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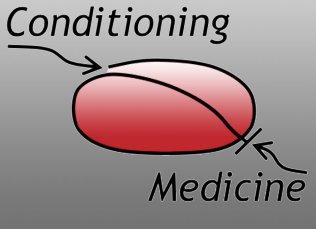

EDITORIAL| OPEN ACCESS

Negative Conditioning: Confounding the benefits of preconditioning and postconditioning

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Over the last decades, the number of research groups actively working on mechanisms involved in pre-conditioning and post-conditioning cardioprotection and neuroprotection has increased substantially, and multiple mechanisms and new targets for organ protection against injury and disease have been identified. This enormous interest has also led to the identification of factors, which interfere with the benefits of pre-conditioning and post-conditioning – so called "negative conditioners" that include age, co-morbidities, co-medications, and other factors. This special issue of Conditioning Medicine on Negative Conditioning reviews several different factors, which are known to attenuate the protective effects of pre- and post-conditioning, and also addresses their effects on the signaling pathways underlying conditioning protection.

The confounding effects of diabetes mellitus are highlighted in articles by Jiang et al. in stroke patients, and Wider et al. in the setting of acute myocardial infarction. Jiang et al. review the negative effects of diabetes on clinical outcomes in tissue plasminogen activator-treated stroke patients, underscoring the importance of maintaining glucose homeostasis in these patients to improve health outcomes. Wider et al. review the confounding effects of diabetes mellitus on the cardioprotective efficacy of ischemic conditioning in the setting of acute myocardial infarction, and highlight the importance of taking this co-morbidity into consideration when performing experimental and clinical cardioprotection studies.

Endothelial progenitor cells (EPCs) play wide-ranging roles in maintaining organ homeostasis. Hence, it may not be surprising that negative effects of aging and co-morbidities may also involve the degradation of EPC function. The review by Pradillo et al. surveys the mechanisms in aging, hypertension, diabetes, and obesity that affect EPC function during vascular remodelling in the setting of cardiovascular disease.

Importantly, many of these biphasic effects of "negative conditioners" may operate in mulitple diseases and organ systems, as highlighted by the next two reviews. Selvaraji et al. explore the role of mitochondrial dysfunction in age-related neurodegenerative diseases, suggesting that mitochondria dynamics contribute to the protective pathways activated by brain and heart conditioning, therefore presenting new druggable targets for future therapeutic strategies. In the paper by Ytrehus et al., the authors describe the dual role played by uric acid in the pathophysiology of ischemic events occurring in brain, heart, kidney, and other organs. Their impact on cardioprotection and neuroprotection by ischemic conditioning are also reviewed.

Fundamentally, pre-conditioning is related to the toxicological concept of hormesis, whereby lower doses of a toxin elicit a beneficial response whereas higher doses lead to damaging toxicity. In the final review of this issue, Sun et al. propose a conceptual framework wherein aging (and presumably other negative conditioners) may shift the biphasic hormetic curve of steroids, thus amplifying its pathophysiological effects in diseased organs.

The final paper in this special issue on Negative Conditioning is an original research article by Lan et al., who investigate the deleterious effects of hypertension on the brain and heart vasculome of rats, and explore the role of exercise in potentially reversing some of these negative effects.

In summary, this special issue on Negative Conditioning highlights the diverse effects that age and various vascular comorbidities such as hypertension, diabetes etc. have on the heart, brain, and other organs. In order for preconditioning and postconditioning to be clinically effective, these confounding variables must be taken into consideration. Perhaps most importantly, this special issue reminds us that the scope of the journal is broad, and all papers on aging and the negative effects of comorbidities on cell signaling and pathophysiology should be welcome in the pages of Conditioning Medicine.

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