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EDITORIAL REVIEW

Atherosclerosis and arteriosclerosis in chronic renal failure

Cardiovascular complications are the principal cause of morbidity and mortality in end-stage renal disease patients [1]. Arterial disease is the major underlying factor leading to myocardial infarction and cerebrovascular events [2]. The alterations are related to occlusive lesions usually due to growth of a thrombus at the site of an atherosclerotic plaque. For these reasons, research has concentrated on metabolic and mechanical factors of vascular remodeling associated with atherosclerotic plaques.

There has been far less concern with the alterations of arteries as vascular cushions. This is an important aspect, however, since the function of arteries is not only to conduit blood, but also to cushion the pulsation due to intermittent ventricular contraction and flow generation [3]. These two aspects of arterial function can be dealt with independently since their functional alterations have different origins and consequences. Disorders of conduit function by narrowing the vessel lumen affect the tissues and organs downstream, while disorders of cushioning function by arterial wall stiffening have deleterious effects on the heart upstream [3]. In the present review we would like to introduce current hemodynamic concepts of arterial function and its alterations in end-stage renal disease.

Basic principles

The arterial system has two distinct and separate functions: to deliver blood with minimal loss of mean pressure to bodily tissues and organs, and to smooth the pulsations resulting from intermittent cardiac ejection so that blood flow through these organs is almost steady. The arteries thus act as conduits and as cushions [3].

Conduit function of arteries

The efficiency of conduit function is related to the width of the arteries and the near constancy of mean blood pressure along the arterial tree, the mean pressure drop between the ascending aorta and arteries in the forearm or leg being 2 to 3 mm Hg in a supine position [3, 4]. Alterations of conduit function occur through narrowing or occlusion of arteries with restriction of blood flow and resulting ischemia or infarction of tissues downstream. In basal resting conditions the conduit function is maintained until an artery is narrowed to 20% or less of its original diameter [5]. Atherosclerosis characterized by the presence of plaques is the most common disease that disturbs conduit function. Atherosclerosis is primarily an intimal disease, focal and patchy in its distribution, occurring preferentially in the carotid bifurcation, coronaries, renal arteries, infrarenal aorta, and femoral arteries [6]. Focal compensatory enlargement of arterial lumen occurs at discrete sites of narrowing immediately adjacent to more or less normal areas [7]. Risk factors and mechanisms of atherogenesis are complex. They include smoking, lipid disturbances, thrombogenesis, production of vasoactive substances and growth factors and mediators of inflammation. Besides these humoral factors atherogenesis also depends on mechanical factors such as tensile stress and alterations in shear stress [7–10]. Mechanical factors exert their deleterious effects by several mechanisms including increased permeability of endothelium to macromolecules and activation of the endothelial layer by shear stress alterations. The role of mechanical factors is confirmed by the high prevalence of atherosclerosis in hypertension, with a predilection of atherosclerotic plaques for certains sites characterized by disturbances of flow pattern and shear stress, like orifices, bifurcations, bending or pronounced tapering [6, 7].

Cushioning function of arteries

During systole around 50% of stroke volume is directly forwarded into peripheral circulation, and other 50% is stored in the aorta and major arteries, distending their walls and storing part of the energy then available in the diastole. In diastole the stored energy passively recoils the aorta, pressing the stored blood volume forward into peripheral vessels. This so-called "Windkessel function" transforms pulsatile flow in central arteries to almost a steady flow in the tissues [3]. This cushioning function is very efficient in young and healthy humans, and the extra energy lost on account of the intermittent ventricular ejection is only 10 to 15% greater than if the heart's output were nonpulsatile and continuous [11]. The efficiency of cushioning function depends principally on the viscoelastic properties of arterial walls described in terms of compliance, distensibility or stiffness (inverse of distensibility) [3, 11]. The physical properties of arterial walls will determine the amplitude of pressure waves, their propagation and reflection along the arteries. Ejection of blood from the heart into the aorta generates a primary pressure wave (incident), which is propelled forward to other arteries throughout the body at a given velocity (pulse wave velocity-PWV) [3, 11–13]. PWV increases with arterial stiffening and therefore increases progressively from the ascending aorta to the more distal parts of the arterial tree. The incident pressure wave is reflected at any point of structural or geometric discontinuity of the arterial tree, generating a natural counterpulsation (reflected wave) traveling backward from peripheral reflecting sites towards the ascending aorta [12, 13]. Incident and reflected waves are in constant interaction, and they sum up to determine the amplitude and shape of the measured pulse pressure wave, which depend on the amplitude and phase relationship (the timing) between the component waves. For a given pattern of ventricular ejection, the amplitude and the timing of incident and reflected wave depend on the viscoelastic properties of the arterial wall (arterial stiffness). Arterial stiffening is associated with increased systolic and pulse pressures, both directly by increasing the amplitude of the

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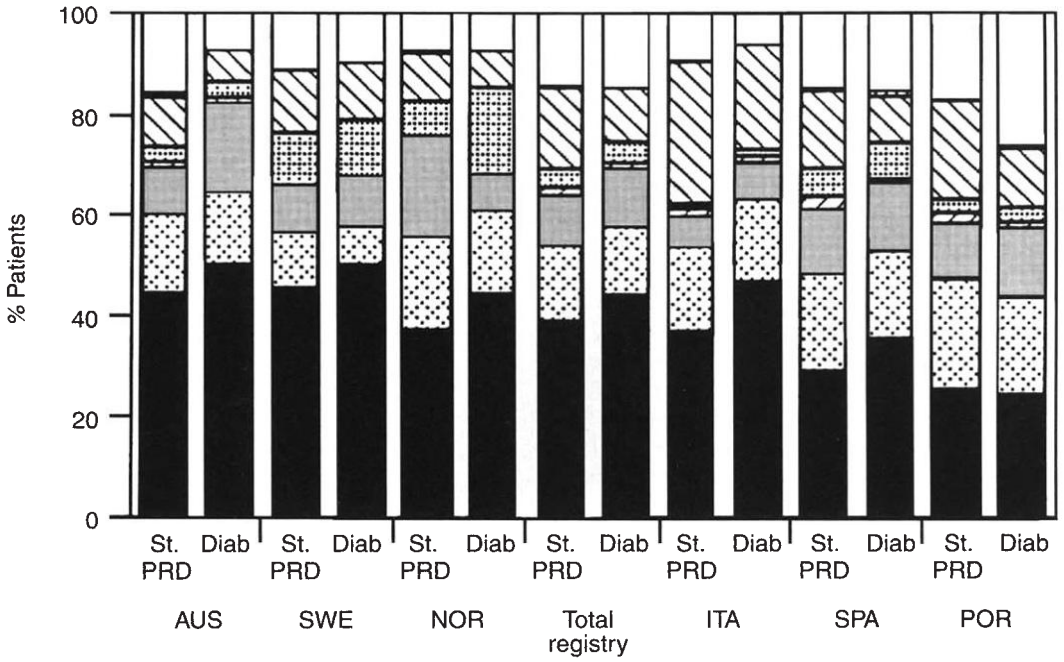

Fig. 1. *Causes of death in patients aged ≥ 60 years at the start of treatment, starting RRT from 1983–1992 (selected countries).* Comparison of mortality factors in European countries with relatively high and low mortality rates, respectively. A small percentage of cardiogenic mortality is observed in some countries with a relatively high mortality rate. Abbreviations are: St, standard patients; Diab, diabetic patients; PRD, primary renal disease; AUS, Austria; SWE, Sweden; NOR, Norway; ITA, Italy; SPA, Spain; POR, Portugal. Symbols are: (□) unknown; (▥) accident; (▧) miscellaneous; (▩) social; (▨) liver; (▣) infection; (⊡) vascular; and (■) cardiac (from Valderrabano et al, Annual Report on Management of Renal Failure in Europe, XXV, 1994; oral presentation at the 23rd ERA-EDTA Congress, Athens, 11–14 June 1995; used with permission).

pressure wave and indirectly by increasing PWV, causing an early return of reflected wave from the periphery to the aorta [3, 11–13]. The direct mechanism is responsible for an increased pulse and systolic pressure in the entire arterial system. Because of the different timing of wave reflections (reflection sites are closer to peripheral arteries than to the aorta), the indirect mechanism predominantly increases aortic and left ventricular pressure in the late systole at the expense of mean diastolic pressure, which is decreased [11, 13]. This results in increased hydraulic load imposed on the left ventricle and a reduction in subendocardial coronary blood supply during diastole [11–15].

Arteriosclerosis is the principal cause altering cushioning function [11]. Arteriosclerosis is primarily a medial degenerative condition that is generalized throughout the thoracic aorta and central arteries, causing dilation, diffuse hypertrophy and stiffening of arteries. Arteriosclerosis is sometimes considered as a "physiological" aging phenomenon that is accelerated by hypertension. Arteriosclerosis results in diffuse fibroelastic intima thickening, an increase in medial ground substance and collagen, and fragmentation of elastic lamellae with secondary fibrosis and calcification of the media. These changes are more pronounced in the aorta and central arteries than in the limb arteries [13].

Taken together, atherosclerosis is a disease that typically disturbs conduit function almost exclusively, while arteriosclerosis does not affect it. Nevertheless, in Western populations these two conditions frequently coexist, since both progress with aging and share several common pathogenetic mechanisms, making the distinction between atherosclerosis and arteriosclerosis sometimes difficult. The development of ultrasound techniques has permitted a direct visualization of small arterial wall segments with direct evaluation of the extent of atheromatous plaques and determination of arterial geometry, with measurements of arterial diameters and intima-media thicknes in plaque-free segments. Thus, the characteristics of arterial lesions at the site of atheromatous plaques yield information concerning pathogenetic factors that are very different from those at non-atherosclerotic sites.

