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PH.D. THESIS

MYOCARDIAL ENERGETIC EFFICIENCY, A NEW TOOL FOR CARDIOVASCULAR RISK ASSESSMENT

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Abstract

Cardiac mechanical energetic efficiency is the ratio of external work (EW) to the total energy consumption. EW performed by the left ventricle (LV) during a single beat is represented by LV stroke work and may be calculated from the pressure-volume loop area (PVLA), while energy consumption corresponds to myocardial oxygen consumption (MVO2) expressed on a per-beat basis. Classical early human studies estimated total mechanical LV efficiency at 20-30%, whereas the remaining energy is dissipated as heat. As practical assessment of LV efficiency poses methodological problems, de Simone et al. proposed a simple surrogate measure of myocardial efficiency, i.e., mechano-energetic efficiency index (MEEi) calculated from LV stroke volume, heart rate and LV mass. In two independent cohorts, including a large group of hypertensive subjects and a population-based cohort (both free of prevalent cardiovascular disease and with preserved ejection fraction), low MEEi independently predicted composite incident adverse cardiovascular events and, specifically, heart failure. The aim of the present thesis is to demonstrate the prognostic ability of low MEEi in different clinical condition and assess its utility as novel noninvasive diagnostic tool.

CHAPTER I

Physiologic cardiac metabolism

The human heart contracts incessantly and requires large amounts of energy to perform its function. Since the accumulation of energy in the form of phosphates within cardiomyocytes is minimal, sufficient to sustain only a few heartbeats, a close relationship between the production of ATP and myocardial contraction is essential for normal cardiac function. Central to the coordination of energy function is the role played by the mitochondria in which the greatest amount of ATP is generated (1).

The heart can use any class of energy substrates: carbohydrates, lipids, amino acids and ketone bodies to produce ATP in the mitochondria. In a normal heart, fatty acids (FA) and carbohydrates are the main energy substrates used ATP production. The entry into the mitochondria of long-chain fatty acids is a process regulated by carnitine-palmitoyl transferase (CPT1), while the oxidation of pyruvate is regulated by the reactions of pyruvate dehydrogenase. In condition of insulin resistance FA uptake is increased and this has been demonstrated to be associated with 25% increase in myocardial oxygen consumption to sustain a given external work. This underline the crucial role of insulin resistance as a possibl determinant of decreased myocardial efficiency, because of the greater energy expenditure required to maintain the external work (2).

Myocardial regulation of fatty acid oxidation

The oxidation of myocardial fatty acids (FAO) is a complex process that provides almost 70% of cardiac ATP, while the remaining portion is produced mostly by substrates such as lactate, glucose and pyruvate (2). The oxidation of fatty acids is less efficient than that of glucose,

theoretically requiring more than 11-12% more oxygen to produce a certain amount of ATP. Several studies on humans and animals show that a high plasma concentration of fatty acids causes an excessive consumption of myocardial oxygen, causing a reduction in the contractile efficiency of the left ventricle. A normo-perfused heart readily extracts and oxidizes circulating fatty acids (FA) in proportion to their arterial concentration. Fatty acids come either from adipose tissue or are released from circulating lipoproteins by hydrolysis by lipoprotein lipase (LPL), so when lipoproteins are hydrolyzed by LPL, a large amount of fatty acids are released, representing the main form of acquirement for the heart. Once in the cytosol, the FAs are first converted into long-chain Acyl-CoA esters: 75% of them are transported to the mitochondria through carnitine palmitoyl-transferase type 1 (CPT-1) where they will undergo β oxidation for generate acetyl-CoA. The use of fatty acids is regulated by different mechanisms, including the activation of PARR- α receptors, which increase the expression of various enzymes involved in FAO, including malonyl-CoA. Malonyl-CoA plays a certain role in the metabolism of fatty acids, since by inhibiting CPT-1, it also inhibits the oxidation of FA.

CHAPTER II

How to measure cardiac efficiency

In order to generate energy, the heart uses the oxidative metabolism of energy substrates. Therefore, there is a close relationship between myocardial oxygen consumption (MVO2) and left ventricular (LV) performance. The efficiency of LV pump function is defined by the relationship between the external cardiac work produced and the amount of energy consumed during contraction. Under normal conditions, the proportion of produced energy used for contraction is ~ 25%, and the residual energy mainly dissipates as heat (2).

In order to calculate myocardial mechanical-energy efficiency, it is necessary to know the energy produced and the oxygen consumed to produce it. Oxygen consumption can be obtained, invasively, by measuring MVO2 (mL O2 · min-1) by multiplying coronary sinus blood flow by the difference in arteriovenous (A-V) oxygen content. Blood flow can be estimated by thermodilution or by doppler after access to the coronary sinus has been performed by cardiac catheterization. The difference in A-V oxygen content can be obtained by determining the oxygen saturation levels between arterial and coronary sinus blood (3) . This method of oxygen determination is considered the gold standard. However, being an invasive method, it is of little utility in clinical practice.

The external work (EW) generated by LV contraction can be estimated by analyzing pressure-volume graph (P-V) of the cardiac cycle, using a conductance catheter placed into the left ventricle. EW is defined by the area contained within the limits of the pressure-volume graph (Fig.1) that can be geometrically approximated as a rectangle with stroke volume as the basis and the end-systolic pressure as the height.

The mechanical-energetic efficiency is obtained by dividing external cardiac work by MVO2.

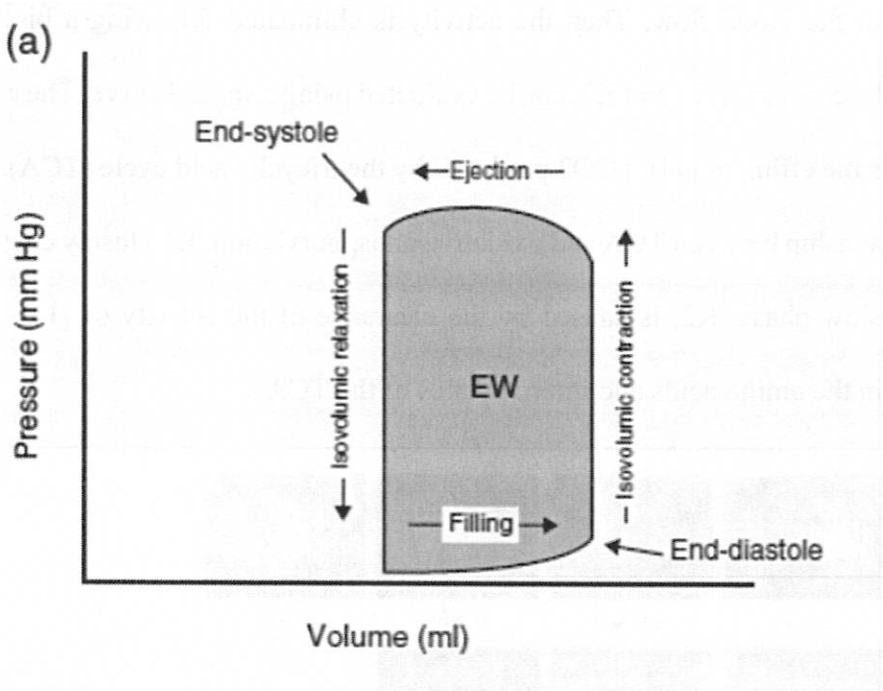

Figure 1: Schematic graph of the single-beat pressure-to-volume relationship. Starting on the right side of the loop, an isovolumetric contraction occurs at the end of diastole, rising pressure until aortic valve opens and the ejection begins. During ejection phase, LV volume decreases, while the pressure changes relatively little. At end ejection, aortic valve closes and left ventricle begins relaxation, which is isovolumetric and characterized by a rapid reduction in pressure, until pressure goes below left atrial pressure. Then, mitral valve opens, LV filling begins and volume increases, with a progressive, small increase in pressure until the end-diastolic volume is reached. The area defined by the pressure-volume loop is the external work.

