Non-invasive estimation of myocardial efficiency using positron emission tomography and carbon-11 acetate – comparison between the normal and failing human heart

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Abstract. The clearance kinetics of carbon-11 acetate, assessed by positron emission tomography (PET), can be combined with measurements of ventricular function for non-invasive estimation of myocardial oxygen consumption and efficiency. In the present study, this approach was applied to gain further insights into alterations in the failing heart by comparison with results obtained in normals. We studied ten patients with idiopathic dilated cardiomyopathy (DCM) and 11 healthy normals by dynamic PET with ^{11}C-acetate and either tomographic radionuclide ventriculography or cine magnetic resonance imaging. A "stroke work index" (SWI) was calculated by: SWI = systolic blood pressure × stroke volume/body surface area. To estimate myocardial efficiency, a "work-metabolic index" (WMI) was then obtained as follows: WMI = SWI × heart rate/*k*(mono), where *k*(mono) is the washout constant for ^{11}C-acetate derived from mono-exponential fitting. In DCM patients, left ventricular ejection fraction was 19%±10% and end-diastolic volume was 92±28 ml/m^2 (vs 64%±7% and 55±8 ml/m^2 in normals, $P<0.001$). Myocardial oxidative metabolism, reflected by *k*(mono), was significantly lower compared with that in normals (0.040±0.011/min vs 0.060±0.015/min; $P<0.003$). The SWI (1674±761 vs 4736±895 mmHg × ml/m^2; $P<0.001$) and the WMI as an estimate of efficiency (2.98±1.30 vs 6.20±2.25×10^6 mmHg × ml/m^2; $P<0.001$) were lower in DCM patients, too. Overall, the WMI correlated positively with ejection parameters ($r=0.73$, $P<0.001$ for ejection fraction; $r=0.93$, $P<0.001$ for stroke volume), and inversely with systemic vascular resistance ($r=–0.77$; $P<0.001$). There was a weak positive correlation between WMI and end-diastolic volume in normals ($r=0.45$; $P=0.17$), while in DCM patients, a non-significant negative correlation coefficient ($r=–0.21$; $P=0.57$) was obtained. In conclusion non-invasive estimates of oxygen consumption and efficiency in the failing heart were reduced compared with those in normals. Estimates of efficiency increased with increasing contractile performance, and decreased with increasing ventricular afterload. In contrast to normals, the failing heart was not able to respond with an increase in efficiency to increasing ventricular volume. The present data support the usefulness of the WMI for non-invasive characterization of cardiac efficiency and may serve as a background for improved evaluation of medical therapy for heart failure.

Key words: Positron emission tomography – Oxidative metabolism – Cardiac efficiency – Heart failure

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Introduction

Mechanical efficiency of the left ventricle is defined as the fraction of total expended energy that is converted into external work [1, 2]. Efficiency can be precisely quantified using invasive measurements of ventricular stroke work as well as myocardial oxygen consumption [2]. Clinically, this parameter could be valuable for the assessment of effects of medical therapy on the heart. This is especially true for the failing heart, where several subgroups of drugs such as vasodilators, inotropic agents, diuretics and β-blockers can be applied and combined. Pharmacological therapy of heart failure is currently monitored by various indexes including symptoms, ventricular contractile performance, haemodynamics and functional capacity, which often reveal conflicting results, making guidance of therapy for the individual patient difficult [3, 4]. By taking into account the energy cost for an

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achieved increase in cardiac output, serial measurements of cardiac efficiency could be used to enhance individual evaluation and optimize therapy. Although this approach has been previously applied in different studies [2, 5–8], its clinical utility has been severely limited owing to the invasive nature of measurements.

Recently, an approach to ventricular efficiency by use of non-invasive imaging techniques has been introduced [9]. Clearance kinetics of carbon-11 acetate, determined by positron emission tomography (PET), can be used to measure tricarboxylic acid cycle flux and thus to determine myocardial oxidative metabolism. A direct relationship between turnover kinetics of ^{11}C-acetate and myocardial oxygen consumption has been demonstrated previously in both animal and human studies [10, 11]. When combined with non-invasive measures of left ventricular performance, PET with ^{11}C-acetate can be used for non-invasive estimation of cardiac efficiency [12].