Atherosclerosis in chronic renal failure

Prevalence and progression of atherosclerosis in uremic patients

Atherosclerosis is a frequent cause of morbidity in patients with end-stage renal disease. Myocardial infarction and cerebrovascular events occupy an important place in the mortality of these patients. This has already been shown in pioneer studies 20 years ago [2, 16, 17] and led to the hypothesis of the existence of an accelerated atherosclerosis [2]. The high prevalence of cardiovascular mortality in chronic hemodialysis patients reported in early reports has been extensively confirmed by numerous subsequent studies [1, 18–25]. Despite significant progress achieved with dialysis technology, there is no evidence for a decrease in the prevalence of atherosclerosis during the last decade, as shown in a recent study by the ERA-EDTA Registry [1]. Based on this report, the cardiovascular mortality rate of chronic dialysis patients, who were stratified into various subcategories according to age, gender, and geographic origin, was approximately 20 times higher than that of the general population, and the cerebrovascular death rate was nearly 10 times higher. The relative risk was thus considerably higher than that of nonuremic diabetic patients

in whom the increase in risk is "only" threefold [26]. Figure 1 shows the high prevalence of cardiovascular mortality in 60-year-old dialysis patients in Europe. It is of interest that the well-known north/south gradient of the general population was observed in the dialysis population as well, that is, there appears to be a much lower prevalence of lethal and non-lethal cardiovascular events in southern Europe than in northern Europe [1]. An increase in the relative risk to develop cardio- and cerebrovascular diseases was also found in recent studies done in dialysis patients in the United States [25, 27, 28], in Latin America [29], and in Japan [23, 30]. A somewhat different conclusion was, however, reached in a recent analysis by the USRD Annual Data Report of the trends in causes of death in dialysis patients for the middle to late 1980s. It showed that the adjusted death rates due to cerebrovascular accidents actually decreased whereas that of cardiac causes increased [31]. It must be stressed that in most studies of cardiovascular mortality no distinction has been made between ischemic and non-ischemic causes. This is of importance since coronary artery-independent mechanisms equally play important roles in the pathogenesis of cardiac failure, including myocardial hypertrophy, valvular disease, intermittent or permanent extracellular volume overload, and anemia [32, 33]. Interestingly, in a methodologically well-done study from the most southern part of Japan [23], the incidence of cerebrovascular events in hemodialysis patients was extremely high (by a factor of 11.5 compared with the general population), whereas that of the cardiac events was not increased (factor 1.1). This incidence clearly is at variance with recent observations made in the U.S. and in Europe.

The hypothesis by Lindner et al [2] of an accelerated atherosclerosis in chronic dialysis patients has been continuously cited since its publication two decades ago. Its validity appeared to be supported by several subsequent reports. Thus, Ibels et al showed in a post-mortem study [34] that dialysis patients exhibited a higher prevalence of atheromatous changes of the carotid and femoral vessel wall, compared with age-matched subjects without renal failure. Very recently, a similar finding has been reported again in a large patient cohort from Japan, using an ultrasonographic technique, in that there was an increased intima/media thickness of the carotid artery in chronic hemodialysis patients, compared with age-matched healthy control subjects (Fig. 2) [30].

However, it remains uncertain whether the atherosclerosis of dialysis patients is effectively accelerated. The high cardiovascular mortality rate is not a proof for an acceleration of the disease process. Many dialysis patients have more or less marked vascular lesions already at the start of dialysis treatment. The risk factors present in the predialysis phase may be of primary importance. Moreover, these patients often exhibit a number of coexistent risk factors, such as arterial hypertension, dyslipidemia, glucose intolerance, and cigarette smoking. These risks clearly are additive. In contrast, in the general population such risk factors may be more often present as single, separate items. Therefore, the reality of accelerated atherosclerosis remains subject to controversy [20, 35, 36]. In fact, this issue represents a preferred matter of discussion at nephrology meetings [37].

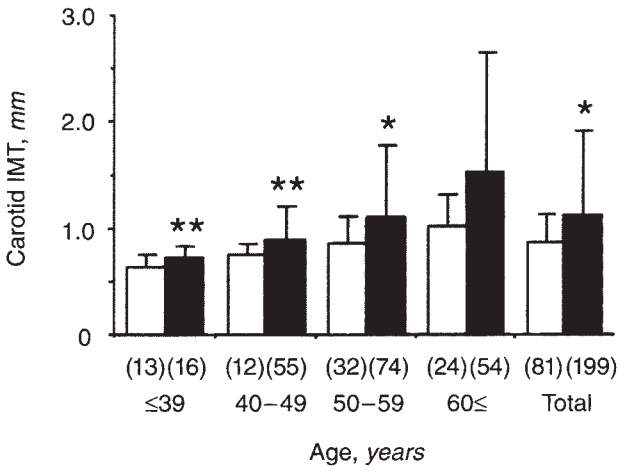

Fig. 2. *Intima/media thickness (IMD) of the carotid artery in healthy control subjects (N = 81; □) and in chronic hemodialysis patients (N = 199; ■).* Columns represent mean (± SD) values split up into different age groups. Parentheses show numbers of subjects. *$P < 0.001$ versus control subjects; **$P < 0.05$ versus control subjects (from Kawagishi et al, *Kidney Int* 48:820–826, 1995, with permission).

Risk factors for atherogenesis in chronically uremic patients

Physical factors. (1.) Tensile stress—arterial hypertension. Evidence that increased tensile stress is important in the pathogenesis of atherosclerosis comes from many observations including the following: atherosclerotic plaques are virtually confined to systemic arteries where the tensile stress is high; the frequency of atheromatous plaques is increased in patients with arterial hypertension; in aortic coarctation, atherosclerosis is accelerated in upper body arteries where the pressure is high, whereas it is decreased in severity in lower body arteries where the pressure is lower; and the development of atherosclerosis in autogenous vein bypass grafts can be experimentally prevented by a rigid external support that counteracts the increase in transmural pressure of the graft [38]. It is not known how increased tensile stress predisposes to atherosclerosis. It seems that high tensile stress enhances the endothelial permeability to macromolecules, thereby directly activating stress-sensitive ion channels.

Undoubtedly, hypertension plays an important role in the pathogenesis of atherosclerosis and vessel alterations associated with ischemia and hemorrhage [25]. A satisfactory control of hypertension is associated with a significant decrease in cerebrovascular morbidity and mortality [39, 40]. The role of hypertension in the pathogenesis of ischemic heart disease is less well established. In several studies, only a borderline effect of blood pressure control, or even the absence of any effect, was observed, whereas in other studies the control of hypertension was associated with an improvement of ischemic cardiac events [39, 40].

Hypertension is a frequent complication in chronic renal diseases, occurring in 80% of patients with end-stage renal disease before initiating dialysis therapy. After the start of dialysis treatment hypertension persists in a large proportion of patients. In particular, the physiologic blood pressure nocturnal dip is frequently absent [41]. An association between high blood pressure and occlusive vessel wall changes was found in chronic hemodialysis patients [25, 42], and a rigorous control of hypertension already at the time of incipient renal failure led to a significant decrease of the incidence of myocardial ischemia after initiation of dialysis therapy [43]. Clinical and epidemiological studies have shown a high prevalence of isolated systolic hypertension in ESRD patients [1, 44–46]. The systolic hypertension was associated with an increase in pulse pressure due to arterial stiffening. It

is of note that in several epidemiological studies increased pulse pressure has been found to be an independent and significant predictor of myocardial infarction and coronary death [47, 48]. As discussed later, increased arterial stiffness could be a factor of myocardial ischemia even in the absence of significant occlusive atheromatous lesions.

(2.) Shear stress and alterations in blood flow. Changes in shear stress may play a role in the pathogenesis of atherosclerosis, but controversy exists whether low or high shear stress would affect the development of atherosclerotic lesions. Fry [8] demonstrated that increased blood flow velocity and wall shear stress enhanced the permeability of the endothelial layers to macromolecules; this can cause erosions of the endothelium and may result in vessel wall injury. On the contrary, Caro and Nerem [9] suggested that low shear stress may adversely affect the mass transport of lipids across the endothelial layer consistently with the development of atherosclerotic plaques at the sites of low shear stress like bifurcations. Lower blood flow velocities and lower shear stress result in a longer particle residence time at blood-vessel wall interface, allowing greater interaction between blood and atherogenic factors as well as facilitating the diffusion of lipids and macromolecules accross the endothelium. Glagov and Zarins suggested that low shear stress induces focal thickening of arterial walls in order to reduce the local diameter and restore wall shear stress [10]. The multiplicity of theories relating changes in shear stress to atherogenesis illustrate the difficulty of measuring *in vivo* the shear stress at the vascular interface in humans. Nevertheless, it appears that fluctuating shear related to secondary non-laminar and pulsatile flow is the major etiologic factor. The role of shear stress alterations on the development of atherosclerosis in ESRD patients has not been specifically investigated, principally due to the difficulty of measuring the level of shear stress in humans.

Metabolic and humoral factors. (1.) Disturbances of lipid metabolism. The uremic syndrome is characterized by a number of quantitative and qualitative derangements of lipoprotein metabolism. The resulting disturbances [49] should, at least theoretically, contribute to the pathogenesis of the atherosclerosis of chronic renal failure.

