

¹¹C-Acetate Clearance as an Index of Oxygen Consumption of the Right Myocardium in Idiopathic Pulmonary Arterial Hypertension: A Validation Study Using ¹⁵O-Labeled Tracers and PET

Yeun Ying Wong^{1,2}, Pieter Raijmakers³, Jasmijn van Campen¹, Willem J. van der Laarse², Paul Knaapen⁴, Mark Lubberink³, Gerrina Ruiter^{1,2}, Anton Vonk Noordegraaf¹, and Adriaan A. Lammertsma³

¹Department of Pulmonology, VU University Medical Center, Amsterdam, The Netherlands; ²Department of Physiology, VU University Medical Center, Amsterdam, The Netherlands; ³Department of Nuclear Medicine and PET Research, VU University Medical Center, Amsterdam, The Netherlands; and ⁴Department of Cardiology, Institute of Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands

Idiopathic pulmonary arterial hypertension (IPAH) results in increased right ventricular (RV) workload and oxygen demand. It has been shown that myocardial oxygen consumption (MVO₂) of the hypertrophied right ventricle of IPAH patients can be measured using PET and ¹⁵O-labeled tracers. This method is, however, not very suitable for routine clinical practice. The purpose of the present study was to assess whether MVO₂ can also be determined in the right ventricle of IPAH patients from the clearance of ¹¹C-acetate, a simple method that is in use for MVO₂ measurements of the left myocardium. **Methods:** Seventeen of 26 IPAH patients performed the total PET study. Nine other patients were scanned only for ¹¹C-acetate. ¹⁵O-H₂O, ¹⁵O-O₂, and ¹⁵O-CO scans were used to derive RV flow, oxygen extraction fraction, and blood volume, respectively, from which RV MVO₂ was calculated. The rate of clearance determined by monoexponential curve fitting (K_{mono}) and the efflux rate constant k_2 were derived from the ¹¹C-acetate scan. The RV rate-pressure product was also determined by means of right heart catheterization, as an index of the RV MVO₂, and was calculated as the product of systolic pulmonary artery pressure and heart rate. **Results:** Both ¹¹C-acetate clearance rates, K_{mono} ($R^2 = 0.41$, $P = 0.006$) and k_2 ($R^2 = 0.45$, $P = 0.003$), correlated with RV MVO₂. They also correlated with RV rate-pressure product (K_{mono} , $R^2 = 0.41$, $P = 0.0005$; k_2 , $R^2 = 0.48$, $P < 0.0001$). **Conclusion:** ¹¹C-acetate clearance rates correlated moderately with quantitative RV MVO₂ measurements in IPAH. Therefore, ¹¹C-acetate PET can be used only as an index of RV oxidative metabolism in IPAH patients.

Key Words: ¹¹C-acetate; ¹⁵O; PET; monoexponential curve fitting; pulmonary arterial hypertension; right ventricle; myocardial oxygen consumption; rate-pressure product

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For correspondence or reprints contact: Adriaan A. Lammertsma, Department of Pulmonology, VU University Medical Center, Van der Boerhorststraat 7, 1081 BT Amsterdam, the Netherlands.

E-mail: aa.lammertsma@vumc.nl

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The oxygen consumption (MVO₂) of the normal right myocardium is less than that of the left heart as a result of a lower afterload (1). In idiopathic pulmonary arterial hypertension (IPAH), elevated pulmonary vascular resistance causes right ventricular (RV) hypertrophy and ultimately fatal RV failure. To gain insight on the pathophysiology of reduced pump function in the failing heart, quantification of MVO₂ is important. A noninvasive method using state-of-the-art PET and ¹⁵O-labeled tracers has been validated as a means to measure MVO₂ accurately (2–4). Using this method, it was recently demonstrated that the right ventricle consumes more oxygen in patients with severe IPAH than in those with mild PAH for generating similar RV power output (5). This method is, however, extensive and time-consuming (4), requiring 3 consecutive PET scans (¹⁵O-H₂O, ¹⁵O-CO, and ¹⁵O-O₂) and an on-site cyclotron to produce the short-lived ¹⁵O tracers (6). PET using ¹¹C-acetate has been proposed as a more practical method to estimate MVO₂. With ¹¹C-acetate being the precursor of acetyl-CoA in the tricarboxylic acid cycle, the rate of ¹¹C-acetate clearance determined by monoexponential curve fitting (K_{mono}) is closely related to MVO₂ of the left heart (4,7–10).

