Journal of Nuclear Medicine, published on January 5, 2023 as doi:10.2967/jnumed.122.264945

Myocardial external efficiency in asymptomatic severe primary mitral regurgitation using 11C-acetate positron emission tomography

Jens Sorensen[1], Johannes Bergsten[2], Tomasz Baron[2,3], Lovisa Holm Orndahl[2], Tanja Kero[1], Tomas Bjerner[1], Eva-Maria Hedin[2], Hendrik J. Harms[1], Rafael Astudillo[4], Frank A. Flachskampf[2]

[1]Department of Surgical Sciences, Nuclear Medicine and PET, Uppsala University, Uppsala, Sweden

[2]Department of Medical Sciences, Cardiology and Clinical Physiology, Uppsala University and Uppsala University Hospital, Uppsala, Sweden

[3]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden

[4]Department of Surgical Sciences, Thoracic surgery, Uppsala University, Uppsala, Sweden

Word count: 4958

Brief title: Myocardial efficiency in mitral regurgitation

Keywords: myocardial efficiency, mitral regurgitation, cardiovascular magnetic resonance, positron emission tomography

Address for correspondence:

Jens Sörensen, MD PhD
PET Centre, Entrance 86, Uppsala University Hospital
751 85 Uppsala, Sweden
Jens.sorensen@pet.uu.se

Abstract

Aims: Subjects with asymptomatic moderate-severe or severe primary mitral regurgitation (MR) are closely observed for signs of progression or symptoms requiring surgical intervention. The role of myocardial metabolic function in progression of MR is poorly understood. We used ^{11}C-acetate positron emission tomography (PET) to non-invasively measure myocardial external efficiency (MEE), which is the energetic ratio of external cardiac work and left ventricular oxygen consumption.

Methods and results: 47 patients in surveillance with MR and no or minimal symptoms prospectively underwent PET, echocardiography and cardiac magnetic resonance imaging (CMR) on the same day. PET was used to simultaneously measure cardiac output, LV mass and oxygen consumption to establish MEE. PET in patients were compared to healthy volunteers (n=9). MEE and standard imaging indicators of regurgitation severity, LV volumes and function were studied as predictors of time to surgical intervention.

Patients were followed median 3.0 years (interquartile range 2.0-3.8) and the endpoint was reached in 22 subjects (47%). MEE in patients reaching the endpoint (23.8±5.0%) was lower than in censored patients (28.5±4.5%, p=0.002) and in healthy volunteers (30.1±4.9%, 0.001). MEE with a cut-off lower than 25.7% was significantly associated with the outcome (hazard ratio of 7.5 (95%CI: 2.7-20.6, p<0.0001) and retained independent significance when compared to standard imaging parameters.

Conclusions: MEE independently predicted time to progression requiring valve surgery in patients with asymptomatic moderate-severe or severe primary MR. The study suggests that inefficient myocardial oxidative metabolism precedes clinically observed progression in MR.

Introduction

Primary mitral valve regurgitation (MR) affects close to 2% of the overall population, increasing to 10% among the elderly. Surgical repair or replacement are the treatments of choice (*1*). Assessment of MR is an important task of cardiac imaging. In clinical routine, this is usually accomplished by integrating echocardiographic findings with the clinical picture (*2*,*3*). For the evaluation of the impact of moderate or severe MR on LV structure and function, LV diameters or volumes, LV ejection fraction (EF) are currently recommended, and cardiovascular magnetic resonance imaging (CMR) is considered the gold standard for such evaluations (*4*). A novel and theoretically attractive measure of LV performance in valvular heart disease is myocardial mechanical external efficiency (MEE), based on positron emission tomography (PET). MEE relates the "mechanical" energetic output of the LV, measured as forward cardiac output times mean arterial blood pressure, to its "chemical" input from oxidative acetate metabolism, measured by PET (*5*). MEE decreases in heart failure (*6*) and in symptomatic primary and secondary MR (*7*-*9*), but data are scarce.

Given the increasing prevalence of moderate and severe MR, and the increasing complexity of therapeutic options (valve replacement, surgical, and different types of interventional repair, including percutaneous edge-to-edge repair), the need to detect an adverse impact on LV performance early has gained urgency. We therefore set out to evaluate the impact of severe asymptomatic primary MR on MEE, its relation to quantitative measures of MR magnitude and LV remodelling by echocardiography and CMR, the standard imaging techniques in MR, and the role of myocardial metabolic integrity in predicting time to progression mandating surgical intervention.