The most important anomalies are: (1) an increase in the serum levels of triglycerides, IDL, cholesterol-rich VLDL and apolipoprotein (apo) B, and apo-B containing lipoproteins consisting of cholesterol-rich lipoprotein-B particles (LP-B) and triglyceride-rich complex lipoprotein-B particles (LP-Bc); and (2) a decrease in HDL-cholesterol (expecially HDL2), a decrease of the ratio of apo-AI/apo-CIII, and a reduction of that of apo-CII/apo-CIII [49–51]. Apo-CIII appears to be particularly important since uremic patients with vascular disease have a significant increase in the apo-CIII concentration of their B-lipoparticles, compared with uremic patients free of vascular lesions [52]. Partially degraded triglyceride-rich LP-Bc has been shown to be strongly associated with the development of small coronary artery atherosclerotic disease [53], whereas the level of cholesterol-rich LP-B was associated with large coronary artery lesions [53, 54].

In addition, there are profound disturbances of the dynamics of cholesterol transport, including a diminished cholesterol transport rate in serum from HDL to VLDL and LDL [55] and an inhibition of reverse cholesterol transport from peripheral cells to the circulation [56]. Several factors are incriminated in these actions, such as a decrease in LCAT enzymic activity [57] and the accumulation of an inhibitor of the cholesterol ester transfer protein (CETP) [58]. A decrease of the LDL receptor number at the cell surface probably contributes to the abnormal lipoprotein metabolism as well [59].

Furthermore, more recently several qualitative lipoprotein changes have been shown to occur, including increased oxidation [60–63], carbamylation [64], and transformation by advanced glycation end-products (AGE) [65]. Oxidative stress occurs not only at the lipid level, but also at the protein level [66], and hypochlorite-modified proteins, including oxidized LDL, are present in human atherosclerotic lesions [67]. However, it must be stressed that there are conflicting data in the literature with respect to excessive oxidation in uremia. Generally speaking, oxidative processes favor the occurrence of atherosclerosis, probably via an interference with normal lipoprotein function and the concomitant production of highly reactive lipid perioxidation products, such as malonaldehyde, forming adducts with free amino groups of lysines and other amino acids of apolipoprotein B [68], and leading to enhanced generation of oxysterols and depression of lipoprotein lipase mRNA and activity in arterial foam cells [69]. A profound immunological response against various epitopes of oxidized LDL generally occurs in patients with atherosclerotic lesions [70, 71]. The identification of the specific epitopes inducing this response probably will be assessable in the near future with the help of natural monoclonal autoantibodies [72].

Oxidized LDL may be taken up more readily in dialysis patients than in healthy subjects because of an increased expression of type I scavenger receptor [73]. An enhanced formation of atheromatous lesions ensues [74]. Similarly, AGE-LDL may be available for uptake into the vessel wall to a larger extent than normal LDL since such transformed particles have a prolonged stay in the circulation [65]. Figure 3 shows the pathologically slowed clearance of AGE-transformed LDL-particles in the experimental animal, compared with that of native LDL particles. AGE-transformed products of any nature, not only lipoproteins, might participate in the genesis of vascular lesions, especially in diabetic patients, via binding to their endothelial receptor, RAGE, the induction of the vascular adhesion molecule VCAM-1 and the attraction of circulating monocytes to the vessel wall [75]. Recently, it could be shown that RAGE was expressed in arterial and capillary endothelial cells of uremic patients, whereas it was not constitutively expressed in endothelial cells sampled from non-uremic control individuals [76].

The role of the triglyceride-rich lipoproteins as cardiovascular risk factor remains controversial. However, hemodialysis patients with coronary heart disease (CHD) generally have increased serum triglyceride levels together with a diminished serum HDL-cholesterol concentration [77]. The results of the CLAS study showed that the progression of myocardial ischemia was associated with increased circulating levels of triglyceride-rich lipoproteins [78]. However, the relatively low degree of hypertriglyceridemia seen in the majority of uremic patients corresponds only to a small increase in cardiovascular risk in the general population without renal insufficiency [79]. On the other hand, there is an association between IDL, cholesterol-rich VLDL and the degree of severity of CHD [80]. In addition, the cholesterol-rich uremic VLDL have a greater atherogenic potential than normal VLDL. Furthermore, clinical conditions with an accumulation of residual lipoparticles and IDL, such as those seen in chronic uremia,

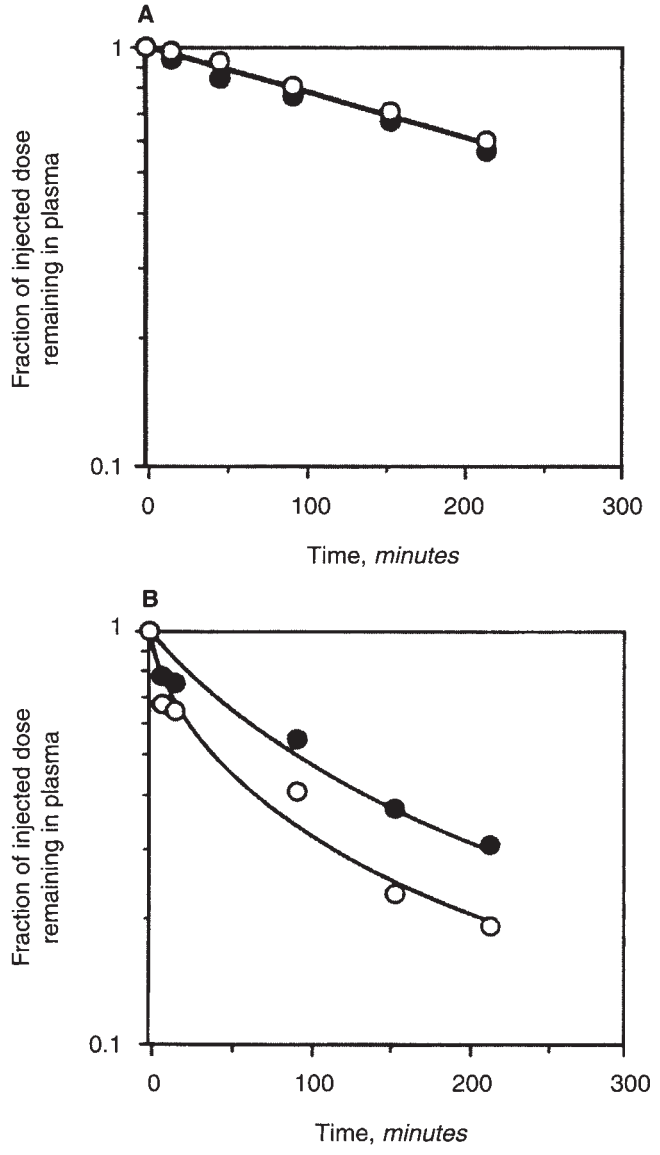

Fig. 3. *Plasma clearance of native and AGL-transformed human LDL in normal control mice (A) and in transgenic mice for the human LDL-receptor (B).* The animals were injected either native LDL (○) or AGE-LDL (●). The control mice without the human LDL receptor exhibit a slow decrease of native as well as of AGE-LDL (A). In contrast, the transgenic mice were able to eliminate relatively rapidly native LDL, but not AGE-transformed LDL. The latter therefore accumulate in serum (from Bucala et al, *PNAS* 91:9441–9445, 1995; with permission).

represent an increased risk for the development of ischemic cardiomyopathy [104].

Only a small number of systematic studies have been done with the most powerful, recently developed exploratory techniques to test the hypothesis of an association between disturbances of lipoprotein metabolism and atherosclerosis in a large population of chronically uremic patients. In the majority of studies with a sufficient sample size that are available to date, only serum levels of total cholesterol and triglyceride levels have been measured for this purpose, and it was found that in most of the patients who had clinical evidence of vascular disease, serum triglycerides were

Table 1. Anomalies of serum lipids and apolipoproteins in chronically uremic patients before the start of dialysis treatment who either had (CVE +) or had not (CVE −) a history of cardiovascular events

Serum levels	CVE + (N = 16)	CVE − (N = 43)
Triglycerides *mM*	2.3 ± 0.3	1.7 ± 0.1[a]
Apolioprotein-B *mg/liter*	1.7 ± 0.13	1.4 ± 0.06[b]
Apolipoprotein-CII *mg/liter*	59 ± 6	44 ± 3[a]
Apolipoprotein-CIII *mg/liter*	224 ± 22	176 ± 12[a]

[a] $P < 0.05$; [b] $P < 0.01$

increased whereas serum total cholesterol was normal. This has led to the conclusion that lipid disturbances probably do not play an important role. However, a relationship between the anomalies of lipoprotein metabolism and atheromatous vessel disease become apparent whenever such anomalies are examined in an appropriate manner. Hence, it has been shown recently that dialysis patients with vascular disease had an increase in serum triglycerides, total cholesterol, and VLDL cholesterol, compared with patients who had no evidence of vascular disease [81]. However, the former also were approximately 15 years older than the latter. Dialysis patients with type I diabetes and a history of myocardial infarction had significantly higher serum levels of total cholesterol and LDL/HDL-ratio than comparable patients without myocardial infarction [26]. In a personal study done at our institution in patients with advanced chronic renal failure who were not yet on dialysis and who were matched for sex and age (Lacour et al, unpublished study), we found significant differences for several lipoprotein parameters between a group of patients who had, and an another group who did not have, clinical evidence of cardiovascular disease (Table 1). There was no difference between the two groups with respect to age, body wt, or plasma concentrations of total cholesterol, HDL cholesterol, apo A or apo E.