It is not known, however, whether ¹¹C-acetate can also be used to estimate RV MVO₂. If so, the use of ¹¹C-acetate PET would make future studies on oxidation in the failing right ventricle more convenient. Recently it was shown for the left ventricle that a single-compartment-model efflux rate constant (k_2) correlated better with the rate-pressure product (RPP), a noninvasive index of myocardial oxygen demand, than K_{mono} (7). However, studies performing a direct comparison of MVO₂ and different methods of ¹¹C-acetate clearance determination in the human right ventricle are lacking. Therefore, the purpose of the present study was to assess whether the RV clearance rates of ¹¹C-acetate correlate with RV RPP and the MVO₂ (in standard units) of the hypertrophied right ventricle in IPAH patients. The MVO₂ data have been presented previously to determine RV efficiency (5,11,12).

MATERIALS AND METHODS

Subjects

Twenty-six patients were included between April 2008 and November 2011. All patients had IPAH according to World Health

Organization group I criteria with either New York Heart Association (NYHA) functional classification II or III–IV (13). The study was approved by the Medical Ethics Review Committee of the VU University Medical Center. All patients signed a written informed consent form. Seventeen patients had paired determinations of MVO_2 obtained from ^{15}O -labeled tracers and ^{11}C -acetate clearance. For the other 9 patients, only an ^{11}C -acetate scan was available and they were included in the correlation between ^{11}C -acetate clearance rate and RPP. They did not undergo ^{15}O scans because of logistic reasons ($n = 3$) or because they participated in another PET study ($n = 6$). All patients had clinically stable IPAH under optimal treatment, except for 2 patients who were newly diagnosed with IPAH NYHA class III and were included before treatment. The change in 6-min walk distance was less than 10% within 6 mo before inclusion. During the study, PAH therapy was continued, which was either single or combination treatment with intravenous prostacyclin, endothelin receptor antagonist, or phosphodiesterase-type 5 inhibition. Exclusion criteria were cardiovascular disease, atrial fibrillation, and anemia (hemoglobin < 12 g/dL). A control group was not included because the normal right myocardium is too thin to be measured reliably using PET and ^{15}O tracers.

PET Scanning Protocol

Patients underwent the scanning protocol within 1 d, consisting of consecutively a ^{15}O - H_2O , ^{15}O - O_2 , ^{15}O -CO, and ^{11}C -acetate scan under resting conditions (ECAT EXACT HR+; Siemens/CTI) or a hybrid PET/CT scan (Gemini TF 64; Philips Healthcare). After a light breakfast 2 h before the first scan, patients fasted until the end of the scanning protocol. The ^{15}O scan protocol has been described previously (5,11,12), and a brief description can be found in the supplemental material (available online at <http://jnm.snmjournals.org>). After the last ^{15}O PET scan and a 2-h break, the patients were repositioned on the scanner bed for a 48-min dynamic emission scan (29 frames) after an intravenous injection of 300 MBq of ^{11}C -acetate in 3-dimensional acquisition mode (7). Six patients had a slightly modified imaging protocol (with the hybrid PET/CT scanner) using a dose of 370 MBq of ^{11}C -acetate followed by a 3-dimensional 50-min dynamic PET acquisition (36 frames). This was followed by a low-dose CT scan (35 mAs) for attenuation correction. Systemic blood pressure, peripheral saturation, and heart rate were monitored at set intervals during the protocol.

Data Analysis

Analysis of ^{15}O data has been described in detail previously (5,12,14), and a brief description can also be found in the supplemental material. For the present study, the volume of interest was the RV

free wall, excluding the septum. ^{11}C -acetate data analysis also has been described previously (7). In brief, a summed image (from 3 to 5 min after injection) was used to reslice the dynamic scan and to define regions of interest for the RV free wall. The ^{11}C -acetate time-activity curve was analyzed by fitting the clearance phase to a single exponential, providing the clearance rate K_{mono} (min^{-1}) (7). In addition, the entire ^{11}C -acetate time-activity curve was fitted to a single-tissue-compartment model as proposed by Van den Hoff et al. (15). This model takes into account both influx and efflux of the tracer and the rate constant k_2 (min^{-1}), reflecting the oxidative flux through the tricarboxylic acid cycle (7). In this analysis, corrections were applied for both spillover from blood to myocardium and partial-volume effects (7). In addition, data reported by Sun et al. (8) were used to apply an average metabolite correction to the ^{11}C -acetate arterial input function.

