

Preliminary Data on the Diagnostic Accuracy of Rubidium-82 Cardiac PET Perfusion Imaging for the Evaluation of Ischemia in a Pediatric Population

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Abstract Evaluation of myocardial perfusion is sometimes necessary in children with congenital heart disease or acquired coronary artery abnormalities. Limited information is available regarding the clinical utility of myocardial perfusion imaging in children. PET imaging with rubidium-82 may provide a convenient clinical means of assessing regional circulatory compromise in pediatric patients with small hearts, due to its improved spatial resolution. Clinically indicated cardiac PET studies obtained in 22 pediatric patients were reviewed by two blinded observers and assigned myocardial perfusion scores using a standard 17-segment model. PET results were correlated with coronary angiography, available in 15 cases, to determine the accuracy of PET scanning for evaluating compromise of the myocardial circulation. Reversible defects consistent with myocardial ischemia were present in 6 of 15 (40%) PET cases. The sensitivity and specificity of cardiac PET for the detection of significant coronary artery disease were 100% and 82%,

respectively. The positive predictive value of cardiac PET was 67%, while the negative predictive value was 100%. Cardiac PET imaging with rubidium-82 appears promising for the noninvasive assessment of myocardial perfusion in the pediatric population. The findings from this small series suggest that prospective study in a larger patient cohort merits consideration.

Keywords Positron emission tomography · Myocardial perfusion

Abbreviations

PET	Positron emission tomography
VSD	Ventricular septal defect
SPECT	Single photon emission computed tomography
EKG	Electrocardiogram
BMI	Body mass index
AS	Aortic stenosis
LAD	Left anterior descending artery
CX	Circumflex artery
RCA	Right coronary artery

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Introduction

The incidence of congenital heart disease is 0.8 per 100 live births, with many of these patients requiring treatment by interventional cardiology or cardiothoracic surgery during the first year of life [10]. In this patient population, a thorough evaluation of myocardial perfusion can be important in therapeutic planning and for assessing mechanical complications affecting epicardial coronary arteries after surgical correction. In addition, various other forms of coronary artery disease occurring in children, such

as Kawasaki disease and transplant vasculopathy, often necessitate functional evaluation of coronary perfusion.

In the pediatric population, the selection of a functional study to noninvasively evaluate myocardial perfusion is limited by several factors. Stress echocardiography with dobutamine administration may be limited in young patients or in patients with high baseline heart rates. Single-photon emission computed tomography (SPECT) myocardial perfusion imaging is limited by poor spatial resolution in patients with small hearts. Furthermore, the use of thallium agents is limited by dosimetric concerns in the pediatric population, while the use of technetium agents is limited by high liver activity, severely compromising evaluation of the inferior wall of the heart in small patients [8]. While the utility of cardiac positron emission tomography (PET) for the evaluation of myocardial perfusion is well established in the adult population, insufficient data exist to validate this method and to define its clinical role in the pediatric population. Advantages of cardiac PET testing in the pediatric population include shorter acquisition times and improved spatial resolution in patients with small hearts. Furthermore, PET imaging with rubidium-82 (^{82}Rb) may permit potentially lower radiation exposure due to its short half-life [4, 6]. No previous study has evaluated the use of rubidium-82 cardiac PET in the pediatric population; therefore, in this pilot study we sought to explore the potential clinical utility of rubidium-82 cardiac PET perfusion imaging in pediatric patients with congenital heart disease or acquired disease potentially affecting the coronary arteries.

Materials and Methods

Twenty-two consecutive pediatric cardiac PET studies performed at the Cleveland Clinic between 2000 and 2007 were analyzed for inclusion in this study. In 15 cases, coronary angiography was available for correlation with PET results.

PET images were obtained at rest and with stress following intravenous injection of ^{82}Rb , with the dose adjusted for the patient's body weight. Effective radiation dose was estimated based on patient age and ^{82}Rb dose, according to published data [6]. In all but one case, the stress images were obtained during pharmacological stress utilizing intravenous dipyridamole infusion (0.56 mg/kg over 4 min). In a single case a dobutamine infusion was utilized; however, this patient did not undergo coronary angiography and, therefore, was excluded from the final analysis.