The non-invasive evaluation of MVO2 is currently limited to the use of positron emission tomography (PET). Acetate labeled with carbon 11 ([11C] acetate) is commonly used in this regard. Figure 2 shows an example of dynamic cardiac PET acquisition with [11C] acetate and the corresponding myocardial time-activity curve. Within minutes of intravenous

injection, the tracer activity in the myocardium reaches a maximum level that is directly proportional to the blood flow. Then the activity is eliminated following a bi-exponential fashion, and the constants, K1 and K2, can be evaluated using a special curve. The rapid phase, K1, represents the efflux of [11C] CO2 produced by the tricyclic acid cycle (TCA), and given the close relationship between TCA and oxidative phosphorylation, K1 closely correlates with MVO2. The slow phase, K2, is caused by the clearance of the activity of [11C], which is incorporated in the amino acids and intermediates of the TCA.

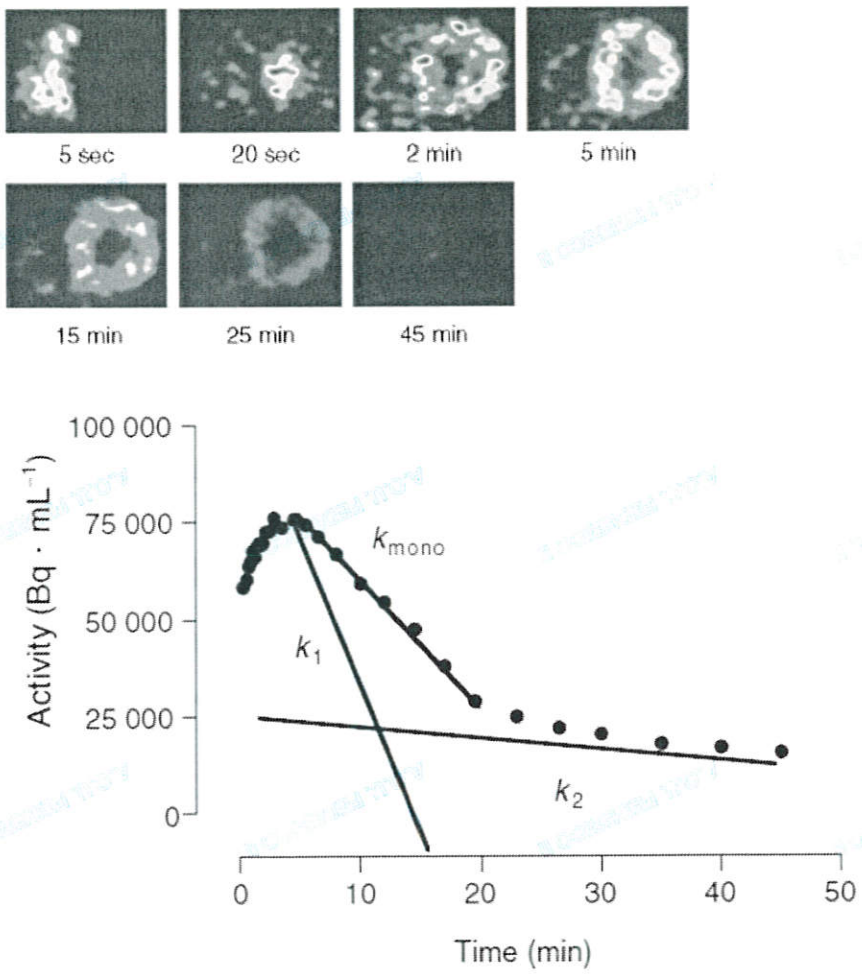

Figure 2: Short-axis view of PET acquisition with [11C] showing the transit of radio-activity through the cavities of the right and left ventricle after the injection of a bolus.

Compared to methods to measure oxidative metabolism, the non-invasive evaluation of the mechanical work produced is relatively simple. To estimate the area contained within the limits of the pressure-volume graph, in essence, it is necessary to know the stroke volume (SV), that is, the end-diastolic (LVEDV) and end-systolic (LVESV) volumes of the left ventricle. Ventricular volumes can result from various imaging techniques, such as magnetic resonance imaging (MRI), echocardiography, or nuclear imaging. LV end-systolic pressure corresponds with good approximation to the systolic arterial pressure of the brachial artery which can be measured using a simple sphygmomanometer. As said, therefore the product of systolic BP by SV is a fairly accurate estimate of external work, representing a rectangular approximation of LV pressure-volume loop.

CHAPTER III

Non-invasive estimate of myocardial energetic efficiency

Estimation of myocardial energetic efficiency (MEE) requires measures of two factors: external work and total energy consumption (4) (5).

The external cardiac work is stroke work, the single-beat pressure-volume loop, and can be non-invasively estimated as

$$SW = BPs \times SV$$

where BPs is systolic blood pressure measured by sphygmomanometer at the end of echocardiographic examination, SV is stroke volume (6). The second term that defines MEE, energy consumption, could ideally be measured by coronary sinus catheterization or non-invasive methods that require complex procedures and calculations (7) (8).

We used the simple 'double product' (DP) validated by previous studies to calculate MVO2 (9) (10):

$$MVO2 = DP = BPs \times HR$$

where HR is the heart rate.

Consequently, MEE can be simplified as follows:

$$MEE = \frac{BPs \times SV}{BPs \times HR} = \frac{SV}{HR}$$

Where HR can be divided by expressed as the time of cardiac cycle by dividing by 60 (4).

Due to the close relationship between MEE and left ventricular mass (LVM) (11), it is convenient express mechanical energy efficiency per gram of LVM, by ratiometrically dividing MEE by LVM (MEEi) that can be expressed as ml / s × g^{-1}.

MEEi as a marker of CVD risk

We have previously demonstrated that in a population of treated hypertensive patients the overall estimated myocardial mechano-energetic efficiency depends on the amount of myocardial mass, in the presence of hypertensive left ventricular (LV) hypertrophy, which is functional to keep normal the global LV myocardial efficiency. However, MEEi is often depressed, paralleling the severity of LV hypertrophy and progressive deterioration of LV function (4). A reduced MEEi negatively affects cardiovascular prognosis, independently of effect of LVH, and reduces the hazard attributable to LVH, therefor contributing to explain the prognostic effect of LVH.

Under this scenario, severity of hypertensive LV hypertrophy is functional to preserve effectively LV performance at the chamber level, when myocardial efficiency is reduced at the level of cardiomyocytes, a condition that contributes significantly to profiling a high-risk cardiovascular phenotype (11).

To better explain how myocardial efficiency might be affected by metabolic abnormalities with have analyzed the impact of obesity, diabetes and metabolic syndrome on MEE in patients with arterial hypertension. From a cohort of 12 503 participants, we demonstrate that MEEi declines in the presence of either metabolic syndrome or diabetes. The impairment is progressive, from the condition free of metabolic syndrome or diabetes to the coexistence of both. Paralleling this progressive decline, patients with metabolic syndrome and diabetes exhibit the highest prevalence of LV hypertrophy and LV concentric geometry

(12). Both studies highlights the concept that MEEi is a useful tool for the assessment of CV risk and able to express both metabolic and structural abnormalities of the myocardium.

During my PhD I have focused my research using MEEi in a different setting of population, looking at its relationship with insulin resistance in non-diabetic patients from the Strong Heart Study, its main determinates and association in population of healthy obese patients from the FATCOR study and finally in a setting of patients at high cardiovascular risk such as those with inflammatory arthritis.