RV Hemodynamics

RV hemodynamics were obtained during right heart catheterization and cardiac MR imaging within 1 wk of the PET study when possible, according to procedures described previously (16). In 3 subjects, for logistic or personal reasons, the interval was 20–55 d between right heart catheterization and PET and 20–36 d between cardiac MR imaging and PET. Because these patients had stable IPAH under drug treatment, the interval was considered acceptable (12). RV RPP, commonly used as an index of myocardial oxygen demand, is defined as the product of systolic pulmonary arterial pressure and heart rate (5). Stroke work index was calculated as the product of stroke volume index and (mean pulmonary arterial pressure – mean right atrial pressure) (17).

Some fluctuation in pulmonary arterial pressure and heart rate may be present within hours to days and will contribute to the variance in the relationships presented in Figures 1 and 2 and Supplemental Figure 1. It can be assumed, however, that variability of pulmonary arterial pressure was relatively small within the study window, given the significant correlation between systolic pulmonary arterial pressure measured 1 d before the PET study and MVO_2 determined during the PET study (5). Within the study period, mean heart rate varied between 60 and 105 bpm, based on 3 separate measurements in 23 of the 26 IPAH patients. The median coefficient of variation of heart rate in these patients was small (4.8%). In addition, heart rate variation did not affect the significance of correlations with RPP.

Statistical Analyses

All results are expressed as mean \pm SD, with ranges given in the tables. Linear regression analysis was used (Prism 5 for Windows; GraphPad Software). A P value of less than 0.05 was considered statistically significant.

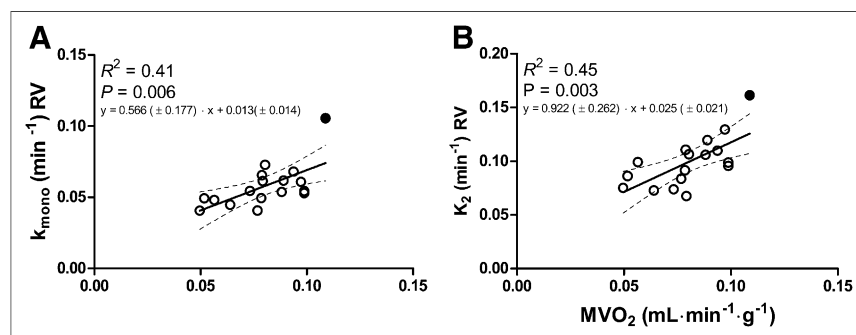


FIGURE 1. (A) K_{mono} and (B) tissue-to-plasma efflux rate constant of ^{11}C -acetate as function of RV MVO_2 . Best fit is represented by thick line. Thinner broken lines represent 95% confidence interval. Equation of regression line is shown within panels (\pm SE). $n = 17$ IPAH patients. Treatment-naïve patient is shown as black dot.

RESULTS

In total, 26 patients (25 women and 1 man) were included. Two of the patients were newly diagnosed with NYHA functional classification III–IV IPAH and were treatment-naïve at the time of inclusion. As such, the study population comprised severely ill patients on the one hand and clinically stable patients on the other hand, resulting in heterogeneity of patient characteristics and hemodynamics (e.g., 6-min walk distance, cardiac output, and RV ejection fraction) (Table 1). The age range was also large. Table 2 summarizes RPP and PET-derived

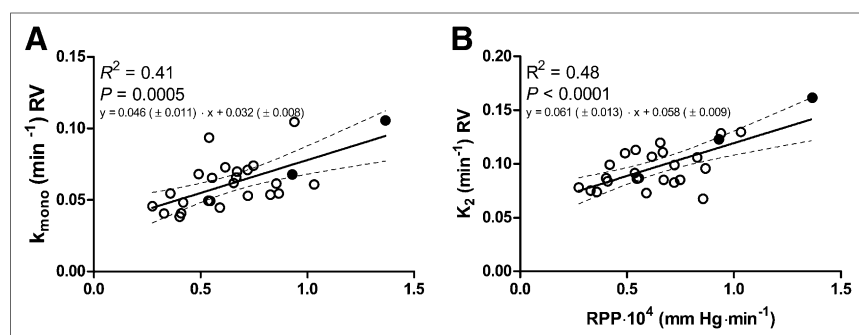


FIGURE 2. (A) K_{mono} and (B) tissue-to-plasma efflux rate constant of ^{11}C -acetate as function of RPP. Best fit is represented by thick line. Thinner broken lines represent 95% confidence interval. Equation of regression line is shown within panels (\pm SE). $n = 26$ IPAH patients. Two treatment-naïve patients are shown as black dots.

