Assessment of myocardial oxidative metabolism in aortic valve disease using positron emission tomography with C-11 acetate

C-11 acetate has recently been introduced as a tracer of myocardial oxidative metabolism with the use of positron emission tomography. To evaluate this approach in the pressure- or volume-loaded heart, C-11 acetate clearance rate constants were determined in 22 patients with chronic aortic valve disease and in nine normal subjects. Global myocardial C-11 clearance was significantly higher in patients with predominant aortic stenosis ($n = 11$) or aortic regurgitation ($n = 11$) than in normal subjects (0.069 ± 0.017 min^{-1} and 0.072 ± 0.010 min^{-1} compared with 0.050 ± 0.004 min^{-1}, $p < 0.05$) and correlated significantly with the rate-pressure product corrected for mean aortic valve gradient ($r = 0.73$, $p = 0.0001$) for all studies. However, analysis of patient subgroups demonstrated that this correlation held only for aortic stenosis ($r = 0.79$, $p < 0.005$ for gradient-corrected rate-pressure product). Additionally, C-11 clearance was strongly correlated with the product of heart rate and mean wall stress in patients with aortic stenosis ($r = 0.89$, $p < 0.005$) but not in patients with aortic regurgitation. Normalization of C-11 acetate clearance rate constants for gradient-corrected rate-pressure product were significantly lower in patients with loaded ventricles, particularly in the presence of a low ejection fraction, compared to normal subjects. Possible mechanisms include myocardial adaptation through hypertrophy or depressed contractility, which would both tend to reduce oxygen consumption under any given load. Serial comparison of C-11 acetate kinetics and noninvasive indexes of oxygen demand may provide assessment of disease progression in pathologic ventricular loading. (AM HEART J 1992;123:653.)

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Assessment of myocardial oxygen consumption has formerly required complex and invasive techniques. However, noninvasive characterization of myocardial oxidative metabolism has recently become possible with the introduction of C-11 acetate as a metabolic tracer for use with positron emission tomography.[1-3] Results of experimental studies in animals have demonstrated that C-11 acetate is taken up avidly by the myocardium and that subsequent clearance of C-11 activity from the heart is strongly correlated with myocardial oxygen consumption per unit mass of tissue (MVO_2).[4, 5] These promising results have led to the evaluation of this agent as a tracer of oxidative metabolism in humans. In normal subjects studied at rest and during exercise[6] and at rest and during dobutamine infusion,[7] there was a close correlation between C-11 acetate clearance rate constants and the rate-pressure product. This parameter is itself a validated correlate of myocardial oxygen consumption by the normal human heart.[8-10] Besides being a means to directly and noninvasively assess myocardial oxygen consumption, C-11 acetate clearance kinetics also provide assessment of regional variation in oxidative metabolism.[11] This facility is unique since invasive assessment of myocardial oxygen consumption only provides assessment of global oxygen extraction. Results of these validation studies in normal humans suggest that C-11 acetate may be a useful experimental tool for evaluating oxidative metabolism in cardiac disease. However, reports of the utility of this method for the evaluation of pathologic conditions of the heart have been limited to a study involving a small number of patients after myocardial infarction.[12]

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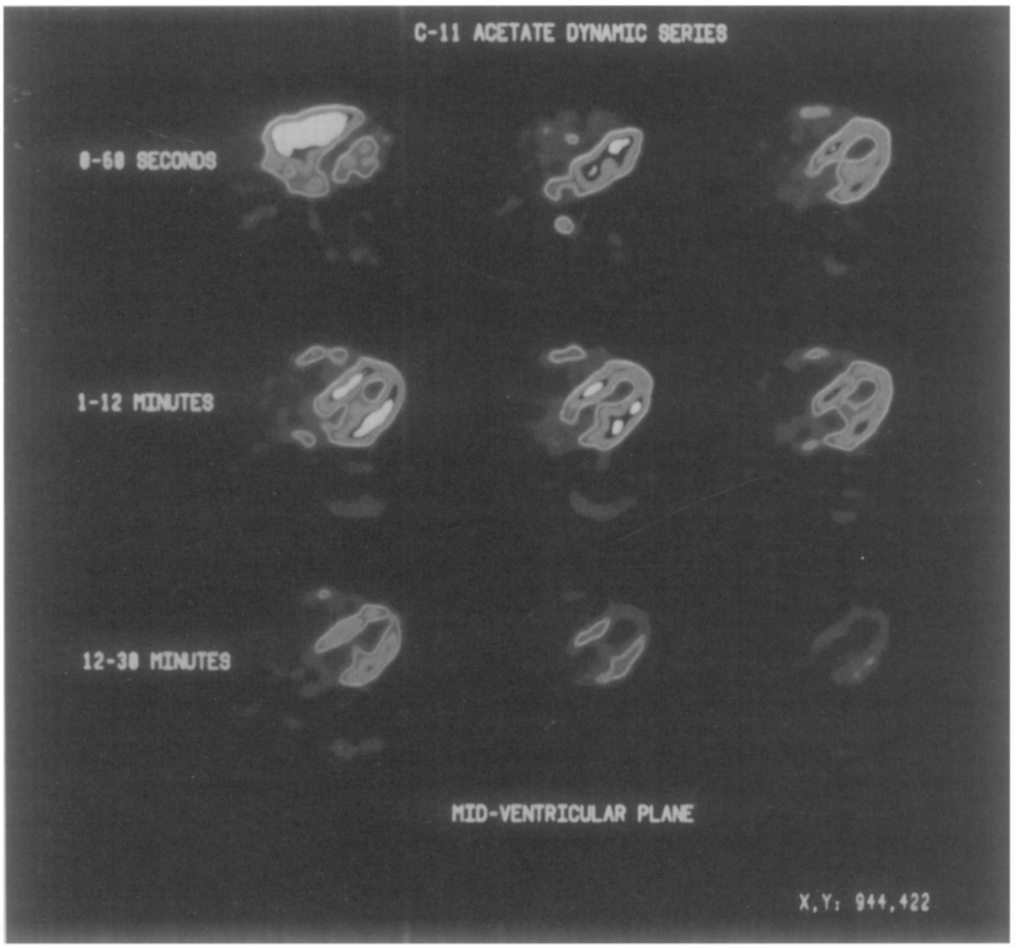


Fig. 1. Dynamic series of decay-corrected C-11 acetate images displayed in single midventricular transaxial plane. In the first frame *(top left)* C-11 activity is mainly in blood. Later there is rapid blood pool clearance and avid myocardial extraction. By the final frame *(bottom right)* there has been substantial clearance of myocardial C-11 activity, reflecting metabolism of C-11 acetate via tricarboxylic acid cycle.