Myocardial Mechano-Energetic Efficiency and Insulin Resistance in non-diabetic members of the Strong Heart Study cohort

Mancusi C, de Simone G et al. Cardiovasc Diabetol. 2019 Apr 30;18(1):56.

In the present analysis, we tested the hypothesis that MEEi progressively deteriorates for increasing degrees of insulin resistance in non diabetic participants from the Strong Heart Study (SHS). The Strong Heart Study is a longitudinal epidemiologic cohort study for cardiovascular disease and its risk factors among American Indians. The study population included resident members in 13 communities in Arizona, Oklahoma, and South/North Dakota. (13). In its initial stages, the SHS included three components. The first was a survey to determine cardiovascular disease mortality rates from 1984 to 1994 among tribal members aged 35-74 years of age residing in the 3 study areas (the community mortality study). The second was the clinical examination of 4,500 eligible tribal members. The third component is the morbidity and mortality (M&M) surveillance of these 4,500 participants. The SHS has completed three clinical examinations of the original Cohort Phase I: 1989-1991; Phase II: 1993-1995; 1998-1999, respectively. Due to the importance of genetics in the occurrence of CVD, the SHS expanded into the genetic epidemiology area. In the Phase III study, in addition to the Cohort examination, the study conducted a pilot family study. The family pilot study recruited approximately 30 families (10 per field center) which consisted of more than 900 family members. Due to the success of the pilot study, was funded to conduct a full-blown family study, the Strong Heart Family Study (SHFS) to investigate the genetic contributions to CVD and its risk factors. Phase IV genetic studies emphasized genetic linkage analysis to localize genes that contribute to CVD risk. In Phase IV, an additional 18 to 25 extended families (a total of about 900 members at least 15 years

of age) were recruited from each of the field centers from 2001 – 2003. This provides a total of 3,776 individuals from 94 families, of whom 825 are Phase III participants re-examined in Phase IV (14). We selected non diabetic participants (i.e. no history of diabetes and plasma glucose<126 mg/dL) from the Strong Heart Study (SHS) initial cohort (2nd exam) and the Strong Heart Family Study (SHFS) cohort (4th exam, age range 18-93), with available data on fasting glucose and fasting insulin levels, and free of prevalent CV disease, as already done in a previous study (15). Detailed descriptions of the study design and methods of the SHS and SHFS have previously been reported (16). Obesity was classified as BMI ≥30 kg/m2. Arterial hypertension was defined by BP≥140/90 mmHg or current antihypertensive treatment (17). Fasting plasma glucose, lipid profile and other laboratory variables were measured by standard methods, as previously reported (15). Degree of insulin resistance was assessed using HOMA-IR. Glomerular filtration rate (GFR) was estimated by the simplified Modification of Diet in Renal Disease formula. Echocardiograms were performed using phased-array, commercially available echocardiographs, with M-mode, two-dimensional and Doppler capabilities, and read off line using working stations equipped with frame-grabber to measure on stop-frame images, as previously reported in detail (18). LV mass, and LV mass index (by normalization for height in $m^{2.7}$) were estimated (18). Relative wall thickness was computed as a dimensionless ratio between posterior wall thickness and LV internal radius, as the measure of LV concentricity (19). Stroke volume (SV) was calculated as the difference between LV end-diastolic and end-systolic volumes by the z-derived method, and allometrically normalized by height (16). Cardiac output was calculated by SV times heart rate and allometrically normalized by height (16). Ejection fraction and midwall shortening were calculated as previously reported (16). The population sample was divided into quartiles of HOMA-IR and exploratory statistics were performed to analyze the linear trend among the different degrees of insulin

resistance for age, sex, heart rate, blood pressure, BMI, risk profile (including obesity, lipid profile, kidney function), and LV structural and functional parameters (LV mass index and relative wall thickness, stroke index, cardiac index and ejection fraction). ANCOVA was used to study the relation of MEEi with HOMA-IR quartiles, adjusting for age, sex, obesity and hypertension. Because in this population, including members of the SHFS cohort, the level of family relatedness could be significant, we also adjusted analysis for a standard kinship coefficient, based on the level of relatedness within family. Continuous variables were used to model independent correlates of MEEi, including HOMA-IR, kinship coefficient, age, sex, systolic BP, plasma cholesterol, triglycerides, waist circumference and two markers of inflammation, fibrinogen and PAI-1. The study population comprised 3128 non-diabetic participants (age 47±17 years, 1807 women, 1447 obese, 870 hypertensives). Table 1 shows that with increasing HOMA-IR patients were older, more likely to be women, obese and hypertensive (all p for trend <0.001). With increasing HOMA-IR, there was also a clear trend toward a progressive increase in blood pressure and heart rate and worse lipid profile (all p for trend <0.001).

Table 1: Demographics and metabolic risk profile in quartiles of HOMA-IR				
	≤1.71 (n=784)	1.72-2.75 (n=776)	2.76-4.66 (n=785)	≥4.67 (n=783)
Age (years) *	44±18	46±18	48±16	48±16
Sex (% women) †	52	58	59	62
Hypertension (%)†	18	28	31	35
Obesity (%)†	12	37	58	78
Body mass index (kg/m^2) †	*25±4*	*29±5*	*31±5*	*35±7*
Waist circumference (cm) †	88±12	99±12	103±13	113±15
Systolic BP (mmHg) †	119±18	122±17	124±16	126±17
Diastolic BP (mmHg) †	72±11	75±11	76±10	77±10
Heart rate (bpm) †	67±11	68±11	69±11	70±11
GFR_{MDRD} (ml/min/1.73m^2) *	94±27	92±25	92±47	93±27
Cholesterol (mg/dl) *	181±38	190±38	192±37	185±36
HDL-c (mg/dl) †	55±17	50±15	46±13	42±12
Triglycerides (mg/dl) †	105±55	139±87	161±92	166±105
Fibrinogen (mg/dL) †	335±70	348±74	360±76	367±77
PAI-1 (ng/mL) †	40±47	48±36	57±40	71±47

Legend. BP blood pressure, GFR glomerular filtration rate, HDL high density lipoprotein, PAI plasminogen activator inhibitor-1.

Whereas no effect was observed in ejection fraction, increasing in HOMA-IR was associated with progressive increase in LV mass index, stroke index and cardiac index and decline of midwall shortening (all $p<0.0001$) (Figure 3).