Methods

A total of 47 asymptomatic or mildly symptomatic patients, (class I or II according to New York Heart Association (NYHA) Functional Classification), confirmed by bicycle exercise testing, with severe degenerative and chronic primary MR by echocardiographic criteria (*2*) were evaluated and included in the study between October 2013 and March 2018 at the Department of Cardiology, Uppsala University Hospital. Patients with other concomitant moderate or severe valve disease, non-sinus rhythm, history of coronary artery disease, chronic renal disease, symptomatic and/or severe lung disease, and method-specific contraindications were excluded. All patients underwent ^{11}C-acetate PET, echocardiography and CMR on the same day. CMR and PET were performed one hour apart with no intake of food or fluids between scans to avoid hemodynamic alterations. Additionally, a group of healthy volunteers (n=9) underwent same-day ^{11}C-acetate PET and echocardiography. The healthy volunteers had no signs or symptoms of cardiovascular disease or other chronic diseases. The study was approved by the Regional Ethical Review Board at Uppsala University (Dnr 2012/543) and all subjects provided written informed consent.

Positron emission tomography (PET)

PET/CT scanning was performed with a GE Discovery ST16 or DMI20. Following a scout CT scan, a low-dose CT scan (120 kV, 20 mAs) was performed. After this, a 27-minute list mode emission scan was performed, starting simultaneously with automated injection of 5 MBq/kg bodyweight ^{11}C-acetate as a 5 mL bolus (1 mL s^{-1}) in an antecubital vein, followed by a 30 mL saline flush (2.0 mL s^{-1}). The collected list mode emission data was used to create a dynamic image series consisting of 29 time-frames using all data with 5 second frames lengths during the

first minute. PET data were analysed using software developed in-house (*8*) with full automation (Figure 1).

MEE was calculated by a standard formula (incorporating caloric conversion factors) as proposed by Bing et al in 1949 (*10*):

$$MEE\ [\%] = \frac{MAP \times forward\ SV \times HR \times 1.33 \times 10^{-4}}{MVO_2 \times LVM \times 20}$$

with MAP: mean arterial pressure (mmHg), SV: stroke volume (mL/beat), HR heart rate (beats/min), MVO_2: mean myocardial oxygen uptake (mL/g/min), LVM: LV mass (g).

The dynamic PET data set was used to measure forward cardiac output (aortic flow) with an indicator dilution approach, as previously described (*8,11*). Heart rate and blood pressures were measured non-invasively at the time of PET scanning. Heart rate was used to calculate forward stroke volume from forward cardiac output. The full dynamic data set was used to obtain the denominator of the MEE equation, mean MVO_2 and LV mass, as previously described (*8,12*). PET post-processing was fully automated and produced identical results when iterated. Test-retest results using this technique were previously published, showing a 9% coefficient of variance for MEE in healthy volunteers (*13*).

Echocardiography

Echocardiography (Vivid-7, General Electric Vingmed, Horten, Norway) was performed according to current guidelines. All studies were performed by experienced sonographers and interpreted by a single experienced physician.

LVEDV, LVESV and LV ejection fraction (EF) were assessed using the biplane Simpson's method. LA volume was calculated by the biplane area length method. LVEDV, LVESV and LA volume were indexed to the body surface area. Total stroke volume was calculated as the difference between LV end-diastolic and end-systolic volumes. Aortic forward stroke volume was calculated using the Doppler velocity time integral method, using the aortic annulus diameter for LV outflow tract diameter. Mitral regurgitant volume (RegVol) was estimated by both by the PISA-method and by the volumetric method (total stroke volume – forward stroke volume). LV global longitudinal strain was measured by strain rate imaging.

Cardiovascular magnetic resonance (CMR)

CMR studies were performed using an Ingenia 3 T whole body scanner (Philips Healthcare, Best, The Netherlands) with an $80 mT \cdot m^{-1}$ gradient system. Short- and long-axis cine images were acquired using a steady-state free precession pulse sequence. LV volumes and mass were manual segmented from short-axis stack images using long-axis images to define the basic slice. End-diastolic endocardial and epicardial contours were propagated with manual re-adjustments performed as required. Papillary muscles and adnexal muscle tissue were included in LV mass. Phase-contrast images were acquired perpendicular to the proximal ascending aorta to quantify aortic flow (forward stroke volume), using a semiautomated algorithm. Images were analysed using commercial software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). Mitral regurgitant volume (RegVol) was calculated by subtracting aortic forward stroke volume from total LV stroke volume. End-systolic wall stress was estimated using the thick-wall sphere model (*14*), for which end-systolic cavity pressure was substituted with systolic brachial pressure

obtained at PET. A CMR-based MEE ($MEE_{CMR/PET}$) was constructed by using aortic forward stroke volume and LV mass from CMR with MAP, HR and mean MVO_2 from PET.

Outcomes

For outcomes analysis, patients were followed regularly at our clinic or affiliated hospitals until March 2021. Time from inclusion to mitral valve intervention was recorded. The decision for mitral valve intervention was at the discretion of a multidisciplinary conference and in most cases (19 of 22) triggered by a combination of echocardiographic progression of MR and heart failure symptoms.

