Reference Ranges for LVEF and LV Volumes from Electrocardiographically Gated ^{82}Rb Cardiac PET/CT Using Commercially Available Software

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Electrocardiographic gating is increasingly used for ^{82}Rb cardiac PET/CT, but reference ranges for global functional parameters are not well defined. We sought to establish reference values for left ventricular ejection fraction (LVEF), end systolic volume (ESV), and end diastolic volume (EDV) using 4 different commercial software packages. Additionally, we compared 2 different approaches for the definition of a healthy individual. **Methods:** Sixty-two subjects (mean age ± SD, 49 ± 9 y; 85% women; mean body mass index ± SD, 34 ± 10 kg/m²) who underwent ^{82}Rb-gated myocardial perfusion PET/CT were evaluated. All subjects had normal myocardial perfusion and no history of coronary artery disease (CAD) or cardiomyopathy. Subgroup 1 consisted of 34 individuals with low pretest probability of CAD (<10%), and subgroup 2 comprised 28 subjects who had no atherosclerosis on a coronary CT angiogram obtained concurrently during the PET/CT session. LVEF, ESV, and EDV were calculated at rest and during dipyridamole-induced stress, using CardIQ Physio (a dedicated PET software) and the 3 major SPECT software packages (Emory Cardiac Toolbox, Quantitative Gated SPECT, and 4DM-SPECT). **Results:** Mean LVEF was significantly different among all 4 software packages. LVEF was most comparable between CardIQ Physio (62% ± 6% and 54% ± 7% at stress and rest, respectively) and 4DM-SPECT (64% ± 7% and 56% ± 8%, respectively), whereas Emory Cardiac Toolbox yielded higher values (71% ± 6% and 65% ± 6%, respectively, $P < 0.001$) and Quantitated Gated SPECT lower values (56% ± 8% and 50% ± 8%, respectively, $P < 0.001$). Subgroup 1 (low likelihood) demonstrated higher LVEF values than did subgroup 2 (normal CT angiography findings), using all software packages ($P < 0.05$). However, mean ESV and EDV at stress and rest were comparable between both subgroups (p = NS). Intra- and interobserver agreement were excellent for all methods. **Conclusion:** The reference range of LVEF and LV volumes from gated ^{82}Rb PET/CT varies significantly among available software programs and therefore cannot be used interchangeably. LVEF results were higher when healthy subjects were defined by a low pretest probability of CAD than by normal CT angiography results.

Key Words: ^{82}Rb; cardiac PET/CT; left ventricular ejection fraction; electrocardiographic gating

Myocardial perfusion imaging with ^{82}Rb-gated PET/CT is gaining acceptance as an important imaging modality for the evaluation of coronary artery disease (CAD) because it provides improved diagnostic quality, certainty, and accuracy over conventional cardiac SPECT (*1–5*). In addition, cumulative evidence supports the prognostic value of ^{82}Rb PET in predicting adverse cardiac outcomes (*6–10*).

Current PET systems allow for routine electrocardiographically gated rest–stress acquisition protocols with ^{82}Rb. However, when compared with the extensively validated gated myocardial SPECT technique, there is less evidence for the usefulness and validity of the functional parameters—left ventricular ejection fraction (LVEF), end-systolic volume (ESV), and end-diastolic volume (EDV)—derived from gated ^{82}Rb PET.

Prior studies supported the usefulness of functional parameters from ^{82}Rb PET, but the studies were performed in mixed populations of individuals with and without CAD, mostly using a single software package (*6,10–13*). Hence, information about the reference range of functional parameters from gated ^{82}Rb PET remains scarce.

Additionally, it has been demonstrated for SPECT that significant variations among commercially available software packages for the quantification of LVEF, ESV, and EDV exist, and therefore interchangeable use of these software algorithms was not recommended (*14–16*). And finally, some controversy exists about the best way to define a healthy population. Although most prior studies used a low likelihood of CAD, others used normal results of coronary angiography (*17*).

The main aim of our current study was to address these open issues in ^{82}Rb-gated PET by obtaining global functional parameters in a healthy population using the 4 most frequently applied software products for functional nuclear imaging analysis and comparing 2 different approaches of defining a healthy population.