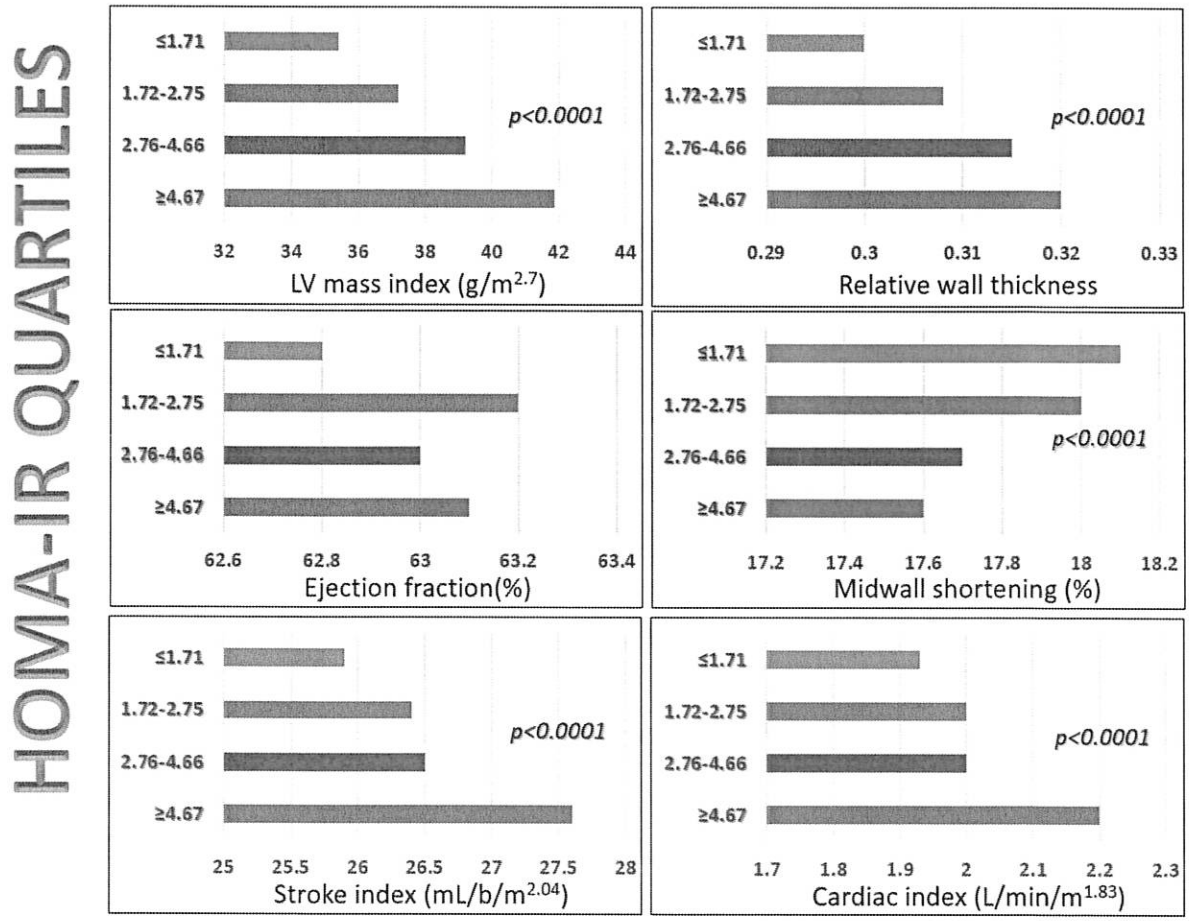

***Figure 3**: LV geometry, systolic function and performance in quartiles of HOMA-IR.*

After adjusting for the kinship coefficient, age, sex, obesity and hypertension, MEEi progressively decreased with increasing HOMA-IR (Figure 4).

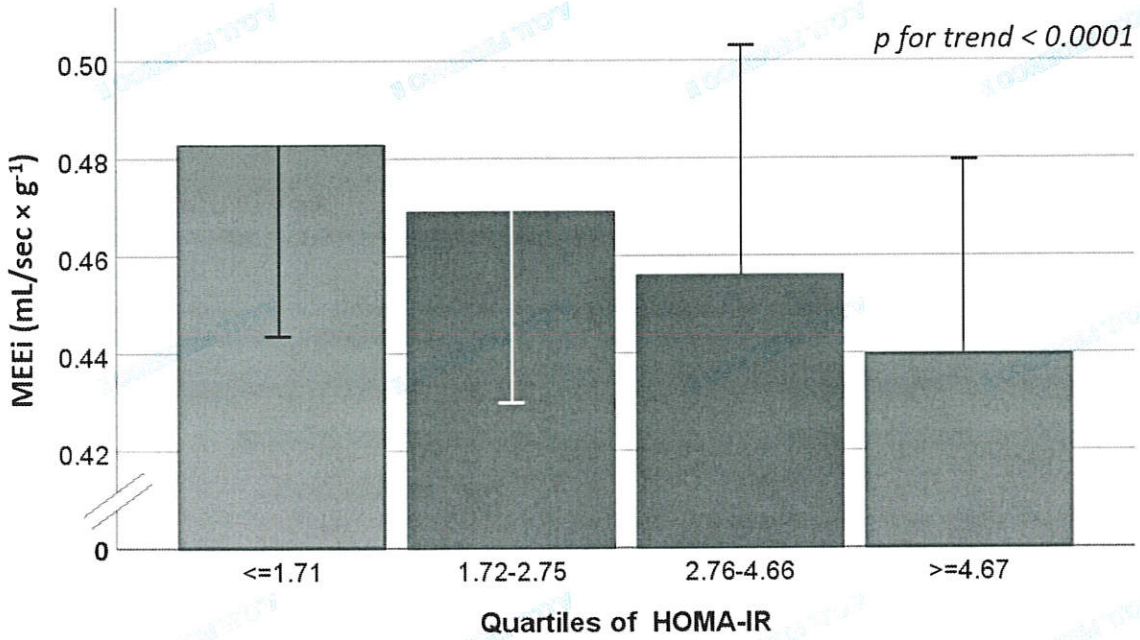

Figure 4: Least square means of MEEi for quartiles of HOMA-IR (insulin resistance), after adjusting for family relatedness, age, sex, obesity and hypertension. MEEi progressively decreases with increasing HOMA-IR.

In sequential multivariable regression models, the correlation of MEEi with HOMA-IR was adjusted for many potential covariates (Table 2). First, we run the model including family relatedness. This regression model demonstrated that the negative relation between MEEi and HOMA-IR was independent of the significant effect of kinship coefficient. In the additional models by adding sequentially demographics, risk factors and markers of inflammation, HOMA-IR remained highly significant (all $p < 0.0001$).

Table 2: Models of multiple linear regression between HOMA-IR and MEEi, adjusting for kinship coefficient and subsequently for age and sex, risk factors and finally markers of inflammation.

	Adjusted for kinship coefficient		**+Adjusted for age and sex**		**+Adjusted for CV risk factors**		**+Adjusted for markers of inflammation**	
	Standardized β-coefficients	p≤	Standardized β-coefficients	p≤	Standardized β-coefficients	p≤	Standardized β-coefficients	p≤
Kinship coefficient	0.295	0.0001	0.069	0.003	0.079	0.0001	0.087	0.0001
HOMA-IR	-0.166	0.0001	-0.176	0.0001	-0.078	0.0001	-0.070	0.0001
Age (years)			-0.342	0.0001	-0.236	0.0001	-0.239	0.0001
Sex (M/F)			0.155	0.0001	0.130	0.0001	0.144	0.0001
Systolic BP (mmHg)					-0.151	0.0001	-0.151	0.0001
Cholesterol (mg/dL)					-0.037	0.055	-0.039	0.042
Triglycerides (mg/dL)					-0.042	0.025	-0.034	0.069
Waist circumference (cm)					-0.196	0.0001	-0.156	0.0001
GFR_{MDRD} (ml/min/1.73m^2)					0.013	0.462	0.016	0.357
Fibrinogen (mg/dL)							-0.077	0.0001
PAI-1 (ng/mL)							-0.075	0.0001

Association of Myocardial Energetic Efficiency with Circumferential and Longitudinal Left Ventricular Myocardial Function in Subjects with Increased Body Mass Index (the FATCOR Study)

Mancusi C, Midtbø H et al. J Clin Med. 2021 Apr 8;10(8):1581.

Aim of the present study was to explore the association of MEEi with parameters of LV systolic function in adults with increased BMI and free from cardiovascular disease. The current analysis used data from the FAT associated CardiOvascular dysfunction (FATCOR) study, which was conducted from 2009 to 2017 at Haukeland University Hospital, Bergen, Norway. Inclusion and exclusion criteria for the study have been published previously (20). In short: the FATCOR study included 620 women and men aged 30-65 years with a BMI >27.0 kg/m2 free from prevalent cardiovascular disease. Exclusion criteria were previous myocardial infarction, gastrointestinal disorder, severe psychiatric illness or inability to communicate in Norwegian language. The participants were recruited by a primary health care center with a particular research interest in obesity, mostly based on an advertisement in a local newspaper. A total of 127 participants were excluded due to incomplete echocardiographic data (n=51), insufficient echocardiographic image quality (n=49) or hardware mismatch for analysis of global longitudinal strain (GLS, n=25), missing information on Doppler Stroke volume (SV, n=13) or withdrawal of informed consent (n=2).