Statistical methods

Categorical variables are presented as numbers and frequencies. Continuous variables are presented as mean ± standard deviation (SD) or as medians and interquartile ranges (IQR). Correlations were assessed using linear regression. The agreement of corresponding parameters from PET and CMR were studied using Bland-Altman plot analyses and the significance of bias with paired T-tests.

PET results in patients were compared to healthy volunteers using T-tests. The relation of outcome data towards MEE and standard imaging parameters were analysed by univariate Cox proportional hazards. Multivariate Cox models were experimentally performed using the best MEE cut-off and significant univariate predictors from echocardiography (ESV, RegVol, Tricuspid jet max velocity) or CMR (EDV, ESV, RegVol).

P-values < 0.05 were considered significant. Statistical analyses were performed using JMP Version 16 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism version 9 (GraphPad Software, La Jolla, CA, USA).

Results

Clinical and laboratory findings are shown in Table 1. The mean age in the study population was 59.4±11.0 years and 91% (n=44) were men. All patients met echocardiographic criteria for severe degenerative mitral regurgitation at the time of inclusion. The most common valve defect was an isolated or dominant P2-segment prolapse of the posterior leaflet (78%, n=39), followed by Barlow's disease (14%, n=7)

A history of hypertension was present in 60% (n=28). Symptoms were categorised as NYHA class I in 89% (n=42) and class II in 11% (n=5) at referral. One patient did not complete the CMR scan due to claustrophobia; this patient did undergo PET. Healthy volunteers (n=9, 54±8 years, 3 males) had no history of cardiac disease and had normal echocardiographic findings.

Myocardial efficiency

Table 2 shows the results of MEE and associated PET measurements in healthy volunteers, compared to MR patients. There were significant differences in age and sex distribution among the groups. Average MEE in patients (26.3±5.3%) was significantly reduced compared to healthy volunteers ((30.1±5.0%, p=0.048; for details see Table 2. MEE in patients who reached an end-point was lower than in censored patients (mean difference -4.6% (95%CI: -7.4; -1.8), p = 0.002,

while MEE in censored patients was similar to healthy volunteers (mean difference -1.7% (95%CI: -5.4%; 2.1), p=0.37), as shown in Figure 2.

Results of linear correlation analyses of MEE with parameters from echocardiography and CMR are shown in Table 3, showing inverse weak, but significant correlations with indices associated with regurgitation, remodelling severity and LV global longitudinal strain. Notably, MEE did not correlate with left ventricular EF or end-systolic wall stress.

The MEE equation includes forward stroke volume and LV mass, here obtained by PET by an automated image analysis procedure. Both these parameters were also available from the same-day CMR in MR patients, and cross-modality correlations and agreement were good (forward stroke volume: r=0.88 (95%CI 0.79-0.93), p<0.0001, and bias=-1±8 mL, p=0.52; LV mass: r=0.91 (95%CI 0.84-0.95), p<0.0001, and bias=0±15 g, p=0.9). When CMR-based forward stroke volume and LV mass were inserted into the MEE equation the correlation remained good (r=0.76 (95%CI 0.61-0.86), p<0.0001), but MEE values from PET alone were higher (bias= 4.6±3.5%, p<0.0001). A residual analysis showed that differences in both forward SV and LV mass contributed significantly to MEE variance. Use of two different PET scanners in the study did not impact bias towards CMR-based MEE.

Clinical outcomes

Median duration of follow-up was 2.7 years (IQR 1.9-3.2). The endpoint of surgical intervention was reached in 21 subjects. One subject progressed and developed characteristic symptoms, and was recommended for intervention but the patient rejected surgery; this patient suffered cardiovascular death 5 years after inclusion and the time-point of recommendation for surgery

was used as an end-point surrogate. Thus, the final number of subjects considered reaching the end-point in statistical analyses was 22.

The indication for intervention was at the discretion of the treating physicians and followed guidelines available at the time of the study (*15*). Occurrence of symptoms during surveillance was noted in 17 of 22 (77%) in whom surgery was eventually recommended.

Univariate analysis showed that MEE as a continuous variable predicted outcome; a decrease of MEE by 1% increased the relative hazard of the outcome within the next year by 19% (hazard ratio 0.84 (95% CI 0.75-0.93); p=0.0004). ROC analysis provided an MEE cut-off for event prediction at 25.7%, close to the lower limit of normalcy, which was associated with a risk ratio of 7.5 (95%CI: 2.7-21), p<0.0001) in a univariate Cox model. A Kaplan-Meyer plot is shown in Figure 2B.

Table 3 shows univariate baseline predictors of outcome by Cox proportional hazards analysis from echocardiography and CMR. $MEE_{CMR/PET}$ performed similar to MEE from PET alone, both as a continuous variable (hazard ratio 0.85 (95%CI 0.77-0.93) and as a binary cut-off, established as $MEE_{CMR/PET}$ <22.2% (hazard ratio 5.9 (95%CI 2.0-17.8).

