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Commentary

Exercise regulates cardiac metabolism: Sex does matter

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Cardiac substrate utilization remains a critical focus for the research community.[1] Research has acknowledged the role of metabolic flexibility in the development and progression of cardiac dysfunction during a variety of diseases and conditions.[2,3] Under resting basal conditions, the heart relies on fatty acid metabolism as the primary energy source with glucose, lactate, ketone bodies, pyruvate, acetate, and branched-chain amino acids contributing as substrates depending on substrate availability, hormonal status, and myocardial conditioning.[4] In addition to pathological states, physiological states, such as acute exercise, induce dynamic changes in substrate metabolism, including nearly a 10-fold increase in myocardial oxygen consumption.[3,5] To meet the increased demand for energy during and after a bout of exercise, the heart muscle must exhibit metabolic flexibility and selectively utilize different substrates for adenosine triphosphate production. Moreover, metabolic substrate adaptations depend on the frequency, intensity, duration, and mode of exercise while multiple metabolic fluxes, such as the use, storage and mobilization of substrates must be coordinated to maintain energy homeostasis.[1,2] Although many different processes of exercise-induced regulation and metabolic remodeling have been identified,[3–5] the effect of exercise on cellular metabolism and the landscape of metabolic pathway regulation in response to both acute exercise and chronic exercise training remain unclear.

Research evaluating changes in cardiac metabolism in response to chronic exercise training have produced inconsistent findings related to the contribution of glycolysis, glucose oxidation, and lipid oxidation in the hearts of exercise-adapted mice.[4,5] The reasons for these discrepant findings in the physiological metabolic adaptations to exercise training are numerous and likely depend on the frequency, intensity, duration, and mode of exercise. For example, glucose oxidation, palmitate oxidation, and myocardial oxygen consumption were unchanged with moderate-intensity exercise training in mice, while high-intensity exercise training resulted in increased glucose oxidation, and decreased palmitate oxidation and oxygen consumption rates.[6] In addition, the choice of animal model, including strain and sex, as well as the methodology used to assess metabolism are likely critical variables.[4,5,7] Adding to the complexity, sex-specific differences in cardiac metabolism and the response to pathological stress have been reported.[8] For example, female mice exhibit more pronounced cardiac hypertrophic responses than their male counterparts,[9] suggesting that response to exercise training is a complex multi-component network, impacted by many factors, including sex hormones.[10,11] Moreover, exercise-induced adaptive regulation of metabolism is important for maintaining mitochondrial function, as alterations in glucose catabolism can lead to mitochondrial respiration disturbances.[5] However, the mechanisms underlying these mitochondria adaptions in response to exercise remain obscure. While the effects of acute and chronic exercise on cardiac muscle are multifarious, reflecting the divergent responses to hormonal factors, the specific cellular, molecular, and metabolic mechanisms that underlie those adaptations remain elusive. Therefore, understanding sex-specific changes in cardiac metabolic pathways and substrate utilization due to acute and chronic exercise, particularly at varying exercise intensities, can contribute to the development of exercise interventions and sex-specific therapeutic approaches to treat cardiovascular disease.

In this issue of the *Journal of Sport and Health Science*, Kyle Fulghum and colleagues[12] evaluated potential sex

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differences in cardiac metabolism in response to an acute bout of exercise of varying intensities on a motorized treadmill. In the study, FVB/NJ mice were used based on their reported high treadmill exercise performance capacity.[13] Changes in circulating substrates (lactate, ketone bodies, and glucose) were measured at the end of a single bout of treadmill exercise of low, moderate, and high intensity and after 1 h of recovery. The authors found that the circulating substrates, lactate and 3-hydroxybutyrate, responded differently to variable exercise intensities immediately after acute exercise in both sexes but circulating glucose remained relatively stable. These changes in the levels of circulating lactate and ketone bodies that influence cardiac metabolism have been previously reported by the same group.[5]

Moreover, the authors also found that circulating lactate levels in male and female mice increased during high intensity exercise but returned to baseline within 1-h post-exercise. Blood glucose concentrations and 3-hydroxybutyrate levels varied between males and females. While the glucose concentration was only slightly decreased at 1-h post-exercise, circulating 3-hydroxybutyrate levels were significantly increased in the female mice while there were no changes in the male mice. This finding of elevated 3-hydroxybutyrate levels in female mice after an exhaustive bout of exercise has recently been reported.[14] These results are consistent with a previous report about sex-dependent hormonal differences, suggesting that the gonadal endocrine system could have a substantial effect on exercise and post-exercise metabolism.[10] Overall, these findings indicate that metabolic responses following acute exercise are profoundly determined by sex.

