

# Increased uptake of specific metabolic substrates during cardiac resynchronization therapy despite no change in arterial concentrations: the very definition of metabolic flexibility

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**This commentary refers to ‘Metabolic flexibility and reverse remodelling of the failing human heart’, by P.G. Green *et al.*, <https://doi.org/10.1093/eurheartj/ehaf033> and the discussion piece ‘Questionable metabolic flexibility during cardiac resynchronization therapy’, by F.W. Prinzen and G.J. van der Vusse, <https://doi.org/10.1093/eurheartj/ehaf818>.**

We thank Drs Prinzen and van der Vusse for their interest in our study.<sup>1</sup> Despite the small sample size which both we and the Editorial<sup>2</sup> acknowledged, we would highlight this is amongst the most comprehensive invasive phenotyping study of human heart failure ever undertaken. The data from Figure 3B is based on 11 (not 7) patients using the least sensitive laboratory measure of total non-esterified fatty acid (NEFA) concentration. The more precise lipidomic analysis of long chain FA uptake for example (Figure 3D) contains 363 measurements and is highly significant ( $P < .001$ ) as is the correlation with long-term reverse remodelling ( $n = 231$ , from seven patients,  $P < .001$ , Supplementary Table 3).

Regarding their first point, we agree that an increase in FA uptake and reduction in respiratory quotient (RQ) during intralipid infusion are reflective of increased arterial supply of FA relative to that during insulin/glucose infusion and show this clearly. However, a further significant increase in FA uptake is seen once stabilized on intralipid following cardiac resynchronization therapy (CRT) pacing (Figure 3D) with no change in arterial FA concentration, and perhaps more importantly, a significant increase in FA uptake is also seen following CRT pacing when the heart is stabilized on insulin/glucose, without changes in and during a low

arterial FA concentration (Supplementary Figure 1A). Hence, we have shown that the heart is able to switch substrate use according to supply and CRT pacing—the very definition of metabolic flexibility.

In terms of the change in RQ with CRT, this is also addressed in the discussion of the paper. The increase in NEFA uptake is modest in relative terms compared with glucose uptake (Figure 4A) and associated with an increase in cardiac work without an increase in oxygen uptake during CRT. This may not be sufficient to result in a measurable change in RQ with a relatively modest increase in FA utilization improving cardiac function without significantly reducing cardiac efficiency. Given that a fall in median RQ was observed but with high variability in the data (Table 2), the study also may be underpowered to detect a significant reduction. Cardiac resynchronization therapy did not increase the production of toxic intermediary metabolites associated with FA metabolism (such as triacylglycerol, diacylglycerol, and ceramides) on insulin/glucose or intralipid. Indeed, there is no data in humans to suggest lipotoxicity is a causative driving force in heart failure, and increasing FA use appears acutely beneficial in human non-ischaemic heart failure.<sup>3</sup>

The third point regarding correlation not indicating a causal relationship is pertinent, and we emphasize that we were careful not to claim causality. We agree that reverse remodelling initiated by CRT is a complex process that induces downstream changes in ion channel expression, calcium handling, adrenergic responsiveness, and metabolism. However, much work needs to be done to tease out and understand the contribution of each of these factors, and whilst Drs Prinzen and van der Vusse are perfectly entitled not to pursue metabolic limitations to this process, we believe that many other research groups and funding bodies will.

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## Declarations

### Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

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