In previous studies, this non-invasive approach has been validated against invasive measurements of ventricular efficiency [12]. Additionally, beneficial effects of afterload reduction using nitroprusside [13] and of the inotropic agent dobutamine [12] for patients with heart failure have been described using a "work metabolic index" derived from PET and echocardiography as a non-invasive estimate of cardiac efficiency. Little, however, is known about the work metabolic index in normal individuals and changes in the failing heart compared with the normal heart.

Thus, it was the aim of the present study to further validate this non-invasive approach for the estimation of cardiac efficiency, and to gain additional insights into alterations in the failing human heart. Results in patients with heart failure based on idiopathic dilated cardiomyopathy were compared with results in a group of healthy normals. Additionally, interrelations between the work metabolic index and loading conditions as well as ejection parameters were investigated in both groups.

Materials and methods

Patients and study design

Twenty-one individuals (11 men, 10 women; age 52±10 years) underwent PET with ^{11}C-acetate for determination of myocardial oxygen consumption, combined with non-invasive assessment of left ventricular contractile function.

A subgroup of ten patients (eight men, two women; age 53± 11 years) suffered from chronic idiopathic dilated cardiomyopathy (DCM). Diagnosis was based on the absence of significant coronary artery disease or primary valvular heart disease during cardiac catheterization. Due to symptomatic heart failure, a standard medication including ACE inhibitors, β-blockers and furosemide had to be continued throughout the study.

Additionally, an age-matched group of 11 healthy normals (four men, seven women; age 51±9 years) without clinical or electrocardiographic evidence of cardiac disease and without any cardioactive medication was studied.

Prior to inclusion in the study, all patients signed written informed consent forms approved by the ethical committee of the medical faculty of the TU München.

Positron emission tomography

[1-^{11}C]acetate was synthesized according to Pike et al. [14]. PET imaging was performed using an ECAT EXACT or ECAT 951 scanner (CTI/Siemens, Knoxville, Tenn.). The performance characteristics of these scanners have been described previously [15, 16]. After adequate positioning, a transmission scan of 10–15 min was acquired using external rod sources for correction of photon attenuation. Subsequently, 300–500 MBq of ^{11}C-acetate was injected as a slow bolus over 30 s, and a dynamic imaging sequence of 21 frames over 30 min (10×10, 1×60, 5×100, 3×180, 2×300 s) was initiated. Heart rate and blood pressure were monitored continuously throughout the imaging procedures by ECG and arm cuff measurements.

Assessment of left ventricular function

Measurement of left ventricular function was carried out on the same day either before or directly after PET imaging. In normals, electrocardiographically gated magnetic resonance imaging (MRI) was used to avoid radiation exposure. In patients with dilated cardiomyopathy, radionuclide ventriculography combined with single-photon emission tomography (SPET) was chosen because assessment of ventricular function during exercise, which cannot be performed with an MR scanner, was required for clinical purposes in addition to rest imaging. Both techniques have been shown to be reliable and reproducible [17, 18], and results have been demonstrated to correlate closely [18].

MRI was performed using a 1.5-T Philips Gyroscan ACS2 or NT (Philips Medical Systems, Best, The Netherlands). Short-axis multislice multiphase cine gradient-echo sequences were applied with electrocardiographic triggering of R waves to cover the cardiac cycle in 12 phases. The entire left ventricle was imaged from apex to base in 12 slices with a thickness of 7–10 mm and a 128×128 pixel matrix.

For radionuclide ventriculography, autologous erythrocytes were labelled with 800–1000 MBq of technetium-99m by a combined in vivo/in vitro technique, and re-injected after purification. Following 5 min to allow for equilibrium, patients were positioned in a rotating triple-headed gamma camera (Multispect 3, Siemens, Erlangen, Germany), and an electrocardiographically gated tomographic acquisition at rest (12 phases, 120° acquisition angle, 20 views, 40 s per view, 64×64 matrix) was performed.