PET images were viewed using an ESoft 4.0 Workstation (Siemens Medical Solutions, Inc, and Toshiba Medical Systems Corp.) and 4D-MSPECT v3.1 software (University

of Michigan, Ann Arbor). PET images were reviewed semiquantitatively by two blinded observers and assigned myocardial perfusion scores using a standard 17-segment model [9]. Differential tracer uptake $>15\%$ between stress and rest was considered clinically significant. Coronary angiograms were reviewed by a single blinded observer using Philips Inturis Suite, CCF Prototype software (Philips Medical Systems). Coronary artery stenoses $\geq 70\%$ of the luminal diameter were considered significant. In smaller children stenoses between 50% and 70% were considered possibly significant due to the smaller diameter of the reference vessel. Clinical information, including age, height, weight and clinical diagnosis, was obtained both from the patients' electronic medical records and, when necessary for completeness, from hospital chart review. The results of the PET studies were correlated with coronary angiography to determine the accuracy of PET scanning for evaluating myocardial perfusion.

Results

Two illustrative cases are presented in Figs. 1 and 2. The first case is of a 15-year-old boy with a history of transposition of the great arteries (TGA) and status post arterial switch surgery as a neonate. The patient had suffered from syncope, leading to a referral for PET perfusion imaging. The PET perfusion images revealed extensive anterior and lateral wall ischemia, and left heart catheterization revealed occlusion of the left main coronary artery at its ostium and collateral filling of the left system from the right coronary artery (Fig. 1a). Following surgical correction, a repeat PET study demonstrated no myocardial ischemia and only a mild fixed defect in the lateral wall (Fig. 1b).

The second case example is that of a 6-year-old boy with a large ventricular septal defect (VSD) and single-ventricle physiology. The patient was referred for imaging due to left ventricular dysfunction on echocardiogram. The patient's PET study demonstrated a fixed septal defect consistent with his known VSD, as well as right ventricular hypertrophy. No inducible ischemia was present (Fig. 2). On subsequent cardiac catheterization, the coronary arteries were normal.

The final analysis included 15 cases in which coronary angiography was available for correlation with PET results. Clinical characteristics and results of PET testing and coronary angiography for all patients are reported in Table 1. Age of patients ranged from 8 months to 18 years and weight ranged from 5.4 to 104.6 (average, 34.2) kg. Patients' clinical diagnoses included TGA post arterial switch, Kawasaki disease, transplant vasculopathy, aortic valve disease, single ventricle, and various coronary artery anomalies.

