus, the distensibility coefficient was reduced in these hemodialysis patients although they were younger than the control subjects.

Furthermore, the mechanical vessel wall properties of the common carotid artery were studied in 10 additional hemodialysis patients (age 37.4 ± 4.0 years, range 23 to 55 years) before and after ultrafiltration during hemodialysis (Table 3). It was known from previous hemodialysis that these patients did not respond to ultrafiltration with a significant fall of blood pressure. This observation was confirmed during the study. In spite of a weight loss of almost 4 kg due to ultrafiltration, systolic and diastolic blood pressure did not change significantly (Table 3). However, there was a substantial decrease of end diastolic

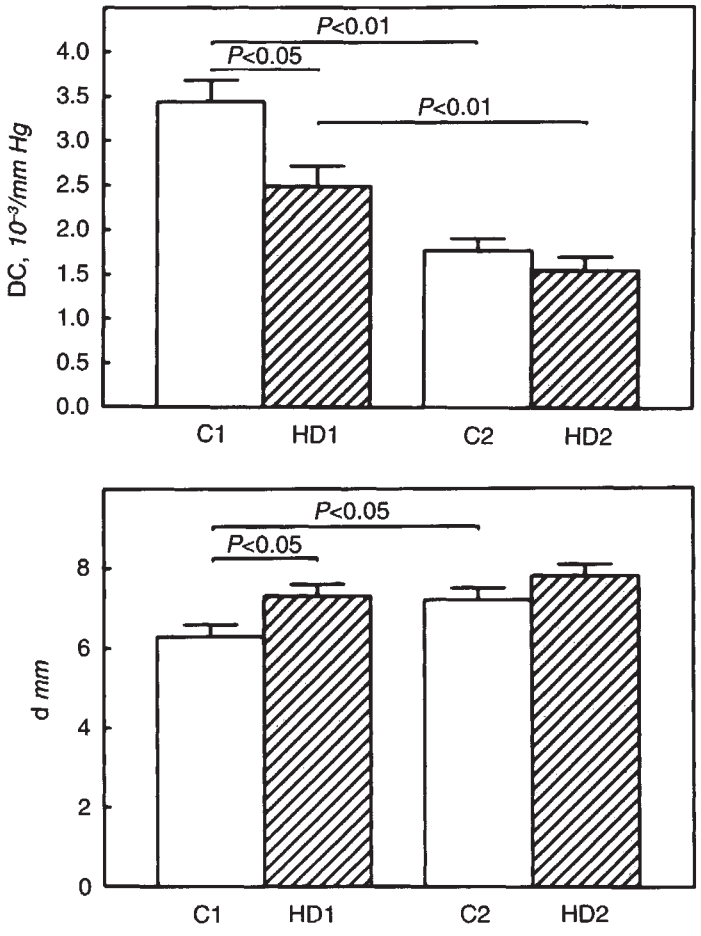

Fig. 1. *Mean ± SEM of distensibility coefficient (DC, A) and end diastolic diameter (d, B) in young and older normotensive hemodialysis patients (HD1, HD2) and in age-matched controls (C1, C2).*

diameter of the common carotid artery with no or only insignificant changes of vessel wall parameters (Table 3).

Table 3. Ultrafiltration (UF), body weight (body wt), systolic blood pressure (BPS), diastolic blood pressure (BPD), end diastolic diameter (d), relative diameter increase during the cardiac cycle (dist1), systolic increase in common carotid artery diameter per mm Hg pulse pressure (dist2), cross sectional compliance (CC) and distensibility coefficient (DC) before and after ultrafiltration (UF) during hemodialysis

	Before UF	After UF	*P*
Body wt *kg*	66.5 ± 2.9	62.7 ± 2.6	[a]
BPS *mm Hg*	149 ± 10	144 ± 12	NS
BPD *mm Hg*	89 ± 6	85 ± 7	NS
d *mm*	7.8 ± 0.4	7.2 ± 0.4	[a]
dist1 *%*	6.5 ± 1.2	6.3 ± 1.4	NS
dist2 *%/mm Hg*	0.12 ± 0.026	0.11 ± 0.019	NS
CC 10^{-3} *mm²/mm Hg*	86 ± 12	83 ± 8	NS
DC 10^{-3}*/mm Hg*	2.14 ± 0.44	2.26 ± 0.45	NS

Data represent mean ± SEM of 10 patients.
[a] $P < 0.01$

Discussion

The data for vessel diameter, cross sectional compliance and distensibility coefficient of the common carotid artery measured in this study in control subjects are comparable with the values determined by other investigators [8, 14]. In a group of 13 normotensive volunteers aged 20 to 35 years, van Merode, Kiezer and Reneman measured a common carotid artery diameter of 6.4 ± 0.2 mm [15]. In ten women whose age ranged from 19 to 24 years, van Merode et al determined a distensibility coefficient of 3.96 ± 1.0 10^{-3}/mm Hg (mean ± SD) and a cross sectional compliance of 100 ± 15 10^{-3} mm²/kPa. In a study of Baumgart et al [8], in 15 normotensive volunteers 21 to 56 years old, a relative distension per mm Hg pulse pressure of 0.15 ± 0.04%/mm Hg was determined.