measures of RV MVO_2 . There was a significant correlation between K_{mono} and MVO_2 (Fig. 1A). A similar correlation was found between k_2 and RV MVO_2 (Fig. 1B). K_{mono} and k_2 also correlated significantly with RPP (Figs. 2A and 2B). There was no significant correlation between stroke work index and either K_{mono} or k_2 ($R^2 = 0.06$, $P = 0.22$, and $R^2 = 0.11$, $P = 0.11$, respectively).

DISCUSSION

The main findings of this study are that the rate of clearance of ^{11}C -acetate correlates with both MVO_2 , as measured using PET and ^{15}O -labeled tracers, and RPP in the hypertrophied RV wall of IPAH patients, with little difference between K_{mono} and k_2 .

The significant correlation between ^{11}C -acetate clearance rate K_{mono} and MVO_2 in the hypertrophied right ventricle is in agreement with previous studies on the left myocardium in both control subjects ($r = 0.71$, $P = 0.02$) and patients with chronic myocardial infarction ($r = 0.89$, $P < 0.001$) (4,7–10).

Little is known about the rate of clearance of ^{11}C -acetate from the normal right ventricle. Two previous studies reported a mean K_{mono} value of $0.040 \pm 0.003 \text{ min}^{-1}$ and $0.043 \pm 0.009 \text{ min}^{-1}$ in the normal right ventricle of control subjects, versus patients with heart failure or dilated cardiomyopathy, who had a mean K_{mono} of $0.055 \pm 0.005 \text{ min}^{-1}$ and $0.051 \pm 0.007 \text{ min}^{-1}$, respectively (9,18). It has been proposed that the higher clearance rate of ^{11}C -acetate in these patient groups with left heart failure is likely

due to an increased RV workload in left ventricular (LV) heart failure—that is, due to secondary pulmonary hypertension (9). In addition, Ukkonen et al. demonstrated in patients with congestive heart failure that higher oxidative metabolism in the right ventricle relative to that in the left ventricle was related to an increased ventilatory drive, reflected by the slope of increase of ventilation relative to carbon dioxide production, which in turn was associated with increased mortality in these patients (19). Therapeutic interventions for LV heart failure, such as exercise training in dilated cardiomyopathy patients, were shown to also have a positive effect on RV oxidative metabolism, with a significant reduction of RV K_{mono} (20).

Similarly, cardiac resynchronization therapy in patients with idiopathic dilated cardiomyopathy also enhanced RV oxidative metabolism and metabolic reserve during stress (21). Despite differences in patient population and methodology, RV K_{mono} values in the present IPAH patients are in agreement with these previous studies, reflecting increased oxygen demand of the right myocardium as a result of increased afterload in IPAH.

Previously, a significant correlation between MVO_2 and RPP of the total RV wall ($R^2 = 0.55$, $P = 0.0004$) in IPAH patients was demonstrated (5).

Caution is needed when the ^{11}C -acetate clearance rate is used for absolute quantification of MVO_2 . Clearance of ^{11}C -acetate can be affected by metabolic shifts in remodeling RV myocardium in IPAH, because in the failing myocardium, other processes may result in an uncoupling between MVO_2 and adenosine diphosphate phosphorylation—for example, by increased production of NO and reactive oxygen species (22). The assumed tight coupling of the rate of clearance of acetate via the tricarboxylic acid-to-oxygen use in the respiratory chain, as found in the normal heart, may be absent in diseased myocardium. In such cases, ^{11}C -acetate clearance may severely overestimate adenosine triphosphate re-synthesis and underestimate MVO_2 . On the other hand, earlier studies with healthy volunteers and experimental canine studies showed that changes in the availability of myocardial metabolic substrates or ischemia, without changes in hemodynamics, did not

TABLE 1
Clinical Characteristics and Hemodynamics at Time of Inclusion

Characteristic	Mean \pm SD ($n = 26$)	Range
Age (y)	48 \pm 18	26–73
Mean right atrial pressure (mm Hg)	8 \pm 6	0–27
Pulmonary capillary wedge pressure (mm Hg)	9 \pm 3	2–14
Mean pulmonary arterial pressure (mm Hg)	52 \pm 14	34–91
Cardiac output (L·min ⁻¹)	5.1 \pm 1.3	2.8–7.6
Heart rate (bpm)	77 \pm 14	56–102
Pulmonary vascular resistance (dyne·s·cm ⁻⁵)	704 \pm 317	313–1,419
Stroke work index (mm Hg·mL·m ⁻²)	1,258 \pm 428	325–2,063
RV ejection fraction (%)	33 \pm 17	11–66
6-min walk distance (m)	448 \pm 125	93–637

Eleven patients were in NYHA class II and 15 were in class III.