All participants completed a standardized questionnaire reporting their medical history and use of any medication. Clinic blood pressure (BP) was measured in accordance with guidelines using an Omron M4 sphygmomanometer (Omron Healthcare Co. Ltd., Hoofdorp, Netherlands) with an appropriately sized cuff. Pulse pressure was calculated as the difference between clinic systolic and diastolic BP. A Diasys Integra II apparatus

(Novacor, Cedex, France) was used for 24-h ambulatory blood pressure monitoring. An average 24-h systolic BP ≥ 130 mmHg and/or 24-h diastolic BP ≥ 80 mmHg was considered elevated. Hypertension was considered present if the 24-h ambulatory BP was elevated or the participants reported use of antihypertensive medication (17). Tetrapolar bioelectric impedance analysis (Tanita-TBF- 300A, Tanita Corporation of America, Arlington Heights, USA) was used for body composition analysis. Obesity was defined as BMI 30.0 kg/m2. In accordance with the criteria from the American Diabetes Association (21), diabetes mellitus was considered present if fasting blood glucose ≥7 mmol/L, 2-h blood glucose ≥11.1 mmol/L after a 75-g oral glucose test, or a glycated hemoglobin A1c ≥ 6.5%. Insulin resistance was assessed by the homeostasis model assessment-insulin resistance index (HOMA-IR). Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Echocardiography was performed with a GE Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway) following a standardized imaging protocol. The images were analyzed using Image Arena software version 4.4 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) in the Echocardiography Core Laboratory at the University of Bergen, Bergen, Norway. As recommended for clinical trials, the initial image analyses were quality assured by proof reading by a single expert reader. The joint American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines for chamber quantification were applied for quantitative echocardiography (22). LV mass was indexed for height2.7 as recommended in obesity. SV was calculated by PW-Doppler at the aortic valve hinging points. Midwall fractional shortening (MFS) was calculated using a previously reported formula. MEEi was calculated as previously reported. Speckle tracking echocardiography analysis of LV peak systolic longitudinal strain was done offline on a workstation equipped with EchoPac BT 202 (GE Vingmed Ultrasound, Horten, Norway) with excellent reproducibility (16). Peak systolic

longitudinal strain was assessed in the apical 2-, 3- and 4-chamber views using the automated imaging function. The endocardial border was traced automatically, and end-systole was defined by aortic valve closure. After software processing the quality of tracking was assessed visually, and if the tracking was poor the segment was excluded. Global longitudinal strain (GLS) was calculated as the average peak systolic longitudinal strain in the 17 LV segments (23).

Data were analyzed using SPSS (version 21.0; SPSS, Chicago, Illinois, USA). The study cohort was divided into MEEi quartiles. The lowest MEEi quartile was considered as low MEEi (<0.41 mL/g/sec). Analysis of variance was used to compare continuous variables among MEEi quartiles, using polynomial linear contrast for trend analysis. The $\chi 2$ distribution was used to compare categorical variables and Kendall's t–b was used for trend analysis. Univariable and multivariable regression analyses were used to identify the association of MEEi with circumferential and longitudinal LV myocardial systolic function (MFS and GLS) after adjusting for age, sex, BMI, presence of hypertension, HOMA index, serum triglycerides, LV mass and concentric geometry. These results are reported as odds ratio (OR) and associated 95% confidence intervals (CI). A p-value of <0.05 was considered statistical significant in all analyses.

A total of 480 patients were included in the analysis (mean age 47±9 years, 61 % women, 63% obese, 74% hypertensive). Lower MEEi quartile was confirmed to be associated with greater proportion of men, obesity and hypertension (all p for trend <0.05). Lower MEEi quartile was also associated with worse lipid profile and higher HOMA-IR index (all p for trend <0.05). Ejection fraction, MFS and GLS decreased and LV mass and concentric geometry increased in parallel with lower MEEi quartile. In univariable analyses, lower MEEi quartile was paralleled by increasing serum triglycerides level and LV mass, and by lower LV systolic myocardial function assessed by MFS and GLS (Fig. 5).

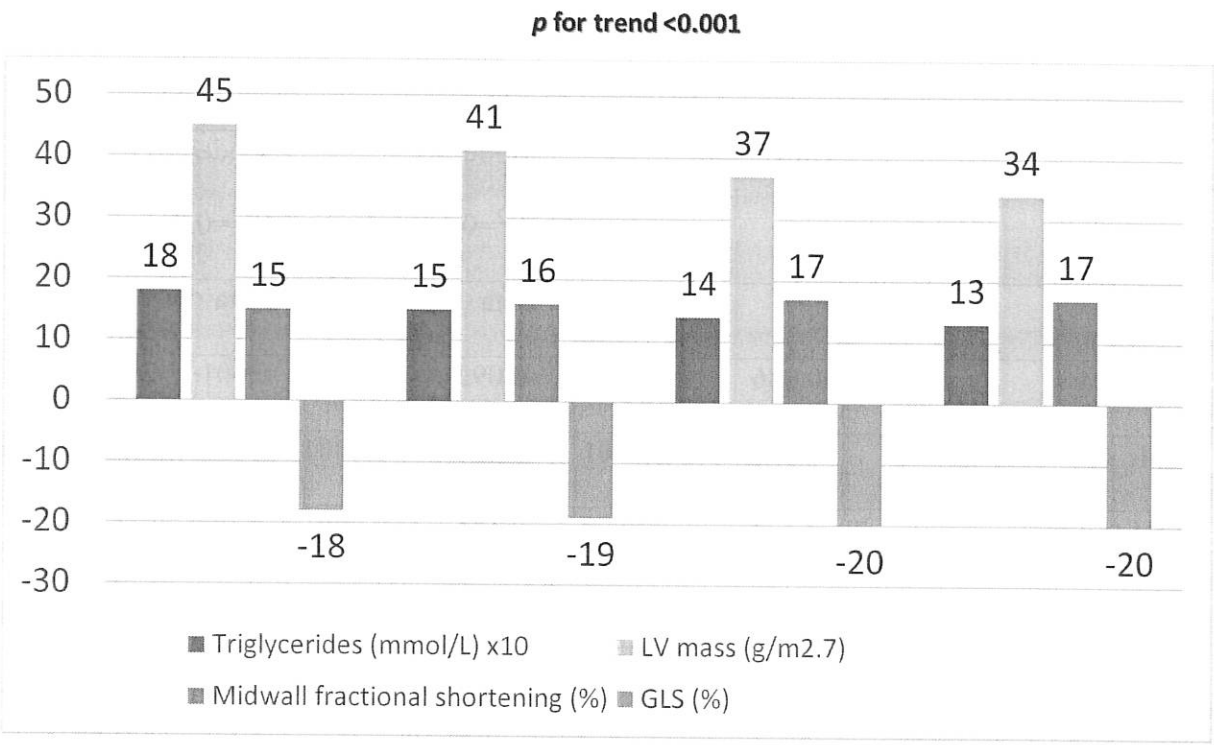

Figure 5. Levels of triglycerides, LV mass, midwall fractional shortening and global longitudinal strain (GLS) among quartiles of MMEi.

