

## Systemic Tetrahydrobiopterin (BH<sub>4</sub>) Levels and Coronary Artery Disease

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Dear Sir,

The vascular endothelium has important secretory, metabolic, and immunologic functions. The impairment of such functions is an early step in the pathogenesis of several diseases including atherosclerosis [1], and endothelium-dependent vasodilation induced by nitric oxide (NO) is certainly a key function. Tetrahydrobiopterin (BH<sub>4</sub>) is intimately involved in NO-mediated vasomotion. The exact role of BH<sub>4</sub> in NO catalysis remains debated, but may include stabilization of the active conformation of the enzyme, action as an allosteric effector enhancing substrate binding, coupling of substrate oxidation to NADPH consumption thereby reducing the ratio of superoxide to NO production, and posttranscriptional stabilization of NO synthase mRNA [2, 3]. In addition, BH<sub>4</sub> is a potent antioxidant and scavenger of oxygen-derived free radicals [2, 4]. Impaired NO production and increased free radical formation have been observed in several diseases predisposing to atherosclerosis [4]. In states of BH<sub>4</sub> depletion, endothelium-located NO synthase switches from NO to superoxide production. Thus, a local BH<sub>4</sub> deficiency in endothelial cells may be of major importance in the pathogenesis of a dysfunctional endothelium as a mechanism of oxidative vascular injury [3]. This consideration is corroborated by several in vitro and

**Table 1.** BH<sub>4</sub> levels in 17 patients with normal coronary vessels and in 17 patients with 3-vessel disease

	Normal coronary vessels	3-Vessel disease
Patients	17	17
Age, years	54.4 ± 12.0	64.1 ± 9.0*
Sex (f/m)	3/14	3/14
<i>History</i>		
Smoking/pack-years	10/22.2 ± 17.0	14/49.6 ± 28.7
Hypertension	4	9
Diabetes	1	2
Hypercholesterolemia	12	14
Positive family history	8	14
<i>Medication</i>		
Platelet inhibitors	11	15
Beta-blockers	5	12
Statins	3	5
<i>Laboratory</i>		
Glucose, mmol/l	5.71 ± 1.32	5.82 ± 1.66
Total cholesterol, mmol/l	5.64 ± 1.13	5.70 ± 1.11
Creatinine, μmol/l	79.0 ± 9.5	84.1 ± 13.2
C-reactive protein, mg/l	0.38 ± 1.5	3.64 ± 5.5*
BH <sub>4</sub> , nmol/l	6.05 ± 1.40	5.69 ± 1.84

Values are presented either as number of subjects or mean ± SD.

\* p < 0.05.

<sup>1</sup> Measured as total biopterin (sum of BH<sub>4</sub>, BH<sub>2</sub>, and biopterin).

in vivo studies showing that exogenous BH<sub>4</sub> may indeed restore impaired NO production during acute or chronic endothelial dysfunction [4]. However, whether or not this local BH<sub>4</sub> deficiency is reflected by decreased circulating BH<sub>4</sub> levels is unknown at present.

We therefore quantified serum BH<sub>4</sub> levels as total biopterin (sum of BH<sub>4</sub>, and oxidized forms BH<sub>2</sub> and biopterin) with fluorimetric detection by HPLC after acidic oxidation [5] in 17 patients with angiographically proven 3-vessel disease and in 17 patients with angiographically normal coronary arteries; the latter were evaluated for chest pain (5), arrhythmia (4), valvular heart disease (3), cardiomyopathy (2), cardiac tumor (1), or preoperatively before noncardiac surgery (2). Only subjects without impairment of renal function, immunologic disorder, or cancer were eligible. The results are given in table 1.

Although circulating total biopterin levels were slightly lower in patients with 3-ves-

sel coronary artery disease compared to subjects without coronary atherosclerosis, this difference was small and did not reach statistical significance ( $p = 0.53$  for intergroup comparison using the two-tailed unpaired *t* test). In contrast, C-reactive protein was higher in 3-vessel disease, presumably reflecting the well-known inflammatory component of atherosclerotic disease [1]. From these data we conclude that a local BH<sub>4</sub> deficiency with atherosclerotic vessels does not seem to be reflected by systemically decreased total biopterin concentrations. Therefore, the determination of circulating total biopterin levels is helpful neither in the diagnosis nor in the quantification of coronary artery disease. Furthermore, the measurement of systemic total biopterin concentrations is probably not useful for the selection of patients who would profit from BH<sub>4</sub> administration, which has been shown to improve endothelial dysfunction and to reduce the progression of atherosclerosis [3, 4].

## References

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