Data analysis

Positron emission tomography. Attenuation-corrected transaxial PET images were reconstructed by filtered backprojection and a Hanning filter with 0.3 cycles/bin cutoff frequency. A previously validated volumetric sampling tool [19] was then applied to a summed data set of frames 11–13 of the dynamic imaging sequence to create polar maps of static myocardial activity distribution at 2–4 min after injection of ^{11}C-acetate. These polar maps were normalized to their maximum and used for qualitative assessment of regional myocardial perfusion [20].

Myocardial sectors defined by the polar map were then transferred to the whole dynamic imaging sequence, and time-activity

curves were obtained. The early phase of tracer washout in these curves was fitted mono-exponentially to obtain the constant *k*(mono) as a previously validated measure of oxidative metabolism [11], expressed in another polar map. The average of *k*(mono) for the whole map was calculated to define global myocardial oxygen consumption.

Ventricular function. MR images were analysed using commercially available software (MASS, University of Leiden, The Netherlands). Contours for endocardial borders were drawn manually in every phase of slices from the apex to just below the valve plane. Then, end-diastolic and end-systolic volumes were calculated from the summation of these slices in the end-diastolic and end-systolic phases.

For radionuclide ventriculography, SPET data were reconstructed by filtered backprojection (Butterworth filter, 5th order, cutoff frequency 0.5 cycles/bin). A previously validated volumetric sampling tool was used to detect endocardial borders in end-systolic and end-diastolic phases, and to calculate left ventricular volumes [18].

Calculation of haemodynamic parameters and estimation of myocardial efficiency

End-diastolic and end-systolic volumes were used to calculate the left ventricular ejection fraction (LVEF) and stroke volume. Cardiac output was then obtained by muliplying stroke volume by heart rate (HR). Systemic vascular resistance (SVR) was estimated as mean arterial blood pressure divided by cardiac output and converted to dynes×s/cm^5 [21].

Left ventricular stroke work was estimated by a stroke work index (SWI), the product of stroke volume index (SVI; stroke volume divided by body surface area) and peak systolic blood pressure.

Mechanical efficiency of the left ventricle is generally defined as the relation between cardiac work and oxygen consumption. To non-invasively estimate myocardial efficiency, stroke work data were combined with data from ^{11}C-acetate PET [9], and the work-metabolic index (WMI) [12] was calculated by:

$$\mathrm{WMI} = \frac{\mathrm{SWI} \times \mathrm{HR}}{k(\mathrm{mono})} (\mathrm{mmHg} \times \mathrm{ml} / \mathrm{m}^2), \quad (1)$$

where *k*(mono) is the myocardial clearance constant for ^{11}C derived from PET, SWI is the stroke work index and HR is the heart rate.

Statistical analysis

Values are expressed as mean ± standard deviation. The unpaired Student's *t* test was applied to compare results in normal and failing hearts. Simple linear regression analysis was used to describe correlations between continuous variables in the entire patient population and in subgroups of patients. A *P* value <0.05 was defined as significant.

Results

Haemodynamic and functional parameters

Results of haemodynamic and functional parameters for normals and cardiomyopathic patients are summarized in Table 1. As expected, LVEF, stroke volume and cardiac output were markedly reduced in DCM patients, and end-diastolic and end-systolic volumes were significantly increased. As a consequence of medical therapy, blood pressures and the rate-pressure product in DCM patients were significantly lower compared with normals, while there was no difference in heart rate. Despite medication with ACE inhibitors, however, SVR remained significantly higher in DCM patients. Finally, as a result of lower stroke volume and lower systolic blood pressure, the SWI also was significantly lower in DCM patients compared with normals.

Kinetics of ^{11}C-acetate

Static images of early ^{11}C-acetate uptake as a qualitative measure of myocardial perfusion were homogeneous and did not reveal evidence of perfusion defects (defined as regional uptake <50% of the maximum) in any individual.