In multivariable analysis lower MEEi was independently associated with older age, male sex, presence of hypertension and increase triglycerides level (all $p<0.05$). After adjusting for these factors as well as for LV geometry, lower MEEi remained independently associated with lower LV myocardial function by MFS and GLS, but not with ejection fraction (all $p < 0.05$) (Table 3).

Table 3. Covariables of MEEi in uni- and multivariable linear regression analyses						
	Univariate		Model 1 (R^2=0.14)		Model 2 (R^2=0.31)	
	Beta	p	Beta	p	Beta	p
Age (years)	-0.086	0.058	-0.092	0.991	0.001	0.991
Male sex	**-0.240**	**0.0001**	**-0.234**	**0.0001**	-0.059	0.130
BMI (kg/m^2)	**-0.174**	**0.0001**	**-0.181**	**0.0001**	-0.068	0.173
Hypertension (n/y)	**-0.189**	**0.0001**	**-0.098**	**0.038**	-0.037	0.393
HOMA IR	**-0.130**	**0.005**	-0.054	0.238	-0.065	0.121
Triglycerides (mmol/L)	**-0.167**	**0.0001**	**-0.089**	**0.05**	**-0.085**	**0.04**
LV mass (g/m$^{2.7}$)	**-0.492**	**0.0001**	--------	--------	**-0.392**	**0.0001**
Concentric geometry (n/y)	**-0.204**	**0.0001**	--------	--------	0.034	0.481
MFS (%)	**0.322**	**0.0001**	--------	--------	**0.128**	**0.01**
GLS (%)	**-0.231**	**0.0001**	--------	--------	**-0.129**	**0.003**

Abbreviation: BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance index; LV, left ventricle; MFS, midwall fractional shortening; GLS, global longitudinal strain.

Predictors and prognostic role of low myocardial mechano-energetic efficiency in chronic inflammatory arthritis.

Cioffi G, Mancusi C et al J Hypertens. 2021 Jan;39(1):53-61.

We designed this prospective study to assess: (a) the values of MEEi in a large population of patients with with rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA), compared with those of a non-RA/AS/PsA comparison group analyzed for primary prevention purposes; (b) the clinical and echocardiographic variables associated with the status of "low-MEEi"; (c) whether the RA/AS/PsA cluster per se is a condition associated with low-MEEi independently of confounding factors; (d) whether low-MEEi is a prognosticator of adverse CV outcome in these patients.

The study population comprised non-institutionalized subjects > 18 years of age with rheumatoid arthritis (RA) diagnosed according to the 2010 ACR/EULAR classification criteria (24), psoriatic arthritis (PsA) and anchylosing spondylitis (AS) diagnosed by the CASPAR and the ASAS criteria as recently summarized by Rudwaleit and Taylor (25). Participants were consecutively recruited from March 2014 to March 2016 at the Division of Rheumatology, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona (Italy) in which patients underwent clinical, laboratory and echocardiographic evaluations. Participant rheumatologists were provided with a form designed to capture all essential CV risk factor information, laboratory, data on the clinical expression of inflammatory disease and current medical therapy (including medications for CV risk factors control). All subjects were free of symptoms/signs of cardiac disease. Exclusion criteria were a history of myocardial infarction or documented coronary heart disease (CHD), myocarditis or heart failure, diagnosed by clinical, electrocardiographic evaluation at rest and by the results of exercise/scintigraphy/echo-stress test, alcoholic or primary cardiomyopathy, prior myocardial

revascularization, significant valve heart disease, atrial fibrillation. All patients gave written informed consent signing a specific institutional consent form, the study was approved by Ethical Committees of the Verona University and conforms to the ethical guidelines of the Declaration of Helsinki as revised in 2000.

The degree of activity of RA disease was evaluated by the clinical disease activity index (CDAI) score (24). Patients with a CDAI score >10 were defined as subjects with activated pattern of the disease having moderate-high disease activity. Congestive heart failure was defined as the presence of signs and symptoms of either right (elevated jugular venous pressure, hepato-jugular reflux, fluid retention) or LV failure (exertional dyspnea, paroxysmal nocturnal dyspnea, cardiac enlargement, gallop rhythm, pulmonary venous congestion) or both, confirmed by non-invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction. CHD was diagnosed by clinical, electrocardiographic evaluation at rest and by the results of exercise/scintigraphy/echo-stress test. Ischemic stroke was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist, lasting more than 24 hours and caused by ischemia; transient ischemic attack (TIA) was defined as a focal neurological deficit of sudden onset and diagnosed by a neurologist, lasting less than 24 hours; peripheral thromboembolism (TE) was defined as the occlusion of blood flow by an embolus, outside the brain and heart by the responsible physician.

The pre-specified primary end-point of the study was a composite of CV death or CV hospitalization due to both cardiac events (unstable angina, myocardial infarction, severe chest pain due to acute pericarditis, heart failure, percutaneous coronary intervention and coronary artery bypass grafting), and non-cardiac vascular events (stroke, TIA, TE, peripheral vascular intervention and stent thrombosis). Secondary study end-point was a composite of all-cause death or all-cause hospitalization. For each patient, the follow-up was stopped at the time of the first event or death. All clinical events were examined by an independent end-point

classification committee. Each clinical event was diagnosed and classified by two expert clinicians who analysed in detail the clinical reports, validated the endpoints and formally generated the information which migrated into the database. Hospitalizations and vital status were recorded every 3 months during the scheduled visited for clinical check or during hospital access for managing pharmacological therapy or by telephone calls. Follow-up ended at 30 September 2019. All anamnestic data and those gathered during follow-up were recorded in the patient's e-chart and then subsequently migrated to the data warehouse. The variables useful for calculating MEEi were part of the standard echocardiographic evaluation scheduled for all patients at enrolment.

For the purposes of this study we selected a first control group of patients named "*non-RA/AS/PsA comparison group*" which was compared with the study group of patients with RA/AS/PsA; it was composed of 216 patients without RA/AS/PsA, selected for having similar age, gender, body mass index (BMI), prevalence of hypertension and diabetes to RA/AS/PsA patients.

A second control group of patients named "*healthy controls*" was formed by 145 healthy subjects without any CV risk factor who were consecutively referred to our center for an echocardiographic evaluation in primary prevention. Data of these patients were only used for calculating MEEi and define the status of "low-MEEi".

Transthoracic echocardiography was performed following a standardized protocol. M-Mode, 2D, color Doppler and spectral Doppler images were acquired, stored and forwarded for final interpretation by two expert sonographers. LV mass, and LV mass index (by normalization for height in $m^{2.7}$) were estimated (22). LV hypertrophy was defined as LV mass $\geq$ 49.2 $g/m^{2.7}$ for men and $\geq$ 46.7 $g/m^{2.7}$ for women (22). Relative wall thickness was computed as a dimensionless ratio between posterior wall thickness and LV internal radius both measured at end-diastole, as the measure of LV concentricity. Stroke volume (SV) was calculated as the

difference between LV end-diastolic and end-systolic volumes by the z-derived method, and allometrically normalized by height (16). Ejection fraction (LVEF) and stress-corrected midwall fractional shortening (sc-MFS) were calculated as previously reported (26). Rationale for using sc-MFS as appropriate and accurate index of LV systolic function in RA/AS/PsA patients has been previously explained in detail (27). LV diastolic parameters were assessed following the international recommendations for the evaluation of LV diastolic function published in 2016 by Nagueh et al. (28). MEEi was estimated as previously reported. The relations between MEEi and clinical and echocardiographic variables were evaluated by univariate and multivariate linear regression analyses. Variables included into the statistical models were age, systolic blood pressure (SBP), BMI, diabetes, hypertension, LV mass, LV relative wall thickness, LV sc-MFS. Chronic inflammatory arthritis (yes vs no) was considered only for the model A. Furthermore, the study population was stratified by status of "low-MEEi" at baseline. The cut-off value for low-MEEi was a priori identified as 0.32 ml/s/g $^{-1}$ (the 5th percentile of MEEi calculated in the 145 healthy controls). Finally, univariate and multivariate Cox regression analyses was performed to assess whether low-MEEi was a condition associated with the primary clinical endpoint (composite of CV death or CV hospitalization). The following variables were considered at univariate analysis: Age, GFR, LV mass, MEEi, duration of inflammatory disease, hypertension, diabetes, dyslipidemia, female gender, BMI, LV diastolic dysfunction, LV concentric geometry. The first four variables listed above were included as covariates in the final multivariate model. All analyses were performed using statistical package SPSS 19.0 (SPSS Inc. Chicago. Illinois) and statistical significance was identified by two-tailed $p < 0.05$.