Echocardiographic and CMR-based severity of mitral regurgitation were also predictive (p<0.05) in univariate Cox analyses (Table 3). Furthermore, and likely mediated by guideline-based management, LV volumes by standard imaging were significantly predictive of outcomes. LV ejection fraction, end-systolic wall stress and global longitudinal strain had no significant association towards outcome.

MEE remained a significant independent predictor when adjusted for any of the standard imaging parameters, more pronounced when the cut-off MEE<25.7% was used. Table 4 shows the results

of two experimental Cox multivariate models, in which MEE<25.7% was adjusted for the parameters with the highest univariate predictive capacity from either echocardiography or CMR. In a Cox model of MEE corrected for anamnestic presence of hypertension, MEE remained highly predictive (p=0.0002), while history of hypertension did not reach statistical significance (p=0.9).

Discussion

Our study shows for the first time the relation of MEE with MR severity, LV remodelling, and progression requiring surgical intervention in asymptomatic severe primary MR. Importantly, the predictive value of MEE was proportional and persisted after correction for standard objective estimators of MR severity, suggesting that MEE offers information that is orthogonal to the estimators recommended in current guidelines. These observations suggest that reduction of myocardial efficiency precedes progression to symptomatic MR requiring intervention.

MEE predicted outcome independently of standard clinical, laboratory, echocardiographic and CMR parameters collected at the time of PET. This can be partially explained by the fact that MEE is calculated from parameters that are typically not part of standard guideline-oriented MR evaluation, such as cardiac forward work and myocardial oxygen consumption. However, none of the functional parameters used in the MEE equation were significant predictors of outcome on their own.

Clinically, our data confirm the prognostic impact of well-established regurgitation parameters such as RegVol and LV volumes for both echocardiography and CMR. LVEF did not correlate

with MEE in this cohort and was not predictive, probably because LVEF was within the normal range in all subjects.

Tricuspid jet velocity and left atrial volume, the echocardiographic estimates of backward volume loading recommended in guidelines, were both significantly correlated with MEE and significant predictors in univariate analyses. Both, however, lost predictive significance when adjusted for MEE in multivariate models. A potential explanation for these results is that a poorer metabolic efficiency might have a culprit role in reducing diastolic LV function, which drives the backward failure and results in earlier symptom occurrence.

The experimental multivariate Cox analyses showed that end-systolic volume from echocardiography, but not from CMR, had independent predictive capacity. This is confusing, since CMR is the gold standard. A potential explanation could be that treating physicians had access to serial echocardiography data according to guidelines, but were blinded to CMR and PET.

Although MEE showed independent predictive value for outcomes, the modest size of our cohort, as well as the limited availability of ^{11}C-acetate PET, does not allow us to predict the potential future role of MEE in the routine management of patients with asymptomatic severe mitral regurgitation. Still, the orthogonal perspective on progression offered by MEE might be useful for research into optimizing decision-making algorithms based on clinical data and for developing surrogate markers of MEE from standard imaging modalities. One such opportunity could be to study MEE in MR patients with concomitant cardiovascular or metabolic diseases to see if co-morbidities contribute to MR progression by augmenting disturbances in oxidative metabolism beyond what is caused by volume overload. Hypertension is common in MR and

patients who suffer from both disease entities are potentially prone to more rapid symptomatic progression, but there is no clear evidence for benefit of anti-hypertensive therapy (*16*). MEE is lowered in hypertension with LV hypertrophy (*17*), which would suggest that a history of hypertension might predispose a reduction of MEE in MR and contribute to the more rapid symptomatic progression in a subset of patients found in this study. Based on this hypothesis, we tested the association of hypertension and MEE for predicting progression but found no significant interaction in this cohort.

In patients with overt heart failure, MEE is significantly associated with LV hypertrophy and end-systolic wall stress (*6*). Among the individual parameters used in the MEE equation, LV mass was the only one that was significantly increased in MR patients, compared to healthy controls in our study. The hypertrophy seen in MR is generally regarded as an adaptive mechanism that reduces wall stress, secondary to LV dilatation. We did not find any association of end-systolic wall stress towards MEE or outcome, probably because the hypertrophic adaptation matched the dilatation sufficiently overall. However, this adaptation is apparently not sustainable in a subset of MR patients and causes a lowered metabolic efficiency even before major adverse changes in wall stress and systolic function occur. This may relate to metabolic alterations found in failing myocardium, including in the setting of MR (*18*), and points to a poorly understood variation in phenotypic susceptibility. MEE was in the normal range in MR subjects that did not experience early progression in spite of LV hypertrophy, suggesting that early adaptations to chronic volume overloading in subjects without increased susceptibility include a potentially improved efficiency of oxidative metabolism. This is analogous to previous findings in subjects with LV hypertrophy due to aortic stenosis and pressure overload, where MEE was in the normal range until symptom occurrence (*19*).