The clearance constant *k*(mono) was significantly correlated with the rate-pressure product as a predictor of oxygen demand (r=0.76; P<0.001), and, albeit less markedly, with the SWI (r=0.47; P=0.03). Concordantly, with reduced overall work, global *k*(mono) was signifi-

Table 1. Haemodynamic and functional parameters

Variable	Healthy normals (n=11)	DCM (n=10)	P value
Heart rate (min^{-1})	75±14	70±13	0.42
Systolic blood pressure (mmHg)	134±14	106±18	0.01
Diastolic blood pressure (mmHg)	83±11	71±14	0.04
Mean aortic pressure (mmHg)	100±11	83±15	0.01
Rate-pressure product (mmHg/min)	10082±2190	7471±1909	0.01
LVEF (%)	64±7	19±10	<0.001
LVEDVI (ml/m^2)	55.0±8.2	92.1±27.6	<0.001
LVESVI (ml/m^2)	19.7±5.2	76.5±29.9	<0.001
Stroke volume index (ml/m^2)	35.3±6.0	15.6±5.8	<0.001
Cardiac output (l/min)	5.10±1.34	1.97±0.70	<0.001
SVR (dynes×s/cm^5)	1672±465	3638±1085	<0.001
Stroke work index (mmHg × ml/m^2)	4736±895	1674±761	<0.001

DCM, Dilated cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; SVR, systemic vascular resistance

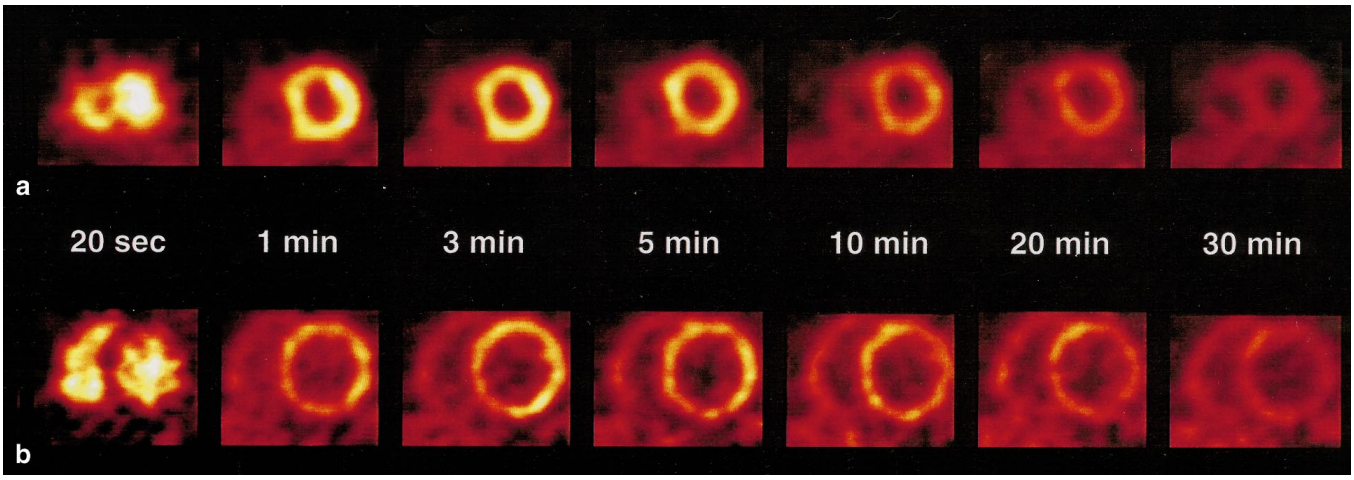


Fig. 1. Kinetics of ^{11}C-acetate in a healthy normal individual (**A**) and a patient with DCM (**B**). Depicted are representative mid-ventricular short-axis slices showing the anterior wall at the top, the septum on the left, the lateral wall on the right and the inferior wall at the bottom at various time points after tracer injection. Early after injection, activity is present in the blood pool of both ventricles. Subsequently there is a rapid wash-in into the myocardium paralleling myocardial perfusion. Thereafter, a slow washout reflecting metabolic turnover in the tricarboxylic acid cycle can be observed

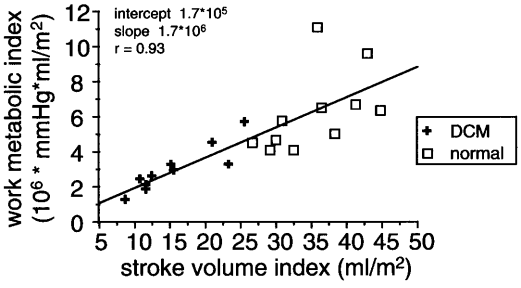


Fig. 3. Regression plot for the WMI as an estimate of cardiac efficiency and the ejection parameter stroke volume index (SVI)

cantly lower in DCM patients than in normals (0.040±0.011/min for DCM vs 0.060±0.015/min for normals; P=0.003). Examples of the kinetics of ^{11}C-acetate in normal and failing hearts are depicted in Fig. 1.

