Resting cardiac energy metabolism is inversely associated with heart rate in healthy young adult men

Gabriele Fragasso, MD,[a] Francesco De Cobelli, MD,[b] Roberto Spoladore, MD,[a] Antonio Esposito, MD,[b] Anna Salerno, MD,[a] Giliola Calori, MD,[a] Claudia Montanaro, MD,[a] Francesco Maranta, MD,[a] Guido Lattuada, PhD,[c,d] Alberto Margonato, MD, FESC,[a] Alessandro Del Maschio, MD,[b] and Gianluca Perseghin, MD[c,d] ***Milano, Italy***

Background 31-Phosphorus-magnetic resonance spectroscopy may provide pathophysiological insights into the high-energy phosphate metabolism of the myocardium as measured by phosphocreatine to adenosine triphosphate (PCr/ATP) ratio. Aim of the present study was to determine in vivo the relation between cardiac PCr/ATP ratio and heart rate in normal male subjects.

Methods One hundred twelve apparently healthy, young male individuals (age 34 ± 10 years) were prospectively evaluated. They underwent cardiac cine magnetic resonance imaging to assess left ventricular (LV) function and morphology and 3D-ISIS ^{31}P-magnetic resonance spectroscopy of the LV to assess the PCr/ATP ratio (a recognized in vivo marker of myocardial energy metabolism). Data were analyzed after segregation by tertiles of the resting PCr/ATP ratio.

Results A significant inverse association between PCr/ATP ratios and resting heart rate was observed (Spearman ρ: r=–0.37; $P < .0001$). PCr/ATP ratios were also inversely associated with body mass index, diastolic blood pressure, wall mass and with insulin resistance, but in multiple regression analysis heart rate was found to be independently related to PCr/ATP.

Conclusions The present study shows that resting heart rate is proportionally lower across tertiles of increasing PCr/ATP ratio of the LV in apparently healthy young male individuals, supporting the hypothesis that heart rate is a major determinant of cardiac energy stores. These findings may explain the prognostic role of heart rate in the general population as evidenced by previous large epidemiological studies. (Am Heart J 2011;162:136-41.)

There has been recently increasing interest in heart rate as a risk factor for cardiovascular disease. An elevated resting and post-exercise heart rate has been shown to be an independent predictor of cardiovascular morbidity and mortality[1-3] and is associated with a greater incidence of sudden cardiac death.[4-5] High heart rate may indicate sympathetic nervous system activation[6] which, in the long-term, may contribute to the build-up of metabolic risk factors for cardiovascular disease.[7] Additionally, high sympathetic tone is known to interfere in cardiac substrate utilization,[8] mainly by peripheral catecholamine-induced release of free fatty acids (FFA) [9] and increased myocardial oxidative stress.[10] Therefore, increased heart rate may be just a marker of a complex pathophysiological process.[11]

In normal myocardium, the concentrations of the high energy phosphate compounds adenosine triphosphate (ATP) and phosphocreatine (PCr) are tightly controlled over a range of performance because ATP production by mitochondrial oxidative phosphorylation is closely coupled to ATP utilization by cytosolic adenosine triphosphatases.[12] Adenosine triphosphate is the direct energy source for energy-consuming reactions in the cell, whereas PCr acts as an energy storage compound and, in addition, as an energy transport molecule in the "creatine kinase-PCr energy shuttle."[13] Previous clinical studies using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) to measure PCr/ATP ratios in human myocardium have shown that this ratio is reduced in hypertrophied and, even more so, in failing human myocardium.[14-21]

The aim of this study was to assess the link between basal heart rate and myocardial metabolism in normal subjects.

Methods

Patients

One hundred twelve consecutive normal volunteers (age 34 ± 10 years) were recruited within the outpatient services of the

From the [a]Cardio-Thoracic and Vascular Department - Clinical Cardiology, Istituto Scientifico-Universita' Vita/Salute San Raffaele, Milano, Italy, [b]Department of Radiology, Istituto Scientifico-Universita' Vita/Salute San Raffaele, Milano, Italy, [c]Internal Medicine—Istituto Scientifico H San Raffaele, Milano, Italy, and [d]Department of Sport, Nutrition and Health—Università degli Studi di Milano, Milano, Italy.