^{11}C-acetate PET has been used to study MEE at a later stage in MR progression in small studies of symptomatic primary (*7*) and secondary (*9*) mitral regurgitation, showing MEE improvements after surgery in parallel with normalisation of forward stroke volume. In the current study, external cardiac work and forward stroke volume in patients who reached the endpoint was not significantly different from patients who were censored or from healthy volunteers, and symptom burden was minimal, suggesting that our cohort were studied at an earlier disease state than previous ^{11}C-acetate PET studies in MR. Moreover, it is difficult to draw conclusions from comparisons between our study and previous knowledge because guideline criteria for recommending surgical intervention have become more aggressive in the recent decade. Hence, studies with serial PET measurements might be required to understand the dynamics of myocardial metabolic efficiency, during progression leading to an intervention and during recovery after surgery, and to what extent the presumably distinct predictive value of MEE found in this study can be used for therapeutic decision-making or as an outcome surrogate in drug trials. For such studies, PET-MEE has the advantage of simultaneous acquisition and automated analysis of all required parameters. The data show, however, that combined CMR and PET with careful avoidance of hemodynamic alterations between scans is not inferior to PET alone for predictive purposes, but MEE quantification appear to be method-dependent.

Limitations

Several limitations of our study should be recognized. The number of patients included is modest, but nevertheless this is potentially the largest study evaluating primary mitral regurgitation severity with same-day PET, echocardiography and CMR. Most importantly, this is a study in

patients with moderate-to-severe or severe primary MR, which does not address lesser degrees of MR or secondary MR.

An important fundamental limitation was the nature of our end-point, which was mitral valve intervention. The decision to proceed with intervention followed current guidelines at the time of the study and thus was triggered by the emergence of symptoms or NT-proBNP increase, progressive LV dilatation, or reduction in LVEF exceeding guideline-specified echocardiographic limits, or some combination of these features. Hence, it is not surprising that volumetric indices like RegVol and LVEDV were prognostic of outcomes. One patient was recommended for surgery, but declined and died of cardiovascular causes. Of interest, this patient had the lowest MEE (15.7%) of all subjects in the cohort. Removal of this patient from outcome analyses did not change results or conclusions.

We acknowledge that MEE is a simplified approach to measuring myocardial efficiency and comparisons to invasive approaches with pressure-volume loop analyses and direct measurement of MVO_2 are relevant for future studies. Pump work did not include the product of regurgitant volume and end-systolic left atrial pressure; it is unclear if this addition would alter the predictive value of MEE.

Conclusion

MEE by ^{11}C-acetate PET was reduced in asymptomatic chronic degenerative mitral valve in proportion to the severity of MR measured by multiparametric echocardiography and CMR, and MEE predicted time to progression triggering surgical intervention, independently of standard imaging parameters of MR severity, LV function and size.

Key points

Question: What is the role of myocardial efficiency of oxidative metabolism (MEE) measured with ^{11}C-acetate PET in progression of asymptomatic moderate-severe or severe primary mitral valve insufficiency?

Pertinent findings: MEE was proportional to standard imaging indicators of regurgitation severity and volume overload. MEE was independently predictive of time to progression requiring surgical intervention.

Implications for patient care: MEE might provide an objective and early indicator of deteriorating myocardial energetics in mitral valve disease.

Acknowledgments

This study was supported by research grants Nr. 20130631 and Nr. 20190593 from the Swedish Heart-Lung Foundation, Stockholm, Sweden.

Conflicts of Interest: Nothing to Disclose.

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;368:1005-1011.

2. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013;14:611-644.

3. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017;30:303-371.

4. Myerson SG, d'Arcy J, Christiansen JP, et al. Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification. *Circulation.* 2016;133:2287-2296.

5. Sorensen J, Harms HJ, Aalen JM, Baron T, Smiseth OA, Flachskampf FA. Myocardial Efficiency: A Fundamental Physiological Concept on the Verge of Clinical Impact. *JACC Cardiovasc Imaging.* 2020;13:1564-1576.

6. Hansen KB, Sorensen J, Hansson NH, et al. Myocardial efficiency in patients with different aetiologies and stages of heart failure. *Eur Heart J Cardiovasc Imaging.* 2022;23:328-337.

7. Chow BJ, Abunassar JG, Ascah K, et al. Effects of mitral valve surgery on myocardial energetics in patients with severe mitral regurgitation. *Circ Cardiovasc Imaging.* 2010;3:308-313.

8. Harms HJ, Hansson NHS, Kero T, et al. Automatic calculation of myocardial external efficiency using a single (11)C-acetate PET scan. *J Nucl Cardiol.* 2018;25:1937-1944.