In a recent study from Italy in which chronic hemodialysis patients were examined using carotid ultrasonography, a significant association was observed between the intima/media thickness of the vessel wall and the serum concentration of LDL cholesterol [82]. In contrast, in two other recent ultrasonographic studies done in dialysis patients no association was found, based on multivariate regression analysis, between the degree of severity of atheromatous lesions of the carotid and the femoral artery and the serum levels of a variety of lipid parameters, including apo-AI, apo-B, total or HDL cholesterol, LDL cholesterol, and triglycerides [30, 83]. Similarly, in a recent personal study (unpublished results) no difference in commonly measured serum lipid levels was observed between hemodialysis patients with or without ultrasonographically-proven atheromatous plaques of the carotid artery (Table 2). However, in none of these studies was a comparison made between lipid parameters and clinically evident cardio- or cerebrovascular events. Morover, the plaques could be the result of long-standing lipid abnromalities that have been changed with the advent of uremic or dialysis. For instance, the serum level of total cholesterol decreases in the case of malnutrition. Consequently, this parameter probably loses its predictive value for vascular risk [84].

Another independent, genetically-determined vascular risk factor in the general population is the serum level of lipoprotein(a) or Lp(a) [85]. However, its predictive value remains controversial

Table 2. Atheromatous plaques prevalence and comparison of clinical parameters in ESRD patients

Parameters	Plaques absent $N = 45$	Plaques present $N = 62$
Age *years*	43.9 ± 14.4	61.7 ± 13.5[a]
Sex *M/F ratio*	1.42 ± 0.50	1.31 ± 0.47
Body surface area m^2	1.68 ± 0.26	1.70 ± 0.16
Systolic BP *mm Hg*	144.0 ± 24.8	151.6 ± 33.0
Diastolic BP *mm Hg*	87.0 ± 13.9	78.6 ± 14.6[a]
CCA diameter *mm*	5.91 ± 0.79	6.64 ± 0.87[a]
CCA IMT *μm*	722 ± 107	838 ± 87[a]
CCA distensibility $KPa^{-1} \cdot 10^{-3}$	21.5 ± 9.5	12.9 ± 6.4[a]
Aortic PWV *cm/second*	908 ± 163	1247 ± 352[a]
Total cholesterol *mmol/liter*	5.03 ± 1.00	4.87 ± 1.54
HDL cholesterol *mmol/liter*	1.07 ± 0.35	1.12 ± 0.47
Triglyceride *mmol/liter*	1.90 ± 0.98	1.93 ± 0.87
Fibrinogen *g/liter*	4.20 ± 0.88	5.67 ± 1.00[a]
Smoking status *packet · years*	5.15 ± 11.00	16.00 ± 22.00[a]

Data are mean ± SD.

Abbreviations are: CCA, common carotid artery; IMT, intima-media thickness; PWV, pulse wave velocity

[a] $P < 0.01$

[86]. Apparently, the risk increases in case other lipidic risk factors are present, such as increased LDL, apoB, or decreased HDL [85, 87]. A correlation between low molecular apo(a)-phenotypes and CHD has been found in several studies [88]. The potential value of serum Lp(a) as a risk factor has been examined in uremic patients by numerous authors in recent years. In practically all these studies an increase of serum Lp(a) was found in a more or less large proportion of the patients examined [83, 89–93]. Figure 4 shows the increase of the percentage of uremic patients at our institution with high serum Lp(a) levels, compared with age- and sex-matched healthy control subjects [93]. This increase was partially reversible after successful renal transplantation [93]. Moreover, a recent report showed that the serum Lp(a) concentration was increased most often in hemodialysis patients with low serum albumin levels, that is, in patients with malnutrition, as compared to a normal serum Lp(a) concentration in dialysis patients with normal serum albumin [94].

The increase of serum Lp(a) in end-stage renal disease appears to be limited to patients with the high molecular isoform of the various Lp(a) phenotypes [92]. In accord with the findings in the population at large, higher serum Lp(a) concentrations were also found in uremic patients with a history of ischemia [90, 91]. Surprisingly, a correlation existed on the one hand between the serum level of Lp(a) and the number of ultrasonographically demonstrated lesions of the carotid artery, and on the other hand between the apo(a) phenotype and the presence of atheromatous vessel changes [83].

The complex relationship between serum Lp(a) and atherogenesis in chronic renal failure requires further scrutiny [85, 86]. A recently proposed mechanism for the induction or aggravation of atheromatous lesions by Lp(a) is an impairment of vascular relaxation by oxidized Lp(a) [95]. The latter may involve the formation of O_2^- radicals, the production of which has been shown by some groups to be enhanced in chronic renal failure patients [96]. Enhanced oxidation not only occurs at the lipid level, but also at the protein level [66]. Table 3 summarizes the most important atherogenic factors associated with lipoprotein metabolism.

(2.) Disturbances of glucose metabolism. Uremic patients suffer from a variety of anomalies of carbohydrate metabolism. Insulin resistance has been a well-known feature for many years. The myocardial tissue is involved as well since insulin-dependent glucose uptake is diminished in experimental uremia [26]. Insulin resistance also is in part responsible for the disturbed activation of lipoprotein lipase and the accumulation of VLDL and IDL in renal failure. In the experimental animal, this anomaly can be corrected by the administration of exogenous insulin [97]. It is also frequently improved after the start of intermittent hemodialysis treatment [98]. On the other hand, the increased glucose input into the organism under CAPD treatment may have an atherogenic potential via the induction of a variety of lipid disturbances, such as an increase in the production of VLDL with hypertriglyceridemia and a decrease in HDL cholesterol [99]. It is of note that the recently described, so-called "metabolic syndrome" of patients with essential hypertension, in particular in association with obesity, relies on the hypothesis of a relationship between insulin resistance and an increased tendency to develop atherosclerotic vascular disease [100]. Hyperinsulinemia recently has been shown to be an independent risk factor for ischemic heart disease [101].

It is well known that diabetic patients with advanced renal failure have a mediocre vascular prognosis. This could be related not only to the numerous metabolic anomalies linked to this pathologic condition, but also to the induction of tissue damage via slow, irreversible changes in extracellular molecules due to hyperglycemia-induced covalent modification. The best studied example of such changes is covalent modification of proteins by advanced glycation end products (AGEs). The endothelial cell is a primary target site. Reactive oxygen species, which may be excessively formed in uremic patients, particularly under specific hemodialysis conditions, contribute to sugar-adduct autoxidation and AGE formation. Interestingly, inhibition of oxidant pathways by antioxidants is capable of preventing intracellular AGE production [102].

(3.) Hyperhomocysteinemia. Homocysteine can exert toxic effects on vascular endothelium via an acceleration of LDL autooxydation [103] or via a mechanism favoring vascular thrombosis [104]. Recently, homocysteine has also been shown to enhance vascular smooth muscle cell proliferation, via an induction of cyclin A [105]. Chronic renal failure is associated with an increase in the plasma homocysteine level [106]. This is true for patients before [107] as well as after the start of dialysis therapy [42, 108]. The increase generally persists after successful renal transplantation [109]. Hyperhomocysteinemia has been recognized as an important vascular risk factor in the general population [110, 111]. Figure 5 demonstrates the prevalence of carotid artery stenosis as a function of plasma homocysteine levels in non-uremic patients. Recently, a similar relationship has been reported for hemodialysis patients [42] and kidney graft recipients [109]. An insufficient intake of folic acid could be the main cause of homocysteine accumulation [110]. In addition, under hemodialysis treatment, a state of relative folic acid deficiency can occur easily since folic acid is a water soluble, dialyzable vitamin that is regularly cleared during the dialysis session [112]. However, according to a recent report only the total and the free forms, but not the reduced form, of plasma homocysteine are increased in chronically uremic patients [108], and only the reduced form is supposed to act as a