Work metabolic index

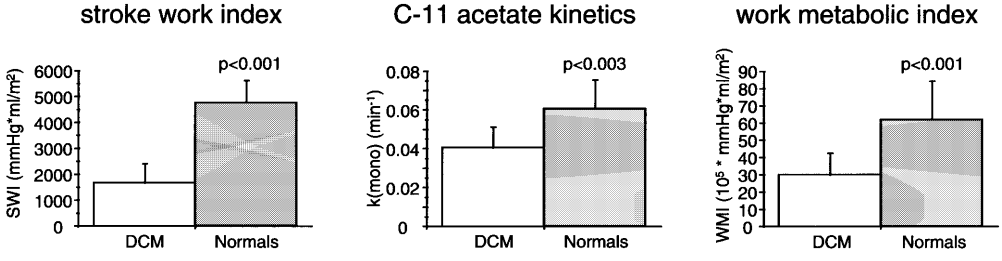
Compared with the reduction in cardiac work, the difference for k(mono) between the two groups was less pronounced, resulting in significantly lower values for the WMI as an estimate of cardiac efficiency in DCM patients (2.98±1.30 vs 6.20±2.25×10^6 mmHg × ml/m^2; P<0.001) (Fig. 2).

Differential relationship of the work metabolic index to ejection parameters and loading conditions

A highly significant positive correlation of the ejection parameters LVEF and stroke volume with the WMI was found (r=0.73, P<0.001 for LVEF and r=0.93, P<0.001 for SVI) (Fig. 3). Furthermore, SVR as a measure of ventricular afterload was significantly inversely correlated with the WMI (r=–0.77, P<0.001) (Fig. 4).

The relations between left ventricular end-diastolic volume index (LVEDVI), as a parameter of ventricular preload, and the WMI were different for normals and DCM patients: In normals, there was a weak positive correlation between LVEDVI and WMI, which did not reach statistical significance (r=0.45; P=0.17). In DCM patients, on the other hand, there was a non-significant negative correlation coefficient for WMI and LVEDVI (r=–0.21; P=0.57), with a substantial difference in slope compared with normals (Fig. 5).

Fig. 2. Values for stroke work index (SWI), the ^{11}C-acetate clearance rate constant k(mono) and the work-metabolic index (WMI) in groups of normals and patients with DCM



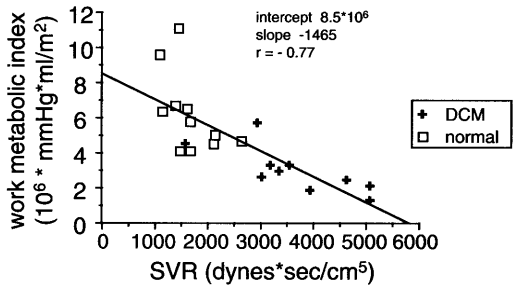


Fig. 4. Regression plot for the WMI as an estimate of cardiac efficiency and systemic vascular resistance (SVR), a parameter reflecting ventricular afterload

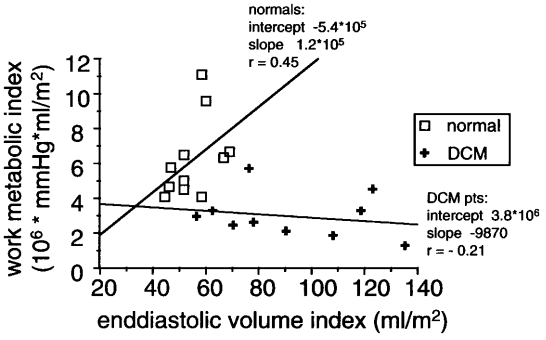


Fig. 5. Regression plot for the WMI as an estimate of cardiac efficiency and left ventricular end-diastolic volume as a measure of preload. Regression lines for normals and patients with DCM are depicted separately. Note the significant difference in slope

