Therapy With Nitrates: Increasing Evidence of Vascular Toxicity*

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The organic nitrates came into use in the therapy of cardiovascular disease well over a century ago. At that time, and for decades thereafter, they were administered acutely to relieve symptoms of myocardial ischemia and pulmonary congestion. With the later introduction of long-acting preparations in an effort to prevent symptoms of ischemia and/or left ventricular dysfunction, the problem of tolerance during continuous dosing was soon documented. There has since been a tremendous focus of investigation concerning the etiology of tolerance and methods to prevent it.

In the mid 1990s it was reported that therapy with nitroglycerin was associated with increased free radical production by the endothelium and that this biochemical response appeared to play an important role in the development of tolerance (1). This observation, the "free radical hypothesis" of the etiology of tolerance, was followed by a rapid increase in our understanding of the impact of organic nitrates on both vascular biochemistry and vascular function. Animal models of nitrate exposure have now documented that sustained exposure to organic nitrates, particularly glyceryl trinitrate (GTN), is associated with: 1) increased superoxide anion production, with this increase apparently arising from a number of enzymatic sources (1–3); 2) increased tissue content of endothelin-1, possibly mediated by increased production of angiotensin II (4); 3) activation of protein kinase C (4); 4) development of abnormalities in L-arginine transport with subsequent abnormalities in endothelial nitric oxide synthase function (5,6); and 5) abnormalities in the function of mitochondrial aldehyde dehydrogenase (7).

At the same time, human experimentation has documented that sustained therapy with GTN is associated with an increase in the vascular sensitivity to vasoconstriction (8) and evidence of abnormal responses to endothelium-dependent vasodilation in a number of vascular beds (9,10). It should be emphasized that most experimental work to date has involved GTN, with little information published concerning the impact of other organic nitrates. Some observations have suggested that there may be important differences between different organic nitrates. For example, it has been suggested that pentaerythritol tetranitrate does not appear to cause increased free radical production (11) and that this characteristic is associated with less evidence of hemodynamic tolerance (12) as well as improved endotheliumpdependent vasomotor responses during sustained therapy (13).

In this issue of the Journal, Hink et al. (14) from Thomas Münzel’s laboratory, provide more data concerning the far-reaching biochemical effects of nitroglycerin therapy on vascular biochemical homeostasis. Their observations document that relatively short-term continuous GTN therapy in both rats and rabbits was associated with the development of important abnormalities in the function of prostacyclin synthase (PGI2-S), the enzyme responsible for the synthesis of prostaglandin-I2, a compound with potent vasodilatory and antiplatelet effects. Their observations serve to remind us that some of the acute vasomotor effects of nitrates are mediated through the stimulatory effects of either GTN and/or the active metabolite nitric oxide on PGI2 production (15). More importantly, they identify yet another apparent adverse effect of sustained GTN therapy on vascular homeostasis and function. Their data document that sustained GTN therapy is associated with a marked decrease in PGI2-S activity, with subsequent reduction in PGI2 production. The inhibitory effect of GTN exposure on PGI2-S function appears to be mediated by increased tyrosine nitration of PGI2-S, a reflection of increased peroxynitrite formation, which is demonstrated to occur during sustained nitrate exposure.

What is not addressed in the current publication is the relative importance of the oxidative damage to PGI2-S in the development of nitrate tolerance and the abnormalities of vascular function observed in vivo during nitrate therapy. During the past several years, a number of important cellular enzyme systems have been shown to develop impaired function in response to sustained therapy with GTN, including membrane-bound oxidases (16), endothelial nitric oxide synthase (3,17), arginine transporters (6) and, most recently, mitochondrial aldehyde dehydrogenase (7). In each case, these abnormalities appear to result in or be caused by increased bioavailability of superoxide anion and related reactive oxygen species. Unfortunately, the relative importance of these functional abnormalities remains uncertain. Indeed, it remains unclear which, if any, of the observed changes are primary events versus secondary phenomena related to the increase in radical production caused by the nitrate. Directly relevant to this question is the fact that the fundamental mechanism that triggers the increase in superoxide anion production remains unknown. It has
been suggested that this may result directly from the biotransformation and denitriﬁcation of GTN (and, potentially, other organic nitrates) (18); however, there has been no deﬁnitive documentation of this process. Further understanding of the fundamental mechanisms involved is required before the exact cascade of events will be unraveled and the relative importance of these multiple observed biochemical abnormalities determined.

Despite these factual uncertainties, the potential implications of these ﬁndings are intriguing. The data provided by Hink et al. (14) suggest that sustained GTN therapy is associated with a decrease in production of PGI2, with the subsequent loss of important vasodilator and antiplatelet effects. Furthermore, it is possible that inhibition of PGI2-S, with a consequent increase in the concentration of prostaglandin-H2, may also be associated with an increase in the synthesis of thromboxane-A2, with its potent vasoconstrictor and platelet activation effects. However, the majority of patients with coronary artery disease are prescribed the cyclooxygenase inhibitor acetylsalicylic acid, which reduces the production of many prostaglandins, including both PGI2 and thromboxane-A2. The dose dependency of the inhibitory effect of acetylsalicylic acid on platelet and vascular prostaglandin production and the relevance of this to the beneﬁcial effects of acetylsalicylic acid in the therapy of coronary artery disease has been debated for decades (19). In light of these factors, it cannot be concluded with certainty that the inhibitory effect of GTN on PGI2-S is necessarily associated with adverse effects on clinical outcome. Nevertheless, the authors correctly point out that this combination of effects, particularly when combined with the inhibitory effect of GTN on endothelial nitric oxide function, sets a stage where GTN therapy is associated an inhibition of the production the two most important endogenous vasodilator, antithrombotic and antiproliferative signaling pathways in vascular tissue.

There is growing evidence that sustained nitrate therapy, particularly with GTN, is associated with a multitude of adverse effects on vascular biochemistry and function. Some ﬁve years ago, our group noted that some of the vascular changes observed during sustained nitrate therapy were potentially atherogenic (20). Despite these concerns, we still have almost no information concerning the impact of chronic nitrate therapy on long-term clinical outcomes. Trials of the organic nitrates in angina have been small with short-term follow-up periods. Larger trials, in the postinfarction setting, have used short follow-up periods and the impact of nitrate therapy independent of hydralazine in the setting of chronic heart failure remains ambiguous (21,22). Interestingly, when retrospective analyses have been performed examining the impact of nitrate therapy in the postinfarct period, negative results have been observed (23). These observations, when combined with the obvious negative impact of nitrate therapy on endothelial function, should drive us to more carefully examine our chronic use of these agents in patients with a variety of cardiovascular diseases.

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