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Oral presentation

Nitric oxide resistance at the platelet level: pathophysiology and therapeutic implications

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Background

Nitric oxide (NO) functions as a negative regulator of platelet aggregability, predominantly via activation of soluble guanylate cyclase (sGC); this is also relevant to the clinical efficacy of NO donors in management of acute coronary syndromes. However, we have discovered that acute coronary syndromes are associated with attenuation of platelet responsiveness to NO donors, independent of the phenomenon of nitrate tolerance. The phenomenon of platelet NO resistance has been documented to occur in association with a number of coronary risk factors (hypertension, diabetes, hyperlipidaemia) and also in non-ischaemic forms of heart disease.

Epidemiology and prognostic impact

In general, we have documented that severe NO resistance was seen particularly in patients with unstable angina pectoris [1]. However, NO resistance also occurred in the presence of hyperglycaemia [2], in aortic stenosis (independent of the presence of coronary disease), in polycystic ovarian syndrome [3], and in untreated heart failure [4]. Among patients with unstable angina, NO resistance was an independent predictor of morbidity and mortality [5].

Mechanistic considerations

Platelet NO resistance reflects a combination of "scavenging" of NO by reactive oxygen species and (potentially reversible) impairment of sGC function. Evidence for a role for superoxide (O_2^-) in modulating NO resistance includes close correlations with whole blood O_2^- content [2], and partial reversal with SOD [6]. We have also documented an impairment of platelet sGC function in patients with stable angina pectoris [6]. However, phosphodiesterase activity did not appear to modulate NO resistance.

Therapeutics of NO resistance

We examined the effects of perindopril in patients with previously untreated congestive heart failure [7]; treatment was associated with partial restoration of SNP responses. The "metabolic" anti-anginal agent perhexiline restored platelet responsiveness to NO in patients with refractory angina, with parallel improvements in symptomatic status [8]. In diabetics, treatment of hyperglycaemia with intravenous insulin infusion also ameliorated platelet NO resistance. As an alternative approach, we are currently testing the hypothesis that NO resistance may be circumvented either by nitroxyl donors, or "direct" sGC stimulators (BAY 41-2272) and sGC activators (BAY 58-2667). Theoretically, these sGC activators offer the advantage of circumventing both NO "scavenging" and inactivation/oxidation of sGC.

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