Baseline clinical and echocardiographic characteristics of the 432 patients with RA/AS/PsA are shown in Table 4. They were prevalently middle-aged patients with a long duration of disease, near half with a diagnosis of hypertension and/or dyslipidemia which were

quite well controlled by means of pharmacological therapies. Moderate-high activity of disease was found in one third of them at baseline evaluation whereas about two third were receiving biologic disease modifying anti-rheumatic (DMARDs) therapy. LV concentric geometry was found in more than half of patients, LV hypertrophy in more than one quarter, as well as LV diastolic dysfunction. The mean value of MEEi was 0.35 ± 0.11 ml/sec/g^{-1}.

When compared to the 216 subjects of the control group, patients with RA/AS/PsA showed higher prevalence of dyslipidemia and were more frequently active smokers, had higher serum C protein reactive levels and were taking more frequently statins. Looking at the echocardiographic features, RA/AS/PsA patients had smaller LV volumes, higher LV mass and prevalence of concentric LV geometry, lower sc-MFS and MEEi (near one quarter) than patients of the comparison group. MEEi was low (defined in the statistical analysis paragraph as < 0.32 ml/sec/g^{-1}) in 164 patients (38% of the RA/AS/PsA patients whose MEEi mean value was 0.25 ± 0.05 ml/sec/g^{-1}). Patients who had low-MEEi were older with greater BMI, higher prevalence of hypertension and diabetes mellitus than those who had not. Echocardiographic characteristics diverged substantially between the two groups. The former had higher LV mass, prevalence of LV concentric remodeling/hypertrophy, lower sc-MFS and more frequently LV diastolic dysfunction than the latter. No difference in LVEF was found between the two study groups.

Table 4. Main characteristics of the 432 study patients with chronic inflammatory arthritis divided according to the presence of low MEEi and those of the 216 patients used as comparison group.

Variables	Low MEE NO (n=268)	Low MEE YES (n=164)	p	Total study population (n=432)	Comparison group (n=216)	p
Clinical and laboratory						
Age (years)	56 ± 12	59 ± 12	0.04	57 ± 12	59 ± 14	0.09
Female gender (%)	66	59	0.12	64	58	0.08
Body Mass index (Kg/m2)	25.3 ± 4.1	27.0 ± 4.8	< 0.001	26.0 ± 4.5	25.4 ± 4.3	0.10
Waist circumference (cm)	91 ± 12	97 ± 13	< 0.001	93 ± 12	91 ± 11	0.05
Obese (%)	12	23	0.003	16	12	0.06
Systolic blood pressure (mmHg)	134±17	134±16	0.88	134±17	133 ±16	0.21
Diastolic blood pressure (mmHg)	83 ± 9	82 ± 10	0.78	83 ± 9	82 ± 8	0.30
Hypertension (%)	39	61	< 0.001	46	43	0.36
Dyslipidemia (%)	55	59	0.48	56	28	<0.001
Active smoker, %	31	41	0.04	34	12	<0.001
Diabetes (%)	6	13	0.008	9	11	0.36
Glomerular filtration rate (ml/min/1.73m2)	94 ± 22	93 ± 24	0.94	94 ± 23	87 ± 19	0.06
Total cholesterol (mg/dl)	194 [175-222]	198 [179-227]	0.39	195 [173-215]	191 [175-219]	0.43
Cholesterol LDL (mg/dl)	109 [89-128]	112 [88-133]	0.56	110 [93-135]	118 [95-139]	0.20
Triglycerides (mg/dl)	106 [78-155]	110 [79-143]	0.10	108 [75-137]	115 [90-156]	0.32
C reactive protein (mg/l)	2.9 [0.7-7.5]	2.1 [0.5-6.9]	0.10	2.7 [1.0-6.3]	1.1 [0.03-2.1]	0.03
Clinical disease activity index	9.7 ± 8	11.7 ± 8	0.11	10.5 ± 9	-	
Moderate-high disease activity (%)	29	37	0.13	32	-	
Disease duration (years)	12.3 ± 9.8	13.5 ± 10.1	0.24	12.6 ± 9.9	-	
LV end-diastolic volume (ml/m2)	51 ± 10	47± 12	0.003	49 ± 11	51 ± 12	0.01
Relative wall thickness	0.42 ± 0.06	0.50 ± 0.07	< 0.001	0.45 ± 0.07	0.38 ± 0.05	<0.001
Concentric LV geometry (%)	43	89	< 0.001	59	16	<0.001
LV mass index (g/m 2.7)	42 ± 11	48 ± 12	< 0.001	44 ± 11	39 ± 9	<0.001
LV hypertrophy (%)	21	38	< 0.001	28	13	<0.001
LV ejection fraction (%)	66 ± 6	65 ± 7	0.06	66 ± 7	64 ± 9	0.06
Stress-corrected MFS (%)	94 ± 16	73 ± 11	< 0.001	86 ± 15	99 ± 14	<0.001
MEEi (ml/sec/g-1)	0.42 ± 0.08	0.25 ± 0.05	< 0.001	0.35 ± 0.11	0.45 ± 0.10	<0.001
E / A ratio (trans-mitral flow)	1.04 ± 0.38	0.86 ± 0.26	< 0.001	0.96 ± 3.0	0.96 ± 2.9	0.96
E / E' ratio	6.2 ± 1.6	6.4 ± 1.8	0.20	6.3 ± 1.7	6.4 ± 2.1	0.42

ACEi = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin T1 receptor blockers; CCP = Cyclic Citrullinated Peptide; DMARDs = disease modifying anti-rheumatic; LV = Left Ventricular; MEEi: mechano-energetic efficiency MFS = midwall fractional shortening; NSAIDs = non-steroidal anti-inflammatory drugs.

Likely due to the unfavourable phenotypic profile, angiotensin-converting enzyme inhibitors or angiotensin T1 receptor blockers (ACEi/ARBs) were more frequently prescribed in patients with low-MEEi. A first logistic regression analysis aimed to assess whether RA/AS/PsA disease was associated with MEEi included both patients with RA/AS/PsA (n = 432) and non-RA/AS/PsA patients of the comparison group (n = 216, total n = 648 subjects). This analysis showed that the condition "RA/AS/PsA disease" was closely and independently related to lower MEEi together with older age, higher SBP, LV relative wall thickness, LV mass, and lower sc-MFS. In the Model B we considered only 432 patients with RA/AS/PsA. The variables emerging as correlates of lower MEEi were higher SBP, LV relative wall thickness, LV mass, and lower sc-MFS. The following variables were associated with this condition at univariate analysis: older age, higher SBP and BMI, hypertension, diabetes mellitus, LV concentric geometry, lower sc-MFS and LV diastolic dysfunction. The independent predictors of low-MEEi in RA/AS/PsA patients resulting from the multivariate analysis were older age, higher SBP, diabetes mellitus, LV concentric geometry and lower sc-MFS. During a median follow-up of 36 [21–48] months, a primary end-point occurred in 37 patients (8.6%): 22 of 164 patients who had low-MEEi (13.4%) and 15 of 268 patients (5.6%) who had not (p = 0.004). Secondary endpoint occurred in 128 patients (29.6%): 64 of 164 patients who had low-MEEi (39.0%) and 64 of 268 patients (23.9%) who had not (p = 0.008). No death occurred during the follow-up. During follow-up 37 CV hospitalization occurred. The presence of low-MEEi was associated with the occurrence of primary end-points both in univariate and in multivariate Cox regression analysis together with older age, lower GFR and higher LV mass (Table 5). Secondary endpoint was predicted by low-MEEi at univariate analysis and was of borderline statistical significance as independent prognosticator of all-cause events (HR 1.42 [CI 0.99-2.05], p = 0.052) when the model was adjusted for age (HR 1.02 [CI

1.00-1.04], $p = 0.03$), LV mass (HR 1.01 [CI 1.00-1.02], $p = 0.04$) and duration of RA/AS/PsA disease (HR 1.02 [CI 1.00-1.04], $p = 0.04$).