Submitted October 15, 2010; accepted April 11, 2011.

Reprint requests: Gabriele Fragasso MD and Gianluca Perseghin MD, Division of Metabolic and Cardiovascular Sciences, Istituto Scientifico San Raffaele, Via Olgettina 60, 20132 Milano, Italy.
E-mails: gabriele.fragasso@hsr.it, perseghin.gianluca@hsr.it

0002-8703/$ - see front matter

doi:10.1016/j.ahj.2011.04.012

Center of Nutrition/Metabolism of the San Raffaele Scientific Institute. All study subjects were apparently healthy, with no previous history of diabetes, hypertension, dyslipidaemias, vascular events, dilated cardiomyopathy, pathological ejection fraction, and resting electrocardiographic (ECG) markers of cardiac ischemia and no features compatible with the NYHA classes for heart failure. They were not taking any medications. Habitual physical activity was established in all study subjects with a questionnaire based on 3 components: physical activity index (PAI) at work, sport during leisure time, and physical activity during leisure time excluding sports, as we have previously reported.[22] Recruited subjects gave their informed written consent after explanation of purpose, nature and potential risks of the study. The protocol was approved by the ethics committee of the Istituto Scientifico San Raffaele.

Experimental procedures

Subjects were instructed to consume an isocaloric diet and to abstain from heavy exercise activity for 3 days before the magnetic resonance imaging (MRI)-MRS studies. All volunteers underwent the protocol at 7:30 to 9:30 AM on Wednesdays in the resting state after a 10 hours overnight fasting period.

Cardiac ^{31}P-MRS

Cardiac ^{31}P-MRS was performed at rest using a 1.5 T whole-body scanner (Gyroscan Intera Master 1.5 MR System; Philips Medical Systems, Best, The Netherlands). ^{31}P spectra were obtained by means of a 10-cm-diameter surface coil used for transmission and detection of radio frequency signals at the resonance frequency of ^{31}P (at 1.5 T, 25.85 MHz) as previously described.[22-24] Briefly, after appropriate positioning of the surface coil on the chest, localized homogeneity adjustment was performed using the body coil and ECG-triggering by optimizing the ^{1}H-MRS water signal. Afterwards, the transmitter-receiver was switched without time delay to the ^{31}P frequency and manual tuning, and matching of the ^{31}P surface coil was performed to adjust for different coil loading. The radio frequency level was adjusted to obtain a 180° pulse of 40 ms for the reference sample at the centre of the ^{31}P-surface coil. The acquisition of ^{31}P-MR spectra was triggered to the R-wave of the ECG, with a trigger delay time of 200 milliseconds and a recycle time of 3.6 seconds. Image selected in-vivo spectroscopy (ISIS) volume selection in three dimensions (3D-ISIS) based on 192 averaged free induction decays was employed. The volume of interest was oriented avoiding inclusion of chest wall muscle and diaphragm muscle (typical volume size: 5 [caudo-cranial] × 6 × 6 cm^3). Acquisition time was 10 minutes. Adiabatic frequency-modulated hyperbolic secant pulses and adiabatic half-passage detection pulses were used to achieve inversion and excitation over the entire volume of interest. Examination time was 40–45 minutes.

