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EDITORIAL COMMENT

Plasma Homocysteine, Coronary Risk Factors and Serum Nitrite in Coronary Artery Disease and Vascular Syndrome X

One of the earliest events in the development of atherosclerosis is believed to be endothelial dysfunction (1). In addition, however, patients without established coronary artery disease but with risk factors for its development also have evidence of endothelial dysfunction (2). Such risk factors include elevated levels of low-density lipoproteins (LDL), reduced levels of high density lipoproteins (HDL), free radicals from tobacco, hypertension, diabetes mellitus, acquired and genetic hypercoagulable states, and infectious organisms (2-4). These cardiovascular risk factors, by inducing endothelial-cell injury and dysfunction, contribute to the development of atherogenesis. Furthermore, many of these risk factors are known to act in synergy with regards to their effects on endothelial dysfunction and the development of atherosclerosis. In addition to these so-called traditional risk factors, elevated levels of homocysteine have also been associated with endothelial dysfunction. Homocysteine has been shown to be toxic to the endothelium (5), to be prothrombotic (6), and to decrease the availability of nitric oxide (7). Elevations of plasma homocysteine have been associated with increased age, menopause, genetic defects in the enzymes involved in homocysteine metabolism, nutritional deficiencies in vitamin co-factors and other systemic diseases (8). Numerous prospective and case-controlled studies have shown hyperhomocysteinemia to be an independent risk factor for atherothrombotic vascular disease (9). Finally, another group of patients who may demonstrate evidence of endothelial dysfunction are those with the so-called cardiac syndrome X. This condition is characterized by a history of typical angina pectoris, presence of ischemic-like ST segment changes on exercise testing and neither obvious epicardial coronary disease nor inducible spasm on coronary arteriography (10). Abnormal vascular reactivity seems to be a predominant feature of this syndrome (11), although there is controversy as to whether or not this abnormal vascular reactivity is endothelium dependent or independent (12). Many studies have suggested an imbalance between endothelin-1 and NO release in patients with this syndrome (11,13, 14), but the precise mechanism for this imbalance remains an area of intense investigation.

Endothelial dysfunction is characterized by a number of changes. Cell surface markers involved in adhesion – such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion (ICAM-1) – are up-regulated, and production of cytokines, chemokines and other growth factors is increased (1, 15, 16). As a result, there is increased adhesiveness of platelets and leukocytes to the endothelium, increased vascular permeability and a local procoagulant state. In addition, endothelial dysfunction is associated with loss of NO bioavailability due to either reduced formation or accelerated degradation of NO (17). Besides being a potent vasodilator, NO counteracts leukocyte adhesion to the endothelium (18, 19), prevents vascular smooth muscle proliferation (20), and inhibits platelet aggregation (21). These biologic actions of NO make it an important component in the endogenous defense against vascular injury, inflammation, and thrombosis, all key events involved throughout the course of atherosclerosis. Thus, loss of the functional integrity of the endothelium, as is commonly seen in the presence of cardiovascular risk factors, plays a critical role in all stages of atheroscerlosis from lesion initiation to plaque rupture (17).

In the current issue of AKD, Soysal et al (22). report on the relationships between the various cardiac risk factors, homocysteine levels and the presence of endothelial dysfunction in three well-characterized groups of patients representing a spectrum of atherosclerosis – namely, patients with established CAD, patients with cardiac syndrome X and appa-

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rently healthy subjects. The authors make a number of interesting oberservations. Firstly, they re-assuringly confirm many of the known relationships between homocysteine and both CAD and CAD risk factors. Importantly, however, they do this after rigorously excluding patients with co-morbidities known to raise homocysteine levels. Secondly, they report reduced nitrite levels in patients with established CAD as well as those with risk factors, including those with elevated homocysteine levels. The finding of an inverse relationship between homocysteine and serum nitrite levels suggests a potential mechanism for endothelial dysfunction in patients with hyperhomocysteinemia that is consistent with present theories about the deleterious effects of homocysteine on nitric oxide bioavailability. Thirdly, and perhaps most interestingly, the authors also demonstrate the lack of a relationship between either homocysteine levels or serum nitrite levels and cardiac syndrome X – setting this group apart from those with established CAD. The latter finding might suggest the lack of endothelial dysfunction in patients with cardiac syndrome X. Although most studies in fact do suggest the presence of endothelial dysfunction in this patient population (11,13,22,23), there are other studies that do not (12, 24). One limitation of the current study is the use of nitrite levels as the sole measure of endothelial dysfunction. In addition to nitrite levels, the measurement of other markers of endothelial dysfunction (such as VCAM-1 levels, brachial artery flow measurements, or vasomotor response to pharmacologic or physical stimuli) in this group of patients would have been most useful. It is noteworthy that Soysal and colleagues specifically excluded patients with one or more features of the so-called metabolic syndrome X (characterized by abdominal obesity, hypertriglyceridemia, low HDL cholesterol, insulin resistance, hyperinsulinemia, and hypertension). Since many of these clinical characteristics are themselves associated with endothelial dysfunction (25), their exclusion from this study controls for any potentially confounding variables and further strengthens the findings of these investigators.