Table 5: Variables independently related to the pre-specified primary end-point of the study (a composite end-point defined as death or hospitalization from cardiovascular causes): Univariate and multivariate Cox regression analysis.

	Univariate			Multivariate		
Variables (226 patients)	**HR**	**Confidence intervals**	***p***	**HR**	**Confidence intervals**	***p***
Age (years)	1.06	1.03 – 1.09	< 0.001	1.04	1.01 – 1.07	0.007
GFR (ml/min/1.73 m^2)	0.98	0.96 – 0.99	0.002	0.98	0.97 – 0.99	0.03
LV mass ($g/m^{2.7}$)	1.01	1.00 – 1.02	0.001	1.01	1.00 – 1.02	0.008
Myocardial MEEi (≤ vs > 0.32)	2.56	1.31 – 5.00	0.006	2.23	1.13 – 4.38	0.02
Duration of disease (years)	1.03	0.99 – 1.07	0.06			
Hypertension (yes vs no)	1.90	0.98 – 3.70	0.06			
Diabetes (yes vs no)	1.94	0.81 – 4.67	0.13			
Dyslipidemia (yes vs no)	1.92	0.92 – 3.99	0.08			
Female gender	1.13	0.57 – 2.26	0.72			
Body mass index (Kg /m2)	1.00	0.93 – 1.07	0.99			
LV diastolic dysfunction (yes vs no)	1.79	0.92 – 3.50	0.09			
LV concentric geometry (yes vs no)	1.94	0.91 – 4.11	0.08			

Legend: GFR glomerular filtration rate, LV left ventricle, MMEi myocardial energetic efficiency.

Discussion

Myocardial energetic efficiency is a non-invasive and useful tool for the evaluation of patients at high cardiovascular risk, useful to improve our understanding of metabolic abnormalities and related systolic dysfunction and cardiovascular prognosis.

In the first study we demonstrates that in the non-diabetic participants of the SHS cohort with normal ejection fraction and free of prevalent CV disease, insulin resistance is a significant contributor of the variance of myocardial mechano-energetic efficiency per gram of LV mass. The effect of insulin resistance could be demonstrated to be independent of major CV risk factors, including hypertension, lipid profile and central obesity, all factors linked to metabolic syndrome that could mediate the direct relation between insulin resistance and myocardial energetic efficiency. MEEi progressively declines with increasing levels of insulin-resistance, a relation that is maintained also after multiple adjustments for potential confounders. We had already seen that in the treated hypertensive patients of the Campania Salute Network registry (12), metabolic syndrome and type 2 diabetes were associated with the lowest levels of MEEi, with the worst performance found when diabetes and metabolic syndrome coexisted. The hypothesis that insulin resistance could be the reason was near obvious and, interestingly, we could confirm this hypothesis in the non-diabetic population-based cohort of the SHS. In another analysis in the SHS cohort, using acute myocardial infarction as a competing risk event, we found that the hazard of heart failure with type 2 diabetes was even higher than with arterial hypertension (29). Despite the presence of many cardiovascular characteristics associated with incident heart failure, type 2 diabetes remained a potent determinant of risk of heart failure, indicating that non-hemodynamic characteristics participate to the biological profile at risk of heart failure (30). Our study suggests that abnormality of mechanisms of production of energy related to insulin-resistance might be an important link to explain evolution toward heart failure.

Following the same path we have demonstrated that LV systolic function, assessed by MFS and GLS is independently related to MEEi among adults with increased BMI and free from CV disease form the FATCOR study. Low MEEi also parallels worse metabolic profile, higher prevalence of abnormal LV geometry, as also shown in previous studies in different populations, expanding previous results on metabolic and hemodynamic correlates of reduced myocardial efficiency and improving our understanding of the association of obesity with heart failure. Our results demonstrate that in patients with increased BMI but free from CV disease, at a given level of LV mass the left ventricle works inefficiently with high energy wasting, a condition associated with high CV risk phenotype. We demonstrate that systolic myocardial dysfunction is also part of this adverse cardiometabolic phenotype. Interestingly low MEEi is associated with both reduced MFS and GLS, strongly suggesting that both longitudinally and circumferentially dysfunction contribute to determine reduced efficiency in obese/overweight individuals as previously reported (31).

Central obesity and insulin resistance are among the main determinants of reduced MEEi. Both conditions and closely related to low-grade inflammation which is typical of patients with inflammatory arthritis (32) (33). Thus we decided to investigate whether assessment of MEEi could be useful in the context of patients with chronic inflammatory arthritis to refine cardiovascular risk profile. We demonstrated that the values of myocardial MEEi measured in a large population of patients with RA/AS/PsA is significantly lower than those of a non-RA/AS/PsA comparison group analyzed in primary prevention; RA/AS/PsA per se is a disorder which predicts lower MEEi levels, independently of the confounding factors; the condition of "low-MEEi" is recognizable in more than one-third of RA/AS/PsA patients and is predicted by older age, higher SBP, diabetes mellitus, LV concentric geometry and lower LV systolic function. Finally low-MEEi is an independent prognosticator of adverse CV outcome in these patients. Thus MEEi is a simple non-

invasive ultrasound-guided parameter which is appropriate and feasible in patients with chronic inflammatory arthritis. These patients are at increased risk of CV morbidity and mortality and should be undergone an accurate CV assessment based on validated prognostic tools (34). More than one-third of these patients analyzed in primary prevention has low-MEEi which is associated with traditional CV risk factors and abnormalities in LV geometry and systolic function. Consistently, low-MEE emerges as a powerful prognosticator of adverse CV events in these patients, and could be use in clinical practice for stratifying RA/AS/PsA patients with different likelihood of events and easing their clinical management.

Other studies have focused on the possible utility of MEEi as a diagnostic and prognostic tool in different clinical condition. Recently it has been demonstrated that in patients with primary aldosteronism myocardial MEEi is lower as compared with essential hypertensive patients. A reduced MEEi may reflect an impairment of production and utilization of energy in the myocardium, which could lead to the occurrence of cardiovascular complications and therefore these findings may contribute to explain the increased risk of cardiovascular events in patients with primary aldosteronism (35).
Patients with Nonalcoholic fatty liver disease (NAFLD) have raised risk of cardiovascular diseases and MEEi is reduced in this setting independently of impaired insulin resistance, demonstrating that other metabolic abnormalities may contribute to impaired myocardial efficiency (36).

In conclusion MEEi is a novel and useful tool for the evaluation and risk stratification in different clinical condition. Being a non-invasive and simple measurement its applicability in epidemiological studies may help in advancing knowledge in the field of epidemiology and cardiovascular prevention.

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