Discussion

In summary, non-invasive estimates of stroke work and oxygen consumption were reduced in the failing heart compared with normals. In relation to the reduction in work, the decrease in oxidative metabolism was less pronounced, resulting in lower values for the WMI as an estimate of cardiac efficiency. For all individuals, the WMI decreased with decreasing contractile performance, and also decreased with increasing peripheral vascular resistance, reflecting ventricular afterload. In normals, an increase in the WMI was observed with increasing end-diastolic volume as a measure of preload. The failing heart, however, was not able to respond with an increase in efficiency to increasing end-diastolic volumes. The present data support the usefulness of the WMI for non-invasive characterization of ventricular efficiency and may serve as a background for improved evaluation and monitoring of medical therapy for heart failure.

Differences in haemodynamics, myocardial oxidative metabolism and non-invasively estimated efficiency between the normal and failing heart

Dilated cardiomyopathy is characterized by increased left ventricular end-diastolic and end-systolic volumes combined with reduced ejection parameters such as LVEF, stroke volume and cardiac output [22]. As a counter-reaction to decreased output, systemic vascular resistance is increased to maintain peripheral circulation [23]. These haemodynamic alterations are confirmed in the present study. Peripheral resistance remained elevated in our group of cardiomyopathic patients despite medication with ACE inhibitors, which counteract vasoconstriction associated with the activated renin-angiotensin system in heart failure [24]. The observed reduction in blood pressure was most likely also due to medical therapy in the heart failure group.

It has been demonstrated in various patient groups that clearance constants for ^{11}C-acetate are correlated with estimates of cardiac work [10–12, 25–27]. Thus, corresponding to reduced stroke work in the failing heart, kinetics of ^{11}C-acetate indicated moderately reduced oxidative metabolism compared with normals. The reduction in oxidative metabolism, however, was less pronounced than the reduction in stroke work, resulting in a decrease in the WMI. As this parameter was introduced to reflect the energy cost for a given level of work, the reduction suggests decreased efficiency of cardiac performance in patients with dilated cardiomyopathy.

The present study is the first to compare non-invasive estimates of efficiency in the failing and normally functioning heart. Various factors may account for reduced efficiency in heart failure: First, molecular and cellular alterations in idiopathic dilated cardiomyopathy may contribute to these findings. Changes in the myocardial ratio between phosphocreatine and ATP have been identified in severe dilated cardiomyopathy, suggesting abnormalities of energy metabolism [28]. Alterations of protein constituents of the myofilaments such as decreased actomyosin ATPase rate, reduced cross-bridge cycling rate and shortening velocity have also been identified [29, 30]. These changes may result in higher oxygen demand for a given level of work. Alterations of the cardiac sympathetic nervous system have also been described [31, 32], which may influence contractility and metabolism in the failing heart. A direct relationship between these abnormalities and cardiac efficiency, however, has not yet been investigated.

Secondly, changes in ventricular loading conditions and contractility have been shown to affect cardiac efficiency [1, 8]. Lower estimates of efficiency in the present study therefore could be secondary to haemodynamic and contractile alterations in the failing heart.

Interaction between estimates of efficiency and ventricular loading conditions in the normal and failing heart

Dependence of ventricular efficiency on contractility, preload and afterload has been described previously by invasive measurements [8]. Using a non-invasive ap-

proach, the present data support a positive relationship between efficiency and ejection parameters as estimates of contractility. These results confirm previous findings based on ^{11}C-acetate kinetics in an animal model [9], and provide a rationale for the use of inotropic substances in heart failure therapy, which may increase not only the output but also the efficiency of the cardiomyopathic heart [12].

Maximal efficiency requires not only an adequate ejection fraction but also a high end-diastolic ventricular volume. A positive relationship between preload, which is defined by end-diastolic volume, and efficiency has been described previously [1, 8, 9]. This relation is confirmed in the present study for the normal heart; in contrast to the normal heart, however, the failing heart did not react with an increase in efficiency with increasing volume load. This loss of reactivity may be the expression of an intrinsic molecular pathophysiological mechanism in dilated cardiomyopathy, where ongoing dilatation is a part of the disease process.