MATERIALS AND METHODS

Patients and Study Design

We retrospectively reviewed our database, seeking patients who underwent gated ^{82}Rb myocardial perfusion PET/CT for the evaluation of CAD between January 2006 and March 2009 at the Johns Hopkins Hospital. We included only patients with normal myocardial perfusion ^{82}Rb PET/CT findings and no history of CAD, cardiomyopathy, valvular disease, or significant arrhythmias. Individuals fulfilling criteria for 1 of 2 different subgroups were included: subgroup 1 consisted of subjects with a low clinical pretest (≤10%) probability of CAD as defined by Diamond and Forrester (18). Subgroup 2 consisted of individuals who underwent coronary CT angiography (CTA) as part of their PET/CT session, had good image quality, and showed complete absence of any coronary atherosclerosis on CT.

A total of 62 subjects were identified, 34 for subgroup 1 and 28 for subgroup 2. This retrospective analysis was granted exempt status by the Johns Hopkins Institutional Review Board.

Acquisition Protocol

All patients were imaged using a Discovery STRx PET/CT system (GE Healthcare), equipped with an integrated lutetium yttrium orthosilicate crystal PET component and a 64-slice CT component. A low-dose CT scan (120 kV, 40 mA) was acquired for attenuation correction of PET emission data before rest acquisition.

Rest Acquisition. ^{82}Rb-chloride (1,480–1,850 MBq [40–50 mCi]) was infused intravenously from a strontium–rubidium generator as a slow bolus over 30 s, and a 2-dimensional list-mode PET scan was obtained over 8 min.

Stress Acquisition. Dipyridamole (0.56 mg/kg) was administered over a period of 4 min. A second dose of 1,480–1,850 MBq (40–50 mCi) of ^{82}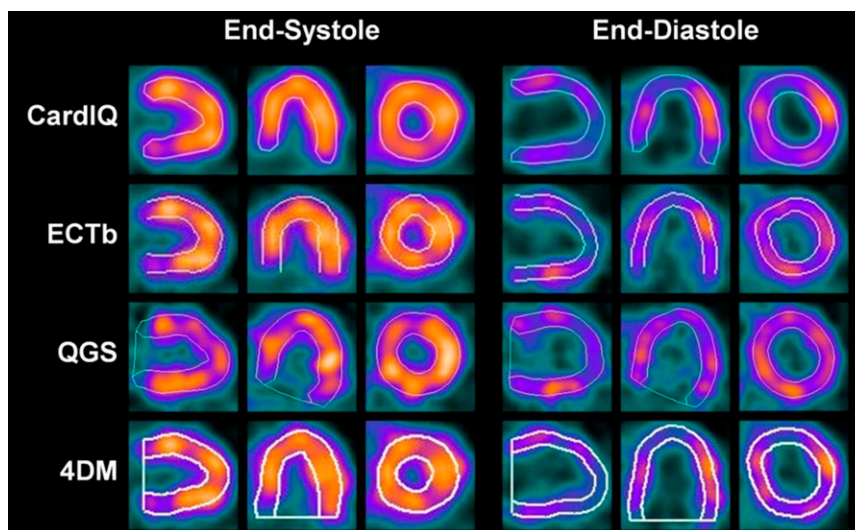Rb-chloride was infused 4 min after the end of dipyridamole, followed by an 8-min 2-dimensional list-mode acquisition. The rest and stress PET data were checked for accurate alignment with the low-dose CT scan, and software-based realignment was performed for attenuation correction if necessary (19). List-mode data were resampled to static (90-s prescan delay) and gated (8 bins per cardiac cycle) images (13).

CTA Acquisition. When performed, contrast-enhanced CTA was initiated immediately after the end of PET. Most patients (20/28) were premedicated with oral metoprolol (50–100 mg, 30 min before the start of PET/CT) to reduce heart rate below a target of 65 beats per min. Seventeen subjects underwent prospectively gated (step-and-shoot) CTA, and the remaining 11 individuals underwent conventional helical CTA, as described previously (20).

Data Analysis

Attenuation-corrected PET images were reconstructed by an iterative algorithm (ordered-subset expectation maximization, 2 iterations, 21 subsets), with postprocessing filtering (Butterworth, order 10; cutoff, 0.25 cycles/bin). Four commercially available products—the CardIQ Physio package (a dedicated PET software; GE Healthcare) and the 3 major SPECT software packages (Emory Cardiac Toolbox [ECTb; Syntermed, Inc.], Quantitative Gated SPECT [QGS; Cedars-Sinai Medical Center], and 4DM-SPECT [4DM; INVIA, LLC])—were used for further analysis of electrocardiographically gated datasets. No dedicated PET version of the latter 3 software packages was available. This analysis included oblique reorientation of the datasets on the transversal planes, first parallel to the septum and then parallel to the inferior wall; definition of valve plane (automatically processed by all 4 algorithms), with manual adjustment in the case of inadequate anatomic delineation, except for QGS (which did not have a manual correction option); quality control of automated contour detection; and software-derived calculation of LVEF, ESV, and EDV from rest and stress datasets. Figure 1 shows specific examples of contour findings for all 4 software programs. To assess for sex differences, left ventricular (LV) volumes were normalized to body surface area by dividing ESV and EDV (ESV index and EDV index [in mL/m^2], respectively) by body surface area.

