

## New tricks for an old drug

See doi:10.1053/euhj.2002.3296 for the article to which this Editorial refers

In this issue, Willoughby and colleagues report the effects of perhexiline on the sensitivity of platelets to the antiaggregatory effects of nitric oxide<sup>[1]</sup>. Nitric oxide potently inhibits the aggregation of platelets via a cyclic GMP dependent mechanism. This group of workers has previously shown that platelets from patients with both stable angina and unstable coronary syndromes exhibit impaired *ex vivo* sensitivity to the antiaggregatory effects of the nitric oxide donor sodium nitroprusside, this abnormality being particularly marked in patients with unstable coronary syndromes<sup>[2]</sup>. Platelet nitric oxide resistance may play an important role in platelet thrombus formation in unstable coronary syndromes<sup>[3]</sup>. Previous work by the group has suggested that this resistance to the antiaggregatory effects of nitric oxide on platelets might occur from one or both of two mechanisms. First, by increased nitric oxide clearance as a result of increased superoxide production. Second, via a reversible inhibition of platelet guanylate cyclase<sup>[4]</sup>. Platelet NO resistance has also been documented in association with insulin resistance in obesity<sup>[5]</sup>. In certain situations, including heart failure and coronary artery disease there may also be 'resistance' to the vascular smooth muscle effects of nitric oxide<sup>[6,7]</sup>. Because this resistance results in a parallel shift of the dose-response relation it is only identified by examining the vascular response to submaximal doses of NO donors. Nitric oxide resistance may contribute to the endothelial dysfunction seen in these conditions. It is not known whether the mechanisms responsible for vascular smooth muscle and platelet nitric oxide resistance are the same, and whether the two phenomena parallel each other.

The present study was prompted by the group's previous observation that in a multivariate analysis, perhexiline treatment predicted greater platelet nitric oxide sensitivity in patients with angina<sup>[2]</sup>. Perhexiline is an antianginal now little used in Europe because of reports of hepatotoxicity and neurotoxicity in the 1970s and 1980s. Nevertheless, several reports have shown it to be a potent anti-anginal, both as monotherapy and as an adjunct to conventional antianginal therapy<sup>[8,9]</sup>. It is metabolized by a P450 enzyme system for which there is polymorphic variation, and toxicity can be avoided by measuring plasma levels and maintaining them within the range

0.15–0.6  $\mu\text{g} \cdot \text{ml}^{-1}$ <sup>[10]</sup>. There has been a resurgence in its use for both refractory angina and unstable angina in Australia over the past decade or so, in light of its efficacy and acceptable safety profile with appropriate monitoring of plasma levels. Recent studies have suggested that the principal mechanism responsible for its antianginal efficacy may be metabolic. It is a potent inhibitor of the enzyme carnitine palmitoyltransferase-1 (CTP-1) which is involved in mitochondrial uptake of long chain fatty acids<sup>[11]</sup>. This results in a reduction in myocardial fatty acid  $\beta$  oxidation, and an increase in glucose utilization at a reduced oxygen cost for energy production<sup>[12]</sup>. Other metabolic agents are also available which cause a shift in substrate utilization<sup>[13–16]</sup>.

In this non-randomized study the authors examined the effects of initiating perhexiline on platelet nitric oxide sensitivity in 30 patients with refractory but stable angina and 50 patients with unstable coronary syndromes. As would be expected on the basis of the existing literature, perhexiline administration was associated with marked improvements in anginal frequency in both groups. Although perhexiline did not change the basal aggregation of platelets to ADP *ex vivo* in either patient group, after 3 days administration, there was a substantial increase in the antiaggregatory effects of sodium nitroprusside in both patient groups—implying increased platelet nitric oxide sensitivity. In a group of 12 patients with acute coronary syndromes who were not given perhexiline, there was no change in either platelet aggregation in response to ADP or in its inhibition by sodium nitroprusside over the same time interval. In an elegant series of investigations the authors demonstrate that the increased nitric oxide sensitivity is associated with increased platelet cGMP generation and that the extent of improvement in platelet NO responsiveness predicted clinical symptomatic response. They demonstrated that co-incubation of isolated neutrophils with perhexiline abrogated the superoxide 'burst' in response to fmlp, but they conclude that most of the effect of perhexiline on platelet NO responsiveness may be via reversal of platelet guanylate cyclase generation. They present two lines of evidence to support this. First, 3 days of perhexiline therapy did not change whole blood superoxide generation. Second, the beneficial effects on platelets were observed even in platelet-rich plasma, which has minimal potential for superoxide generation. Perhexiline has insulin-sensitizing actions<sup>[17]</sup>, and the authors speculate whether this

may contribute to the phenomenon. Platelet NO resistance occurs in the setting of insulin resistance associated with obesity<sup>[5]</sup>. Oxidative stress cannot be excluded, however, as a mechanism of reversible guanylate cyclase inhibition. In another study intravenous vitamin C augmented platelet NO responsiveness in patients with CHF<sup>[18]</sup>. By improving insulin sensitivity, perhexiline might increase intracellular antioxidant status and this may contribute to the restoration of guanylate cyclase activity. Cellular uptake of vitamin C is insulin dependent and occurs against a 10-fold concentration gradient<sup>[19]</sup>. Intracellular vitamin C is a key factor in restoring the antioxidant potential of intracellular antioxidants including reduced glutathione and vitamin E<sup>[20,21]</sup>.

This paper provides important insights into the mechanism of action of perhexiline. In addition to its metabolic antianginal effects, restoration of the antiaggregatory effects of nitric oxide may potentially have an important therapeutic role in patients with acute coronary syndromes.

Perhexiline is now being used quite widely in Australia for both refractory angina and unstable coronary syndromes. Perhaps the time has come for cardiologists outside Australia to reconsider the use of 'metabolic agents'. This paper suggests that perhexiline may potentially modify platelet thrombus formation as well as reducing myocardial oxygen requirement. These mechanisms might potentially lead to a reduction in major adverse clinical events in patients with acute coronary syndromes. A trial may be warranted to examine this important issue. We do not know whether these effects on platelet NO sensitivity are shared by the other 'metabolic' agents.

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