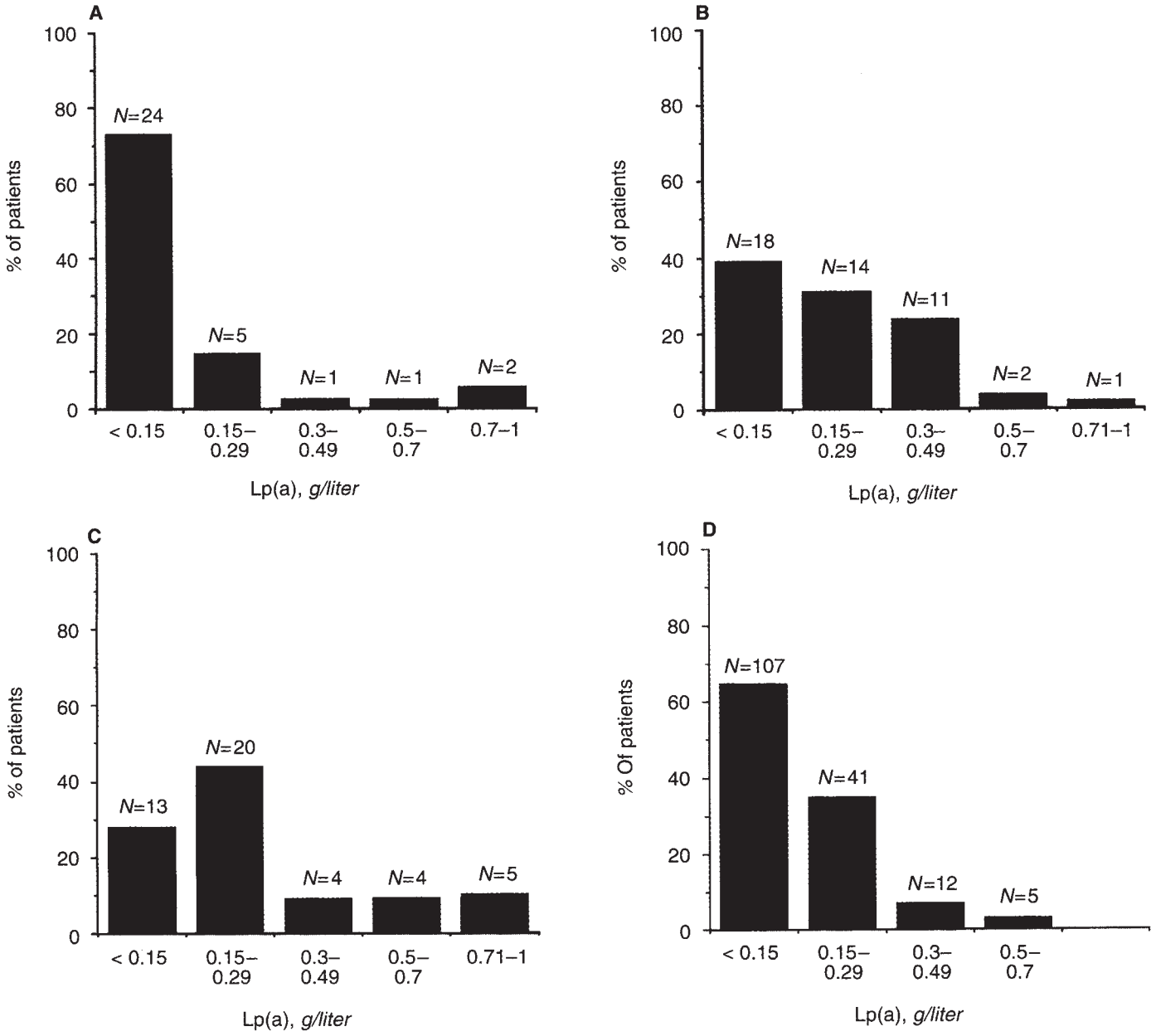

Fig. 4. *Percentage of* (**A**) *healthy control subjects (N = 33),* (**B**) *chronically uremic patients not yet on dialysis (N = 46),* (**C**) *hemodialysis patients (N = 46), and* (**D**) *renal transplant recipients (N = 165) with increasing serum Lp(a) levels from left to right.* A clear-cut shift to the right is seen in the patients, which is particularly marked in the hemodialysis patient population (after [93], with slight modifications).

pro-atherogenic factor. Another recent report found plasma homocysteine levels to be elevated in many patients, despite adequate blood folate levels, suggestive of an altered homocysteine metabolism (Note added in proof, A). Of note, an association has recently been found in dialysis patients between total plasma homocysteine and occlusive vascular disease [42]. It is possible that in renal failure reduced plasma homocysteine is formed in increased amounts which subsequently could be rapidly oxydized [108], due to the increased oxydative stress activity in uremia [96]. Interestingly, treatment with supraphysiologic doses of folic acid, vitamin B6 and vitamin B12 can decrease or even normalize plasma homocysteine levels in dialysis patients [113].

(4.) Cigarette smoking. The major role of cigarette smoking needs not be discussed in any detail. Chronically uremic patients are by no means protected against the deleterious effects of tobacco consumption [30, 114].

Other potential risk factors. (1.) Disturbances of calcium and phosphorus metabolism. Complicated atheromatous lesions with vascular calcifications probably have a greater prevalence in uremic than in non-uremic patients. Following percutaneous transluminal catheter angioplasty (PTCA), the one-year reocclusion rate was as high as 70% in dialysis patients, which is considerably higher than in other patient categories with an increased vascular risk, including non-uremic diabetic patients

Table 3. Potentially atherogenic factors related to the disturbed lipoprotein metabolism chronic renal failure

(1) Static quantitative and qualitative anomalies
- ✳ Increase of the serum levels of:
  - -triglycerides
  - -intermediary lipoproteins (IDL)
  - -cholesterol-rich low-density lipoproteins (VLDL)
  - -apolipoprotein-B (apo-B)
  - -Lp(a)
- ✳ Decrease of the serum levels of:
  - -cholesterol in high-density lipoproteins (HDL-cholesterol)
  - -apo-AI/apo-CIII ratio
  - -apo-CII/Apo-CIII ratio
- ✳ Physical changes of lipoproteins
  - -oxydation
  - -carbamylation
  - -transformation through "advanced glycation end-products" (AGE-transformation)

(2) Dynamic anomalies
- ✳ Diminished reverse cholesterol transport
  - -decrease of LCAT, LPL and HTGL enzyme activities
  - -accumulation of an inhibitor of cholesterol ester transfer protein (CETP)

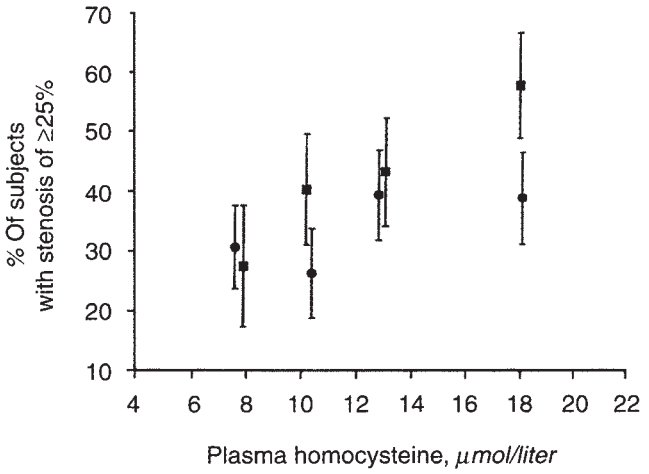

Fig. 5. *Age-corrected prevalence maximal extracranial carotid artery stenosis of ≥25 percent in men (■) and women (●), as a function of quartiles of plasma homocysteine concentration (from Selhub et al, N Engl J Med 332:286–291, 1995; used with permission).*

[26]. The calcification of atheromatous plaques probably is favored by an increased calcium-phosphate product, be it in association with secondary hyperparathyroidism or with adynamic bone disease. This is also true for the higher risk of developing aortic valve calcification [115]. Recently, a significant relation was also found in dialysis patients between the degree of carotid intima/media thickness and the plasma levels of phosphate and parathyroid hormone [30]. Vascular calcifications may be favored by long-term vitamin D therapy [116]. Clearly, a satisfactory control of calcium and phosphate metabolism is mandatory not only for an optimal skeletal stability but also with respect to vascular risk. Finally, arterial hypertension also promotes vascular calcium deposit, as has been recently shown for the coronary artery in asymptomatic men [117].

(2.) Vitamin E deficiency. Several pieces of evidence have emerged in favor of a potential enhancing role of vitamin E deficiency in the occurrence of coronary heart disease of the population at large [118, 119]. The protective role suggested from these epidemiologic studies is in apparent contradiction with a first large intervention study where the administration of vitamin E for several years was not associated with a decrease in the cardio- or cerebrovascular mortality of Finnish smokers in a recently published intervention study [120]. However, the primary end-point of that study was different, namely the prevention of cancer. A recent randomized, controlled trial of vitamin E administration to patients with coronary heart disease concluded that such a treatment substantially reduced the rate of non-fatal myocardial infarction [121]. However, in that study there was no apparent benefit on overall cardiovascular deaths either. Clearly, further work will be required to show the patient groups for whom these findings are applicable [121].

Vitamin E could afford protection against cardiovascular disease by several mechanisms, including antioxydative properties allowing to limit lipoprotein oxydation [122], inhibitory effects on platelet adhesion and aggregation [123] and on monocyte adhesion to the endothelial cell [124], antiproliferative effects on vascular smooth muscle [125] and intracellular effects on the monocyte leading to a decreased ability to release oxygen radicals and cytokines such as IL-1β [126]. To date, there is only limited evidence in favor of a vitamin E deficiency state in uremic patients. In one recent study there was no difference in the vitamin E content of LDL between three uremic groups, including patients either in the predialysis state, under hemodialysis, or under CAPD treatment [63]. However, subclass analysis of these patients revealed that prolonged dialysis treatment was associated with a decrease of the vitamin E content in LDL. The underlying cause has not been elucidated. In particular, the possible role of malnutrition has not been excluded. Since the efficiency of vitamin E to protect uremic LDL against oxidation appears to be diminished, relatively high doses of the vitamin are likely to be required to obtain that protection [63]. In another recent study, serum vitamin E was not different between hemodialysis patients and healthy subjects, although the content of tocopherol in red blood cells and in HDL was lower in the dialysis patients [127].