In this study we evaluated the use of positron emission tomography with C-11 acetate in 22 patients with chronic aortic valve disease to compare C-11 acetate clearance kinetics in the pressure- and volume-loaded heart with those found in normal subjects, assess the homogeneity of oxidative metabolism within the loaded ventricle, and determine the relationship between C-11 acetate clearance and routinely available hemodynamic and echocardiographic parameters of left ventricular oxygen demand.

METHODS

Study population. The study protocol was approved by the Human Subject Protection Committee of the University of Michigan Medical Center. All patients and normal control subjects were studied only after they granted informed written consent. The patient population included 22 patients (14 men and eight women) with chronic aortic valve disease and no evidence of coronary artery disease. These patients were between the ages of 34 and 85 years and were being considered for aortic valve replacement. All were clinically stable and had no change in medications during the study interval. Elective coronary angiography had been performed in all patients within 1 month of the positron emission tomography. None had coronary stenoses of greater than 50% of the luminal diameter or regional wall motion abnormalities suggesting prior myocardial infarction.

Patients were classified as having either predominant aortic stenosis or aortic regurgitation based on their clinical diagnosis, which incorporated a knowledge of physical examination, echocardiographic, and cardiac catheterization findings. Eleven patients were considered to have predominant aortic stenosis and 11 were considered to have aortic regurgitation as the dominant valvular lesion. Patients were compared with nine healthy male volunteers, 22 to 28 years of age. These subjects had no known cardiac disease based on clinical history, physical examination re-

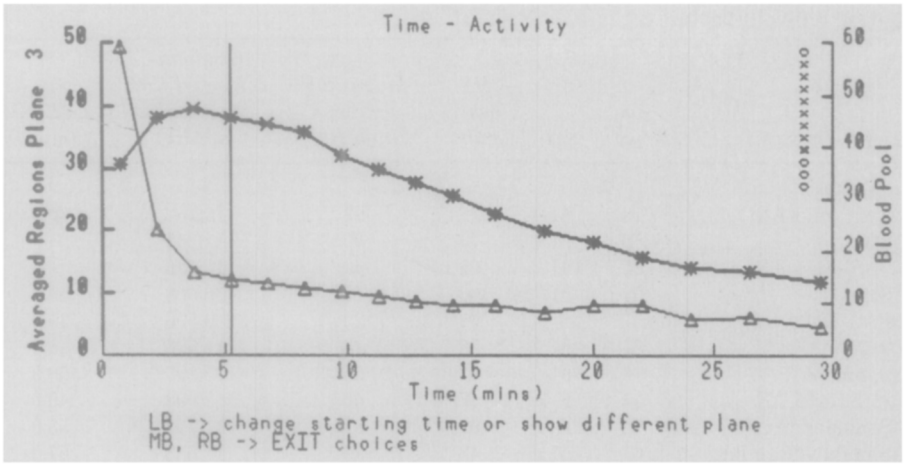


Fig. 2. Typical C-11 acetate time-activity curve (corrected for decay) displayed for left ventricular myocardial region of interest. Early rapid clearance phase of myocardial clearance curve was fitted by means of least-squares monoexponential curve fitting routine. Lower curve represents blood pool activity, which decreases rapidly and substantially early after intravenous administration.

sults, and ECG findings. All were considered to be at low risk for coronary artery disease. Echocardiographic studies were performed in four of these subjects and results were normal.

Noninvasive assessment of left ventricular oxygen demand. The rate-pressure product and left ventricular wall stress are readily available and commonly used noninvasive parameters of left ventricular oxygen demand.[8-10, 13] Heart rate and cuff systolic blood pressure values obtained at the beginning of the C-11 acetate positron emission tomographic study were multiplied to calculate the rate-pressure product. In patients with aortic stenosis, the brachial systolic blood pressure value may underestimate left ventricular systolic pressure and consequently a correction was made for the aortic valve gradient in determination of the rate-pressure product. In all patients with evidence of aortic stenosis, the sum of the systolic blood pressure and the mean aortic valve gradient was used as an approximation of left ventricular systolic pressure. A "gradient-corrected" rate-pressure product was then obtained by multiplying the heart rate at the time of the positron emission tomography by this parameter.

All patients had undergone echocardiography shortly before the positron emission tomographic study. In 15 patients positron emission tomography and echocardiography were done within 24 hours of each other. Among the seven remaining patients, the interval between the studies was less than 1 week in three patients and less than 6 weeks in four (range 4 to 40 days). The mean aortic pressure gradient was calculated by integrating the Doppler peak aortic flow velocity spectral envelope.[14] The left ventricular ejection fraction was determined by two-dimensional echocardiography with Simpson's rule in the 20 patients.[15] A left ventricular ejection fraction of less than 50% was considered abnormal. In patients with technically adequate echocardiograms for assessment of wall thickness and left ventricular dimensions (n = 18), mean left ventricular wall stress index[16] and left ventricular mass[17] were also calculated. Comparisons were made with four normal subjects who had undergone echocardiographic studies.

Positron emission tomography with C-11 acetate. C-11 acetate was synthesized by means of a modification of previously described methods.[1] All C-11 acetate studies were performed with a whole-body positron emission tomography scanner (Siemens 931, Siemens Gammasonics Inc., Hoffmann Estates, Ill.), which allows simultaneous imaging of 15, transaxial slices, 6.75 mm thick. Transmission images were obtained for 15 minutes and were used to correct for the effects of tissue attenuation on the emission images. Dynamic positron emission tomographic imaging was then performed for 31 minutes after intravenous administration of 740 MBq (20 mCi) of C-11 acetate. Ten frames of 90 seconds' duration were obtained, followed by five frames of 120 seconds' duration and two frames of 180 seconds' duration.