Cardiac MRI

MRI studies were performed with the above described scanner using an enhanced gradient system with a maximum gradient strength of 30 mT/m and a maximum gradient slew rate of 150 mT m^{-1} s^{-1}. The Cardiac Research software patch (operating system 9) was used. The examination was performed using a five-element cardiac phased-array coil, and retrospective ECG-triggering was obtained with vectorcardiogram system and using standard MRI methodology as previously described.[22-24]

^{31}P-MRS analysis

^{31}P-MR spectra were transferred to a remote SUN-SPARC workstation for analysis. The spectra were quantified automatically in the time domain, using Fitmasters. The ATP level was corrected for the ATP contribution from blood in the cardiac chambers based on a previous study.[15] Depending on the repetition time (TR), phosphocreatine/ATP (PCr/ATP) ratios had to be corrected for partial saturation effects, and T1-values obtained from inversion recovery experiments on the human left ventricle (LV) were used. Based on these data and a TR of 3.6 seconds, a saturation correction factor of 1.35 was obtained and applied to all "blood corrected" myocardial PCr/ATP ratios.[25] An estimate of the signal-to-noise ratio of each spectrum was obtained from the relative Cramer-Rao SD calculated for the PCr/ATP, which is a commonly reported index of accuracy of the spectral quantification.[26]

MRI analysis

Image analysis was performed using an image-processing workstation (EasyVision; Philips Medical Systems) by using the cardiac analysis software package as previously described.[22-24]

Analytical determinations

Glucose concentration was measured with the glucose oxidase method (Beckman Coulter, Fullerton, CA). Triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) were measured as previously described.[22-24] Plasma insulin (intra-assay and inter-assay coefficient of variation <3% and 6%, respectively; cross-reactivity with C-peptide and proinsulin <1%) was measured with radioimmunoassay (Linco Research, St Charles, MO).[22-24] We estimated insulin resistance (homeostatic model assessment [HOMA-IR]) as previously described.[27] Heart rate was assessed continuously in an automated fashion during the entire period of the cine MRI acquisition, and the cardiac analysis software package delivered the average values: the final heart rate value was obtained on a 20-minute time period during which the study was acquired. To standardize the procedure, all patients were left supine in the resting position under the coil for 10 minutes before starting the study acquisition.

Statistical analysis

Data in text, tables, and figures are mean ± SD. Analysis was performed using the SPSS software (version 13.0; SPSS Inc, Chicago, IL). One-way analysis of variance (ANOVA) or Kruskal-Wallis non-parametric test were used to compare variables between tertiles of PCr/ATP ratio depending on the distribution of the data. Bonferroni post hoc test was used. Statistical significance was defined as a $P < .05$. The relationship between PCr/ATP ratio and the anthropometric, clinical, and laboratory features and LV morphologic and functional parameters were examined by two-tailed Person's correlation coefficients; also, in this case, nonparametric correlation coefficient was obtained using Spearman's ρ when appropriate. To ascertain how important was the relative contribution of anthropometric, clinical, and laboratory features and of LV morphologic and

Table I. Anthropometric, clinical and laboratory features of study subjects by tertiles of PCr to ATP ratio

	Tertile I	Tertile II	Tertile III
PCr/ATP	1.55 ± 0.18 range: 1.08-1.79	2.03 ± 0.13 range: 1.80-2.23	2.49 ± 0.24 range: 2.24-3.15
Age (years)	33 ± 7	34 ± 10	34 ± 12
Weight (kg)	82 ± 15*	78 ± 10	72 ± 9
Height (cm)	176 ± 7	178 ± 6	176 ± 7
BMI (kg/m^2)	26.3 ± 4.4*	24.8 ± 3.5	23.5 ± 2.8
PAI	7.9 ± 1.4	8.1 ± 1.7	8.5 ± 1.5
Systolic BP (mm Hg)	123 ± 10	124 ± 8	123 ± 9
Diastolic BP (mm Hg)	83 ± 7*	83 ± 8	77 ± 8
Total cholesterol (mg/dL)	186 ± 36	203 ± 48	182 ± 34
HDL-C (mg/dL)	50 ± 13	60 ± 15	56 ± 13
Triglycerides (mg/dL)	120 ± 115	100 ± 84	85 ± 40
Glucose (mmol/L)	5.1 ± 0.5*	5.1 ± 0.4*	4.8 ± 0.5
Insulin (μU/mL)	14.5 ± 5.9	13.7 ± 4.3	11.6 ± 6.7
HOMA-IR	3.3 ± 1.2*	3.2 ± 1.1	2.5 ± 1.3
FFA (mmol/L)	0.59 ± 0.21	0.58 ± 0.21	0.61 ± 0.22
Creatinine (mg/dL)	1.13 ± 0.78	0.97 ± 0.48	0.97 ± 0.23

