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Commentary: One plus one does not always equal two: Mitochondrial cardioprotection

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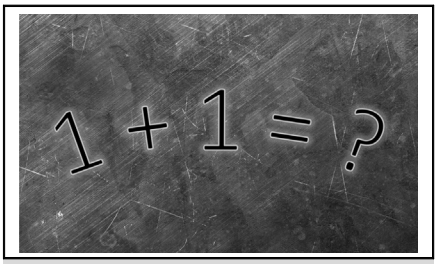

One plus one is equal to…?

CENTRAL MESSAGE

Mitochondrial cardioprotection pathways are difficult to predict and may not always lead to the expected result.

Several mitochondrial pathways have been targeted to find the Holy Grail for cardioprotection. In their recent paper, Ahmad and colleagues[1] investigated the cardioprotective properties of diazoxide (DZX) and mitochondria-targeted s-nitrosating agent separately and in combination. Based on their in vitro and ex vivo studies, the authors concluded that these 2 substances provide cardioprotection when administered separately, but this effect is reduced when combined. This is an intriguing finding, as one would expect a synergistic effect instead of a potential mutually exclusive mechanism of action (Figure 1). This study provides some insight into the mechanisms of action of DZX, a drug that has been studied for its possible cardioprotective effects in preclinical models.[2]

However, while intriguing, their hypotheses would benefit from being approached from a categorical and empirical perspective. First, the use of an in vivo model would add to the translational clinical significance of these results. In the present study, their functional data are derived from a 90-minute ex vivo cardiac reperfusion period. Previous reports have shown that 120 minutes of reperfusion provide the best reliable assessment of infarct size in hearts perfused on a Langendorff apparatus.[3] Another point to consider is the fact that mitochondrial function was not evaluated at the end of the experiment. Mitochondrial isolation and ATP content would further confirm their findings. In addition to these limitations, physiological differences between murine models and humans should be considered. In fact, mice have been shown to exhibit increased levels of xanthine oxidase (which is absent in humans or other animal models such as rabbits), an enzyme that is directly involved in the formation of reactive oxygen species and may be implicated in the cardioprotective effect of DZX and mitochondria-targeted s-nitrosating agent.[4] Finally, the authors state that they used both male and female mice. As acknowledged by them, it would be interesting to evaluate any sex-specific observations, given that mitochondrial oxygen consumption and Ca^{2+} are modulated by sex and play a significant role in the sex-based response to ischemia-reperfusion.[5]

Nevertheless, this interesting study adds another path down the road that will ultimately lead to understanding

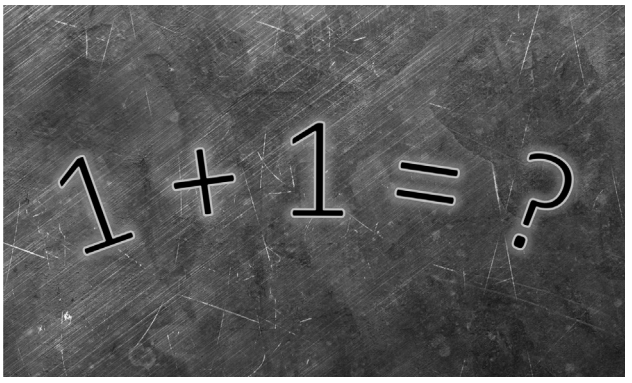

FIGURE 1. One plus one is equal to…?

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the whole picture of mitochondria and cardioprotection. The authors should be commended for their work, and future follow-up studies on these preliminary observations are keenly awaited.

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