A single midventricular transverse transaxial plane was chosen from the 15 available planes. The decay-corrected dynamic series of C-11 acetate images for this plane was displayed, and regions of interest were assigned on the frame with the best myocardial definition. Generally this was approximately 4 to 6 minutes after administration of the tracer (Fig. 1). Myocardial regions were assigned for the septum, anterior wall, and free lateral wall. For consistency between studies, the apical left and right ventricular junction and the posteromedial papillary muscle were used as arbitrary landmarks demarcating these regions. An additional region of interest was assigned for the entire left ventricular myocardium in this plane. These regions of interest were then extrapolated to all frames of the dynamic series, thereby defining regional and global left ventricular myocardial time-activity curves (Fig. 2). Monoexponential least-squares curve fitting of the early rapid phase of myocardial clearance was used to derive C-11 clearance half-times in seconds.[6] C-11 clearance rate constants (k min^{-1})

Table I. Data from individual subjects

Group	Clinical diagnosis	Age (yr)	Sex	HR (beats/min)	Mean AoV gradient (mm Hg)	Gradient-corrected RPP (beats/min. mm Hg)	LVEDD (mm)	Echo LVEF (%)	k min^{-1}
Patients with aortic stenosis									
1237	Moderate AS, mild AR	72	M	72	23	10,152	60.0	30	0.0616
3026	Severe AS	58	M	73	50	11,242	—	64	0.0743
3698	Moderate AS, mild AR	85	M	62	49	10,726	—	60	0.0659
5307	Severe AS	62	M	66	61	12,606	50.0	50	0.0829
5855	Moderate AS	57	F	58	22	9,396	39.0	60	0.0514
6808	Moderate AS	81	M	96	48	14,976	45.0	46	0.0676
6869	Severe AS, mild AR	70	M	91	55	15,197	50.0	79	0.0566
7124	Moderate AS, mild AR	55	F	67	56	12,998	48.0	55	0.0609
7818	Severe AS, moderate AR	72	F	62	67	11,718	53.0	55	0.0695
7840	Severe AS, mild MR, mild AR	61	M	48	79	11,568	57.0	60	0.0553
9855	Severe AS	75	F	122	42	22,936	57.0	20	0.1145
Patients with aortic regurgitation									
1313	Moderate AR, MS, mild AS	63	F	103	30	17,922	54.0	45	0.0785
2531	Severe AR	77	M	53	—	9,010	69.0	60	0.0623
2573	Mild AR, mild MR	38	M	72	—	9,072	64.0	63	0.0622
4463	Severe AR, mild-moderate AS and MR	34	M	83	29	12,533	64.0	59	0.0860
5417	Mild-moderate AR, mild AS	67	M	76	20	11,400	77.0	8	0.0574
6157	Severe AR	50	M	88	—	10,736	64.0	—	0.0610
7006	Moderate AR, severe MR	68	F	58	12	7,656	68.0	50	0.0863
9313	Moderate-severe AR	63	F	74	—	14,652	58.0	55	0.0683
8285	Severe AR	42	M	71	—	8,875	66.0	—	0.0681
9899	Moderate-severe AR	61	M	75	—	12,900	76.0	50	0.0811
9953	Moderate AR	74	F	72	—	11,664	56.0	63	0.0720
Normal subjects									
3148	Normal	29	M	60	0	6,840	—	—	0.0484
9631	Normal	22	M	57	0	6,156	—	—	0.0529
9086	Normal	22	M	43	0	5,160	—	—	0.0507
1950	Normal	22	M	50	0	6,000	—	—	0.0504
8442	Normal	26	M	62	0	6,820	—	—	0.0452
9154	Normal	28	M	60	0	6,000	—	—	0.0554
6942	Normal	28	M	64	0	6,656	—	—	0.0460
1382	Normal	26	M	56	0	6,272	—	—	0.0548
3359	Normal	26	M	60	0	6,720	—	—	0.0501

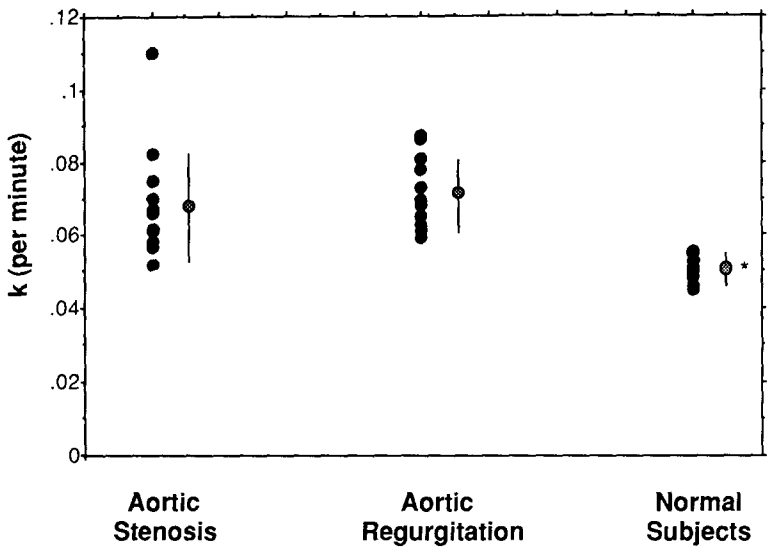
Echo, Echocardiography; *AS*, aortic stenosis; *AR*, aortic regurgitation; *MS*, mitral stenosis; *MR*, mitral regurgitation; *AoV*, aortic valve; *HR*, heart rate; *LVEF*, left ventricular ejection fraction; *LVEDD*, left ventricular end-diastolic dimension; k min^{-1}, C-11 acetate clearance rate constant.

were obtained by dividing the natural logarithm of two by the C-11 clearance half-time in minutes. In animal studies C-11 acetate clearance rate constants have been shown to be directly proportional to myocardial oxygen consumption in milliliters per minute per gram of tissue[4, 5] and are thus independent of left ventricular mass.