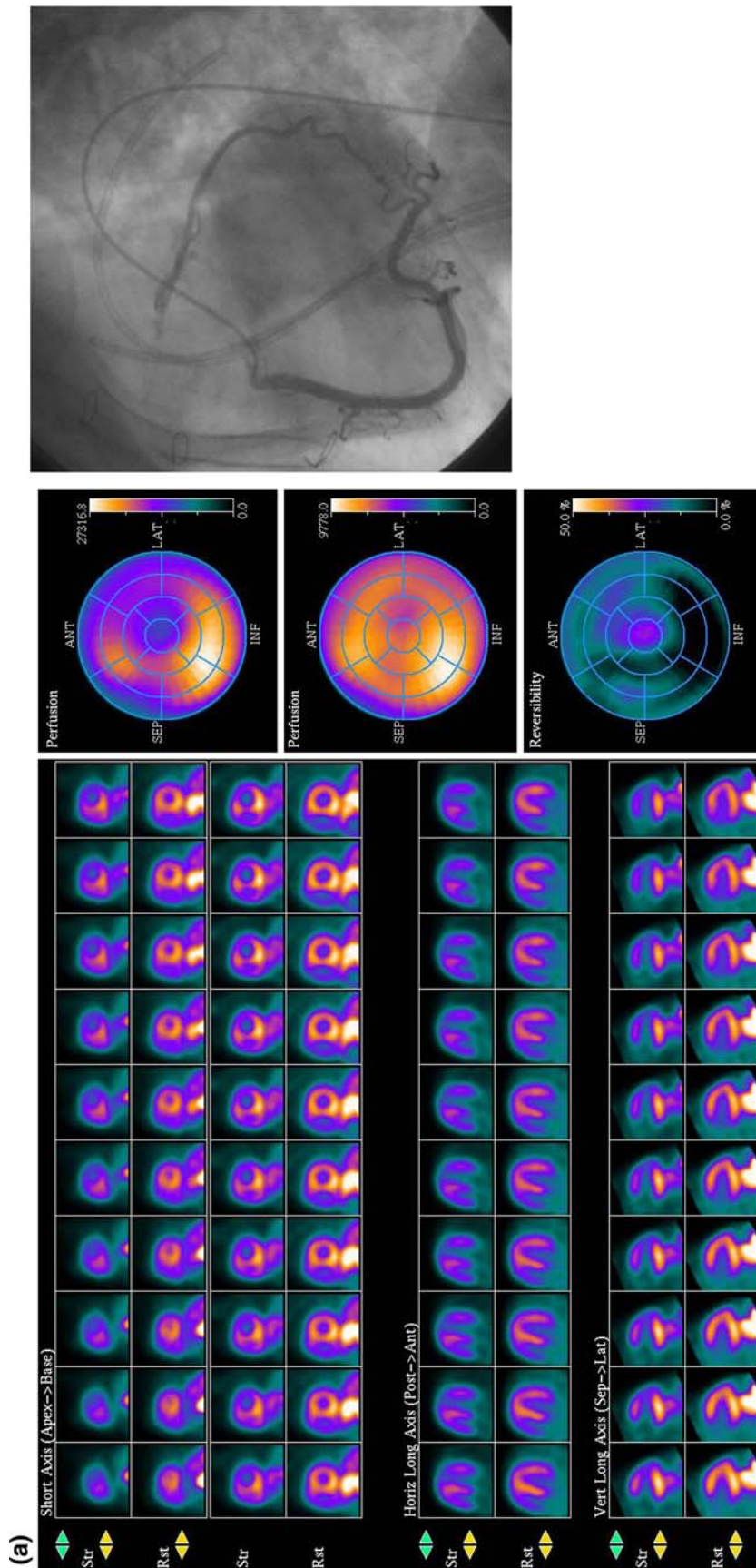


Fig. 1 A 15-year-old boy with transposition of the great arteries status post arterial switch and occlusion of the left main coronary artery. **(a)** An abnormal PET study prior to surgical repair of the left main coronary artery. **(b)** PET study with no evidence of myocardial ischemia following surgical repair