In summary, Soysal et al. should be commended for a well-conducted, statistically sound study in a group of very well characterized patients. Their data is intriguing and strongly supports the current view on cardiac risk factors, homocysteine and endothelial dysfunction. In addition, however, their data also provides some mechanistic insight into the potential mechanisms of endothelial dysfunction in hyperhomocysteinemia and also continues to fuel the controversy regarding the presence or absence of endothelial dysfunction in patients with cardiac Syndrome X.

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References

1. Ross R. Atherosclerosis–an inflammatory disease. N Engl J Med. 1999; 340: 115-26.
2. Vita JA, Treasure CB, Nabel EG, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990; 81: 491-7.
3. Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. J Am Coll Cardiol 1994; 24: 1468-74.
4. Reddy KG, Nair RN, Sheehan HM, Hodgson JM. Evidence that selective endothelial dysfunction may occur in the absence of angiographic or ultrasound atherosclerosis in patients with risk factors for atherosclerosis. J Am Coll Cardiol 1994; 23: 833-43.
5. Harker LA, Ross R, Slichter SJ, Scott CR. Homocysteine-induced arteriosclerosis. The role of endothelial cell injury and platelet response in its genesis. J Clin Invest 1976; 58: 731-41.
6. Hajjar KA. Homocysteine-induced modulation of tissue plasminogen activator binding to its endothelial cell membrane receptor. J Clin Invest. 1993; 91: 2873-9.
7. Upchurch GR Jr, Welch GN, Fabian AJ, et al. Homocyst(e)ine decreases bioavailable nitric oxide by a mechanism involving glutathione peroxidase. J Biol Chem 1997; 272: 17012-7.
8. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998; 338: 1042-50.
9. The Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002; 288: 2015-22.
10. Kemp HG Jr. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. Am J Cardiol 1973; 32: 375-6.
11. Piatti P, Fragasso G, Monti LD, et al. Acute intravenous L-arginine infusion decreases endothelin-1 levels and improves endothelial function in patients with angina pectoris and normal coronary arteriograms: correlation with asymmetric dimethylarginine levels. Circulation 2003; 107: 429-36.

12. Bottcher M, Botker HE, Sonne H, Nielsen TT, Czernin J. Endothelium-dependent and -independent perfusion reserve and the effect of L-arginine on myocardial perfusion in patients with syndrome X. Circulation 1999 ; 99: 1795-801.
13. Piatti P, Fragasso G, Monti LD, et al. Endothelial and metabolic characteristics of patients with angina and angiographically normal coronary arteries: comparison with subjects with insulin resistance syndrome and normal controls. J Am Coll Cardiol 1999; 34: 1452-60.
14. Kaski JC, Elliott PM, Salomone O, et al. Concentration of circulating plasma endothelin in patients with angina and normal coronary angiograms. Br Heart J 1995; 74: 620-4.
15. Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell 1994; 76: 301-14.
16. Ley K, Tedder TF. Leukocyte interactions with vascular endothelium. New insights into selectin-mediated attachment and rolling. J Immunol 1995; 155: 525-8.
17. Behrendt D, Ganz P. Endothelial function. From vascular biology to clinical applications. Am J Cardiol 2002; 90(Suppl): 40L-8L.
18. Gauthier TW, Scalia R, Murohara T, Guo JP, Lefer AM. Nitric oxide protects against leukocyte-endothelium interactions in the early stages of hypercholesterolemia. Arterioscler Thromb Vasc Biol 1995; 15: 1652-9.
19. Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogenous modulator of leukocyte adhesion. Proc Natl Acad Sci U S A 1991; 88: 4651-5.
20. Cornwell TL, Arnold E, Boerth NJ, Lincoln TM.Inhibition of smooth muscle cell growth by nitric oxide and activation of cAMP-dependent protein kinase by cGMP. Am J Physiol 1994; 267: C1405-13.
21. de Graaf JC, Banga JD, Moncada S, Palmer RM, de Groot PG, Sixma JJ. Nitric oxide functions as an inhibitor of platelet adhesion under flow conditions. Circulation 1992; 85: 2284-90.
22. Soysal D, Sumru S, Susam İ. The association of plasma homocysteine, cardiac risk factors and serum nitrite in patients with coronary artery disease, cardiac syndrome X and healthy subects. Anadolu Kardiyol Derg 2003; 3: 26-34.
23. Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. N Engl J Med 1993; 328: 1659-64.
24. Desideri G, Gaspardone A, Gentile M, Santucci A, Gioffre PA, Ferri C. Endothelial activation in patients with cardiac syndrome X. Circulation 2000; 102: 2359-64.
25. Piatti PM, Monti LD, Conti M, et al. Hypertriglyceridemia and hyperinsulinemia are potent inducers of endothelin-1 release in humans. Diabetes 1996; 45: 316-21.

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