Finally, an inverse relationship between afterload and efficiency, which has been described in previous studies [8, 9, 13], is also confirmed by the present data. Lower vascular resistance is expected to reduce myocardial oxygen demand, which would counterbalance increased output requirements. With the concomitant increase in stroke work, higher efficiency can be expected. Acute reduction of afterload by nitroprusside has already been demonstrated to increase the efficiency of the failing heart [7, 13].

Interindividual differences in loading conditions and cardiac output may contribute to the degree of variability of the WMI in normals which was observed in the present study. Furthermore, the significant reduction in the WMI in the failing heart may largely be attributed to a combination of substantial alterations of these determinants.

The WMI is an estimate of cardiac efficiency based on the results of ^{11}C-acetate PET. In contrast to precise measurements of efficiency, which require complex invasive procedures and which are not widely clinically used owing to their invasive character, the WMI is acquired non-invasively and has been validated previously [12]. For the assessment of cardiac performance in heart disease, indexes of efficiency may be of incremental value over clinical and haemodynamic variables because information about the metabolic cost for haemodynamic performance is included. The results of the present study further support the feasibility of this non-invasive approach for the estimation of efficiency. Owing to its non-invasive character, the WMI may be especially helpful for serial applications to determine drug effects and optimize heart failure therapy.

In the future, non-invasive trials could be designed to assess beneficial effects on efficiency of long-term medication with drugs such as established β-blockers and ACE inhibitors, the recently introduced angiotensin antagonists [33], or a combination of these.

Limitations

Some methodological limitations have to be taken into account:

First, the WMI is an estimate of global efficiency which may not be valid in the presence of regional heterogeneities. To avoid influences of major regional differences on metabolic or mechanical function, only heart failure patients with idiopathic dilated cardiomyopathy were studied. Additionally, assessment of perfusion and function did not reveal any regional abnormalities.

Secondly, compared with an invasive assessment, arm cuff measurements provide only rough estimates of blood pressure and may be of limited reliability. It is also of note that non-invasively calculated stroke volume reflects both forward volume and a potential regurgitating volume through mitral insufficiency which may exist secondary to dilated cardiomyopathy. However, differences between groups and correlations for the WMI with other parameters were still significant, supporting the feasibility of this approach. Patients with primary mitral valve disease were not included in the study.

For improved reliability and observer independence, MRI and gated blood pool SPET were chosen instead of echocardiography to determine ventricular function. For clinical reasons, two different techniques were used in normals and heart failure patients. Potential differences between these techniques could have contributed to observed differences between the groups. However, we have previously demonstrated that volumes determined by both methods correlate excellently, with correlation coefficients being above 0.9 [18]. A slope of 0.98 in this comparison suggested that an underestimation of volume by MRI may be relevant only for very high absolute values [18]. MRI, however, was used in normals in the present study, in whom high volumes are not observed. Additionally, with respect to estimates of efficiency, underestimation of stroke volume would only result in lower WMI, but results for normals (based on MRI) were still significantly higher than those in heart failure patients, suggesting that methodological differences do not play a major role.

Finally, for ethical reasons and owing to their clinical state, cardiomyopathic patients could be studied under a standard medication only, which may have influenced the results. Differences between normal and failing hearts, however, were still identified and interpretable. This study was not designed to determine characteristic effects of specific drugs used for medical therapy of heart failure. Based on the results of the present study, larger clinical trials may be designed in the future to characterize effects of various new therapeutic approaches on estimates of efficiency in the failing heart.

Conclusion

The work-metabolic index, or WMI, an estimate of cardiac efficiency derived from ^{11}C-acetate PET and functional imaging by MRI or tomographic radionuclide ventriculography, was significantly impaired in the failing heart compared with normals. Overall, a positive correlation with ejection parameters and an inverse correlation with ventricular afterload were observed. Furthermore, the WMI tended to increase with increasing preload in normals, while such an effect could not be observed in heart failure. The results suggest that non-invasive estimation of myocardial efficiency may be a valuable diagnostic tool. This approach may be useful to evaluate cardiac effects of various substances and to optimize therapy of heart failure in the future.

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