Statistical analysis. Values for groups are presented as mean ± one standard deviation. Mean values of continuous factors were compared for the two patient subgroups by means of unpaired *t* tests. Pearson's correlation was used to test the association of two continuous factors. Analysis of variance was performed to assess differences between patient and normal subject populations. Comparison of regional C-11 acetate clearance rate constants within individual subjects was performed with analysis of variance for repeated measures by means of Scheffe's F test method. Probability levels of <0.05 were considered statistically significant.

RESULTS

Population characteristics. Data for individual patients and normal subjects are displayed in Table I. The clinical, hemodynamic, and echocardiographic data characterizing each of the subgroups in the study are presented in Table II. In both groups of patients the gradient-corrected rate-pressure product was significantly higher than the rate-pressure product in the normal subjects. Patients with aortic regurgitation had significantly higher left ventricular end-diastolic diameters than patients with aortic stenosis, but left ventricular wall stress, mass, and



*P<0.05 compared with Aortic Stenosis and Aortic Regurgitation

Fig. 3. Average C-11 acetate clearance rate constants in patients with either predominant aortic stenosis or predominant aortic regurgitation were significantly higher than values in normal subjects. Mean values *(hatched circles)* and standard deviation for each group are displayed.

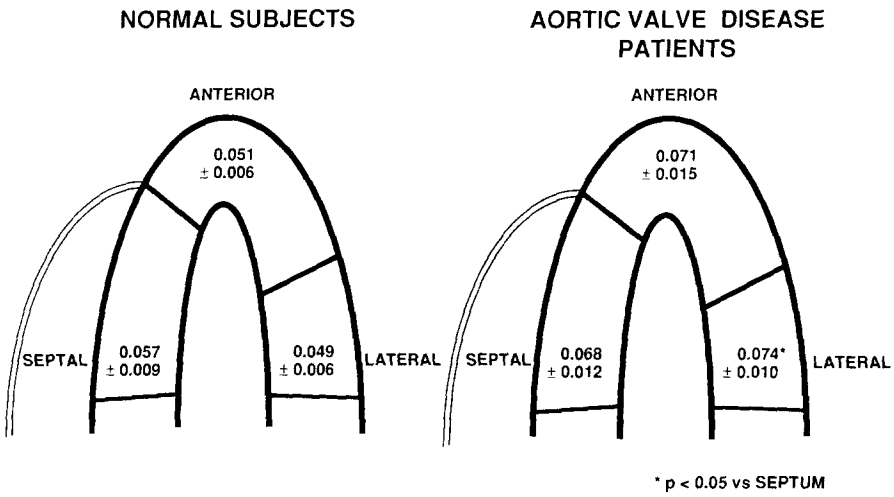


Fig. 4. Myocardial regions of interest were defined for septum, anterior wall, and lateral wall of left ventricle on single midventricular plane. Apical junction of left and right ventricles was used as border between septum and anterior wall. Posteromedial papillary muscle was used as junction of anterior and lateral walls. Average regional C-11 clearance rate constant data from nine normal subjects are presented on the left and from all patients with aortic valve disease on the right. Regional C-11 acetate clearance rate constants were not significantly different between patients with pressure or volume overload but were significantly higher in all regions compared with those values recorded in normal subjects ($p < 0.05$).

ejection fractions were not significantly different in the two patient subgroups.

Global C-11 acetate clearance rate constants by group. There was greater variation of global C-11 acetate clearance rate constants within both patient subgroups than in the normal subjects. As expected under the conditions of increased loading observed in the patient population, global left ventricular C-11 acetate clearance rate constants in patients with either pressure or volume overload were significantly higher than the rate constants in normal subjects. C-11 acetate clearance rate constants averaged 0.069 ± 0.017 min^{-1} for patients with predominant aortic stenosis and 0.072 ± 0.010 min^{-1} for patients

Table II. Characteristics of patients and normal subjects by diagnostic subgroup

Group	*N*	*Age (yr)*	*Male:Female*	*HR (beats/min)*	*Mean AoV gradient (mm Hg)*	*Gradient-corrected RPP (beats/min mm Hg)*
Aortic stenosis	11	68 ± 10*	7:4	74 ± 21	50 ± 17†	13,047 ± 3,750*
Aortic regurgitation	11	58 ± 15*	7:4	75 ± 14*	8 ± 12	11,493 ± 2,976*
Normal subjects	9	25 ± 3	9:0	57 ± 7	—	6,292 ± 544

HR, Heart rate; *AoV*, aortic valve; *RPP*, rate-pressure product (heart rate × [systolic blood pressure + mean AoV gradient]); *LVEF*, left ventricular ejection fraction; *LVEDD*, left ventricular end-diastolic dimension; *LV*, left ventricular; *k* min^{-1}, global C-11 acetate clearance rate constant.
*$p < 0.05$ compared with normal subjects.
†$p < 0.05$ compared with patients with predominant aortic regurgitation.

Table III. Characteristics of patients and normal subjects by left ventricular ejection fraction subgroup

Group	*N*	*Age (yr)*	*AS:AR*	*HR (beats/min)*	*Mean AoV gradient (mm Hg)*	*Gradient-corrected RPP (beats/min. mm Hg)*	*LVEDD* (normal 37-57 mm)*
LVEF ≥ 50%	15	62 ± 13†	8:7	68 ± 11‡	32 ± 29	11,529 ± 2,107†,‡	58 ± 10
LVEF < 50%	5	72 ± 7†	3:2	93 ± 20†	33 ± 12	15,477 ± 5,168	59 ± 12
Normal subjects	9	25 ± 3	0:0	57 ± 7	—	6,292 ± 544	—

HR, Heart rate; *AoV*, aortic valve; *RPP*, rate-pressure product (heart rate × [systolic blood pressure + mean AoV gradient]); *LVEF*, left ventricular ejection fraction; *LVEDD*, left ventricular end-diastolic dimension; *LV*, left ventricular; *k* min^{-1}, global C-11 acetate clearance rate constant.
*Echocardiographic data from 12 patients with LVEF ≥50% and four patients with LVEF >50%.
†$p < 0.05$ compared with normal subjects.
‡$p < 0.05$ compared with patients with LVEF <50%.

with predominant aortic regurgitation compared with 0.050 ± 0.004 min^{-1} in normal subjects ($p < 0.05$) (Fig. 3 and Table II). Although gradient-corrected rate-pressure products were slightly higher in patients with aortic stenosis than in patients with aortic regurgitation, C-11 acetate clearance rate constants were slightly lower on average in the group with aortic stenosis. Although neither of these trends reached statistical significance, these data emphasize that factors other than the rate-pressure product may affect myocardial oxygen consumption.