9. Sugiki T, Naya M, Manabe O, et al. Effects of surgical ventricular reconstruction and mitral complex reconstruction on cardiac oxidative metabolism and efficiency in nonischemic and ischemic dilated cardiomyopathy. *JACC Cardiovasc Imaging.* 2011;4:762-770.

10. Bing RJ, Hammond MM, et al. The measurement of coronary blood flow, oxygen consumption, and efficiency of the left ventricle in man. *Am Heart J.* 1949;38:1-24.

11. Harms HJ, Tolbod LP, Hansson NH, et al. Automatic extraction of forward stroke volume using dynamic PET/CT: a dual-tracer and dual-scanner validation in patients with heart valve disease. *EJNMMI Phys.* 2015;2:25.

12. Harms HJ, Stubkjaer Hansson NH, Tolbod LP, et al. Automatic Extraction of Myocardial Mass and Volume Using Parametric Images from Dynamic Nongated PET. *J Nucl Med.* 2016;57:1382-1387.

13. Hansson NH, Harms HJ, Kim WY, et al. Test-retest repeatability of myocardial oxidative metabolism and efficiency using standalone dynamic (11)C-acetate PET and multimodality approaches in healthy controls. *J Nucl Cardiol.* 2018;25:1929-1936.

14. Alter P, Rupp H, Rominger MB, Klose KJ, Maisch B. A new methodological approach to assess cardiac work by pressure-volume and stress-length relations in patients with aortic valve stenosis and dilated cardiomyopathy. *Pflugers Arch.* 2008;455:627-636.

15. Vahanian A, Iung B. The new ESC/EACTS guidelines on the management of valvular heart disease. *Arch Cardiovasc Dis.* 2012;105:465-467.

16. Katsi V, Georgiopoulos G, Magkas N, et al. The Role of Arterial Hypertension in Mitral Valve Regurgitation. *Curr Hypertens Rep.* 2019;21:20.

17. Laine H, Katoh C, Luotolahti M, et al. Myocardial oxygen consumption is unchanged but efficiency is reduced in patients with essential hypertension and left ventricular hypertrophy. *Circulation.* 1999;100:2425-2430.

18. Conway MA, Bottomley PA, Ouwerkerk R, Radda GK, Rajagopalan B. Mitral regurgitation: impaired systolic function, eccentric hypertrophy, and increased severity are linked to lower phosphocreatine/ATP ratios in humans. *Circulation.* 1998;97:1716-1723.

19. Hansson NH, Sorensen J, Harms HJ, et al. Myocardial Oxygen Consumption and Efficiency in Aortic Valve Stenosis Patients With and Without Heart Failure. *J Am Heart Assoc.* 2017;6.

Table 1. Baseline patient characteristics.

Clinical data (n=47)	
Age, years	62±10
Male sex, n (%)	43 (91)
Body surface area, m^2	2.0±0.2
Body mass index, kg/m^2	25±3
History of hypertension, n (%)	28 (60%)
NTproBNP, ng/L (median, IQR) (URL <230)	99(67;183)
Medication at inclusion:	
Renin-angiotensin-aldosterone-system inhibitors	25 (53%)
Beta-receptor inhibitors	9 (19%)
Calcium channel inhibitors	7 (15%)
Diuretics	4 (9%)
Digoxin	2 (4%)

Table 2. ^{11}C-acetate PET/CT comparison of healthy controls and asymptomatic severe primary mitral regurgitation

	Healthy controls	MR	P-value
N	9	47	
Sex (M/F)	3/6	43/4	**0.0002**
Age (y)	55±8	62±10	**0.03**
Heart rate (min^{-1})	62±10	59±10	0.50
Mean arterial pressure (mmHg)	97±11	100±13	0.42
PET parameters:			
Cardiac Index (L/m^2)	2.8±0.4	2.5±0.3	0.054
Forward SV index (mL/m^2)	45±5	43±7	0.29
MVO_2 (mL/min/100g)	10±2	10±2	0.50
LV mass index (g/m^2)	55±8	83±16	**<0.0001**
External work ($J/min/m^2$)	35±3	34±8	0.32
LV energy consumption ($J/min/m^2$)	114±22	163±45	**<0.0001**
MEE (%)	30±5	26±5	**0.048**