(3.) Vasoactive, endothelium- and platelet-derived compounds. Strictly speaking, endothelial and platelet dysfunction most often is the consequence of the noxious action of many of the risk factors that have been discussed, and not a risk factor by itself. The vessel wall produces a variety of locally active vasoconstrictor and vasodilator substances, some of which exert pro-atherogenic or anti-atherogenic actions. The former include the endothelins, and the latter several prostaglandin derivatives such as prostacyclin and nitric oxide (NO or EDRF). The plasma level of endothelin-1 is increased in uremic patients, before as well as after the dialysis session [128, 129]. To what extent its increase in the circulation reflects local endothelin-1 concentration and the propensity to favor atheromatous changes of the vessel wall, remains to be seen. Prostacyclin production by the vessel wall is increased in chronic renal failure whereas the synthesis of thromboxane by platelets is diminished [130]. Enhanced synthesis and activity of NO synthase leading to increased NO production has been shown to occur with hemodialysis using cellulosic membrane, but not polymethylmethacrylate membrane [131]. On the other hand, the formation and retention of the competitive inhibitor of NO synthase, asymetric dimethyl-L-arginine, may favor a decrease in NO generation [132]. Furthermore, NO also

could be more rapidly inactivated in dialysis patients, due to the excessive generation of oxygen-derived free radicals [96]. This process is particularly pronounced in diabetics and can be reversed by administering the antioxidant, vitamin C [133]. It is of note that hemodialysis patients may have a relative [134], and less frequently an absolute [135], ascorbic acid deficiency. Collectively, the physiologic equilibrium between locally formed vasoactive compounds clearly is perturbed in the uremic state, either intermittently or chronically.

A variety of other factors reflect an activation and/or dysfunction of the vascular endothelium in chronic renal failure in association with changes of the coagulation system, such as increased plasma levels of von Willebrand factor, plasminogen activators, thrombomodulin, fibrinogen, proconvertin and the inhibitor of type-1 plasminogen activator [114, 136, 137].

(4.) Cytokines. Some cytokines such as interleukin-1 have been ascribed pro-atherogenic actions as well [138]. The balance between IL-12 and IL-10 production might contribute to the level of immune-mediated tissue injury in atherosclerosis [139]. The enhanced generation of a variety of cytokines in uremic patients and in particular the activation of monocytes and platelets through the contact with bioincompatible dialysis membranes could favor atherosclerosis, according to this hypothesis [26].

(5.) Miscellaneous factors. Estrogens exert a protective action against the development of atheromatous vessel changes, probably not only via a more favorable constellation of plasma lipoproteins, but also via an inhibition of LDL-oxidation [140]. Estrogens probably act in a similar way in uremic patients who frequently exhibit a relative estrogen deficiency.

In the general population, angiotensinogen—and less convincingly the ACE enzyme—have been proposed to be two other risk factors [86]. However, a possible role of these factors has not yet been demonstrated in chronic renal failure.

The vitamin B6 deficiency frequently observed in uremic dialysis patients [112] could also favor the occurrence of atherosclerosis, as is the case in non-renal patients in whom a negative relation has been found between the plasma level of pyridoxal-5′-phosphate (the co-enzyme of vitamin B6) and the prevalence of extracranial carotid artery stenosis [110].

The progression from the advanced atherosclerotic lesion to vessel occlusion involves neutrophil (PMN) adhesion to the vascular endothelium. Neutrophils exert both scavenger and damaging effects, via the increased expression of adhesion molecules, including ICAM-1 and L-selectin. Neutrophil-depleted and ICAM-1–deficient mice have been shown to be relatively resistant to stroke [141]. In hemodialysis patients, neutrophil L-selectin decreases during the dialysis session with cellulosic membrane whereas plasma L-selectin increases, possibly in association with pulmonary leukoaggregation and neutrophil activation [142]. Such intermittent changes of neutrophil function could have relevance for the progression of atherosclerotic vessel disease.

Viral infections, which occur more frequently in uremic patients than in the general population, could play a role as well, as has been seen with cytomegalovirus (CMV) or adenovirus infection, possibly via the induction of vascular smooth muscle cell proliferation secondary to changes of lipid metabolism, immunologic injury, or impairment of vessel repair of atherosclerotic lesions [143–145; Note added in proof, B]. Prior exposure to CMV infection has been recently shown to be a strong independent risk factor for restenosis after coronary angioplasty and atherectomy [146].

The prolonged administration of immunosuppressive drugs such as corticosteroids and cyclosporine also must be considered. Both compounds may be atherogenic via their negative effects on lipoprotein metabolism, that is an increase in circulating total cholesterol and triglycerides [147].

Cyclosporine may also increase the development of atherosclerotic lesions via its suppression of cell-mediated immunity [148]. In addition, cyclosporine has been suspected to exert a stimulating effect on Lp(a), although a study done by our group failed to confirm this contention, at least for the case of renal transplant recipients [93].

Diuretics and antihypertensive drugs such as thiazides and beta adrenergic receptor blockers also could theoretically be atherogenic since they often induce an increase in serum triglyceride and LDL-cholesterol concentration and/or a decrease in LPL activity [149, 150]. Their positive effect in terms of blood pressure control must, however, be regarded as more important than their potentially negative effects via minor changes of lipoprotein metabolism [151].

The regular administration of heparin leads to a depletion of the pools of the two major lipolytic enzymes, LPL and HTGL through an intermittent liberation during each hemodialysis session [152]. Moreover, heparin interferes with the action of the third key enzyme of lipoprotein metablism, namely LCAT, via an excessive liberation of free fatty acids. The use of low molecular weight heparin is able to prevent such negative effects [153, 154].

Antiatherogenic mechanisms. (1.) Uremia and dialysis dependent factors. As mentioned above, the predominance of locally synthesized vasodilatory and antiatherogenic compounds such as prostacyclin and NO theoretically should be protective against atherosclerosis. The same is true for the diminished liberation of thromboxane and the mitogenic factor PDGF by platelets [26].

Anemia could be considered to be partially protective against atherogenesis because anemia interferes with the interaction of platelets with the arterial wall, decreasing platelet aggregation, thereby decreasing the risk of thrombogenesis. However, in a recent prospective study done in a large cohort of dialysis patients anemia had no independent association with the development of ischemic heart disease, whereas it was associated with clinical and echocardiographic cardiac disease, as well as with overall mortality [155].

Vitamin A levels are often increased in chronic renal failure [156]. Since the most common substrate of vitamin A is β-carotene, and since several epidemiological and animal studies suggest that β-carotene supplements are associated with a decreased risk for coronary artery disease [157], one could speculate that uremic patients are relatively protected via elevated plasma vitamin A. However, in a recent randomized, double-blind, placebo-controlled study the long-term supplementation of 22,071 physicians with beta carotene had no effect on the incidence of cardiovascular disease [158]. Moreover, it must be stressed that in chronic renal failure patients in whom the circulating vitamin A-binding protein is increased, retinol-binding protein is also elevated [159], so that free plasma vitamin A levels are probably normal [160].

The frequently diminished plasma concentrations of the most active vitamin D metabolite, calcitriol, which has been shown to be proatherogenic, also might be considered to be a rather favorable condition [26].

Table 4. Atherogenic risk factors in chronic renal failure

(1) Generally recognized risk factors
–hypertension
–pathologically altered lipoproteins
–increased serum homocysteine levels
–cigarette consumption
(2) Other potential risk factors
–disturbances of calcium phosphate metabolism
–vitamin E deficiency
–excessive local generation of pro-atherogenic substances (angiotensinogen, endothelin-1, thromboxane B, cytokines)
–viral infections
–estrogen deficiency
drugs (antihypertensive and immunosuppressive agents, heparin)
(3) Potentially protective factors
–decreased formation of thromboxane, calcitriol
–increased liberation of prostacyclin
–biocompatible (versus bioincompatible) dialysis membrane
–moderate alcohol consumption (wine)
(4) Co-morbid states aggravating ischemia
–myocardial hypertrophy
–anemia
–hypotensive episodes during the dialysis session
–arteriovenous fistula with excessive blood flow rates

Table 5. Common carotid artery geometry and functional indexes in ESRD and controls

Parameters	Controls $N = 55$	ESRD $N = 107$
Age *years*	48.4 ± 14.9	54.4 ± 16.9
Sex *M/F ratio*	1.41 ± 0.50	1.37 ± 0.49
Body surface area m^2	1.84 ± 0.24	1.68 ± 0.20[b]
Systolic BP *mm Hg*	144.0 ± 21.9	149.0 ± 30.7
Diastolic BP *mm Hg*	86.9 ± 13.7	81.7 ± 14.8[a]
CCA diameter *mm*	5.64 ± 0.69	6.37 ± 0.91[b]
CCA IMT μm	720 ± 88	794 ± 111[b]
CCA distensibility $KPa^{-1} \cdot 10^{-3}$	21.4 ± 10.9	15.9 ± 8.7[b]
Aortic PWV *cm/second*	987 ± 179	1117 ± 340[b]
DTTI/STTI %	170.0 ± 28.9	150 ± 31.9[b]
Subjects with atheromatous plaques %	21.8	57.9[b]

Data are mean ± SD. Abbreviations are: CCA, common carotid artery; IMT, intima-media thickness; PWV, carotido-femoral pulse wave velocity; DTTI/STTI, subendocardial viability index. This Table is from [145], expanded data.
[a] $P < 0.05$; [b] $P < 0.01$

The treatment of uremic patients with biocompatible, highly permeable dialysis membranes could theoretically oppose atherogenesis by exerting a positive influence on lipid metabolism, for instance through an improved function of the LPL enzyme or a decrease of apo-CIII [161].

(2.) Uremia independent factors. To date, the regular, moderate intake of alcohol, especially of wine, is considered by many authors as a favorable measure against the development of atheromatous lesions [162]. One of the various, as yet hypothetical, mechanisms proposed in the literature is an inhibition of LDL oxydation by phenolic substances contained in wine [163]. Another possible mechanism is a decrease in platelet aggregation [164]. The relatively high wine consumption in the southern part of Europe compared with that in the northern part could explain, at least in part, the north-south gradient of the prevalence of atherosclerosis, which also has been found in dialysis patients despite a much higher frequency of ischemic syndromes in the latter [1]. However, reduced risk of coronary heart disease is also seen with moderate consumption of other alcoholic beverages [165]. Reduced risk is observed only in individuals with increased LDL-cholesterol levels, not in those with normal or low levels [166].