Regional C-11 acetate clearance rate constants. In normal subjects C-11 acetate clearance rate constants were on average higher in the septal region of interest than in the lateral wall. This difference did not reach statistical significance. In contrast, C-11 clearance rate constants were significantly higher in the lateral wall than in the septum in patients with pathologically loaded ventricles ($p < 0.05$), although the difference was small averaging 8%. These data are presented in Fig. 4.

Comparison of C-11 acetate clearance with parameters of left ventricular oxygen demand. If results of all studies (patients and normal subjects) were included, there was a significant correlation between global C-11 acetate clearance rate constants and the gradient-corrected rate-pressure product (Fig. 5). Exclusion of patients with volume overload as a result of aortic regurgitation improved the correlation between global C-11 acetate clearance rate constants and the gradient-corrected rate-pressure product and increased the slope of the regression. Indeed whereas global C-11 acetate clearance rate constants in patients with aortic stenosis were significantly correlated with the gradient-corrected rate-pressure product values ($r = 0.79$, $p < 0.005$), no significant correlation was found between these parameters in the 11 patients with predominant aortic regurgitation. Similarly there was a significant but weaker correlation between C-11 acetate clearance rate constants and heart rate for all studies ($r = 0.63$, $p < 0.005$) and in patients with aortic stenosis ($r = 0.69$, $p < 0.05$), but not in patients with aortic regurgitation as their dominant valve lesion.

In the 18 patients and four normal subjects from whom echocardiographic findings were available, C-11 acetate clearance rate constants were loosely but significantly correlated with the mean wall stress index ($r = 0.64$, $p < 0.005$). C-11 acetate clearance rate constants were more strongly correlated with the product of heart rate and mean wall stress index ($r = 0.73$, $p < 0.001$), consistent with the importance

LVEDD (normal 37-57 mm)	*Echo LVEF (%)*	*Mean LV wall stress index*	*LV mass (gm)*	*k min^{-1}*	*k/RPP × 100,000*
51 ± 6†	53 ± 16	278 ± 86	322 ± 88	0.069 ± 017*	0.54 ± 0.09*
65 ± 7	50 ± 17	292 ± 76	358 ± 136	0.072 ± 010*	0.65 ± 0.19
—	—	184 ± 15	—	0.050 ± 004	0.81 ± 0.11

Echo LVEF (%)	*Mean LV wall stress index**	*LV mass (gm)*	*k min^{-1}*	*k/RPP ×1,000,000*	*k/HR-stress index product ×1,000,000*
59 ± 7‡	255 ± 74	366 ± 122	0.070 ± 0.011†	6.3 ± 1.7†	4.3 ± 0.9‡
30 ± 16	355 ± 64†	303 ± 100	0.075 ± 021†	5.0 ± 0.7†	2.3 ± 0.4†
—	183 ± 15	—	0.050 ± .004	8.1 ± 1.1	4.6 ± 0.8

of heart rate as an index of myocardial oxygen demand.[10] As with the comparisons between C-11 acetate clearance rate constants and rate-pressure product and with heart rate, a strong correlation was observed between C-11 acetate clearance rate constants and the heart rate–wall stress index products for the nine analyzed patients with aortic stenosis ($r = 0.89$, $p < 0.005$) (Fig. 6), but no significant correlation was found in the nine patients with aortic regurgitation.

Assuming that C-11 acetate clearance rate constants reflect myocardial oxygen consumption, the relationship between C-11 acetate clearance rate constants and noninvasive parameters of oxygen demand in individual subjects and patients should be similar unless that parameter inaccurately reflects true oxygen demand in the loaded heart or oxygen supply and demand are uncoupled because of ischemia. Accordingly C-11 acetate clearance rate constants were normalized for gradient-corrected rate-pressure product in all individual studies. Normalized C-11 clearance rate constants were significantly lower for patients with aortic stenosis than for normal subjects (Table II). Normalized C-11 clearance rate constants in patients with aortic regurgitation were higher than in patients with aortic stenosis but lower than in normal subjects. These differences did not reach statistical significance. These data suggest, however, that the gradient-corrected rate-pressure product may overestimate oxygen demand in chronic overload of the left ventricle and particularly in aortic stenosis. Possible mechanisms include myocardial adaptation to chronic loading by left ventricular hypertrophy, which would tend to decrease wall stress[18, 19] and hence oxygen demand[13] at any given pressure load, or as an alternative depressed myocardial contractility, which would cause a relative decrease in oxygen consumption with respect to loading conditions.[10] The former possibility is supported by the observation that C-11 acetate clearance rate constants normalized for the left ventricular wall stress index were on average no higher in aortic stenosis than in aortic regurgitation ($2.62 \pm 0.7 \times 10^{-4}$ vs $2.61 \pm 0.66 \times 10^{-4}$, p = NS).

Comparison of C-11 acetate clearance rate constants in patients with and without low left ventricular ejection fractions. The role of depressed myocardial contractility in association with aortic valve disease could not be directly assessed in the absence of measured parameters of contractility but was indirectly evaluated by comparing C-11 acetate clearance rate constants in patients with and without reduced left ventricular ejection fractions as determined by two-dimensional echocardiography in 20 patients (Table III). Because most patients (n = 15) had well-preserved ejection fractions and the proportion of patients with aortic stenosis and aortic regurgitation in each group was not significantly different, all patients were combined for this analysis.

