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Association between Cardiac High-Energy Phosphate Metabolism and Whole Body Metabolism in Healthy Female Adults

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Short tittle: Cardiac High-Energy Phosphate and Whole Body Metabolism

Key Points

- Decline in cardiac metabolism and whole body metabolism may lead to heart failure in later life.
- Cardiac metabolism is associated with whole body metabolism.
- No significant association between cardiac high-energy phosphate metabolism and whole body metabolism in women.
- The present study provides a better understanding of the interaction between the heart and body metabolism and the strategy for modulating cardiac metabolism to treat heart failure.

Key words: Cardiac high energy phosphate, Metabolism

Abstract

Decline in cardiac high-energy phosphate metabolism [phosphocreatine-to-ATP (PCr/ATP) ratio] and whole body metabolism increase the risk of heart failure and metabolic diseases. The aim of the present study was to assess the relationship between PCr/ATP ratio and measures of body metabolic function. A total of 35 healthy women (56 ± 14.0 years of age) underwent cardiac ^{31}P magnetic resonance spectroscopy to assess PCr/ATP ratio - an index of cardiac high-energy phosphate metabolism. Fasting and 2-hour glucose levels were assessed using oral glucose tolerance test. Indirect calorimetry was performed to determine oxygen consumption and resting metabolic rate. There were no significant relationships between PCr/ATP ratio and resting metabolic rate (r=-0.09, p=0.62), oxygen consumption (r=-0.11, p=0.54), fasting glucose levels (r=-0.31, p=0.07), and 2-hour plasma glucose (r=-0.10, p=0.58). Adjusted analysis for covariates including age, body mass index, fat mass, and physical activity, had no significant influence on the relationship between PCr/ATP ratio and body metabolism. In conclusion, the lack of relationship between cardiac PCr/ATP ratio, glucose control and metabolic rate may suggest that overall metabolic function does not influence cardiac high-energy phosphate metabolism.

Introduction

Heart failure is estimated to affect 26 million people globally and its prevalence is expected to rise in coming decades (Savarese & Lund, 2017). Consequently, it poses a problem in terms of financial burden of the healthcare system. In United Kingdom, 1-2% of health care expenditure is spent on heart failure while an estimated annual cost of $31 billion was used in United States in 2012 (Cowie, 2017; Mozaffarian et al., 2016). Heart failure is characterized by deterioration of contractile function resulting to inability of the heart to meet the body demands (Ventura-Clapier *et al.* 2004). The disequilibrium between cardiac supply and demand has led to the concept of energy starvation, in which the heart is compared to an engine out of fuel, that is central to the development of heart failure (Neubauer, 2007). Changes of the cardiac metabolism's components occur in heart failure and may contribute to its development (Neubauer, 2007; Ventura-Clapier *et al.* 2011). Cardiac high-energy phosphate metabolism is responsible for an intricate metabolic stability, maintaining an almost constant concentration of phosphocreatine (PCr), which is considered as an energy storage compound, and adenosine triphosphate (ATP), which is the main source of energy, when cardiac workload increases (Neubauer, 2007). PCr/ATP ratio is a powerful index of cardiac high-energy phosphate metabolism measured by phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) (Esterhammer et al., 2014). Decline in PCr/ATP ratio has been reported in heart failure, supporting energy starvation to play a role in the development of heart failure (Beer et al., 2004; Hardy *et al.* 1991; Ingwall & Weiss, 2004; Neubauer, 2007). Diabetes is heavily linked with heart failure (Nichols *et al.* 2004). The Framingham study (Kannel *et al.* 1974) observed four and eight times increase of heart failure incidence in diabetic men and women, respectively compared to non-diabetics. In absence of diabetes, increased glucose levels were found to increase the risk of heart failure (Nielson & Lange, 2005). On the other hand, abnormalities in glucose metabolism can also occur in heart failure

patients and if not treated may worsen the prognosis (Tenenbaum & Fisman, 2004). Several studies (Neubauer, 2007; Nielson & Lange, 2005) have demonstrated alterations in cardiac energetics and body metabolism that can affect heart failure but there is limited evidence reporting interaction between cardiac and whole body metabolism. Thus, the present study aims to evaluate the relationship between cardiac PCr/ATP ratio and measures of overall body metabolic function. According to the energy starvation theory, the failing heart is analogous to a weak and tired horse, and if appropriately nourished, it will be able to recover and work (Neubauer, 2007). Treating heart failure by targeting energy metabolism can be a promising strategy, but it is still under investigation. Addressing the interaction between cardiac and whole body metabolism may enhance further research to address the question whether using interventions known to improve body metabolism will also lead to improved cardiac metabolism which as a potential target to treat heart failure (Neubauer, 2007).