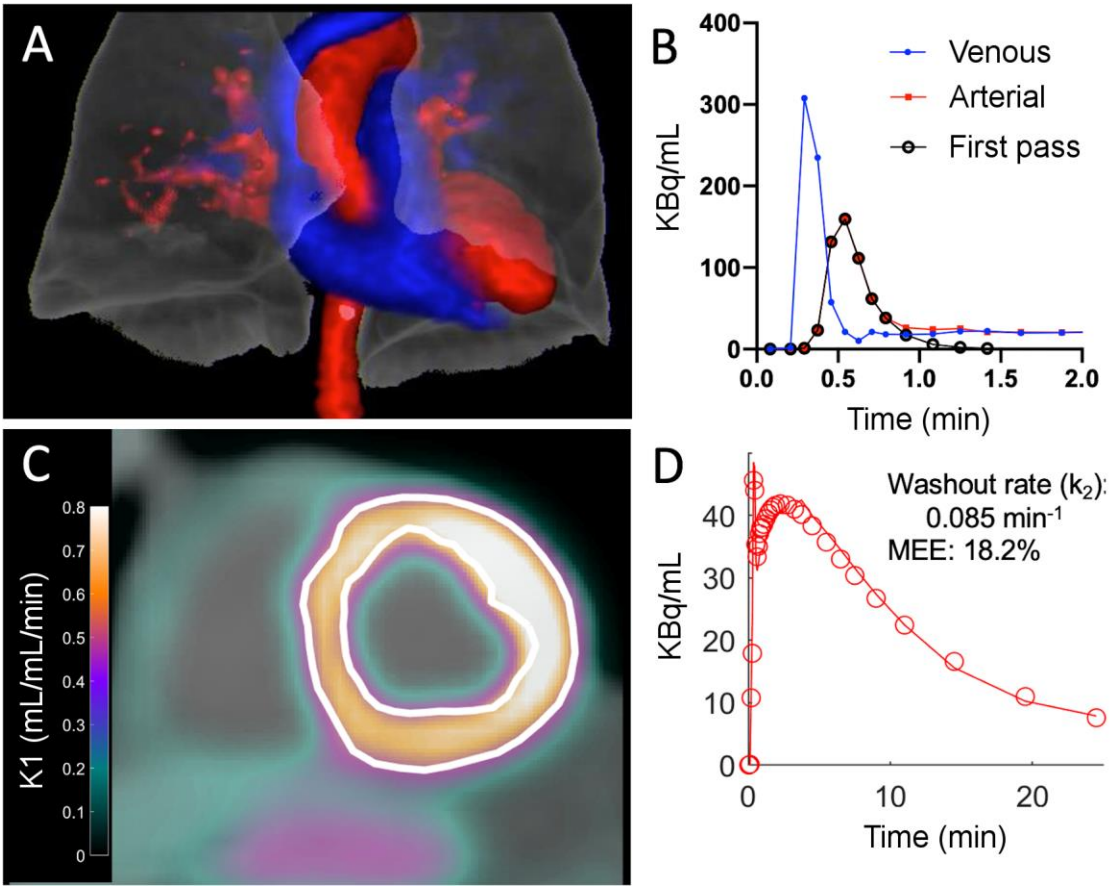
Table 3. Echocardiography and CMR: mean values, linear correlations with MEE and univariate Cox proportional hazard analysis.

Parameter	Mean±SD	Pearson r correlation with MEE (P-value)	Hazard ratio (95%CI)	P-value
Echocardiography:				
LV end-diastolic diameter (cm)	5.5±0.5	-0.35 (0.02)	2.9 (1.3-6.9)	0.01
LV end-systolic diameter (cm)	3.4±0.4	-0. 24(0.10)	3.0 (1.0-9.6)	0.05
Left atrial volume index (mL/m^2)	35 (IQR 31-52)	-0.53 (0.0001)	1.01 (1.00-1.03	0.08
Tricuspid max jet velocity (m/s)	2.6±0.4	-0.51 (0.0003)	6.2 (2.5-15.2)	0.0002
EROA (cm^2)	0.65±0.39	-0.40 (0.005)	2.2 (0.89-4.6)	0.09
Regurgitant volume by PISA (mL)	106±60	-0.37 (0.01)	1.01 (1.00-.01)	0.07
LVEDV index (mL/m^2)	98±18	-0.51 (0.0003)	1.05 (1.02-.07)	0.0002
LVESV index (mL/m^2)	34±7	-0.35 (0.01)	1.13 (1.06-.21)	0.0001
LV ejection fraction (%)	66±4	-0.13 (0.35)	0.97 (0.88-.07)	0.48
Regurgitant volume volumetric mL)	51±31	-0.44 (0.002)	1.02 (1.01-.04)	0.001
LV global longitudinal strain (%)	-21.5±2.6	0.44 (0.003)	0.93 (0.79-.09)	0.37
Cardiac Magnetic Resonance imaging:				
LVEDV index (mL/m^2)	122±26	-0.53 (0.0002)	1.03 (1.01-.04)	0.001
LVESV index (mL/m^2)	39±11	-0.47 (0.001)	1.08 (1.04-.12)	0.0004
Regurgitant volume (mL)	81±35	-0.47 (0.001)	1.02 (1.00-.03)	0.01
Regurgitant fraction (%)	47±12	-0.54 (0.0001)	1.08 (1.03-.13)	0.001
LV ejection fraction (%)	68±4	0.09 (0.57)	0.91 (0.82-.02)	0.1
End-systolic wall stress (kPa)	20±4	-0.10 (0.53)	1.08 (0.96-.22)	0.21
$MEE_{CMR/PET}$ (%)	22±5	0.76 (<0.0001)	0.85 (0.77-.93)	0.0002