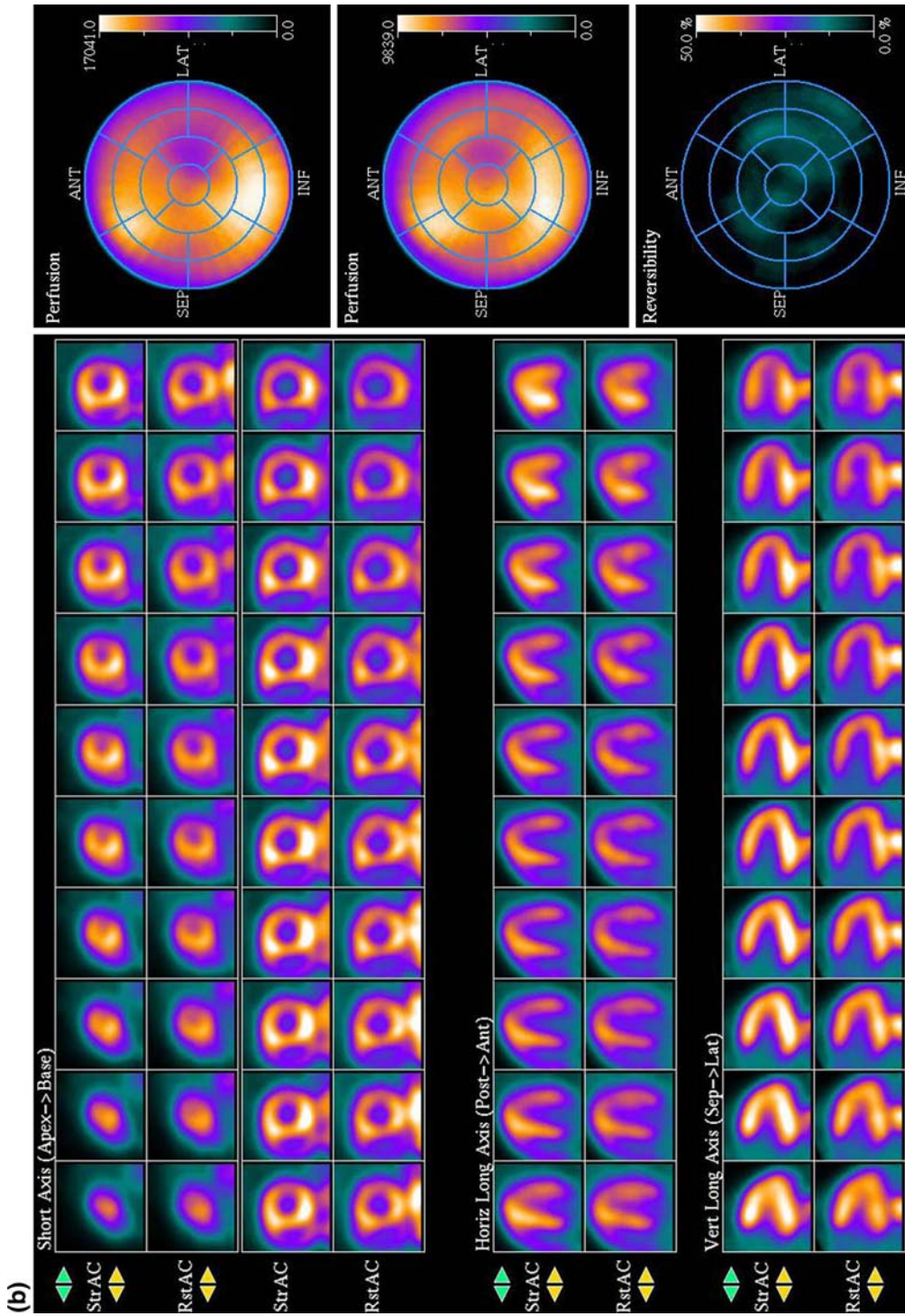


Fig. 1 continued

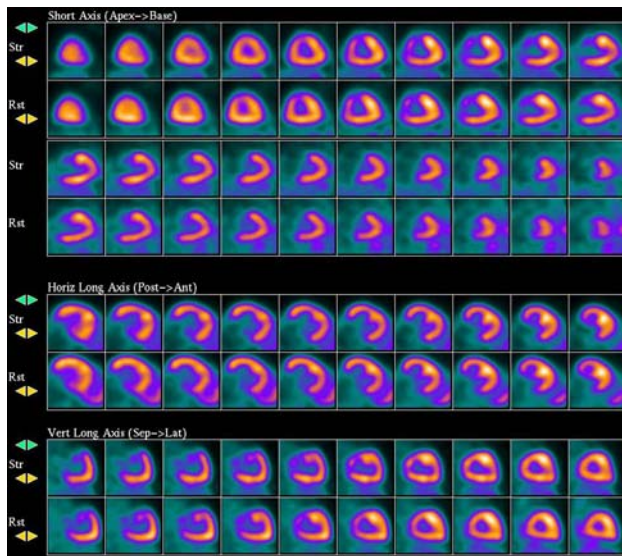


Fig. 2 A 6-year-old boy with a large ventricular septal defect (VSD) and single-ventricle physiology. PET imaging reveals absent septal perfusion and right ventricular hypertrophy

No significant arrhythmias or hemodynamic instability was observed with dipyridamole stress in this population. PET perfusion abnormalities were present in 7 of 15 cases. A fixed perfusion defect was observed in 1 patient, and reversible defects consistent with ischemia were present in 6 of 15 (40%) of cases. Coronary angiography revealed significant coronary stenosis in four of six (67%) cases undergoing left heart catheterization with PET study indicating ischemia, and confirmed a lack of flow-limiting coronary disease in nine of nine (100%) cases in which the PET study did not indicate myocardial ischemia. The sensitivity and specificity of cardiac PET for the detection of significant coronary artery disease in this pediatric population were 100% and 82%, respectively. The positive predictive value (PPV) of cardiac PET was 67%, while the negative predictive value (NPV) was 100% in this population.

