Potentiating mitochondrial aldehyde dehydrogenase 2 to treat post-infarction heart failure

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This editorial refers to ‘Aldehyde dehydrogenase 2 activation in heart failure restores mitochondrial function and improves ventricular function and remodelling’ by K.M.S. Gomes et al., pp. 498–508, this issue.

Heart failure (HF) is common after acute myocardial infarction (MI) with an estimated one in five individuals aged 65 years or older who experience a first MI subsequently developing HF over the next 5 years.1 While a temporal trend towards reduction in HF hospitalizations post-MI has been noted, survival remains poor even in the era of primary reperfusion therapy, multiagent neurohormonal modulation and device implantation, with a 1-year mortality for patients hospitalized for HF after MI of over 45%.2

Complex changes in ventricular geometry ensue within hours of MI—particularly for transmural infarcts—and progress well beyond the acute episode in a process termed ventricular remodelling.3 The degree of ventricular remodelling—described by parameters such as left ventricular (LV) end-systolic volume—has emerged as a key predictor of long-term survival post-MI.4 All therapies proved to beneficially alter HF clinical outcomes, including renin–angiotensin–aldosterone system (RAAS) inhibition, beta-adrenergic receptor blockade, cardiac resynchronization therapy, and LV assist devices, have been associated with LV reverse remodelling, highlighting it as a therapeutic target.5

Modern definitions of cardiac remodelling6 build on earlier, largely morphological descriptions of infarct expansion, progressive ventricular dilatation, and eccentric hypertrophy culminating in systolic failure.3 These reflect complex changes in gene expression, molecular response (altered expression of proteins resulting in impaired sarcoplasmic calcium cycling and abnormal excitation–contraction coupling, increased AT1 receptor expression, and altered β-adrenoceptor function),5,7,8 cellular adaptations (altered myocyte shape, size, and increased levels of apoptosis),9 and interstitial (matrix metalloproteinase (MMP)-mediated extracellular matrix remodelling, RAAS- and TGF-β-mediated fibrosis, activation and recruitment of inflammatory and progenitor cells, and reduced capillary density)10,11 in the pathogenesis and progression of post-MI HF.12

Failure to neutralize these LPP by endogenous antioxidant mechanisms leads to LPP decomposition to form aldehydes, some of which are highly reactive and toxic to the cell, including 4-hydroxynonenal (4-HNE), and malondialdehyde. Both 4-HNE and 4-hydroxyhexanal (4-HHE) are stable, lipophilic and highly reactive electrophiles, which can modify proteins (interaction with cysteine and methionine groups in addition to covalent modification of amide groups of lysine and histidine via Michael addition) generally acting to reduce protein function.16

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Within mitochondria, LPP-derived reactive aldehydes negatively impact activity of complexes I–IV, cytochrome c oxidase, succinate dehydrogenase, and induce mitochondrial permeability transition. Analogous to the effects of upstream progenitor ROS, by originating largely within mitochondria and targeting nearby mitochondrial proteins, pathologically elevated levels of LPP-derived toxic aldehydes are well placed to fuel mitochondrial dysfunction and—in conjunction with effects on inducing cardiomyocyte calcium overload, DNA damage, and potentially via activation of signal transduction—contribute to ventricular remodelling and HF progression post-MI.

It is against this background that Gomes et al. provide evidence in this issue of Cardiovascular Research that enhancing an endogenous cellular defence mechanism against reactive aldehydes improves mitochondrial function and promotes reverse ventricular remodelling in an experimental model of post-MI HF. The study targets aldehyde dehydrogenase 2 (ALDH2), a tetrameric enzyme perhaps best known for its role in metabolizing acetaldehyde as part of ethanol metabolism. ALDH2 is a mitochondrial isozyme member of the NAD(P)+–dependent aldehyde dehydrogenase superfamily present in all taxa which function to metabolize endogenous (e.g. 4-HNE) and exogenous (e.g. the pollutant acrolein) aldehydes to abrogate oxidative stress. Gomes et al. utilize Alda-1, a small molecule allosteric activator of ALDH2 which their group has previously shown to exert cardioprotection in the setting of acute ischaemia—reperfusion injury via inhibition of cytotoxic aldehyde formation.