Methods

A total of 35 healthy women were recruited from local community groups affiliated with Newcastle University. Participants were included in the study if they had (i) no history of cardiovascular diseases, respiratory diseases, and other chronic conditions; (ii) normal glucose tolerance, lipid profile, blood pressure, and electrocardiogram; (iii) body mass index less than 30 kg/m^2. Participants were excluded if they were smokers or former smokers and if they were consuming medications known to affect cardiovascular function. This study was approved by Sunderland Research Committee (09/H0904/55). All participants provided written informed consent according to the Declaration of Helsinki.

Body composition of the participants, such as body mass, and body fat mass, was assessed using air-displacement plethysmography (BodPod, Life Measurement Inc., California, USA).

Physical activity, which is represented by average step count, was measured by a portable multisensory array (Sensewear Pro, Bodymedia Inc., Philadelphia, USA) over a 7-day period and only removed for bathing.

All participants were required to fast overnight before getting their blood samples taken at Clinical Research Facility, Royal Victoria Infirmary, Newcastle upon Tyne the following morning. After the first blood sample collection, which reflects the fasting glucose level, an oral glucose tolerance test was performed. All participants were asked to consume 75 g of oral glucose solution and blood sample was taken two hours later.

Metabolic variables at rest, including oxygen consumption (VO_2), respiratory exchange ratio, and carbon dioxide production (VCO_2), were determined using online gas exchange metabolic system (Metalyzer 3B, Cortex, Leipzig, Germany). Gas exchange measurements were performed in supine position for 10 minutes. Resting metabolic rate was calculated using Weir formula (Weir, 1949) as follows:

$$\text{Resting metabolic rate (kcal/min)} = 3.9 \times VO_2 \text{ (l/ min)} + 1.1\ VCO_2 \text{ (l/ min)}$$

To assess cardiac high-phosphate energy metabolism, participants were scanned using 3T Philips Achieva scanner (Philips, Best, Netherlands) in a prone position. A 10 cm diameter ^{31}P surface coil (Pulseteq, UK) was utilized to transmit and receive the signal. Each participant was positioned into the magnet with the heart at isocenter. The position of the heart was confirmed using imaging from an in-built body coil. Using a cardiac-triggered breath-held field map, shimming was performed to enhance the homogeneity of the main magnetic field. A cardiac gated, slice-selective, one-dimensional chemical shift imaging (1D-CSI) sequence was used. In order to eliminate liver contamination and prevent spectral contamination from the chest wall, a 7 cm slice selective pulse was applied foot-head and spatial presaturation of lateral skeletal muscle was done, respectively. Sixteen coronal phase-

encoding steps were used, generating spectra from 10 mm slices [TR= heart rate; 192 averages at the center of k-space with cosine-squared acquisition weighting; acquisition time~20 min). The locations of the spectral slices were overlaid onto an anatomical image and the first spectrum that arose entirely beyond the chest wall was selected. Quantification of PCr, γ-ATP, and 2,3-diphosphoglycerate (2,3-DPG) peaks was done using AMARES time domain fit routine of jMRUI processing software. The peak area of ATP was corrected for blood contamination by $^1/_6$ of the amplitude of combined 2,3-DPG peak after the fitting. After calculating PCr/ATP ratios, the ratios were corrected for saturation, with T_1 values of cardiac PCr and ATP component taken from previous literature (Jones et al., 2010). Lastly, the flip angle was corrected using a calibration data set and a gadolinium-doped standard of 20 mM phenyl phosphonic acid at the center of the coil.

All statistical analyses were performed using SPSS Statistics V.24.0. Normality of distribution was assessed using Q-Q plots and Shapiro-Wilk test. The relationship between variables of interest was assessed by Pearson's correlation coefficient (r). Partial correlation was also performed to control the covariates including age, body mass index, and physical activity. Data are presented as means ± standard deviation (SD) unless otherwise stated. The level of statistical significance was indicated as $p < 0.05$.

Results

Demographic and physical activity characteristics of the study participants are shown in Table 1. Measures of body metabolic function including resting oxygen consumption, metabolic rate and glucose levels are presented in Table 2.

Analysis of cardiac metabolism using magnetic resonance spectroscopy revealed the mean±SD of cardiac high energy phosphate metabolism (PCr/ATP ratio) of 2.13 ± 0.55.

Association between cardiac high-energy phosphate metabolism and whole body metabolism is illustrated in Figure 1. No significant relationship was found between PCr/ ATP ratio and resting metabolic rate, relative oxygen consumption, fasting plasma glucose levels, and 2-hour plasma glucose levels.

Table 3 shows the results of partial correlation between PCr/ATP ratio and resting metabolic rate, relative oxygen consumption, fasting plasma glucose levels, and 2-hour plasma glucose levels after that being controlled for several covariates. Most correlations still showed weak and negative relationship between the variables even when the analysis was adjusted for age, BMI, fat mass, and physical activity.