To investigate whether biological sex can influence the cardiometabolic phenotype, untargeted metabolomic analyses were conducted on heart tissue harvested from sedentary male and female mice. Surprisingly, the relative abundance of 69 cardiac metabolites was found to be significantly different between sexes. Further analysis revealed higher levels of metabolites (i.e., sphingomyelins, glycerophospholipids, homoarginine, pantothenate, and tryptophan) and lower levels of other metabolites (i.e., acylcarnitines, glycine derivatives, and acetyl CoA) in female compared to male hearts. Overall, these data suggest that biological sex affects the cardiac metabolome of mice irrespective of the exercise effect.

Untargeted metabolomics analyses were also conducted on heart tissue harvested from male and female mice after an exhaustive exercise test and after 1 h of recovery. In total, 30 metabolites changed immediately after exercise or upon 1 h of recovery from an acute bout of high-intensity exercise in female mice. In particular, 3-hydroxybutyrate, isoleucine, and lipid pathway metabolites were significantly increased in the female hearts. This result agrees with previous studies which showed that lipid metabolism may differ between sexes.[11,15] These findings also highlight a potential importance of amino acid mobilization and utilization and lipid biosynthesis in the acute responses to exercise in the female heart. Conversely, in the male murine heart subjected to acute high-intensity exercise, there were few significant changes in metabolite abundance after exercise, with corticosterone being the only metabolite significantly altered. Overall, these findings suggest that female hearts are more metabolically responsive to exercise than male hearts.

Finally, to further explain why exercise had a more pronounced effect on the female cardiac metabolome, the mitochondrial protein fraction was isolated and mitochondrial respiratory function as well as sensitivity to adenosine diphosphate (ADP) was assessed. In general, acute exercise did not influence respiratory function, although state 3 and state 4 succinate-supported respiration tended to be higher in male cardiac mitochondria. Interestingly, ADP sensitivity was generally higher in female mitochondria than in male mitochondria. Because ADP sensitivity could potentially influence mitochondrial function,[16] this could, in part, explain the more pronounced changes in the cardiac metabolome of female compared to male mice following exercise.

Untargeted metabolomics is a top-down research method that obtains data on numerous metabolites and, systematically and comprehensively, analyzes the entire metabolome, seeking to identify differences between the control and experimental group. In the context of the current research, imperatives for future investigations may require experimental verification and exploration of relevant mechanisms. Subsequent in-depth studies are aimed at determining the function of the implicated metabolites as well as the enzymes or genes that regulate them. The present study found higher levels of sphingomyelin, tryptophan, and pantothenic acid in female hearts compared to males. Sphingolipids are a complex lipid mediator family with structural and signaling functions that are crucial components of important vascular regulatory networks.[17] Tryptophan catabolic pathway imbalance has been shown to be predictive of cardiovascular disease.[18] Pantothenate is an essential precursor in coenzyme A biosynthesis, and pantothenate kinase deficiency has been shown to exacerbate ventricular dysfunction in pressure overload causing marked metabolic derangements.[19] The experiments conducted in this study provide convincing evidence that female mice demonstrated greater changes in various metabolites in both sedentary and acute exercise states and appeared to have a higher sensitivity to ADP stimulation in cardiac mitochondria. However, the significance of these sex-dependent differences in cardiac biology and the associated underlying mechanisms remains unclear and require further investigation. Also, further work is needed to examine the functional implications of these metabolites in male and female hearts.

This study provides proof of a divergent, sex-dependent response of cardiac muscle to acute exercise stress, which could further portray different long-term cardiac adaptations to exercise between the sexes. Since sex-dependent differences in cardiac substrate profile account partly for the distinct response of male and female heart to exercise, this could potentially have implications for the clinical diagnosis and treatment of cardiovascular disease based on sex.

Investigation of the effect of metabolites on cardiac structure and function may also provide a valuable direction for future applications of cardiovascular disease biomarker research and prognosis. To conclude, this study is of

paramount importance to the field of cardiac metabolism and exercise physiology as it sheds light on an under-investigated field of cardiac physiology by exploring inherent metabolomic sex differences.

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Authors' contributions

TY, MH, MS, GL, SCK, and JX drafted, reviewed, and edited the manuscript. All authors have read and approved the final version of this manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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