Table 4 summarizes the most important atherogenic risk factors in chronic renal failure.

Arteriosclerosis in chronic renal failure

The arterial system in ESRD patients undergoes structural remodeling very similar to changes with aging, and is characterized by diffuse dilation, hypertrophy and stiffening of the aorta and major arteries (Table 5) [30, 167–169]. Although part of the arterial alterations in ESRD patients are associated with the aging process (Fig. 6), several features of arterial remodeling observed in chronic uremia are different from those of the natural aging process. Remodeling is an active process whose aim is to maintain a constant tensile and/or shear stress. Arterial remodeling usually occurs in response to long-term changes in hemodynamic (physical) conditions, in interaction with locally generated growth factors, vasoactive substances and inflammatory mediators [170]. The endothelium plays a prominent role in the remodeling process.

Hemodynamic factors of arterial remodeling in chronic uremia

Arterial walls and endothelial surface are exposed to the influence of mechanical factors such as flow and pressure stresses. Changes in blood flow and flow velocity alter the shear stress while changes in pulsatile blood pressure alter the circumferential tensile stress. Mechanical stresses alter the properties of arterial wall leading to acute functional or chronic structural adaptive changes [171–176].

Arterial changes associated with alterations in flow. Acute variations in flow and shear stress modulate arterial diameter through the phenomenon of flow dependent vasodilation. When increased during an augmentation in blood flow, shear stress induces an adaptive and functional enlargement of the vessel radius that acts as negative feedback to normalize the stress. This is accomplished through shear stress release of nitric oxyde (endothelium-dependent relaxing factor), hyperpolarizing factor and release of prostacyclin [177–180]. A chronic increase in blood flow modulates the vessel growth by inducing a structural enlargement of the arterial caliber by the reorganization of vascular wall cellular and extracellular components. Experimental studies have shown that reductions in blood flow produced smaller arterial diameters and medial tissue mass, while the creation of arteriovenous fistulas and chronic increase in flow induced dilation of the arteries [171, 172]. In ESRD patients a similar effect of chronically increased blood flow was observed in arteries of the arm bearing dialysis fistula [181]. On the other hand, in ESRD, conditions such as anemia, arteriovenous shunts and overhydration induce a state of chronic volume/flow overload associated with increased systemic and regional blood flow and flow velocity, creating conditions for systemic arterial remodeling [169]. This has been illustrated by cross sectional studies which showed a direct relationship between the diameter of the aorta and of major arteries and blood flow velocity [169], as well as by studies indicating that arterial enlargement could be limited by adequate fluid removal during dialysis [168]. Therefore, it appears that the systemic arterial enlargement observed in ESRD results in part from chronic volume and flow

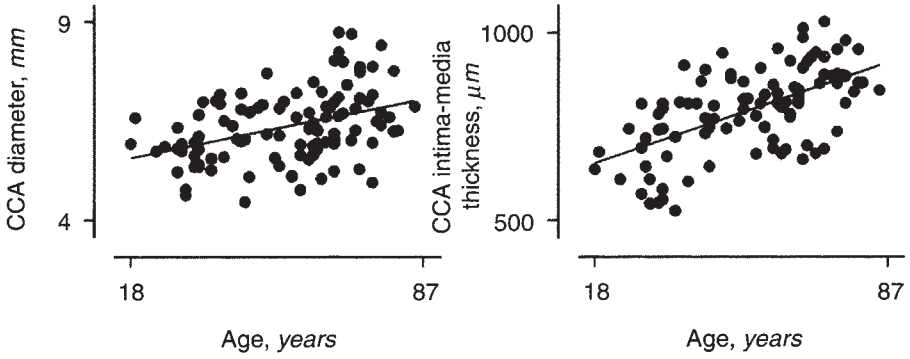

Fig. 6. *Scatter plot showing the correlation between age and common carotid artery (CCA) diameter (A; $r = 0.40$; $P < 0.0001$) and CCA intima-media thickness (B; $r = 0.58$, $P < 0.0001$) in ESRD patients (from London et al, Kidney Int 50:600–608, 1996, expanded data).*

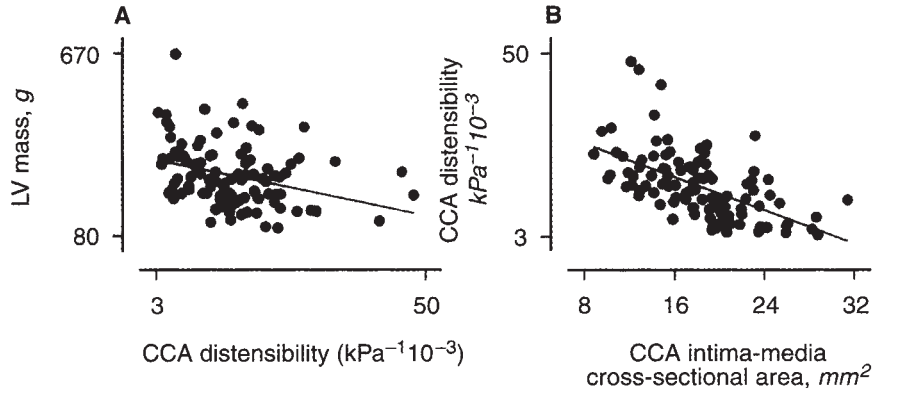

Fig. 7. *Scatter plot showing the correlations between CCA distensibility and left ventricular mass (A; $r = -0.33$, $P < 0.001$) and CCA intima-media cross sectional area and CCA distensibility (B; $r = -0.57$, $P < 0.0001$) in ESRD patients (from London et al, Kidney Int 50:600 to 608, 1996, expanded data).*

overload, and from this point of view differs from changes observed during normal aging.

Arterial changes associated with increase in tensile stress. Tensile stress is an important determinant of the vascular structure. A chronic increase in tensile stress, such as that which occurs during hypertension, induces vascular hypertrophy associated with an increase in the arterial intima-media layer and a decrease in lumen diameter, resulting in an increase in media/lumen ratio [182, 183]. According to Laplace's law whereby wall tension is directly proportional to arterial radius and intraarterial pressure, and inversely proportional to wall thickness, hypertrophy compensates for the increase in blood pressure or radius to maintain normal stress. In comparison with non-uremic patients, the intima-media thickness of major central arteries is increased in ESRD patients [169]. Like in the general population, in ESRD patients arterial wall thickness increases with age, distending pressure, and arterial diameter [169]. The increase in wall thickness is proportional to changes in diameter, and this is a logical consequence of Laplace's law, whereby wall tension is directly proportional to arterial radius. Nevertheless, according to the same law, when the blood pressure increases, and whatever the internal radius, the wall-to lumen ratio should increase in order to normalize the tensile stress. This is observed in nonuremic populations where the wall-to-lumen ratio of arteries has been reported to increase with intravascular pressure [182, 183], but not in ESRD patients [169]. The reason for this difference is not clear. It is possible that conduit arteries have a limited capacity to respond adequately to a combined flow and pressure overload. This was observed on radial artery on the side of arteriovenous fistula in ESRD patients [181] and in experimental conditions. Indeed, in vein grafts subjected to separate mechanical factors such as circumferential stretching and changes in blood velocity, Dobrin, Littooy and Endean [184] demonstrated that changes in flow influence intimal thickening, whereas medial thickening responds to changes in wall stress. Intimal thickening occurs in response to low flow velocity, whereas medial thickening occurs in response to increased parietal tension.

In ESRD, the increase in arterial intima-media thickness (Fig. 7) is associated with decreased arterial distensibility, increased PWV, and early return of wave reflections [169]. Arterial distensibility decreases with increasing blood pressure [3, 13]. In essential hypertensive patients, Laurent et al [185] have shown that the decrease in arterial distensibility was primarily due to higher distending blood pressure rather than to structural modifications, and when adjusted for differences in blood pressure, hypertrophied arteries of essential hypertensive subjects were more distensible and had lower elastic modulus than those of normotensive controls. In ESRD patients decreased arterial distensibility results directly from arterial wall hypertrophy, and incremental modulus of elasticity is increased in comparison with age- and pressure-matched non-uremic controls [169]. The different relationship between hypertrophy and intrinsic elastic properties in nonuremic subjects and ESRD points to qualitative differences in the "hypertrophic process," being in favor of altered intrinsic elastic properties as observed in experimental uremia and *in vitro* in arteries of uremic patients, namely fibroelastic intimal thickening, calcification of elastic lamellae and ground substance deposition [34].