Data are shown as mean ± 1SD.
BP, Blood pressure.
* $P < .05$ versus tertile III (one-way ANOVA and Bonferroni post hoc or Kruskal-Wallis non-parametric test).

functional parameters in predicting PCr/ATP ratio, we used stepwise regression analysis (using F ratio-to-remove of 4 and F ratio-to-enter of 3.996).

Source of funding used to support the research

This work was supported by a liberal donation by Angela Musazzi and Mario Stellato Family. Support by the European Federation for the Study of Diabetes is also gratefully acknowledged.

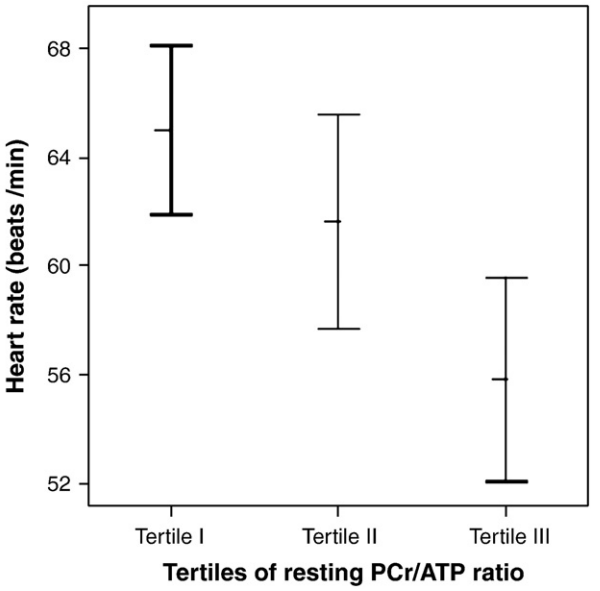
The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

LV PCr/ATP ratio

Study subjects were segregated in subgroups by tertiles of PCr/ATP ratio. The cut-offs were ≤1.79 (tertile I), >1.79 and ≤2.23 (tertile II), and >2.24 (tertile III). The accuracy was excellent: the mean relative Cramer-Rao SD was not different among tertiles (17% ± 7%, 16% ± 5%, and 17% ± 7% in tertiles I, II, and III respectively; $P = .79$). In our setting, the intra-examination coefficient of variation (assessed by studying subjects twice and consecutively on the same session without changing the position of the surface coil) is 6% ± 3%. Inter-examination coefficient of variation assessed during the same temporal period (studied by performing the acquisition in 2 separate occasions, with a time interval of 7 to 19 days with no efforts to minimize variability) was 13% ± 4%.

Figure 1



Tertiles of PCr/ATP ratio and heart rate. Spearman ρ –0.37; $P = .0001$. Data are means ± 95% CI.

Anthropometric and biochemical characteristics of study groups

The anthropometric, clinical, and biochemical features of the individuals within the three tertiles of PCr/ATP ratio are summarized in Table I. Age was not different; meanwhile, body weight and the body mass index (BMI) were higher in the subgroup with the lowest PCr/ATP ratio (tertile I) when compared to the subgroup with the highest PCr/ATP ratio (tertile III). The PAI showed a trend to be different by tertiles of PCr/ATP ratio (7.9 ± 1.4 in tertile I, 8.1 ± 1.7 in tertile II and 8.5 ± 1.5 in tertile III; 1-way ANOVA $P = .081$), and a trend was observed also in the correlation analysis between heart rate and PAI ($r = -0.18$; $P = .067$). Systolic blood pressure was within the reference range and was not different among tertiles; in contrast, diastolic blood pressure was higher in tertile I when compared to tertile III. Total cholesterol, HDL-C, and triglycerides were not different between tertiles. Fasting plasma glucose was higher in tertiles I and II when compared to tertile III; meanwhile, fasting plasma insulin was not different between tertiles even if a trend could be detected (Kruskal-Wallis test; $P = .08$). As a consequence HOMA-IR, as the product of fasting plasma glucose and insulin concentrations, resulted to be significantly different and higher in tertile I when