Discussion

The present study assessed the relationship between cardiac high-energy phosphate metabolism and whole body metabolism. It has been hypothesized that diminished cardiac metabolism plays a major role in the development of heart failure (Neubauer, 2007). Evaluating the association between cardiac and whole body metabolism holds importance as it provides a better understanding of the interaction between the heart and body metabolic processes and their potential malleability with treatments.

The major finding of this study suggests that there is a weak and statistically non-significant relationship between cardiac high-energy phosphate metabolism and measures of whole body metabolic function, including resting metabolic rate, glucose levels, and oxygen consumption. Moreover, after controlling the correlation for covariates (i.e. age, BMI, fat mass, and physical activity), no significant relationship was found between PCr/ATP ratio and whole body metabolic variables.

Available studies that investigated the relationship between cardiac high-energy phosphate to body metabolism were only limited to evaluate the correlation between PCr/ATP ratio to

glucose levels. Patients with type 1 and type 2 diabetes showed a decline in PCr/ATP ratio in comparison to the healthy controls (Metzler et al., 2002; Scheuermann-Freestone et al., 2003). Significant correlation was observed between PCr/ATP ratio and fasting plasma glucose (r^2= 0.55, $p<0.05$), although, no significant correlation was found in healthy subjects, which is in line with the present study (Scheuermann-Freestone et al., 2003). This suggests that presence of disease may enhance interaction between cardiac and body metabolism to be more pronounced. According to a longitudinal study (Nielson & Lange, 2005), increased glucose levels are associated with increased risk of heart failure in non-diabetic adults and it may contribute to the development of heart failure. The possible mechanism to how glucose levels may affect the pathogenesis of heart failure is not known, but based on the present study it can be suggested that cardiac high energy phosphate metabolism may be independent from the mechanisms controlling whole body metabolism (Nielson & Lange, 2005). The effectiveness of therapeutic interventions to improve glucose control has been previously reported (Guazzi *et al.* 2003; Nielson & Lange, 2005). Improvement in insulin sensitivity resulted in improvement in exercise capacity in heart failure, but little evidence is available that improved glucose control can enhance cardiac energetics and function (Guazzi et al., 2003; Nielson & Lange, 2005).

The analyses reveal weak, statistically non-significant relationship between cardiac PCr/ATP ratio, resting metabolic rate and oxygen consumption. This may imply that cardiac high-energy phosphate metabolism is independent from the body metabolic function. No study so far had evaluated relationship between cardiac metabolism and resting metabolic rate. Resting metabolic rate is altered in heart failure patients, although the mechanism was unknown (Poehlman *et al.* 1994). Further analysis included controlling for the covariates i.e. age, BMI, fat mass, and physical activity. However, even after accounting for these potentially confounding factors, results confirmed no significant association between cardiac

PCr/ATP ratio and body metabolism. Lack of association between cardiac high-energy phosphate metabolism and body metabolism suggests that whole body metabolism should not be considered as a marker of cardiac metabolic health. Based on these findings it can be suggested that interventions known to improve whole body metabolism may not lead to improvement in cardiac metabolism.

This study has several potential limitations. The study participants were all women; therefore, the results may not be applicable to men. Furthermore, moderate sample size may increase the risk of statistical error.

In conclusion, the present study indicates a lack of significant relationship between cardiac PCr/ATP ratio and resting metabolic rate, oxygen consumption, and glucose levels. This finding suggests that whole body metabolism has no significant influence on cardiac high-energy phosphate metabolism. Further mechanistic studies are warranted to confirm or refute the lack of association between cardiac and body metabolism. Better understanding of molecular and cellular interactions between metabolic control of the heart and the rest of the body may lead to development to novel therapeutic targets and treatments.

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Additional Information

Competing interests: The authors declare no conflicts of interests.

Author contributions: All authors contributed to the design of the research. K.G.H. and D.G.J. were involved in acquiring the data while P.G.W., K.G.H., and D.G.J. analysed and interpreted the data. All authors have approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Table 1. Anthropometric characteristics of study participants

Variable	Study Participants (n= 35)
Age, years	55.7 ± 14.0
Weight, kg	67.7 ± 11.2
Height, cm	163 ± 5.83
Body mass index, kg/m^2	25.5 ± 3.71
Fat body mass, kg	23.6 ± 9.10
Physical Activity, steps/ day	11532 ± 5422

Table 2. Measurements of whole body metabolism

Variable	Study Participants (n= 35)
Oxygen consumption, mL/min	244 ± 35.9
Oxygen consumption, mL/kg/min	3.68 ± 0.71
Carbon dioxide production, mL/min	221 ± 36.8
Respiratory exchange ratio	0.90 ± 0.07
Resting metabolic rate, kcal/day	1721 ± 255
Fasting plasma glucose, mmol/L	4.87 ± 0.50
2-hour plasma glucose, mmol/L	5.25 ± 1.44