There were two “false-positive” cases, in which a PET study indicated ischemia and coronary angiography did not reveal a flow limiting lesion. The first case involved a patient with surgically corrected TGA and VSD, undergoing PET to evaluate myocardial perfusion following the observation of extensive premature ventricular contractions (PVCs) on ambulatory monitor. The PET study was consistent with lateral wall ischemia, and left heart catheterization revealed an anomalous origin of the circumflex artery from the right coronary artery. The circumflex artery was noted to have a mild dynamic narrowing or “kink” in its proximal segment; however, this was not deemed to be a flow-limiting lesion.

The second “false-positive” case involved a patient with surgically corrected TGA and Kawasaki disease

undergoing PET to evaluate myocardial perfusion following a cardiac MRI revealing an abnormal course of the left coronary artery. The PET study was consistent with ischemia in the left anterior descending artery (LAD) and circumflex territories, and left heart catheterization revealed that the left coronary artery arose from the aorta at an acute angle. However, fractional flow reserve (FFR) was calculated in the LAD and found to be 0.81 (abnormal, <0.75). Therefore, the lesion was deemed not to be flow-limiting.

Discussion

Significant advances in interventional cardiology, cardiothoracic surgery, and pediatric intensive care have led to improved survival and enabled corrective therapy for pediatric patients with complex congenital heart disease. Thorough evaluation of myocardial perfusion is sometimes required in such patients before a therapeutic plan can be pursued, as well as after corrective surgery for various congenital coronary anomalies. In some instances, post-operative evaluation is needed to rule out the possibility of a mechanical complication affecting epicardial coronary arteries. Finally, children with acquired coronary artery disease, such as transplant vasculopathy or Kawasaki disease, may also require functional evaluation of coronary perfusion. Given the lack of strict criteria defining flow-limiting coronary artery lesions visualized by coronary angiography in children, noninvasive means of assessing myocardial perfusion may provide a useful tool to aid in decision-making in this population.

In the pediatric population, the selection of a functional study to noninvasively evaluate for coronary artery stenosis can be difficult. Stress echocardiography with dobutamine may be difficult in young patients or in patients with high baseline heart rates. The utility of dipyridamole stress infusion in the pediatric population, specifically in patients with congenital heart disease, is less well established than in the adult population. However, adult patients with cyanotic congenital heart disease have been shown to exhibit a normal myocardial perfusion reserve in response to dipyridamole stress [2] and the use of dipyridamole stress in the pediatric population has been reported previously [7].

SPECT myocardial perfusion imaging has three main drawbacks in the pediatric population: first, poor spatial resolution (12–15 mm) in patients with a small hearts; second, length of acquisition (25 min for each set of images), necessitating the sedation of younger patients; and third, radiation exposure. PET pharmacologic imaging using ^{82}Rb as a perfusion tracer has three advantages: first, a spatial resolution of 7 mm; second, shorter image acquisition times; and third, potentially lower radiation

