Nature Reviews Cardiology published online 29 July 2014; doi:10.1038/nrcardio.2014.73-c1

Explanations for the 'smoker's paradox' in cardiac resuscitation

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In her Research Highlight (Cardiac resuscitation: The 'smoker's paradox' after in-hospital cardiac arrest. *Nat. Rev. Cardiol.* **11**, 374; 2014),[1] Alexandra Roberts focuses on the large observational analysis by Gupta and colleagues on in-hospital cardiac arrest.[2] According to this analysis, smokers have higher survival rates and better neurological outcome after in-hospital cardiac arrest than nonsmokers.[2] The finding was explained by the investigators as an effect of ischaemic preconditioning,[3] whereby tobacco smoke causes regular hypoxic effects[4] leading to frequent minor ischaemia and subsequent reperfusion.[1–3,5,6] As a result, the tissue becomes preconditioned to reperfusion.[2,3,6] Preconditioning mitigates the paradoxically harmful effects of reperfusion on the tissue, which occur as a result of cardiac resuscitation after major ischaemia or cardiac arrest.[1–3,5,6]

Although the phenomenon of ischaemic preconditioning is a possible explanation for the smoker's paradox, at least two alternative explanations exist. First, in the analysis by Gupta and colleagues, significantly more smokers had a primary diagnosis of acute myocardial infarction than nonsmokers (14.8% vs 9.1%; $P<0.001$).[2] Although the researchers adjusted for this factor in the statistical analysis, the indirect effects were not considered. A primary diagnosis of acute myocardial infarction means that the patient is usually first treated in the emergency room or the cardiac catheterization laboratory, and subsequently transferred to an intensive care ward. In these locations, defibrillators are available and patients are constantly monitored (that is, time to defibrillation is usually short). As a consequence, survival and neurological outcome are better among these patients. This difference is likely to have at least partially contributed to the observed smoker's paradox.

Second, significantly more smokers in the study had previously experienced a myocardial infarction (9.3% vs 4.8%; $P<0.001$), a transient ischaemic attack or stroke (3.8% vs 1.9%; $P<0.001$), or had undergone percutaneous coronary intervention (6.9% vs 2.8%; $P<0.001$), compared with nonsmokers.[2] Although adjustment for these differences was also performed in the statistical analysis, one has to consider that these events determine the medication taken by the patients. After an adverse cardiovascular event, patients typically receive a combination of aspirin (and clopidogrel if a stent has been implanted), a statin, an angiotensin-converting-enzyme inhibitor, a β-blocker, and potentially nitrates.[7] However, the effects of such medication were not considered in the analysis.[2] Owing to the significant difference between smokers and nonsmokers in terms of cardiovascular events, one would expect that a higher percentage of smokers than nonsmokers were taking these medications, which could also have contributed to improved survival and neurological outcome after cardiac arrest.

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Competing interests
The author declares no competing interests.

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