Interobserver reproducibility from 24 cases was determined using 2 independent observers unaware of prior clinical interpretation. One reader repeated the analysis to determine intraobserver

FIGURE 1. Representative horizontal long-axis (first and fourth columns), vertical long-axis (second and fifth columns), and short-axis slices (third and sixth columns), including contours as created by all 4 software packages, during end-systole and end-diastole in representative case.

agreement. In both instances, the analysis consisted of reconstruction and oblique reorientation of the datasets, manual definition of valve plane when needed, and quality control of automated contour detection.

Statistical Analysis

Statistical analyses were performed using SPSS (version 7.5; SPSS, Inc.) for Windows (Microsoft) and StatMate III (ATMS Co. Ltd.). Continuous variables are presented as mean ± SD. One-way, factorial ANOVAs, combined with Scheffé test for post hoc analysis and correction for multiple comparisons, were used to compare functional measures among different software packages. The 2-tailed, unpaired t test was used to assess differences between subgroups of individuals. Categoric variables were compared between groups using χ^2 tests and are presented as percentages. For characterization of inter- and intraobserver variability, Pearson correlation coefficients were calculated. A P value of less than 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

The study group's ($n = 62$) mean age and body mass index were 49 ± 9 y and 34 ± 10 kg/m^2, respectively. Patients' characteristics and hemodynamic parameters are summarized in Table 1. Except for age, no other significant differences existed at baseline between individuals with a low pretest probability of CAD and patients with normal coronary CTA findings. Peak heart rate during dipyridamole was lower in the CTA group; however, other hemodynamic parameters were not significantly different.

Reference Ranges for LVEF, ESV, and EDV

The mean values of LVEF, ESV, and EDV for all 62 patients are summarized in Tables 2 and 3. In general, LV volumes and LVEF measurements showed significant differences among all 4 software packages ($P < 0.001$), with the following exceptions: LVEF was comparable between CardIQ Physio and 4DM, whereas ECTb yielded the highest and QGS the lowest mean LVEF values (Table

2). LV volumes were also significantly different among the software, with some exceptions, as detailed in Table 3.

The response of LVEF to vasodilator stress, a potential marker of disease severity, was relatively similar among the software (Fig. 2).

Comparison of Subgroups of Healthy Subjects

The mean values of normal LVEF in patients with a low pretest probability of CAD (subgroup 1) and normal coronary CTA findings (subgroup 2) are depicted in Figures 3 (rest) and 4 (vasodilator stress), respectively. Subgroup 1 has higher values in almost all settings. When the 20 patients within subgroup 2, which received β-blockade, were compared with the 8 patients of subgroup 2 without β-blockade, no significant differences in LVEF were observed with any of the 4 software packages. ESV and EDV, finally, were not statistically different between the 2 subgroups, although there was a trend for higher ESV in subgroup 2 (data not shown).

Table 4 shows results according to sex. There was a trend for mildly higher LVEFs and smaller LV volumes in women than in the smaller group of men among the different software packages, reaching statistical significance in a few instances.

Reproducibility of Software Measurements of LVEFs and LV Volumes

Intra- and interobserver agreement of LVEF was good for all methods, with correlation coefficients consistently above 0.8 (Table 5). Only ECTb software showed a lower interobserver agreement at rest. ESV and EDV agreements were excellent for all software packages, again except for ECTb, which showed lower intra- and interobserver agreements for ESV.