TABLE 2
RPP and PET-Derived Measures of RV MVO₂

Parameter	Mean ± SD (n = 26)	Range
RV RPP (mm Hg·bpm)	6,567 ± 2,481	2,744–13,668
MVO ₂ (mL·min ⁻¹ ·g ⁻¹ right myocardium) (n = 17)	0.08 ± 0.02	0.05–0.11
K _{mono} (min ⁻¹)	0.062 ± 0.018	0.038–0.106
k ₂ (min ⁻¹)	0.098 ± 0.022	0.068–0.161

affect LV ¹¹C-acetate kinetics, with similar relationships between K_{mono} and either MVO₂ or RPP at normal baseline conditions (23–25).

In the left ventricle of healthy volunteers, Timmer et al. (7) found an improved correlation between LV RPP and the ¹¹C-acetate clearance k₂ (r = 0.75, P < 0.001), as compared with the correlation with K_{mono} (r = 0.46, P = 0.047). Here, we show that the correlation between k₂ and RV RPP was only slightly better than that between K_{mono} and RV RPP (R² = 0.49 vs. R² = 0.41, respectively, Fig. 2). For the left ventricle in the present study population, we found no significant correlations between k₂ or K_{mono} and LV RPP (Supplemental Table 1; Supplemental Figs. 1C and 1D). On the one side, our patient population showed a narrow range of RPP for the left ventricle under resting conditions. On the other side, the failing right ventricle in IPAH results in lower workload for the left heart, which itself may cause altered LV metabolism and mechanical efficiency. A recent study demonstrated that LV cardiomyocytes are atrophic because of unloading and reduced cardiac output in RV failure secondary to chronic thromboembolic pulmonary hypertension (26). It is possible that LV cardiomyocyte atrophy is also present in IPAH, causing smaller differences in LV oxidative metabolic levels and resulting in a lack of correlations between ¹¹C-acetate clearance and LV RPP.

There were several limitations in our study. Measurement error as a result of performing the scanning protocols not simultaneously but in 2 sessions on the same day was unavoidable but may be important. The patient position in the scan may not have been exactly the same in the 2 sessions. Furthermore, there is a possibility that the myocardial metabolism may have altered during the day, as the ¹⁵O PET scans were performed 2 h after a light meal whereas the ¹¹C-acetate PET scan was obtained about 6 h later. The protocol was, however, too extensive to have the patients remain fasting from the midnight before the scanning day till the end of the PET study. The protocol was standardized as much as possible to limit measurement error. In the present study, test–retest variability was not investigated, as adding a scan was not feasible for the present patient population. The reproducibility of ¹¹C-acetate clearance rate measurements in humans has been demonstrated by Armbrrecht et al. (24). The fact that the measurement of pulmonary artery pressure and heart rate for the calculation of RPP was performed on another day may also have contributed to error variance. Finally, we focused only on myocardial metabolic measurements under resting conditions. It is possible that other correlations would appear during exercise or if inotropic drugs were used. Unfortunately, the demanding study protocol and the severity of the disease did not allow strenuous exercise or medical interventions.

CONCLUSION

Clearance of ¹¹C-acetate, expressed as either K_{mono} or k₂, correlated with quantitative RV MVO₂ and RPP measurements in the

hypertrophied right myocardium of IPAH patients significantly, albeit moderately. Given the moderate correlation between RV ¹¹C-acetate clearance with RV MVO₂ and RPP, it must be concluded that the ¹¹C-acetate clearance rate is only an index of RV oxidative metabolism in IPAH patients, which can potentially be used to monitor the efficacy of therapy in IPAH patients.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This work was supported in part by the Netherlands Organization for Scientific Research (VIDI 917.96.306). No other potential conflict of interest relevant to this article was reported.

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