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Correspondence

QJM

Lower cardiac mortality in smokers following thrombolysis

Sir,

In their recent paper,[1] Purcell and colleagues confirm earlier observations that, in comparison to non-smokers, smokers have a higher frequency of reperfusion with thrombolytic therapy and consequently have a lower in-hospital mortality during acute myocardial infarction—the so-called 'smokers' paradox'. The authors conclude that 'smokers may have enhanced systemic fibrinolysis following thrombolysis in acute myocardial infarction'. We believe that this conclusion is not supported by the data, and that alternative and more likely explanations can explain the smokers' paradox.

The authors cite 1-h plasma fibrinogen concentrations as a surrogate marker of the effectiveness of systemic fibrinolysis following thrombolytic therapy with streptokinase. However, although they state that '…current smokers as a group are less likely than non-smokers to have a suboptimal fibrinolytic response to thrombolysis…', there was no difference in 60-min plasma fibrinogen concentrations between smokers and non-smokers as a group: 0.27 (0.14–0.73) vs. 0.31 (0.15–0.67) g/l, respectively; p = NS. Apparent differences were only seen on further subgroup analysis which could alternatively be interpreted as demonstrating that in smokers, systemic fibrinolysis occurred whether the infarct-related artery reperfused or not: plasma fibrinogen concentration 0.27 (0.12–0.61) vs. 0.28 (0.10–0.77) g/l, respectively. Moreover, the lowest plasma fibrinogen concentrations were seen in non-smokers with evidence of reperfusion. In mitigation, smokers have significantly higher basal plasma fibrinogen concentrations,[4] and one could argue that smokers may have had a proportionately greater fall in fibrinogen levels following thrombolytic therapy. Did the authors measure the plasma fibrinogen concentration before initiation of thrombolytic therapy?

We believe that there are at least two other more plausible explanations for the smokers' paradox. First, as the authors allude to in their introduction, the higher reperfusion rate following thrombolytic therapy in smokers[2] is likely to reflect the higher incidence of acute coronary thrombosis—three-quarters of patients with sudden cardiac death due to acute coronary thrombosis are smokers.[3] Moreover, the statement that '…in all studies where it was measured, the severity of residual stenoses in infarct-related vessels after thrombolysis did not differ between smokers and non-smokers' is misleading. In a large cohort of patients (n = 1619) taken from six thrombolytic trials, Grines *et al.*[4] reported that, in comparison to non-smokers, smokers are more likely to have TIMI-3 flow and a greater minimal luminal diameter following thrombolytic treatment. Taken together, these studies strongly suggest that the enhanced reperfusion rate following thrombolytic therapy in smokers relates to a greater contribution of thrombus to the initiation of coronary occlusion and myocardial infarction.

The second explanation relates to the impairment of the acute endogenous fibrinolytic capacity seen in smokers.[5] We have recently demonstrated a major impairment of endogenous tissue plasminogen activator release from the forearm vascular endothelium of healthy young smokers.[6] This finding is consistent with the view that patients with impaired endothelial cell tissue plasminogen activator release are more likely to present with an acute myocardial infarction and to reperfuse with thrombolytic therapy, whereas those with normal endogenous fibrinolytic function are less likely to sustain an acute myocardial infarction and to respond favourably to thrombolysis.

D.E. Newby
N.A. Boon
Department of Cardiology
Royal Infirmary
Edinburgh

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Sir,

We thank Drs Newby and Boon for their provocative contribution, but disagree with a number of the points which they raise.

An association between cigarette smoking, systemic fibrinolysis following thrombolytic treatment and prognosis after myocardial infarction was supported in our study by three lines of evidence.[1] First, a subgroup of non-smokers were defined by persistent ST elevation, higher levels of post-thrombolytic plasma fibrinogen and high early cardiac death. Such a group was not seen among current smokers. Second, multivariate analysis revealed a significant interaction between smoking and plasma thrombolysis as predictors of cardiac mortality which was not seen between other variables. Third, when smoking was assessed as an independent predictor of lower cardiac mortality, the association was independent of all variables except post-thrombolysis plasma fibrinogen. These data strongly support our conclusions but, as we stated, a multivariate analysis of this size should always be considered as hypothesis-generating not hypothesis-proving.

We agree that mean post-thrombolysis fibrinogen did not differ significantly between current, former and non-smokers, although there was a trend towards higher values in non-smokers. However, as Newby and Boon state, pre-thrombolysis fibrinogen levels are known to be higher in smokers with acute myocardial infarction.[2] Therefore our data are consistent with a greater fall in plasma fibrinogen levels in smokers following thrombolysis compared with non-smokers. We did not measure pre-thrombolysis fibrinogen, and know of no study where pre- and post-thrombolysis fibrinogen levels were measured.

Post-thrombolysis fibrinogen levels did not differ between smokers grouped on the basis of ECG evidence of reperfusion, but as we make clear, the systemic fibrinolytic response is only one of many potential explanations for the smoker's paradox. We would not expect it to be the sole predictive variable for reperfusion. It is more interesting that plasma fibrinogen was higher only in the non-smoking group without myocardial reperfusion. This suggests to us that among non-smokers there exists a subgroup who suffer thrombolysis-resistant coronary occlusion as a result of a physiological defect which may include defective systemic fibrinolysis. Following this logic, the smoker's paradox is perhaps more appropriately thought of as the non-smoker's paradox.

In considering alternative explanations to our hypothesis, Newby and Boon quote data regarding sudden death in smokers. However this is an entirely different patient population since the smoker's paradox was observed in studies where patients with acute myocardial infarction reached hospital alive.

Newby and Boon state that our discussion of previously published data is 'misleading', however, a more detailed examination of the literature reveals the reverse to be true. As clearly stated in our introduction, more smokers than non-smokers achieve early complete vessel patency as indicated angiographically by TIMI grade 3 flow.[2–6] Currently the most popular explanation for this phenomenon, and the one to which Newby and Boon prescribe, is that infarct associated coronary occlusions in smokers are composed of a greater proportion of thrombus, as opposed to fixed atherosclerotic narrowing, compared with non-smokers. If that were true we would expect to find more severe residual coronary stenoses remaining following thrombolysis in non-smokers compared with current smokers. We believe that the percentage stenosis is a better guide to residual stenosis than minimal lumenal diameter (MLD), since this latter measurement is clearly influenced by the starting diameter. Newby and Boon quote only 90-min MLD data from the TAMI meta-analysis, but in this study the mean residual % stenosis did not differ significantly between smokers and non-smokers (76% vs. 74%).[2] Moreover, in the larger GUSTO-1 angiographic substudy and the TIMI-4 trial, neither the mean residual % stenosis nor the MLD were found to differ significantly between current and non-smokers.[4,6] These data cast considerable doubt on the more clot-less atheroma theory favoured by Newby and Boon.

Finally, Newby and Boon refer to data showing impaired endothelial fibrinolytic capacity in healthy smokers. This suggests an additional mechanism by which smoking may lead to myocardial infarction, but there is no evidence that subjects with impaired endothelial fibrinolytic activity are more likely to present with acute myocardial infarction, nor that impaired endothelial fibrinolytic activity predisposes to a favourable response to thrombolysis. We believe

that Newby and Boon's hypothesis, while plausible, is not supported by currently available data.

I. Purcell
M. Farrer
Cardiac Medicine
National Heart and Lung Institute
London

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