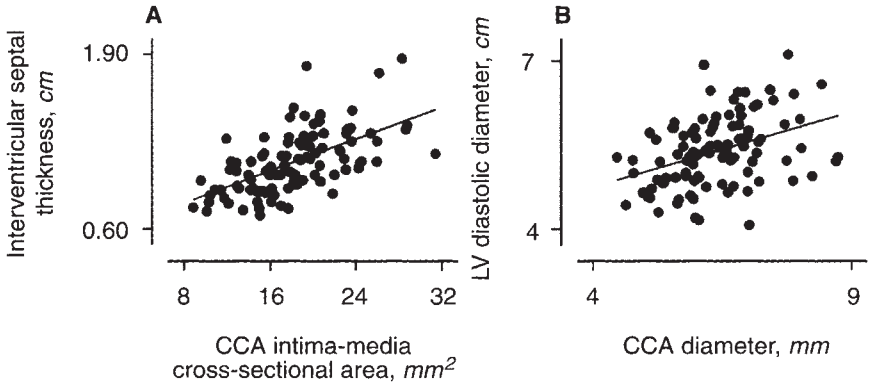

Fig. 8. *Scatter plot showing the correlation between the CCA intima-media cross sectional area and interventricular septal thickness (***A***; $r = 0.59$, $P < 0.0001$) and CCA diameter and left ventricular (LV) diastolic diameter (***B***; $r = 0.39$, $P < 0.0001$) in ESRD patients (from London et al, Kidney Int 50:600–608, 1996, expanded data).*

Nonhemodynamic regulators of arteriosclerotic remodeling in ESRD

It is beyond the scope of the present review to provide a detailed description of factors that modulate the growth of vascular smooth muscle cells and mediators of remodeling in extracellular matrix in general. Numerous growth factors and inhibitors are implicated in the pathogenesis of both atherosclerosis and arteriosclerosis. The role of some factors has already been discussed in the section concerning atherogenesis. In ESRD patients, the number of studies dealing specifically with the role of growth promoters or inhibitors is limited, and usually concern atherosclerosis and not arteriosclerosis. Recent studies performed on endothelial cells *in vitro* have shown that uremic serum has a direct effect on vascular subendothelium, characterized by a less intricate network of fibrils of extracellular matrix, and by a decreased attachment of endothelial cells to that matrix [186]. It would be of interest to analyze the potential effect of active vitamin D compounds on the mechanical properties of the vessel wall. Experimental studies have shown that calcitriol enhances resistance artery force generation *in vitro* [187] and, in concert with nicotine, diminishes arterial distensibility *in vivo* [188].

Consequences of arteriosclerosis for ESRD patients

The most important consequence of arteriosclerosis is arterial stiffening resulting in an increased left ventricular systolic stress and an abnormal relationship between systolic and diastolic tension-time integrals [3, 11, 13]. The principal consequences of these alterations are left ventricular hypertrophy and altered coronary perfusion with a decrease in subendocardial flow [11–15].

The important factors relating the pressure load to LV hypertrophy and altered LV function are the peak and end-systolic pressures in the aorta and central arteries, which are critically dependent on arterial stiffness and the intensity and timing of arterial wave reflections, that is, on the physical properties of arteries [3, 11, 13]. Previous studies have shown that LV hypertrophy in ESRD was correlated to increased pulsatile pressure load due to increased arterial stiffness and wave reflections [46, 167, 189]. Among ESRD patients, significant relations existed between comparable cardiac and vascular parameters [169]. LV diameter and arterial diameters are correlated and significant correlations were observed between the common carotid artery intima-media thickness and/or intima-media cross-sectional area and LV wall thickness and/or LV mass (Fig. 8). These relationships are independent of other factors like age, body surface area, and gender [169]. Moreover, independently from the blood pressure level, the extent of left ventricular hypertrophy is directly proportional to the decrease in aortic distensibility (Fig. 7). However, in ESRD patients a significant correlation was observed between arterial diameter and LV diastolic diameter (Fig. 8), also suggesting the existence of a direct link between arterial dilation and LV hypertrophy [169]. Indeed, the inertial effects are greater in enlarged arteries since larger blood-filled arteries require the heart to produce excess work in order to accelerate blood against larger inertial forces during ejection. An important consequence of LVH is reduction of coronary reserve, and myocardial hypertrophy has long been known as a major factor in the pathogenesis of myocardial ischemia.

The second most important consequence of arterial stiffening is compromised coronary perfusion. Canine studies have shown that aortic stiffening directly decreased subendocardial blood flow despite an increase in mean coronary flow, and that chronic aortic stiffening reduced cardiac transmural perfusion and aggravated subendocardial ischemia [11, 13, 14, 171]. Cardiac ischemia and alterations in subendocardial perfusion are frequently observed in uremic patients despite patent coronary arteries [20, 21]. This has been recently shown in ESRD patients in which the changes in large artery structure and function were associated with decreased diastolic/systolic tension-time integral (subendocardial viability index) (Fig. 9), an index of the propensity for myocardial ischemia when there are altered hemodynamic forces in the absence of occlusive arterial lesions [169]. Due to decreased arterial distensibility and increased PWV, wave reflections return earlier and impact on the incident wave during systole, increasing aortic and CCA pressures, and increasing the LV systolic stress and the systolic tension-time index, an index of LV oxygen and blood demand. On the other hand, the impact of the reflected wave in systole decreases the mean and telediastolic pressures, decreasing the diastolic tension-time index, an index of LV perfusion capacity [3, 13, 14]. Besides the role of abnormal structure and function of aorta and major arteries, these alterations are partly related to structural abnormalities of intramyocardial microvasculature. In uremic rats, Amann et al [190] have shown that diminished myocardial capillary density and thickening of intramyocardial arterioles are due to smooth muscle cell hyperplasia.

At this point of the discussion a special mention should be made concerning the role of anemia in the pathogenesis of arterial disorders and their clinical manifestation. By contributing to maintain volume and flow overload, anemia is an important

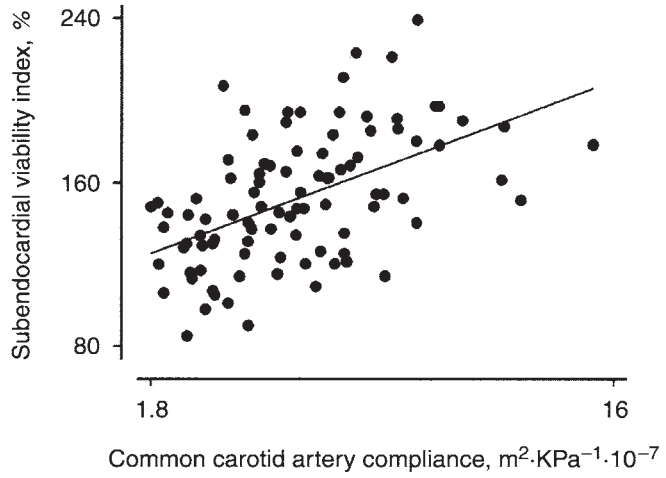

Fig. 9. *Scatterplot showing the correlation between the CCA compliance and subendocardial viability index (diastolic/systolic tension-time ratio) in ESRD patients ($r = 0.51$, $P < 0.0001$) (from London et al, Kidney Int 50:600–608, 1996, expanded data).*

factor in the pathogenesis of left ventricular hypertrophy and its consequences [191–193]. Anemia induces an increased venous return and left ventricular preload, and by contributing to arterial remodeling also increases the ventricular afterload [169]. On the other hand, anemia *per se* induces an alteration of the coronary pressure-flow relationship, inducing an upward shift of the autoregulatory plateau and a decrease in coronary reserve. Therefore, the nearly constant anemia in uremic patients, although it does not appear to contribute *per se* to the development of ischemic heart disease [155], plays an important role in the occurrence of ischemic symptoms, whether or not in conjunction with the presence of atheromatous plaques. This condition is frequently underestimated or even ignored by cardiologists who take care of such patients. Fortunately, the introduction of erythropoietin into clinical practice has improved the therapeutic approach, and myocardial hypertrophy generally regresses and myocardial ischemia may improve [191–193]. Nevertheless, it remains to be determined whether the anemia should be entirely or only partly corrected, since major changes of blood viscosity could alter the shear stress applied to the vascular wall, with unpredictable consequences.

Conclusion and perspectives

The cardiovascular complications of chronic renal failure patients can be schematically ascribed to two different major mechanisms: arteriosclerosis and atherosclerosis. Whereas the latter is a disease that typically disturbs conduit function almost exclusively, the former does not affect it. Most of the underlying mechanisms and risk factors are different, however, some are shared by the two conditions, including arterial hypertension, hormonal disturbances, and dependence on growth factors.

Most of the factors that have been mentioned with respect to the pathogenesis of arteriosclerosis, based on studies in the general population, recently have been shown to play a similar role in patients with end-stage renal disease. In contrast, several of the above evoked mechanisms in the atherogenesis of chronic renal failure remain hypothetical at present. One of the main reasons is that no long-term, well-controlled studies have been available in this area that would have systematically tested, in uremic patients, the importance of factors such as high blood pressure, via the use of antihypertensive drugs, or disturbances of lipoprotein metabolism, via the use of lipid lowering medications. Current clinical practice as to the use of the latter has been extensively reviewed in a recent meta-analysis by Massy et al [194]. The majority of studies have been limited to relating hemodynamic or metabolic parameters to parameters of ischemia. It is only during recent years that a small number of controlled studies has been conducted that were aimed at examining the effect of antihypertensive drugs on static and dynamic parameters of the vessel wall, in particular the pathologically increased arterial stiffness [168, 195, 196]. Thus, London et al [196] could show that the administration for 12 months of either the calcium channel blocker, nitrendipine or the ACE inhibitor, perindopril led to a decrease in arterial pulse wave velocity and pulse wave reflection, indicative of an improvement of vessel wall elasticity. In addition, the administration of perindopril, but not of nitrendipine, was associated with a decrease in left ventricular myocardial mass, primarily via a decrement of the left ventricular volume, although both drugs led to an improvement of left ventricular function.

Controlled long-term studies are time and energy consuming, but they are indispensable to reach valid conclusions on the implications of the numerous factors which theoretically may play a role in the ischemic syndromes of chronic renal failure patients. This is also true for therapeutic interventions such as the use of lipid lowering agents, vitamins, or dietary maneuvers. Prospective, randomized, large-scale trials in uremic patients are urgently required to answer this question.

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