Our data also confirm the results of previous studies, that the vessel wall elasticity is reduced with age [12, 16–18]. In a group of 160 healthy normotensive men at the age of 20 to 69 years, Reneman et al [12] observed a reduced distensibility coefficient, reduced cross sectional compliance and reduced relative systolic diameter change of the common carotid artery in the older subjects.

The present study demonstrates that the vessel wall distensibility of younger hemodialysis patients is significantly reduced in comparison with age-matched controls. In our study, the blood pressure was measured by finger-plethysmography (Finapres®), and blood pressure values of all groups were almost identical. The difference of vessel wall distensibility between the younger hemodialysis group and the age-matched controls seems to be underestimated, because finger-plethysmography may overestimate pulse pressure in younger control subjects. It is well known that pulse pressure is amplified as the pressure wave travels from the ascending aorta to the peripheral arteries [19], but this amplification decreases with age and in the elderly pulse pressure amplitudes are similar in the aorta and in peripheral arteries. Therefore, the vessel wall distensibility in the younger control subjects is probably higher than the values determined in the present study. Recently, it has been shown that the amplification of pulse pressure from the carotid artery to peripheral arteries is decreased in hemodialysis patients due to degenerative changes of the arterial wall [20]. Consequently, the difference of vessel wall distensibility between the younger hemodialysis group and the age-matched control group is probably underestimated in our study.

In the present study, the end diastolic diameter of the common carotid artery was smaller in the younger control subjects than in the younger hemodialysis patients. It was considered that the differences in distensibility coefficients between the two groups could be due to differences in vessel wall diameters. However, in subgroups with almost identical end diastolic diameters of the common carotid artery the distensibility coefficient was significantly lower in hemodialysis patients than in control subjects. Furthermore, volume depletion in hemodialysis patients caused a substantial decrease of carotid artery diameter with no significant increase of the distensibility coefficient. These findings strongly suggest that the reduced distensibility of the common carotid artery observed in younger hemodialysis patients is due to structural changes of the vessel wall. One may assume that other large arteries are affected in a similar way [5].

Intrinsic degenerative changes of the arterial wall are likely the cause of reduced vessel wall distensibility in hemodialysis patients. Ibels et al [21] found a more pronounced intimal thickening and enhanced calcification of the internal elastic lamella and the media ground substance in uremic patients. The

observed histological changes of the arterial wall may be associated with reduced arterial distensibility in uremic patients. However, vessel wall calcification *per se* seems to have little influence on elastic properties of the vessel wall since there is no strong correlation between pulse wave velocity and arterial calcification [5, 22].

The mechanism responsible for the reduced arterial distensibility in hemodialysis patients is not known. Most patients with end-stage renal failure develop hypertension. In hypertensive patients with normal kidney function, a decreased arterial distensibility was found independent of the actual blood pressure levels [3, 4]. Reduced vessel wall distensibility in hypertension seems to be caused by structural changes of the vessel wall [4, 23]. Structural changes of the arterial wall in hypertensive patients consist of thickening of the arterial wall due to smooth muscle hypertrophy concomitantly with an increase of fibrous connective tissue [24, 25]. High blood pressure may therefore also play a major role in the development of reduced vessel wall distensibility in patients with chronic renal failure. Our hemodialysis patients had normal blood pressure values during the two months preceding the study. However, they had been hypertensive for a minimum of one year prior to hemodialysis. Apart from high blood pressure, changes of fluid volume and hypercirculation related to arteriovenous fistula and anemia may cause reduced vessel wall distensibility due to mechanical damage of the arterial wall [26]. Electrolyte disturbances, hyperparathyroidism and uremic toxic effects might also cause changes of the arterial wall. Lipid disorders are frequently observed in hemodialysis patients [27]. Several studies failed to show an effect of hyperlipidemia on arterial compliance [28, 29]. Therefore, lipid disorders appear to be of minor importance for the reduced arterial distensibility in hemodialysis patients.

In our study, the vessel wall distensibility and the vessel diameter were not significantly different in the older hemodialysis patients and in age-matched controls. These results can be explained by the decrease of vessel wall elasticity with age. Similarly, van Merode [14] observed a reduction of vessel wall distensibility in young but not in older subjects with borderline hypertension.

In conclusion, vessel wall elasticity of the carotid artery is decreased in younger hemodialysis patients as compared with age-matched healthy subjects. The enhanced stiffness of the arteries could contribute to the higher incidence of cardiovascular disease in hemodialysis patients.

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