indicating that the unique information that is provided by GDF-15 is related to outcome. In the present chest pain population, we found that GDF-15 adds prognostic information to clinical variables (including age, diabetes, history of myocardial infarction, or heart failure), ECG findings, and biomarker levels (please refer to Table 4 in Ref. 2). We have now performed ROC curve analyses to further assess the incremental prognostic value of GDF-15. These analyses indicate that GDF-15 levels determined on admission add significant prognostic information to an optimized pre-test model that includes information on age, diabetes, history of myocardial infarction or heart failure, ECG findings on admission, and peak cardiac troponin I levels after 2 h. This was reflected by an increase of the c-statistic for the composite endpoint of death or myocardial infarction from 0.79 (95% CI 0.71–0.87) for the optimized pre-test model, to 0.84 (95% CI 0.75–0.90) after addition of GDF-15 (P = 0.063 in this relatively small patient cohort).

In conclusion, GDF-15 emerges as a biomarker that integrates information from established risk markers and that provides unique additional information which is helpful for prognostication, and possibly, for therapeutic decision making in patients with chest pain and suspected ACS.4

References


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Smoker’s paradox in heart failure: might asymmetric dimethylarginine be the possible explanation?

We read with great interest the recent paper by Fonarow et al.1 In the study, they have found in a group of patients with systolic heart failure (HF) that smokers had lower in-hospital mortality compared with non-smokers despite extensive covariate adjustment. The authors called this finding as ‘smoker’s paradox’ with the knowledge that smoking is a well-established and independent risk factor for HF.2

In the paper, it was shown that ischaemic aetiology was less prevalent among smokers compared with non-smokers, although smoking is a well-established marker of ischaemic heart disease. Starting with this point, it is possible to state that non-ischaemic cardiomyopathy was more prevalent among smokers in the study. In the paper, the authors speculated that smoking contributed to decompensation of HF as a result of vasoconstriction, increased venricular filling pressures, and reduced cardiac index.

Hence, abrupt cessation of smoking during hospitalization allowed for the more rapid stabilization and compensation among patients who were smoking up until the time of HF hospitalization. They also speculated that exposure to current/recent smoking had a pre-conditioning-like effect on HF patients allowing better survival during an episode of acute decompensated HF. We think that asymmetric dimethylarginine (ADMA) could be one of the alternative explanations associated with the latter hypothesis.

Endothelial dysfunction, mainly caused by dysregulation of the l-arginine–nitric oxide pathway, is supposed to impact negatively on ventriculovascular coupling, and hence yielding reduced cardiac output and increased peripheral vascular resistance in patients with HF syndromes.3 Asymmetric dimethylarginine, a potent endothelial nitric oxide synthase inhibitor, was shown to be increased in patients with HF.4 Furthermore, it was not only associated with the severity of HF, but also predictive of adverse outcomes in addition to well-known markers.5 In a recent paper by Onat et al.,6 it was shown that ADMA levels were lower among smokers compared with non-smokers. Furthermore, same findings were noted by Eid et al.7 such that they did not have any explanation for beneficial dimethylarginine profile observed in smokers in the elderly population.

We think that in the current paper, the better in-hospital outcome among smokers with HF could partially be explained by the beneficial effect of smoking on ADMA levels, which were shown to impact up on ventriculovascular coupling through endothelial dysfunction.8,9 Herein, we think that ‘smoker’s paradox’ could possibly become apparent due to lower prevalence of ischaemic cardiomyopathy among smokers in the study group (possibly due to statistical chance for the study) and, hence, non-ischaemic cardiomyopathy patients, who were smoking at the time of index hospitalization, might have benefited relatively lower level of endothelial toxin without well-known negative influences of smoking onto atherosclerosis in patients with ischaemic heart disease. In conclusion, it does not seem scientifically wise to state that the hypothesis (that smoking is protective) can probably be refuted immediately. Hence, from the scientific point of view, it might be better to state that something might yield positive results in rare occasions; however, general negative tendency should not bring about


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Smoker’s paradox in heart failure: might asymmetric dimethylarginine be the possible explanation?: reply

We are grateful to Dr Yilmaz et al.1 for their interest in our article on smoking and clinical outcomes in patients with heart failure. They raise several important issues, including an alternative explanation for the findings from OPTIMIZE-HF that smokers hospitalized with heart failure had lower risk adjusted in-hospital mortality, shorter length of stay, and similar early post discharge mortality compared with non-smokers. We concur that, in addition to the potential mechanisms discussed in the manuscript, lower levels of asymmetric dimethylarginine (ADMA) among smokers compared with non-smokers with heart failure is an additional potential explanation. Asymmetric dimethylarginine is elevated in acute and chronic heart failure and, in chronic heart failure, is associated with adverse outcomes. However, it is important to note that a recent prospective study of 118 patients hospitalized with heart failure failed to demonstrate a relationship between plasma ADMA concentration and subsequent clinical outcomes in this patient population. Additional studies are necessary to investigate the ADMA levels in patients hospitalized with heart failure as well as other potential mechanisms for the smoker’s paradox such as a pre-conditioning-like effect with smoking. We also concur that from a scientific standpoint any potential protective effects of smoking in hospitalized heart failure patients should not be refuted immediately, as suggested in the accompanying editorial.3 Paradoxical associations between traditional cardiovascular risk factors and clinical outcomes in patients in patients with established heart failure have been well described, being referred to as ‘reverse epidemiology’.4 Heart failure patients with current or recent smoking exposure may have different intrinsic risk and/or responses to therapy compared with heart failure patients without recent exposure to smoking. Nevertheless, from a clinical perspective, effective smoking prevention and cessation methods should be vigorously employed in all individuals, including those hospitalized with heart failure.

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References


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Regrettably, on page 2272, in Figure 3, the line types of group 4 and group 5 were transposed. The corrected figure is printed below. The authors wish to apologize for this error.