Table 4. Experimental multivariate Cox proportional hazard models of MEE with adjustments for standard outcome parameters from either echocardiography or CMR

Parameter	Hazard ratio (95% CI)	P-value
MEE and echocardiography – whole model P<0.0001		
MEE<25.7%	3.7 (1.1-12.8)	**0.03**
Regurgitant volume volumetric (mL)	1.37 (0.17-13.8)	0.77
LV end-systolic volume index (mL/m^2)	1.08 (1.01-1.17)	**0.03**
Tricuspidal Vmax (m/s)	2.2 (0.70-6.64)	0.17
MEE and CMR – whole model P=0.0002		
MEE<25.7%	5.9 (1.7-20.3)	**0.005**
LV end-diastolic volume index (mL/m^2)	1.00 (0.93-1.07)	0.94
LV end-systolic volume index (mL/m^2)	1.04 (0.95-1.14)	0.39
Regurgitant volume (mL)	1.00 (0.97-1.03)	0.87

Figure 1. **Automatic post-processing of cardiac ^{11}C-acetate PET/CT images.**



A: First-pass analysis after intravenous bolus injection of a few micrograms of ^{11}C-acetate. Arterial clusters (red) indicate left atrium, left ventricle and aorta, while venous clusters (blue) indicate vena cava, right atrium and ventricle, and the pulmonary artery. B: Time-activity curves of the clusters for arterial (red dots) and venous (blue dots) blood, and corresponding isolated first-pass peaks (lines), from which cardiac output and external work (cardiac output x MAP) are calculated as in reference (*11*). C: LV mass is measured by delineating LV endo- and epicardial contours by thresholding the myocardium on a parametric image representing myocardial blood flow (*12*). D: The kinetics of radioactive content over time in myocardium is measured from the region in panel C (*8*). ^{11}C-acetate is trapped intracellularly as ^{11}C-acetyl-Coenzyme A and

converted to ^{11}C-CO_2 by myocardial mitochondriae; the washout rate of radioactivity is directly proportional to MVO_2. Total LV oxygen consumption is measured as mean MVO_2 x LV mass. External work and total LV MVO_2 are converted to Joule and divided, yielding myocardial external efficiency (*8*).

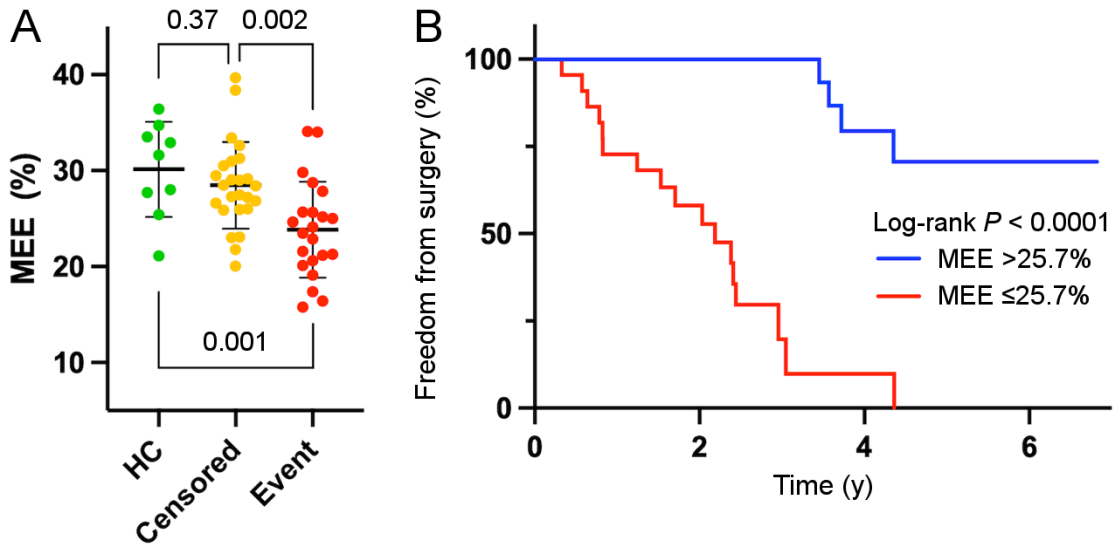


Figure 2. A: Plots of myocardial external efficiency (MEE) comparing healthy controls (HC) and study patients that were followed without (Censored) or with (Event) progression mandating surgical intervention. B: Kaplan-Meier plot showing that patients with MEE below 25.7% at inclusion required valvular surgery significantly faster than patients with MEE above 25.7%.

Graphical abstract