C-11 acetate clearance rate constants were higher in patients with left ventricular ejection fractions <50% than in those with ejection fractions ≥50%

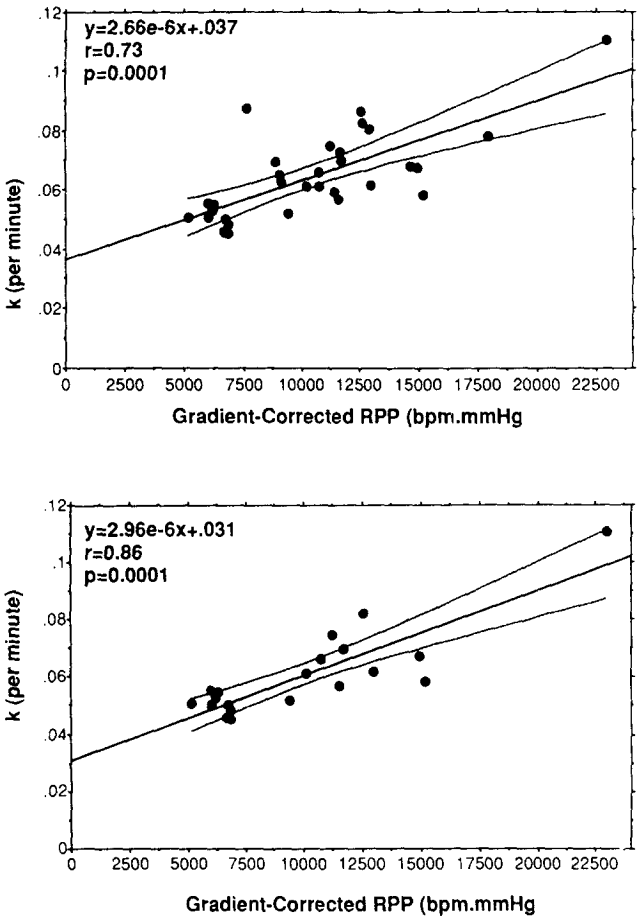


Fig. 5. *Top*, Plot of global C-11 clearance rate constants *(k per minute)* versus rate-pressure product corrected for mean aortic valve gradient determined by Doppler echocardiography in patients with aortic stenosis *(Gradient-corrected RPP)*. Significant correlation was noted, although considerable scatter around regression line was observed. *Bottom*, Exclusion of patients with aortic regurgitation from regression between C-11 acetate clearance rate constants and gradient-corrected rate-pressure product improved correlation between these parameters (95% confidence bands of the mean value of k min^{-1} are displayed).

and normal subjects (Fig. 7 and Table III). However, gradient-corrected rate-pressure products and mean left ventricular wall stress indexes were also higher in patients with depressed ejection fractions and likely account for these differences. C-11 acetate clearance rate constants normalized for gradient-corrected rate-pressure products and for mean left ventricular wall stress tended to be lower in patients with low left ventricular ejection fractions than for patients with preserved left ventricular systolic function. C-11 acetate clearance rate constants normalized for the product of heart rate and mean stress index were not significantly different in patients with normal left ventricular ejection fractions compared with normal subjects. However, C-11 acetate clearance rate constants normalized for the product of heart rate and mean stress index were significantly lower in patients with low ejection fractions than in patients with normal ejection fractions and normal subjects ($2.3 \pm 0.4 \times 10^{-6}$ vs $4.3 \pm 0.9 \times 10^{-6}$ and $4.6 \pm 0.8 \times 10^{-6}$, $p < 0.05$). These data suggest that depressed contractility may partially account for the lower than expected C-11 acetate clearance rate constants based on noninvasive parameters of myocardial oxygen demand.

Besides the global changes observed in C-11 acetate clearance in patients with impaired left ventricular systolic function, the ratio of septal to lateral wall C-11 clearance rate constants was significantly lower in patients with low ejection fractions compared to both normal subjects and patients with normal ejection fractions (0.84 ± 0.09 vs 1.03 ± 0.16 and 0.95 ± 0.07, $p < 0.05$).

DISCUSSION

Myocardial oxidative metabolism represents the cellular expression of the diverse effects of load-independent and load-dependent determinants of myocardial oxygen demand. In the normal heart, simple parameters such as the rate-pressure product are highly correlated with myocardial oxygen consumption.[8-10] However, changes in ventricular geometry and contractility in the pathologically loaded heart may affect the relationship between myocardial oxygen consumption and indirect indexes of oxygen demand. This may limit the utility of such measurements in characterizing myocardial oxidative metabolism under these conditions. The ability to directly assess global and regional oxygen consumption without the need for invasive procedures would have obvious appeal in this setting. Quantification of C-11 acetate clearance kinetics by means of positron emission tomography potentially provides such evaluation,[4, 5, 11] theoretically reflecting all determinants of myocardial oxygen demand including heart rate, wall stress, and contractility.

C-11 acetate clearance kinetics in the pathologically loaded heart. As expected, under the conditions of increased ventricular loading observed in patients in this study, clearance of C-11 activity from the myocardium in patients with aortic stenosis or regurgitation was faster than in the hearts of normal subjects, suggesting increased myocardial oxygen consumption (Fig. 3). Although this is further supporting evidence that C-11 acetate traces myocardial oxidative metabolism, the wide variation in C-11 acetate clearance rate constants in patients with pressure- or

