previous data showing the effectiveness of clopidogrel therapy. An additional critical point mentioned is the random time-point chosen for measurement. In real clinical practice it is not practical to assess platelet function at a specific point of time ± few hours. Therefore, we chose a time-point when maximum platelet inhibition is achieved (∼2 h) after the first administration of a loading dose of 600 mg clopidogrel. After this time-point we (Figure 1) and others did not reveal further attenuation of clopidogrel-dependent platelet inhibition. This is not only true for the total patient cohort but also for the subgroup of patients with ACS. Therefore, assessment of post-treatment platelet function test can be of help to identify risk patients independently from ACS. Therefore, assessment of post-treatment platelet reactivity may help to further improve post-interventional antiplatelet therapy and may point to the necessity of individualized antiplatelet therapy. This has to be verified, however, in clinical trials.

Figure 1 Scatter-plot showing the correlation between time-point of platelet function assay and platelet aggregation in 363 patients with coronary stenting after administration of 600 mg loading dose of clopidogrel. Correlation curves and coefficients are presented for the subgroups of patients with stable angina and acute coronary events. No further attenuation effect of clopidogrel on platelet aggregation was observed at time-points later than 6 h after the loading dose.

References

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Is erectile dysfunction a low-grade systemic inflammatory condition?

Low-grade systemic inflammation is present in insulin resistance, obesity, type 2 diabetes mellitus, hypertension, hyperlipidaemia, and metabolic syndrome X, which predispose to the development of coronary heart disease (CHD).1–3 Conditions in which endothelial dysfunction is present, implying that reduced production of nitric oxide (NO) by endothelial cells could be a common denominator. NO, produced by endothelial cells, is responsible for penile erection. Hence, obesity, type 2 diabetes mellitus, hypertension, hyperlipidaemia, and metabolic syndrome X are likely to be associated with erectile dysfunction. The findings of Montorsi et al. and Vlachopoulos et al. are not only in support of this but also suggest that erectile dysfunction could be a disease of low-grade systemic inflammation. Increase in the levels of inflammatory markers—high-sensitive C-reactive protein (hsCRP), Interleukin-6 (IL-6), IL-1β, tumour necrosis factor-α (TNF-α), endothelial-prothrombotic markers (E-selectin, von Willebrand factor (vWF), tissue plasminogen factor (tPA), plasminogen activator inhibitor-1 (PAI-1), and fibrinogen noted in patients with erectile dysfunction4—suggests that low-grade systemic inflammation is present in these subjects, similar to those seen in insulin resistance, obesity, type 2 diabetes mellitus, hyperglycaemia, and metabolic syndrome X. These findings coupled with the observation that there is a close association between erectile dysfunction and coronary artery disease3 indicate that all these diseases are due to decreased endothelial NO (eNO) generation.

Oral phosphodiesterase-5 inhibitor tadafil, used for the treatment of erectile dysfunction, significantly decreased hypoxia-induced upregulation of TNF-α and IL-1β expression in pulmonary artery,5 indicating that NO has anti-inflammatory actions. Ageing is associated with decreased expression of eNOS synthe (eNOS) and vascular endothelial growth factor (VEGF), whereas that of endothelin-1, a potent vasoconstrictor, increased.6 VEGF increases the ability of endothelial cells to produce NO,7 and its stimulatory effect on penile erection involves phosphorylated eNOS.8 Furthermore, VEGF enhances prostacyclin (PGI2) production,9 eNOS overexpression attenuates myocardial reperfusion injury, and VEGF is essential for NO-mediated angiogenesis.10 These evidences suggest that a co-ordinated expression and synthesis of eNOS, VEGF, and PGI2, and suppression of TNF-α, IL-1, endothelin-1, and other pro-inflammatory molecules are essential to prevent erectile dysfunction, which calls for healthy endothelium.

It is likely that under normal physiological conditions, a balance is maintained between pro- and anti-inflammatory molecules such that optimal NO, PGI2, and VEGF production occurs to prevent erectile dysfunction and to ensure normal blood flow to vital organs, including heart. When endothelial cells fail to produce adequate amounts of NO, PGI2, and VEGF, it could lead to increased secretion of endothelin-1, free radicals (normally NO quenches superoxide anion, whereas excess free radicals inactivate NO and PGI2), and pro-inflammatory cytokines (since NO suppresses the production of TNF, and IL-1) and decreased production and action of VEGF that impair vasodilatation and angiogenesis and cause erectile dysfunction. Hence, measurement of NO, PGI2, VEGF, hsCRP, IL-6, IL-1β, TNF-α, VWF, PAI-1, and fibrinogen in subjects who are at high risk of developing insulin resistance, type 2 diabetes mellitus, hypertension, hyperlipidaemia, and metabolic syndrome X and those with erectile dysfunction may help early detection of low-grade systemic inflammation and in the prevention, prediction, and prognosis of CHD.

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Is erectile dysfunction a low-grade systemic inflammatory condition?: reply

We thank Dr Das for his interest in our work. Taken together, our two studies 1,2 reinforce the notion of a close link between subclinical inflammation/endothelial-prothrombotic activation, erectile dysfunction (ED), and atherosclerotic coronary artery disease. In patients with both ED and CAD, ED precedes the onset of CAD in the majority of patients,1,3 and it is associated with increased inflammatory and prothrombotic activation.1

Thus, in patients with suspected ED or at risk for ED, such as subjects with cardiometabolic risk factors, measurement of inflammatory compounds may contribute to a more comprehensive evaluation of these patients. Other substances, such as the vascular endothelial growth factor proposed by Dr Das, may also be considered. Furthermore, preliminary data from the Sexual Health Unit of Athens Medical School show that ED is associated with high level of adhesion molecules and low level of the N-terminal fragment C-type natriuretic peptide, an endothelium-derived relaxant factor.

At the moment, evidence regarding a possible direct etiological relationship between markers/mediators of inflammation/ prothrombotic activation and ED is limited. However, both ED and CAD are associated with high blood level of these compounds, and, interestingly enough, the adverse effect of each of these conditions (ED or CAD) is independent of the presence of the other condition (CAD or ED), so that men with both ED and CAD have the highest activation of inflammatory and prothrombotic mechanisms.1 In this sense, measuring the level of these compounds may contribute to the following: first, to diagnose vasculogenic ED in patients with ED of unknown etiology. This does not imply that biomarkers may substitute for penile Doppler studies, and, moreover, it presupposes that there is no (or at least much less) inflammatory activation in patients with ED secondary to hormonal, psychological, or neurological abnormalities, which is currently unknown. Secondly, the level of these markers may discriminate men with ED who are also affected by subclinical CAD.4 For both purposes, recognition of appropriate cut-offs is essential.

Our data showed that fibrinogen level or even better the combination of fibrinogen and interleukin-6 levels may be of value for excluding (ruling out) ED. However, specific cut-offs that predict the presence (ruling in) of ED are also needed. An ideal marker must conform with basic criteria recently proposed by Vasan,5 such as pathophysiological relevance, high reproducibility of measurements, incremental value over other known predictors, and, finally, ability to monitor and guide therapy. At the moment, there are no sufficient data to support the routine clinical use of any biochemical marker in the evaluation of ED patients. Clearly, further scrutiny is needed and studies providing insights into the potential role of inflammatory and endothelial substances as markers and risk predictors in subjects with ED are welcome. Especially, because ED stands not only for Erectile Dysfunction, but also for Endothelial Dysfunction and Early Detection as well, as was quoted in the accompanying editorial in the Journal.6

References


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