Seeking to address a different question, namely whether chronic pharmacological activation of mitochondrial ALDH2 can mitigate ventricular remodelling in a rat model of post-MI HF, Gomes et al. convincingly show that administration of Alda-1 for 6 weeks at a time point when adverse LV remodelling and systolic failure are present [4 weeks after coronary artery ligation (CAL)] results in reverse LV remodelling, meaningful levels of improvement in systolic function, and inhibition of both myocardial hypertrophy and cardiac fibrosis. After confirming meaningful levels of improvement in systolic function, and inhibition of both myocardial hypertrophy and cardiac fibrosis. After confirming cardiac aldehydeic overload 10 weeks after CAL, the authors identified reductions in cardiac 4-HNE—protein adducts and total protein carbonyls following treatment with Alda-1 compared with the placebo-treated HF group. While ALDH2 activity was not reduced in the non-Alda-1-treated control HF group, Alda-1 treatment increased cardiac ALDH2 activity by 2.7-fold, with no significant effect on ALDH2 levels which were comparable across all groups, including sham surgical-treated rats. As a corollary of the reduced toxic aldehyde stress in Alda-1-treated hearts, analysis of isolated mitochondria revealed tighter coupling between mitochondrial respiration and oxidative phosphorylation (as reflected by the mitochondrial respiratory control ratio), reductions in mitochondrial ROS release, mitochondrial permeability transition, and cytosolic cytochrome c release, expected to result in less cell death. In seeking to implicate mitigation of 4-HNE’s deleterious effect on mitochondrial function as a key mechanism for HF rescue, Gomes et al. demonstrate a dose-dependent reduction in the mitochondrial respiratory control ratio on exposure to 4-HNE in vitro, predominantly through an effect on State 3 oxygen consumption, which is significantly inhibited by pre-incubation with Alda-1.

The findings of Gomes et al. highlight a role for ALDH2 in the biology of post-MI HF and the beneficial effects of its chronic activation. In seeking to extrapolate these findings to humans, several points need to be considered. The choice of model adopted in the study—CAL in the rat—while well established with a proven track record in the preclinical evaluation of HF therapy, differs in a number of respects from acute coronary syndromes (ACS) in human: considerable variability in infarct size, marked gender difference in acute mortality, permanent ligation with the lack of an initial reperfusion phase (the gold standard therapy for human acute epicardial coronary artery occlusion), and absence of progressive coronary disease resulting in further ACS. These caveats notwithstanding (species difference being the most germane) the potential benefit of ALDH2 potentiation on post-MI HF progression on top of existing neurohormonal antagonism, device therapy, and revascularization are uncertain. Regarding the mechanism for Alda-1-mediated rescue of HF in the model, while the authors’ argument has focused on the mitigation of mitochondrial cytotoxicity from 4-HNE, its neutralizing effect on other chemically stable toxic aldehydes may be relevant, while its potential effects on other biological mechanisms increasingly recognized to play a role in remodelling post-MI, such as inflammation, are unknown. Indirect support for the latter comes from a recent study where ALDH2 knockout mice exhibit greater hepatic inflammation in response to (acet-) aldehydic stress in the form of chronic ethanol exposure.

Is there a drawback to chronic activation of ALDH2? Gomes et al. demonstrate that treatment of healthy rats for 6 weeks did not affect body or organ weight, haemodynamics, or biochemical renal/liver function. In humans, a frequent polymorphism of the ALDH2 allele, termed ALDH2*2, caused by a Glu504Lys amino acid substitution results in inactivation of the enzyme in vivo. ALDH2*2 is especially prevalent in East Asian populations and is responsible for acetaldehyde-mediated flushing and intolerance of alcohol in homozygotes (ALDH2*2/*2) and a milder phenotype in heterozygotes (ALDH2*1/*2), collectively numbering over 540 million worldwide. Notably, Alda-1 activates both wild-type enzyme and restores activity of ALDH2*2 by acting as a chemical chaperone. While speculative, the recent signature for human selection of this variant raises the prospect of jeopardy in overcoming evolutionary selection through chronic activation. Future research may clarify this issue, but will first need to demonstrate the utility of ALDH2 inhibition to ameliorate HF endpoints in man post-MI.

Conflict of interests: none declared.

References

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