Table 3. Partial Correlations between PCr/ATP Ratio and Measures of Whole Body Metabolism

		Resting Metabolic Rate	Relative Oxygen Consumption	Fasting Plasma Glucose	2-h Plasma Glucose
Adjusted for age	r	-0.15	-0.14	-0.10	0.16
	P-value	0.41	0.42	0.58	0.37
Adjusted for BMI	r	-0.09	-0.21	-0.31	-0.08
	P-value	0.63	0.24	0.07	0.65
Adjusted for fat mass	r	-0.09	-0.28	-0.29	-0.06
	P-value	0.63	0.11	0.09	0.74
Adjusted for physical activity	r	-0.14	-0.32	-0.31	-0.03
	P-value	0.45	0.06	0.08	0.86
Adjusted for age, BMI, fat mass, and physical activity	r	-0.25	-0.37	-0.22	0.19
	P-value	0.18	0.43	0.24	0.31

Figure

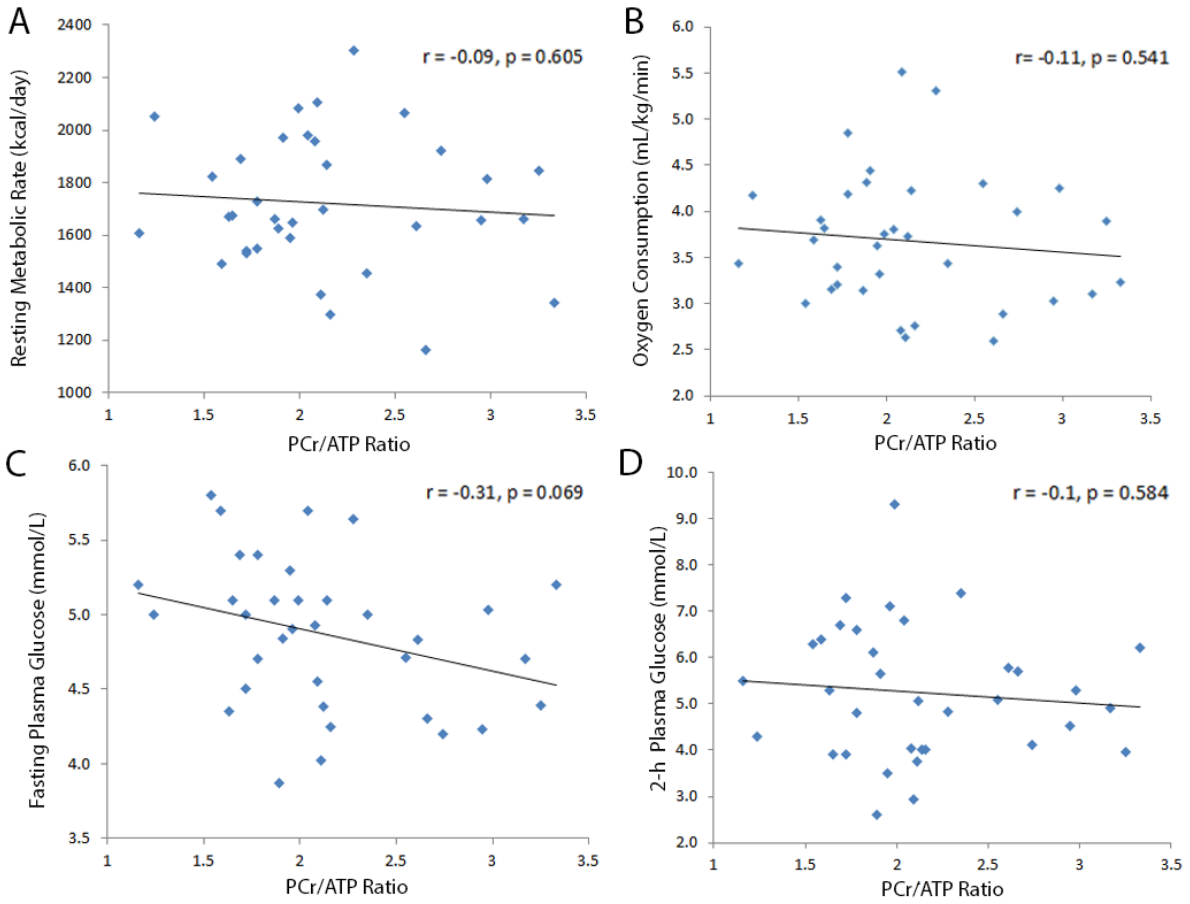

Figure 1. Relationship between cardiac high-energy phosphate metabolism (PCr/ATP ratio) and [A] resting metabolic rate, [B] relative oxygen consumption, [C] fasting plasma glucose levels, and [D] 2-hour plasma glucose levels in all participants.