DISCUSSION

Our study defines reference values and ranges for global functional parameters from gated ^{82}Rb PET/CT, using

TABLE 1. Patient Characteristics and Dipyridamole-Induced Hemodynamic Changes of Study Groups

Characteristic	Subgroup 1 ($n = 34$)	Subgroup 2 ($n = 28$)	P	Total group ($n = 62$)
Mean age ± SD (y)	47 ± 7	52 ± 10	0.039	49 ± 9
Mean BMI ± SD (kg/m^2)	35 ± 12	32 ± 7	0.239	34 ± 10
Women (n)	31 (91%)	22 (79%)	0.161	53 (85%)
African Americans (n)	30 (88%)	24 (86%)	0.958	54 (87%)
Hypertension (n)	22 (65%)	18 (64%)	0.973	40 (65%)
Smoking (n)	18 (53%)	9 (32%)	0.100	27 (44%)
Dyslipidemia (n)	13 (38%)	11 (39%)	0.933	24 (39%)
Diabetes (n)	7 (21%)	10 (36%)	0.184	17 (27%)
Mean baseline heart rate ± SD (bpm)	68 ± 11	64 ± 9	0.131	67 ± 10
Mean peak heart rate ± SD (bpm)	97 ± 14	88 ± 10	0.007	93 ± 13
Mean heart rate change ± SD (bpm)	28 ± 10	23 ± 11	0.063	26 ± 11
Mean baseline arterial pressure ± SD (mm Hg)	97 ± 12	96 ± 15	0.896	97 ± 13
Mean nadir arterial pressure ± SD (mm Hg)	91 ± 11	89 ± 15	0.558	90 ± 13
Mean arterial pressure change ± SD (mm Hg)	6 ± 6	10 ± 17	0.139	8 ± 12

BMI = body mass index; bpm = beat per minute.

TABLE 2. Mean LVEF Using 4 Different Software Packages

Software package (n = 62)	Mean LVEF ± SD (%)		Proposed reference range (mean LVEF ± 2 SDs [%])	
	Stress	Rest	Stress	Rest
CardIQ Physio	62 ± 6	54 ± 7	50–74	40–68
ECTb	71 ± 6	65 ± 6	59–83	53–77
QGS	56 ± 8	50 ± 8	40–72	34–66
4DM	64 ± 7	56 ± 8	50–78	40–72

P < 0.01 for difference among all software packages, except CardIQ Physio and 4DM.

various currently available commercial software products in a typical referral population for PET (high body mass index, mostly women). Our study also provides further insights: it suggests that because values differ among software packages, these values should not be used interchangeably. And it suggests that the criteria used to define subjects for inclusion into a reference database may influence results.

With the exception of CardIQ Physio, which is a dedicated cardiac PET software application, the software products used in this study (ECTb, QGS, and 4DM) are all software that was originally designed for gated SPECT analysis. Our study clearly shows that significant differences may be encountered among these 4 software packages when applied to gated PET data. This finding is consistent with similar observations made in the analysis of gated myocardial SPECT data using those software packages (14). Although CardIQ Physio and 4DM seemed to be most comparable, ECTb consistently yielded the highest and QGS the lowest LVEF values, with a mean LVEF difference of 15% (regardless of stress or rest state) between the 2 software products. Differences in the algorithms for definition of endocardial and epicardial borders and definition of the base and valve planes are the most likely explanation for this observation. For example, QGS uses a 3-dimensional model of the heart without specific geometric assumptions of horizontal or transversal long axes, ECTb uses a 2-coordinate system (cylindric coordinate for basal and mid-myocardial segments but spheric coordinate for the apex), and 4DM requires the heart base to be perpendicular to the chosen long axes (21). Moreover, ECTb and QGS valve-plane definition models assume that the septal wall is shorter than the lateral wall; consequently, the basal limits are independently estimated on each side of the left ventricle, whereas 4DM assumes that the basal limits are the same in the septal and lateral walls (22,23).
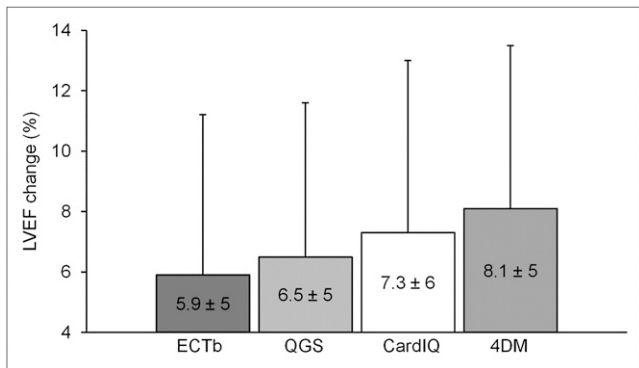
Because of the physical properties of [82]Rb, which has an ultrashort half-life of 75 s and relatively high positron energy, the statistical quality of gated images may be limited. This limitation makes quantification of functional parameters a bigger challenge than when using SPECT or gated PET with other tracers. Nevertheless, reproducibility of the software algorithms was good in our analysis, and the validity of gated [82]Rb PET results was recently demonstrated by us in a comparison with contrast-enhanced CT ventriculography (11). This prior study agreed well with the reference technique but also showed a systematic underestimation of LVEF by PET. The need for defining method-specific reference ranges was emphasized by this prior study, but because of the inclusion of a range of health and disease such reference ranges could not be defined. Our current study provides this missing information; however, most subjects in our study were obese and female. Our results may, thus, be somewhat limited when applied to the general population, but they are representative of the typical population referred for PET because SPECT is limited by artifacts specifically in those individuals.