Table II. Parameters of LV morphology, systolic and diastolic function and heart rate of study subjects by tertiles of PCr to ATP ratio

	Tertile I	Tertile II	Tertile III	One-way ANOVA (*P*)
PCr/ATP	1.55 ± 0.18 range: 1.08-1.7	2.03 ± 0.13 range: 1.80-2.23	2.49 ± 0.24 range: 2.24-3.15	
EDV (mL)	147 ± 25	147 ± 31	147 ± 24	.97
ESV (mL)	58 ± 14	57 ± 18	57 ± 13	.99
EDWM (g)	154 ± 27	149 ± 26	140 ± 21	.05
SV (mL)	88 ± 16	90 ± 17	90 ± 14	.86
EF (%)	61 ± 6	62 ± 6	62 ± 4	.84
CO (L/min)	5.6 ± 1.5	5.5 ± 1.2	4.9 ± 1.0	.087
E-peak filling rate (ml/s)	469 ± 83	472 ± 111	490 ± 86	.61
A-peak filling rate (mL/s)	229 ± 67	230 ± 56	213 ± 72	.47
E/A	2.2 ± 0.6	2.1 ± 0.7	2.6 ± 0.9	.082
DT (milliseconds)	181 ± 34	188 ± 34	192 ± 33	.41
HR (beat/min)	65 ± 9*	62 ± 12*	56 ± 11	**.002**

Data are shown as mean ± 1SD. Boldface indicates statistically significant.
EDV/ESV; End-diastolic/systolic volume; *SV*; stroke volume; *EF*; ejection fraction; *CO*; cardiac output; E/A; early/atrial transmitral flow; DT; deceleration time; HR; heart rate.
* $P < .05$ versus tertile III.

compared to tertile III. Fasting serum FFA and creatinine concentrations were not different between tertiles.

Left ventricular anatomical features

Morphological parameters of the LV are shown in Table II. Even if no subjects were characterized by a pathological LV mass, the end-diastolic wall mass (EDWM) was higher in the tertile I when compared to tertile III in parallel with the higher BMI. Left ventricular volumes assessed either in the end-diastolic and end-systolic phases were not different between tertiles.

Left ventricular function

Systolic function. Parameters of systolic function were not different among tertiles, as summarized in Table II. Ejection fraction, stroke volume, and cardiac output were not different between tertiles of PCr/ATP ratios.

Diastolic function. Parameters of diastolic function are also shown in Table II. No differences were detected between tertiles of PCr/ATP ratio in terms of early and atrial peak filling rates, early/atrial transmitral peak flow rate ratio, and E deceleration time.

Heart rate

The heart rate was measured in the fasting and resting state during the acquisition of cine-MRI and was different between tertiles of PCr/ATP ratio (Table II); it resulted to be higher in the tertiles I and II when compared to tertile III.

Correlation analysis

Anthropometric and biochemical features. PCr/ATP ratio was associated with BMI ($r = -0.25$; $P = .008$), diastolic blood pressure ($r = -0.27$; $P = .014$), fasting plasma glucose ($r = -0.26$; $P = .029$), and HOMA-IR ($r = -0.25$; $P = .034$).

Table III. Results of the multiple regression analysis between PCr/ATP ratio and anthropometric, clinical and metabolic features

PCr/ATP ratio	Variable	*r*	β	*P*
Stepwise multiple regression analysis (including BMI, diastolic BP, HOMA-IR, EDWM and HR)				
Step 1	Heart rate	0.33	–0.333	.004
Excluded variables	BMI		–0.134	.24
	Diastolic BP		–0.133	.27
	EDWM		0.041	.73
	HOMA-IR		–0.11	.36

The selected variables were those associated with PCr/ATP ratio in correlation analysis; Spearman ρ $P < .05$).
HR, Heart rate.