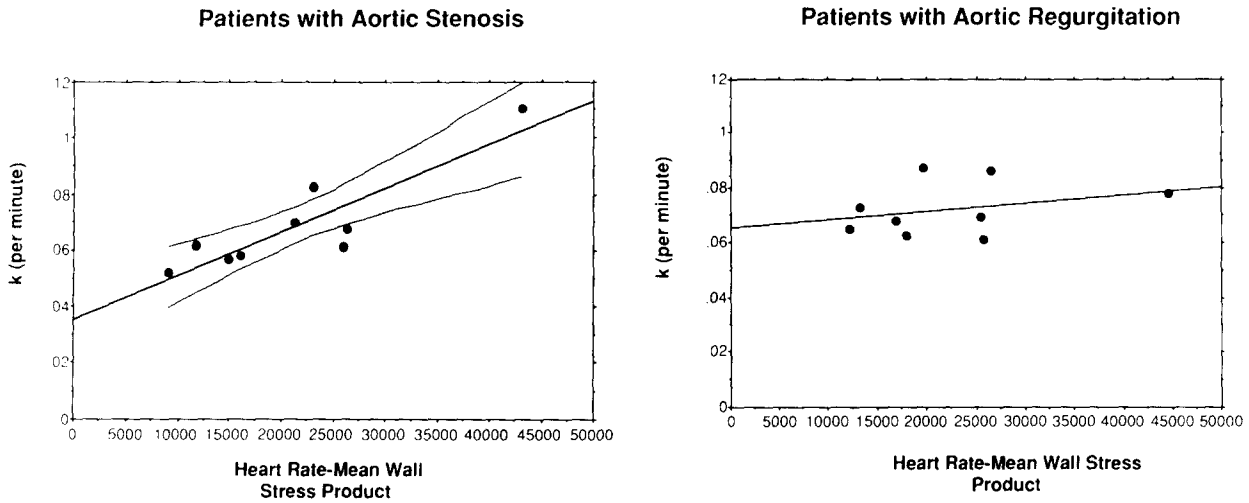


Fig. 6. Plot of global C-11 clearance rate constants versus product of heart rate and mean left ventricular wall stress index determined by echocardiography in nine patients with predominant aortic stenosis *(left)* and nine patients with predominant aortic regurgitation *(right)*. Significant correlation was noted in patients with aortic stenosis (for whom 95% confidence bands of true mean value of k min^{-1} are displayed), but no significant correlation was noted in patients with aortic regurgitation.

volume-loaded hearts and the overlap in patients with and without evidence of contractile dysfunction (Fig. 7) suggest that C-11 acetate clearance rate constants provide limited useful information when viewed in isolation. Inasmuch as myocardial oxygen consumption is closely linked to heart rate and pressure work, normalization of C-11 acetate kinetics to predictors of cardiac oxygen demand may provide identification of work-independent alterations of C-11 acetate kinetics in patients with valvular heart disease.

Relationship of C-11 acetate clearance to noninvasive indexes of myocardial oxygen demand. Although there was a significant correlation ($r = 0.73$, $p = 0.0001$) between C-11 clearance rate constants and the gradient-corrected rate-pressure product, considerable scatter around the line of identity was observed (Fig. 5). This was in marked contrast to the close correlation observed between these parameters in normal subjects studied over a similar range of rate-pressure products attained at rest and during exercise in a study by Armbrecht et al.[6] and at rest and during dobutamine infusion in a study by Henes et al.[7] In both of these studies, correlation coefficients of more than 0.9 were found. This discrepancy may be explained by the technical difficulties of assessing "true" oxygen demand in patients with valvular heart disease. Although echocardiography was performed within hours of the positron emission tomographic study in the majority of patients, small changes in hemodynamic status and heart rate between the studies may have contributed to increased data scatter. On the other hand, rate-pressure product may be less predictive of myocardial oxygen demand in patients with valvular heart disease and C-11 acetate kinetics may more accurately reflect oxygen consumption.

These patients are characterized by varying degrees of left ventricular hypertrophy, dilatation, and function, which are known to affect load independent of myocardial oxygen consumption. Because C-11 acetate kinetics probably reflect all determinants of oxygen demand, changes in contractility or wall stress would alter the relationship between oxygen consumption and rate-pressure product. Patients with aortic regurgitation had a larger range of cavity sizes and left ventricular ejection fractions than patients with aortic stenosis or normal subjects (Table I), thus explaining the lack of significant correlation between C-11 acetate clearance rate constants and the rate-pressure product in the patients.

Independent of the correlation of individual data, the average C-11 clearance rate constants normalized for gradient-corrected rate-pressure product were lower in patients with pressure- or volume-loaded left ventricles than in our normal subjects. A possible explanation for this finding is that myocardial adaptation by hypertrophy may reduce myocardial oxygen demand under conditions of chronically increased loading by reducing wall stress as suggested by results of previous experimental studies.[18] This possibility is supported by the observation that C-11 ac-

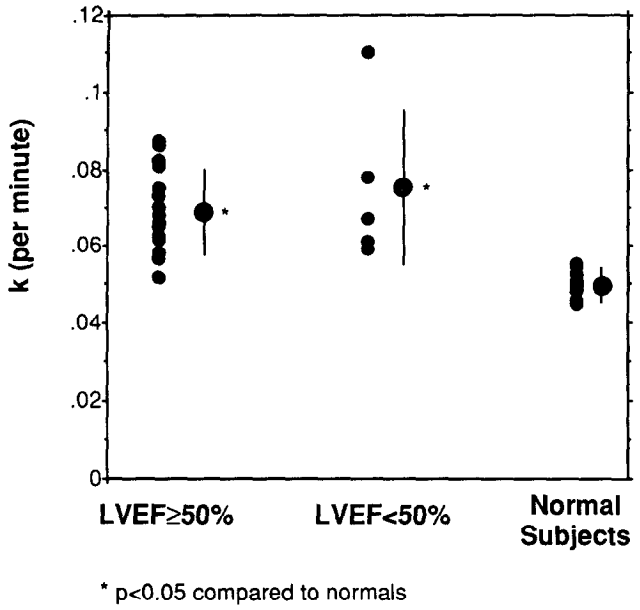


Fig. 7. C-11 acetate clearance rate constants are presented for patients with normal and low left ventricular ejection fractions *(LVEF)* and for normal subjects. Mean C-11 acetate clearance rate constants *(hatched circles)* were slightly higher in patients with LVEF <50%, but there was considerable overlap between patients with normal and low left ventricular ejection fractions.

etate clearance rate constants normalized for left ventricular wall stress were not significantly different and were in fact slightly higher in patients with aortic stenosis compared to those with aortic regurgitation, whereas C-11 clearance rate constants normalized for rate-pressure product were lower in aortic stenosis than in aortic regurgitation. Furthermore, in 15 patients with normal left ventricular ejection fractions, C-11 acetate clearance rate constants normalized for either mean wall stress index or the product of heart rate and the mean wall stress index were not significantly different from values in normal subjects.

