Pathophysiology Underlying Accelerated Atherogenesis in Renal Disease: Closing in on the Target

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The landmark report of Lindner et al. (1) was the first to show that a high proportion of dialysis patients succumb to coronary heart disease. For a long time, however, it was unclear whether or not this observation is fully explained by the high prevalence of classical cardiovascular risk factors (2) or whether pathogenic factors that are specific for renal dysfunction accelerate atherogenesis in uremia and, as we know today, even in states of minor renal dysfunction (3, 4).

Much new information documents not only a high prevalence of coronary atheroma in cross-sectional studies but also a high rate of progression of coronary atherosclerotic lesions in advanced renal failure (5–8). In a recent prospective study, this was found even in patients with minor renal dysfunction (9). Not only is the risk of cardiovascular events higher (10), but the case fatality rate of ischemic cardiac events is also dramatically increased (11,12). This is as far as one could get by observation, according to the famous statement of Claude Bernard: observation is passive science; experimentation is active science. And experimentation in the apo-E−/− mouse recently provided the definite evidence that atherogenesis is specifically accelerated by renal dysfunction (13,14). Two studies documented accelerated growth of atherosclerotic plaques in the aorta. What is remarkable is the fact that this occurred not only after subtotal nephrectomy, but even after uninephrectomy. This finding is of considerable interest in view of the high cardiovascular risk associated with even minor renal dysfunction (3,15,16). Currently, we do not have a smoking gun—yet, but the experimental studies (13,14) have at least identified a strong suspect; the finding of increased staining of aortic endothelial cells for nitrotyrosine even outside of the plaques points to widespread oxidative stress (13) for which there is also evidence in humans (17). But crucial initial steps in atherogenesis remained undefined, and we still do not know whether the atherogenic effect of uremia follows new pathways or just amplifies the response to the atherosclerotic injury. The study of Bro et al. (18) in this issue of JASN sheds new light on this problem by addressing the topic of endothelial adhesion molecules. Expression of adhesion molecules is one of the first steps of atherogenesis and part and parcel of the inflammatory injury to the vessel wall (19).

Bro et al. showed an early and selective increase of ICAM mRNA expression in both lesioned and nonlesioned endothelium, with no change in the expression of selectin and VCAM. A delayed increase of VCAM mRNA was seen selectively in the lesions but not in nonlesioned endothelial cells. The increase was more pronounced in the underlying vascular smooth muscle cells—more consistent with the interpretation that it represents a reaction to plaque formation rather than an initiating pathogenetic mechanism. It had been known in the past that circulating concentrations of ICAM and VCAM are increased in patients with renal failure (20), but these results are difficult to interpret because VCAM is also expressed by nonvascular cells (21) and the biologic activity of the measured product had not been documented. The present study clarifies this point by showing increased expression of these adhesion molecules in the aorta.

The findings raise a number of questions. First, are they consistent with less direct clinical observations? Indeed, early work of Wittko-Sarsat et al. (22) and more recent studies by others have shown increased concentrations of biomarkers of inflammation (hsCRP, IL-6, etc.) and a prothrombotic state (vWF, dimers) in patients with relatively early renal failure (23,24). Increased concentrations of asymmetric dimethyl-L-arginine (ADMA) are also found in renal patients, even when whole kidney GFR is still normal. It had been assumed that normal GFR was maintained by single nephron hyperfiltration. The finding of high ADMA concentrations is highly suggestive of endothelial cell dysfunction with a consecutive decrease in enzymatic ADMA breakdown (25). The bioavailability of the vasoprotective and vasodilatory agent nitric oxide (NO) is also diminished presumably as the result of both diminished synthesis (26) and increased scavenging via reactive oxygen species (ROS). Finally, direct evidence of endothelial dysfunction in renal disease is provided by attenuated endothelial cell-dependent vasodilatation (27,28).

Although the authors have come close to identifying a smoking gun, a second question remains. What is the trigger that causes the inflammatory response? There may be more than one cause, and the usual gang of culprits comes to one’s mind. Since ICAM-1 expression is regulated by NF-κB (29,30), known signal substances activating NFκB such as proinflamm-
matory cytokines, AngII and ET1, oxidized lipids, or AGE may be involved, but a particularly hot candidate is oxidative stress, as suggested by the immunohistochemical finding from Buzzolo et al. (13) of increased expression of nitrotyrosine. Another hot candidate, or at least accomplice, in the initiation or amplification of the response could be C reactive protein (CRP). Deposition of CRP on endothelial cells causes upregulation of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin acting as an initial trigger or an amplifier or both (31). CRP also promotes the release of the chemokine MCP-1 that is involved in leukocyte attraction and transmigration through the endothelial cell layer (32) and the release of the potent vasoconstrictor endothelin-1, which by itself again promotes upregulation of adhesion molecules and MCP-1 on endothelial cells, creating yet another positive feedback loop (33). CRP can also neutralize NO that is produced by endothelial cells (34). NO inhibits platelet and leukocyte activation and prevents vascular smooth muscle cell proliferation. Again CRP inhibits eNOS expression and interferes with downstream effector steps of NO (34). At least in vitro, CRP also upregulates the AT1 receptor, augments AngII-induced proliferation and migration of vascular smooth muscle cells, and increases ROS production, both basal and after stimulation by AngII (35). To date, very little direct evidence for an exaggerated inflammatory reaction in the vessel wall of renal patients has been reported. Nevertheless some preliminary data from our laboratories show deposition of CRP in vessels of uremic animals. The human relevance of these findings is heightened by the observation of more intense deposition of complement C5b9 and CRP in and around coronary plaques of uremic patients. It has been argued that elevated concentrations of factor D amplify the activation of the complement system through the alternative pathway, as documented by Oppermann et al. (37), thus contributing to vascular damage (38).

There is no shortage of further potential culprits, e.g., the CD40/CD40 ligand system (39) and many others, illustrating that the work of Bro et al. (18) has struck a gold mine and will undoubtedly stimulate further studies. Pursuit of this lead might also yield results with potentially far-reaching clinical consequences. The perspective, or at least the hope, is that better definition of the initial steps of accelerated atherogenesis will provide novel targets for treatment. One would be able to test in preclinical studies whether for instance measures to reduce oxidative stress or to interfere with microinflammation are of use, e.g., by administration of vitamin E (40) or aspirin (41).

However, it is quite unlikely that we shall ever find one single golden bullet. Interfering on several levels, i.e., the multifactorial intervention analogous to what has been shown to be highly effective in diabetes (42) might be the final answer, i.e., lipid lowering, rigorous BP control, cessation of smoking, etc., and possibly also antiinflammatory measures.

References

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