LV morphologic and functional features. PCr/ATP ratio was associated with EDWM ($r = 0.23$; $P = .017$) and heart rate ($r = -0.37$; $P < .0001$) (Figure 1).

Stepwise multiple regression analysis. Stepwise regression analysis including the variables significantly associated with the PCr/ATP ratio in the correlation analysis (BMI, diastolic blood pressure, HOMA-IR, EDWM, heart rate) was performed; the analysis selected only the heart rate as independent predictor of PCr/ATP ratio as first step (Table III). Forcing the PAI in the stepwise multiple regression analysis, this was not selected as an independent variable.

Discussion

The results of this study show an inverse correlation between heart rate and resting myocardial high energy phosphates intracellular levels in apparently healthy young male adults. This observation could explain one of the possible mechanisms by which heart rate plays a major role as a cardiovascular risk factor in health and pathological conditions. Large epidemiological studies

have provided a solid body of evidence showing that heart rate is a risk factor in the general population and an independent predictor of cardiovascular mortality in cardiac patients, suggesting that its modification could potentially be beneficial. In fact, apart from the established prognostic role of heart rate in hypertensive patients,[28] in patients with coronary disease[4] and heart failure,[29] several studies have evidenced a progressive increase in all-cause mortality in relation to heart rate also in normal subjects.[30-31] In fact, because resting myocardial high energy phosphate intracellular levels are a marker of cellular energy reserve, their progressive reduction could become particularly significant in the context of manifest cardiac disease.

With respect to other variables known to have an impact on LV PCr/ATP ratio, we put efforts in characterizing the metabolic features of the subjects of our study group because we have previously demonstrated that systemic metabolic parameters were associated with LV energy metabolism. Whole-body insulin resistance in obese individuals[22] and visceral obesity in patients with fatty liver[23] were found to be associated with reduced PCr/ATP ratio. We also measured the LV mass because we have previously reported higher LV PCr/ATP ratio in elite athletes when compared to sedentary individuals in association with exercise-induced LV hypertrophy.[32,33] In this set of data, we confirm that these metabolic and morphologic features are associated with the PCr/ATP ratio; nevertheless, when taken into account in the multivariate analysis, heart rate retained its independent association with cardiac energy metabolism (Table III). Of note, other important factors were under control in our set of data, such as the lipid profile and kidney function, and no association with resting cardiac metabolism was found.

We also want to emphasize that the inspection of our data showed that in this group of subjects without structural heart disease, the measured PCr/ATP ratios were in the range we had previously reported in patients with overt cardiomyopathies; this is the case for individuals within tertile I (average PCr/ATP = 1.55 ± 0.18) despite the fact that systolic and diastolic function parameters were within the normal range. This is an intriguing but not exceptional finding: we, in insulin resistant subjects,[22,23] and others, in patients with type 1[34] and type 2[35] diabetes, reported lower resting PCr/ATP ratios in individuals with metabolic diseases and systolic and diastolic function still in the normal range. We would like to speculate that this sort of data would support the view that abnormalities of cardiac energy metabolism may be detected prior to the subsequent development of cardiac dysfunction; unfortunately, the cross-sectional nature of the present study cannot substantiate this hypothesis, and prospective studies in patients with metabolic diseases are warranted. We also realize that another possible and potentially easier explanation is that the previously reported data with individuals with overt cardiomyopathies and PCr/ATP ratios close to our lower normal limit included, not surprisingly, many patients who were taking on a regular and long lasting basis pharmacological therapies (including β-blockers) potentially able to improve their baseline PCr/ATP ratio to a level close to the lower limit of the normal subjects.