An alternative explanation for apparently decreased myocardial oxygen consumption relative to that expected based on rate-pressure product would be decreased contractility. Since neither rate-pressure product nor wall stress measurements assess contractility, they could theoretically overestimate oxygen consumption in the failing heart. In keeping with this hypothesis, C-11 acetate clearance rate constants normalized for both gradient-corrected rate-pressure product and mean wall stress index were lower in patients with low left ventricular ejection fractions than in patients with preserved ejection fractions, although neither reached statistical significance. However, C-11 acetate clearance rate constants normalized for the product of heart rate and mean left ventricular wall stress index were significantly lower in the five patients with ejection fractions <50% than in patients with normal ejection fractions and also in comparison to normal subjects ($2.3 \pm 0.4 \times 10^{-6}$ vs $4.3 \pm 0.9 \times 10^{-6}$ and $4.6 \pm 0.8 \times 10^{-6}$, $p < 0.05$). Additional studies that use invasive measurement of indexes reflecting the contractile state of the myocardium are required to assess the relationship between C-11 acetate kinetics and myocardial contractility. Initial results of animal studies suggest that changes in myocardial contractility affect cardiac efficiency to a considerable extent, as defined by C-11 acetate kinetics and cardiac work.[20]

Regional C-11 acetate clearance variation with increased global loading. C-11 acetate clearance kinetics provide a unique assessment of regional myocardial oxidative metabolism.[11] In contrast to normal subjects who had marginally higher C-11 acetate clearance rate constants in the septum, both pressure and volume overload were associated with relatively increased C-11 acetate clearance rate constants in the free wall compared to the ventricular septum ($p < 0.05$). The findings in normal subjects are consistent with our previous observations in normal subjects in which more elaborate regional analysis algorithms were used, which showed a small but significant inhomogeneity of C-11 acetate clearance rate constants with relatively increased septal values.[11] Our data suggest that although there is increased loading of the entire ventricle, there may be regional changes in the distribution of myocardial oxidative metabolism, which may reflect either variation in wall stress or regional changes in contractility. The ratio of septal to lateral wall C-11 acetate clearance rate constants was significantly lower in patients with low left ventricular ejection fractions than in normal subjects and patients with normal ejection fractions. Whether such changes in regional oxidative metabolism are useful in determining disease progression requires further definition.

Clinical implications. Treatment of patients with chronic pressure or volume overload of the left ventricle is generally predicated by symptoms. However, there are many clinical settings involving pathologic loading of the left ventricle as a result of valvular disease in which the optimal timing and type of therapeutic intervention remain poorly defined.[21-27] Whereas it is clear that the prognosis after valve replacement is generally good when preoperative ejection fraction is maintained,[28-32] prediction of postoperative function and hence selection of patients for surgery remains problematic in patients with im-

paired left ventricular contractile function.[33] The state of myocardial contractility appears to be a crucial factor in determining the therapeutic outcome of valve replacement in such patients[23, 26, 27, 33-35] but can be difficult to assess in patients with chronic myocardial overload.[23, 36-38]

Conceptually, direct measurement of myocardial oxygen consumption with C-11 acetate combined with determination of load-dependent parameters of myocardial oxygen demand could provide a sophisticated experimental method to derive information regarding the status of load-independent determinants of oxygen demand or myocardial efficiency as we have demonstrated in animal studies.[20] Validation of this approach in humans will require determination of the regression between C-11 acetate clearance rate constants and true myocardial oxygen consumption in the human heart with simultaneous evaluation of load-dependent and load-independent parameters of oxygen demand and external cardiac work.

Limitations. C-11 acetate kinetics have been validated as a marker of myocardial oxygen consumption primarily in normal canine and human hearts. C-11 acetate metabolism may be altered in the failing heart and thus the relationship between C-11 clearance kinetics and oxygen consumption differs from that in the normal myocardium. Results of recent studies indicate that C-11 acetate equilibrates with intermediates of the tricarboxylic acid cycle such as glutamate.[39, 40] Changes in the glutamate tissue concentration therefore may affect the rate of C-11 clearance in the form of C-11 carbon dioxide. Experiments in the acutely ischemic myocardium have demonstrated a maintained relationship between the C-11 clearance rate and MVO_2, but no data comparing C-11 acetate kinetics and directly measured oxygen consumption are available in the failing human heart.[6, 41]

The use of the left ventricular ejection fraction to stratify patients into subgroups presumed to have normal and abnormal contractile function is not ideal, since this parameter does not reflect contractility alone. As can be seen from mean data for patients with and without normal left ventricular ejection fractions (Table III), wall stress tended to be higher in those with a low ejection fraction whereas left ventricular mass tended to be lower. Such features raise the possibility that afterload mismatch[37] may be an important factor in the depressed ejection fraction in these patients rather than depressed contractility. Direct determination of myocardial contractility was not performed in this study, and the presence of depressed contractility as a cause of the relatively reduced C-11 acetate clearance rate constants compared with rate-pressure product and wall stress in patients with low ejection fractions is conjectural but warrants further studies with invasive measurements of contractility.

Conclusions. Positron emission tomography in combination with C-11 acetate provides a unique noninvasive characterization of both regional and global myocardial oxidative metabolism. We have applied this approach to the investigation of patients with aortic valve disease. The data presented suggest that C-11 clearance kinetics after administration of C-11 acetate reflect myocardial oxygen consumption in the pressure- or volume-loaded heart, just as they do in the normal heart.[4-7] However, absolute C-11 clearance rate constant values in a given patient appear to offer relatively little incremental information compared to more readily obtained noninvasive parameters of myocardial oxygen demand, since these values generally reflect loading of the ventricle. If, however, accurate characterization of load-dependent determinants of myocardial oxygen demand were obtained and then compared with myocardial oxygen consumption, as reflected by C-11 acetate clearance, it might be possible to assess the status of load-independent determinants of oxygen demand. Serial comparison of C-11 acetate clearance rate constants with parameters of oxygen demand may provide a means to noninvasively define and follow metabolic performance in the setting of pathologic volume or pressure loading.

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