Xenon: A Noble Member of the Cardioprotection Club

Brief title: Xenon in cardioprotection

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ABBREVIATION LIST

IRI	=	ischemia/reperfusion injury
OHCA	=	Out-of-hospital cardiac arrest
PMI	=	Perioperative myocardial injury
RISK	=	Reperfusion Injury Salvage Kinase
STEMI	=	ST-segment elevation myocardial infarction

INTRODUCTION

Targeting the myocardial injury that paradoxically occurs with the acute reperfusion of ischemic myocardium remains one of the top ten unmet clinical needs in cardiology (1). Although myocardial reperfusion is needed to salvage viable myocardium in ST-segment elevation myocardial infarction (STEMI) patients, it comes at a price. Therapies aimed to protect the heart against ischemia/reperfusion injury (IRI) are known as cardioprotective therapies (2). Despite being mostly tested in STEMI patients, cardioprotective therapies can potentially benefit other patients experiencing acute global IRI, such as those undergoing coronary artery bypass graft or those survivors from cardiac arrest (3).

In this issue of the Journal of American College of Cardiology, Arola *et al.* (4) report that, in comatose survivors of out-of-hospital cardiac arrest (OHCA), inhaled xenon combined with mild therapeutic hypothermia results in a reduction on myocardial injury when compared to that achieved by hypothermia on its own, measured by the delta change of troponin release from baseline to 72 hours after OHCA. After adjustment by independent co-variates, xenon has been proposed as an independent factor attenuating the severity of the myocardial injury after OHCA.

Xenon is a noble gas that has been postulated to mediate pharmacological cardioprotection in previous experimental studies. Xenon's cardioprotective conditioning effect has been linked to the up-regulation of pro-survival kinases recruited by the Reperfusion Injury Salvage Kinase (RISK) pathway, such as Akt and ERK, and has been reported to inhibit the mitochondrial permeability transition pore opening (5–7). Therefore, Arola *et al.* (4) has speculated in their clinical trial that xenon provides protective post-conditioning effect against an ongoing wave of reperfusion injury. Two big questions arise from this statement: (1) how could this gas protect through an acute conditioning-like phenomenon if the mean time from OHCA to initiation of xenon was more than 4 hours? ;

and (2) how could be possible that despite propofol being a well-known cardioprotective agent (8), patients receiving xenon underwent less propofol administration and still presented less myocardial injury? We suspect that the reason is because xenon, rather than acting through the well-known conditioning mechanisms may also act through a RISK-independent pathway. Indeed xenon targets reperfusion injury, as demonstrated by eliciting the protection against IRI when administered at the late phase of reperfusion. It would be very interesting to test whether a pharmacological agent mimicking the conditioning effect present a synergistic effect when administered alongside xenon.

The use of troponin as a surrogate biomarker to predict prognosis and clinical benefits needs to be addressed separately, as arises some questions in OHCA patients that have not set out previously. Before, it is crucial to delineate the difference between myocardial infarct size and perioperative myocardial injury (PMI), both representing an increase of troponin levels in a completely different underlying pathophysiological setting. In STEMI patients, the rise of troponin levels correlates with myocardial infarct size, a well-defined prognostic factor (9), whilst the elevation of troponin levels following coronary revascularization by coronary artery bypass graft is known as PMI and does not necessary seems to be a suitable biomarker for the effect of cardioprotective therapies – i.e. remote ischemic preconditioning has demonstrated to reduce PMI in proof-of-concept studies (10) but has failed to translate this into clinical benefit in subsequent clinical outcomes studies (11). Overall, the conclusions of Arola *et al.* (4) about the efficacy of xenon are based on the assumption that post cardiac arrest troponin release reflects its efficacy to protect the heart against IRI. However, the troponin release originated by a cardiac arrest is closer to reflect the PMI resulting from an acute global insult than to myocardial infarct size resulting from a prolonged insult, and caution should be taken when interpreting the reduction in troponin release by xenon. Taking into account that transient increases in blood troponin concentrations are also observed in

healthy individuals following extenuated exercise, asymptomatic patients, and disease states other than acute coronary syndromes (12), is troponin a noble biomarker?

Sudden death is coming to the fore in cardioprotection and we welcome xenon as a noble member of the club aimed to protect the heart against IRI in multiple settings.

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