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Exercise-induced metabolic adaptations during cardiac rehabilitation: a longitudinal metabolomic investigation on DBS

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ABSTRACT
Ischemic heart disease remains the leading cause of cardiovascular-related mortality worldwide. Despite the well-established benefits of cardiac rehabilitation (CR) through physical exercise after acute myocardial infarction (AMI), the underlying metabolic adaptations remain only partially understood. This study investigated the metabolic responses to CR in AMI patients using untargeted metabolomics and lipidomics on dried blood spots (DBS). Seventeen male patients recovering from a first AMI completed a three-week supervised rehabilitation program. DBS samples were collected before and after training sessions at three time points: first, mid-protocol, and final training. Untargeted analyses were performed using ultra-high performance liquid chromatography coupled with mass spectrometry to assess exercise-induced metabolic shifts. Throughout the CR protocol, progressive adaptation and increase in energy metabolism was observed, probably correlating with enhanced physical performance at the end of CR protocol. On the other hand, short-term lipid changes were detected at the beginning of the CR. Notably, phosphatidylserine (PS) levels increased significantly after the first training session. Since PS typically decreases following myocardial infarction, previous studies suggested that boosting PS (e.g., oral supplementation) may represent a cardioprotective strategy. Our results suggest that training enhances PS biosynthesis, possibly via activation of phosphatidylserine synthase 1 (PSS1), highlighting a potential role of CR in cardiac repair. Furthermore, N-acetyl-L-tyrosine (NAT) levels increased with rehabilitation time. Since NAT induces mitohormesis—an adaptive mitochondrial stress response—in animals, it may be linked to exercise-induced adaptations in humans. In summary, our findings show that CR induces significant metabolic and lipidomic changes in AMI patients, alongside measurable improvements in physical performance. PS and NAT emerged as promising candidate biomarkers for monitoring rehabilitation progress and may contribute to the benefits of CR on post-AMI recovery.

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