Table 1 Clinical characteristics, PET results, and catheterization data

Diagnosis	Age (yr)	Weight (kg)	Height (m)	BMI	PET result	Stress ECG	Coronary angiogram abnormality	Estimated radiation exposure (mrem)
Kawasaki disease	3	17.4	1.03	16.4	Normal	Normal	Normal	1600
Transplant vasculopathy	7	29.1	1.22	19.6	Normal	Normal	Normal	1100
Transplant vasculopathy	8	22.3	1.25	14.3	Normal	Normal	Normal	3000
Moya Moya	8	52.7	1.37	28.1	Normal	Normal	Normal	3000
Surgically corrected TGA, VSD	3	14.3	0.97	15.2	CX ischemia	Normal	Normal	2700
Transplant vasculopathy	8	25.0	1.30	14.8	Normal	Normal	Normal	3700
Surgically corrected TGA	15	48.1	1.61	18.6	LAD CX ischemia	Lateral ST depression	Left main	2500
Surgically corrected ALCAPA	8 mo	5.4	0.67	12.0	LAD CX ischemia	Global ST depression	Left main	1200
Coronary atresia, supraaortic AS	8	25.7	1.28	15.7	LAD CX ischemia	Global ST depression	Left main	2200
Surgically corrected coronary atresia, supraaortic AS	8	26.4	1.26	16.6	Normal	Normal	Normal	2200
Congenital AS	18	104.6	1.75	34.2	LAD CX scar/ischemia	Nondiagnostic	Left main	3000
Postop VSD/single ventricle	6	29.5	1.17	21.6	Fixed septal defect	Nondiagnostic	Normal	2700
Coronary fistula	13	43.0	1.61	16.6	Normal	Normal	Normal	2000
Surgically corrected TGA, VSD, coarctation	10	38.1	1.46	17.9	Normal	Normal	Normal	3300
Kawasaki disease, surgically corrected TGA	7	31.1	1.31	18.1	LAD CX ischemia	Normal	Normal	4000

BMI, body mass index; PET, positron emission tomography; ECG, electrocardiogram; TGA, transposition of the great arteries; VSD, ventricular septal defect; ALCAPA, anomalous left coronary artery from the pulmonary artery; AS, aortic stenosis; LAD, left anterior descending artery; CX, circumflex artery; RCA, right coronary artery

exposure [3]. However, information concerning the clinical utility of ^{82}Rb PET perfusion imaging in the growing pediatric population with complex congenital heart disease is virtually nonexistent.

To our knowledge, this is the first study to evaluate the utility of cardiac PET perfusion imaging with ^{82}Rb in the pediatric population. Limited data exist for the use of ^{13}N ammonia as a PET perfusion tracer in the pediatric population [1, 5]. However, ^{82}Rb has a more energetic positron than ^{13}N ammonia and has not been well evaluated in the pediatric population. Because ^{82}Rb is eluted from a bedside generator, it is available to the increasing number of PET imaging centers that do not have an on-site cyclotron. Thus, use of this perfusion tracer enables PET imaging to be performed at centers which are not as specialized as the traditional academic centers. The present findings indicate that cardiac PET imaging with ^{82}Rb appears safe and effective for the noninvasive assessment of myocardial perfusion in children. These data demonstrate the high sensitivity and specificity of cardiac PET with ^{82}Rb for the evaluation of myocardial perfusion in the pediatric population with complex congenital heart disease or various forms of coronary artery disease. These results should be applicable to pediatric patients with a wide range of congenital and acquired heart conditions, including valvular heart disease, Kawasaki disease, TGA post arterial switch, coronary artery anomalies, and cardiac transplant vasculopathy.

Limitations

This study represents a small, retrospective analysis in a pediatric population at high risk for myocardial perfusion abnormalities due to known coronary artery abnormalities or prior surgical procedures. Interpretation of PET imaging in this population is hindered by the lack of an age-specific normal database. Furthermore, the high pretest probability of coronary abnormalities may skew the correlation between abnormal PET results and flow-limiting coronary artery disease in this high-risk population. Finally, no standard protocol was utilized for ^{82}Rb dosing in this pediatric population. Coronary angiography was utilized as the gold standard in this study. However, coronary angiography was not performed in all cases, even in patients with abnormal PET studies. No additional measures of myocardial perfusion or viability were utilized, and no attempt was made to assess coronary artery function, including coronary vasoreactivity, in this population with a high incidence of coronary artery anomalies and prior surgery.

Conclusion

Cardiac PET imaging with ^{82}Rb appears promising for the noninvasive assessment of myocardial perfusion in children. Cardiac PET can be performed safely, offers high sensitivity and specificity in the pediatric population, and may provide a useful tool to complement coronary angiography in these patients. These results should be applicable to a wide range of congenital and acquired heart conditions, and the findings from this small series suggest that a prospective study in a larger patient cohort merits consideration.

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