Study limitations

The aim of the present study was to evaluate myocardial high energy phosphate intracellular levels and to correlate it to heart rate. The volume of interest used in this work represents a limitation of the study because of the low spatial resolution. However, based on the facts that (1) in preliminary studies using higher spatial resolution (but longer acquisition times), the PCr/ATP ratios were in close agreement and (2) the aim of the study was to assess metabolic alterations involving the entire LV and not to detect local abnormalities within small amount of tissue, we consider as appropriate the use of 3D-ISIS. Because the TR used in this protocol was rather short and the PCr and ATP signals were not fully recovered, the PCr/ATP ratios were corrected for partial saturation effects as described in the methods, and the used T1 values were obtained from inversion recovery experiments reported in the literature.[25] One may think that because the PCr signal decreases at a faster rate than the ATP signal due to its longer T1, this could have a potential impact on our findings. Despite the fact that this issue could not be fully excluded in our study population, we still consider it a remote possibility because numerous previous manuscripts have failed to report a significant change of the PCr/ATP ratio during mild increment of heart rate induced by handgrip exercise,[18] isometric exercise,[36] and leg exercise[37] in healthy volunteers, in whom the procedure was performed in a paired fashion.

Conclusions

The results of this study show an inverse correlation between heart rate and myocardial high energy phosphate intracellular levels in apparently healthy young adults. This observation may indicate one of the potential mechanisms by which, in the long term, heart rate plays a role as a major cardiovascular risk factor in health and pathological conditions. Strategies aimed at reducing heart rate in normal adults may be useful to improve cardiac metabolic efficiency.

References

1. Kannel WB, Kannel C, Paffenbarger Jr RS, et al. Heart rate and cardiovascular mortality: the Framingham Study. Am Heart J 1987; 113:1489-94.

2. Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351-7.
3. Seccareccia F, Pannozzo F, Dima F, et al. Heart rate as a predictor of mortality: the MATISS project. Am J Public Health 2001;91:1258-63.
4. Diaz A, Bourassa MG, Guertin MC, et al. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005;26:967-74.
5. Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;352: 1951-8.
6. Grassi G, Vailati S, Bertinieri G, et al. Heart rate as marker of sympathetic activity. J Hypertens 1998;16:1635-9.
7. Grassi G, Arenare F, Quarti-Trevano F, et al. Heart rate, sympathetic cardiovascular influences, and the metabolic syndrome. Prog Cardiovasc Dis 2009;52:31-7.
8. Bengel FM, Ueberfuhr P, Ziegler SI, et al. Non-invasive assessment of the effect of cardiac sympathetic innervation on metabolism of the human heart. Eur J Nucl Med 2000;27:1650-7.
9. Arner P, Kriegholm E, Engfeldt P, et al. Adrenergic regulation of lipolysis in situ at rest and during exercise. J Clin Invest 1990;85:893-8.
10. Zhang GX, Kimura S, Nishiyama A, et al. Cardiac oxidative stress in acute and chronic isoproterenol-infused rats. Cardiovasc Res 2005; 65:230-8.
11. Balaban RS, Kantor HL, Katz LA, et al. Relation between work and phosphate metabolite in the in vivo paced mammalian heart. Science 1986;232:1121-3.
12. Wallimann T, Wyss M, Brdiczka D, et al. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the "PCr circuit" for cellular energy homeostasis. Biochem J 1992;281:21-40.
13. Bottomley PA. Noninvasive study of high-energy phosphate metabolism in human heart by depth-resolved 31P NMR spectroscopy. Science 1985;229:769-72.
14. Bottomley PA, Weiss RG, Hardy CJ, et al. Myocardial high-energy phosphate metabolism and allograft rejection in patients with heart transplants. Radiology 1991;181:67-75.
15. De Roos A, Doornbos J, Luyten PR, et al. Cardiac metabolism in patients with dilated and hypertrophic cardiomyopathy: assessment with proton-decoupled P-31 MR spectroscopy. J Magn Reson Imaging 1992;2:711-9.
16. Neubauer S, Krahe T, Schindler R, et al. 31P magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease. Circulation 1992;86:1810-8.
17. Conway MA, Allis J, Ouwerkerk R, et al. Detection of low PCr to ATP ratio in failing hypertrophied myocardium by 31P magnetic resonance spectroscopy. Lancet 1991;338:973-6.
18. Yabe T, Mitsunami K, Okada M, et al. Detection of myocardial ischemia by 31P magnetic resonance spectroscopy during handgrip exercise. Circulation 1994;89:1709-16.
19. Conway MA, Bottomley PA, Ouwerkerk R, et al. Mitral regurgitation: impaired systolic function, eccentric hypertrophy, and increased severity are linked to lower phosphocreatine/ATP ratios in humans. Circulation 1998;97:1716-23.
20. Nascimben L, Ingwall JS, Pauletto P, et al. The creatine kinase system in failing and nonfailing human myocardium. Circulation 1996;94: 1894-901.
21. Fragasso G, Perseghin G, De Cobelli F, et al. Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure. Eur Heart J 2006;27:942-8.
22. Perseghin G, Natali G, De Cobelli F, et al. Abnormal left ventricular energy metabolism in obese men with preserved systolic and diastolic functions is associated with insulin resistance. Diabetes Care 2007; 30:1520-7.
23. Perseghin G, Lattuada G, De Cobelli F, et al. Left ventricular energy metabolism is impaired and the intrapericardial and mediastinal fat is increased in young, non-diabetic men with newly found fatty liver. Hepatology 2008;47:51-8.
24. Perseghin G, Fiorina P, De Cobelli F, et al. Cross-sectional assessment of the effect of kidney and kidney-pancreas transplantation on resting left ventricular energy metabolism in type 1 diabetic-uremic patients: a 31P-MRS study. J Am Coll Cardiol 2005;46:1085-92.
25. Lamb HJ, Beyerbacht HP, Ouwerkerk R, et al. Metabolic response of normal human myocardium to high dose atropine-dobutamine stress studied by 31P-NMR spectroscopy. Circulation 1997;96: 2969-77.
26. Lamb HJ, Doornbos J, den Hollander JA, et al. Reproducibility of human cardiac 31P-NMR spectroscopy. NMR Biomed 1996;9:217-27.
27. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-95.
28. Palatini P, Thijs L, Staessen JA, et al. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. Arch Intern Med 2002;162:2313-21.
29. Lechat P, Hulot JS, Escolano S, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. Circulation 2001;103:1428-33.
30. Dyer AR, Persky V, Stamler J, et al. Heart rate as a prognostic factor for coronary heart disease and mortality findings in three Chicago epidemiological studies. Am J Epidemiol 1980;112:736-49.
31. Gillum RF, Makuc DM, Feldman JJ. Pulse rate, coronary heart disease, and death: the NHANES I Epidemiologic Follow-Up Study. Am Heart J 1991;121:171-7.
32. Perseghin G, De Cobelli F, Esposito A, et al. Effect of the sporting discipline on the right and left ventricular morphology and function of elite male track runners; a magnetic resonance imaging and 31P-spectroscopy study. Am Heart J 2007;154:937-42.
33. Perseghin G, De Cobelli F, Esposito A, et al. Left ventricular function and energy metabolism in middle-aged men undergoing long lasting sustained aerobic oxidative training. Heart 2009;95:630-5.
34. Nallur Shivu G, Phan TT, Abozguia K, et al. Relationship between coronary microvascular dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. Circulation 2010;121: 1209-15.
35. Scheuermann-Freestone M, Madsen PL, Manners D, et al. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. Circulation 2003;107:3040-6.
36. Weiss RG, Bottomley PA, Hardy CJ, et al. Regional myocardial metabolism of high-energy phosphates during isometric exercise in patients with coronary artery disease. N Engl J Med 1990;323: 1593-600.
37. Conway MA, Bristow JD, Blackledge MJ, et al. Cardiac metabolism during exercise in healthy volunteers measured by 31P magnetic resonance spectroscopy. Br Heart J 1991;65:25-30.