Reversal of metabolic shift in post-infarct-remodelled hearts: possible novel therapeutic approach

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This editorial refers to ‘Infarct-remodelled hearts with limited oxidative capacity boost fatty acid oxidation after conditioning against ischaemia/reperfusion injury’ by P.-H. Lou et al., pp. 251–261, this issue.

With sophistication and improvement in coronary revascularization therapy, the chances of patients surviving acute myocardial infarction have been increasing. Though the procedure is life-saving, it also predisposes the patients to post-infarction ventricular remodelling and consequent heart failure. Since those patients usually have atherosclerotic lesions not only in the culprit vessel in the infarction but also in some part of the coronary artery, the likelihood of them having re-infarction is substantial. The mortality of patients with re-infarction has been reported to be more than twice as high as that by the first attack, probably due, at least in part, to disrupted in-re-infarction has been reported to be more than twice as high as that by the first attack, probably due, at least in part, to disrupted intrinsic cardioprotective signalling in post-infarct-remodelled hearts. In addition to the change in intracellular signal transduction, it has been well established that a so-called metabolic shift takes place as cardiac hypertrophy and heart failure develop. In healthy hearts, oxidation of fatty acids (FAs) covers >70% of the cardiac energy need, with most of the remainder being accounted for by glucose oxidation. On the other hand, hearts change their substrate preference from FAs towards glucose as remodelling develops in response to diverse stresses. The oxidation of one molecule of FAs yields far more ATP (~129 ATP in the case of palmitate) than glucose (~36 ATP). Therefore, glucose oxidation can hardly compensate for the decrease in ATP synthesis when the oxidation of FAs is even slightly reduced. This metabolic shift may be an adaptive mechanism under a pathological stress condition such as ischaemia/reperfusion, because the oxidation of glucose is ~10% more efficient than that of FAs in terms of oxygen cost. However, shortage of ATP as a consequence of insufficient production is likely to increase the susceptibility of post-infarct-remodelled hearts to cardiomyocyte necrosis and post-ischaemic contractile dysfunction.

Lou et al. demonstrated that post-infarct-remodelled rat hearts, which have limited citric acid cycle capacity and marked deficits in respiratory chain activities, showed marked contractile dysfunction at baseline and severely compromised post-ischaemic functional recovery. The preconditioning mimetic sevoflurane, a volatile anaesthetic, markedly improved the post-ischaemic contractile function in remodelled hearts, which was associated with enhanced energy production by the activation of the oxidation of FAs but not glucose. Interestingly, the fuel was mobilized from accumulated endogenous triglyceride stores. The reversal of substrate preference in post-infarct-remodelled hearts seemed to be mediated by the up-regulation of PGC-1α and sevoflurane-induced activation of long-chain hydroxycetyl-CoA dehydrogenase, which promoted the mobilization of FAs and β-oxidation flux, respectively. Furthermore, infusion of a high concentration of exogenous palmitate also improved post-ischaemic contractile recovery in the remodelled hearts. These findings indicate that boosting FA oxidation, whether the fuel is derived from an endogenous store or exogenous source, may promote post-ischaemic contractile recovery, thus alleviating critical acute heart failure after myocardial infarction in remodelled hearts. The enhanced oxidation of FAs being beneficial may be somewhat provocative, as previous experimental studies using healthy adult hearts demonstrated otherwise: for example, increasing FA oxidation under ischaemia/reperfusion was detrimental, whereas increasing glucose oxidation and concomitantly reducing FA oxidation was beneficial. On the other hand, it has been reported that high levels of FAs increased contractile function during reperfusion following ischaemia in neonatal hearts. As is the case in failing hearts, neonatal hearts are highly dependent on glucose oxidation for energy production. These findings indicate that boosting FA oxidation may be beneficial in hearts in which glucose oxidation predominates, perhaps as the recapitulation of the foetal gene programme.

The findings in the report by Lou et al. are intriguing, but some data should be interpreted with caution. In their study, a relatively short duration of ischaemia (15 min) was employed. Although it is unlikely that the short duration of ischaemia resulted in massive myocardial infarction, at least some cardiomyocytes should undergo necrosis, particularly in remodelled hearts that are less tolerant than normal hearts to ischaemia/reperfusion injury. Since sevoflurane has also been reported to reduce myocardial infarction by activating ATP-
sensitive potassium channels, the infarct-size-limiting effect of this agent may contribute to better contractile recovery. The finding that exogenous palmitate infusion mimicked the effect of sevoflurane may argue against the possibility, but it would still be possible that the protection afforded by sevoflurane was derived from both mobilization of FAs and infarct size reduction. Should that be the case, the effect of sevoflurane purely on enhanced FA oxidation might have been overestimated.

Infarct-remodelled hearts in this study seem to be at the stage of compensated hypertrophy without any sign of decompensated heart failure: reduction in ejection fraction was very mild (57%, compared with 74% in sham-operated hearts), and an infarct scar area was not present in the interventricular septum, indicating that the left anterior descending artery was ligated at a distal part, after branching off septum-perfusing branches. Since mitochondrial function has been reported to increase or not change and then decrease during transition from compensated hypertrophy to heart failure, it is plausible that the metabolic modification by sevoflurane in remodelled hearts also changes depending on the severity of heart failure. Therefore, how sevoflurane affects severely failing remodelled hearts remains unanswered.

As mentioned earlier, the reversal of metabolic shift in protected infarct-remodelled hearts seemed to be mediated by the up-regulation of PGC-1α and sevoflurane-induced activation of long-chain hydroxacyl-CoA dehydrogenase. Candidate molecules that may simultaneously activate these protective mechanisms would be sirtuins, as sirt1 and sirt3 have been reported to deacetylate and activate PGC-1α and long-chain hydroxacyl-CoA dehydrogenase, respectively. The sevoflurane-induced protection was not associated with an increased expression level of either sirt1 or sirt3 (Supplementary material online, Figure S5 in the report of Lou et al.), but the activity of these sirtuins is regulated not only by their protein levels but also by their intracellular localization and NAD+/NADH ratio. The NAD+/NADH ratio decreases during ischaemia because the limiting oxygen supplies during myocardial ischaemia prevent the oxidation of NADH by mitochondrial electron transport chains, and thus NADH builds up. Interestingly, sevoflurane preconditioning, but not ischaemic preconditioning, has been reported to suppress the increase in NADH during ischaemia. Thus, sevoflurane may maintain the activity of sirtuins, and thereby the activity of PGC-1α and long-chain hydroxacyl-CoA dehydrogenase, by preserving the NAD+/NADH ratio during ischaemia/reperfusion.

There are some issues that remain to be addressed for possible translation of this study into the clinical arena. First, it is difficult to administer the agents before the onset of ischaemia in most clinical settings. Thus, it would be crucial to determine the timing, i.e. during ischaemia, reperfusion, or both, for sevoflurane to be present in the myocardium for the protection. Second, protecting hearts with a volatile anaesthetic is useful under controlled respiration, but it may not be practicable in many other clinical situations. Therefore, whether other forms of therapy that boost FA oxidation also afford the protection should be clarified. Finally, it should be elucidated whether the protective mechanisms similarly operate in all remodelled hearts, regardless of severity or aetiology of heart failure. Hopefully, clarification of these issues will better define the significance of modifying metabolic shift to rescue infarct-remodelled hearts from ischaemia/reperfusion injury and help us design a new therapeutic strategy in the future.

Conflict of interest: none declared.

References