TABLE 3. Mean LV Volumes (n = 62) Using 4 Different Software Packages in the Study Group

Software package	ESV (mL)				EDV (mL)			
	Mean ± SD		Proposed reference range (mean ± 2 SDs)		Mean ± SD		Proposed reference range (mean ± 2 SDs)	
	Stress	Rest	Stress	Rest	Stress	Rest	Stress	Rest
CardIQ Physio	28 ± 11*	28 ± 11	6–50	6–50	72 ± 22	61 ± 22	28–116	17–105
ECTb	29 ± 13*	32 ± 13	3–55	6–58	96 ± 31	90 ± 31	34–158	28–152
QGS	40 ± 17	42 ± 17*	6–74	8–76	90 ± 26	82 ± 26	38–142	30–134
4DM	37 ± 16	43 ± 17*	5–69	9–77	100 ± 29	96 ± 30	42–158	36–156

*Paired software with nonsignificant P value. P < 0.01 for differences among all other software measurements.

FIGURE 2. Differences in LVEF response to vasodilator stress among software products (P value was not significant between subgroups).
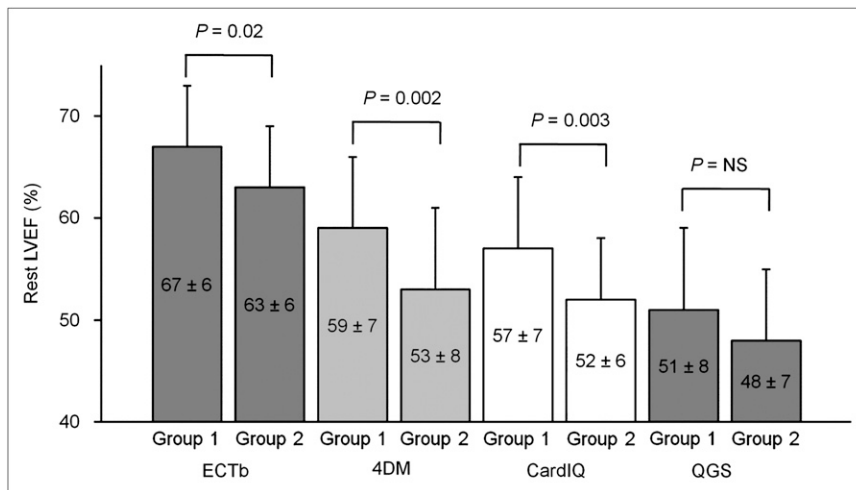
Other authors have described functional parameters using 2 of the software applications included in our study and reported values in similar ranges. Dorbala et al. used the ECTb software in a control group of 44 individuals with a low pretest likelihood of CAD evaluated with ^{82}Rb PET/CT (*12*). In this study the LVEF at rest and stress and the LVEF difference were 62% ± 9%, 69% ± 8%, and 7% ± 7%, respectively. Brown et al. used the QGS package in a mixed population of 87 individuals (15% had history of CAD) and found that the LVEF at rest and stress and the LVEF difference were 47% ± 13%, 54% ± 13%, and 7% ± 7%, respectively, (*13*). Our study, however, is the first—to our knowledge—to compare 4 common software packages directly, in the same patient group. It provides different reference ranges for each package and suggests that no common reference range exists. A resting LVEF of 50%, for example, would have to be considered low or depressed if using ECTb, whereas a resting LVEF of 45% would still be within the reference range for the other types of software. The tendency toward low LVEF values from ^{82}Rb PET has been recognized by some manufacturers, and

novel dedicated algorithms are being developed. Those have not been included in our analysis, and new software may affect clinical practice in the future.
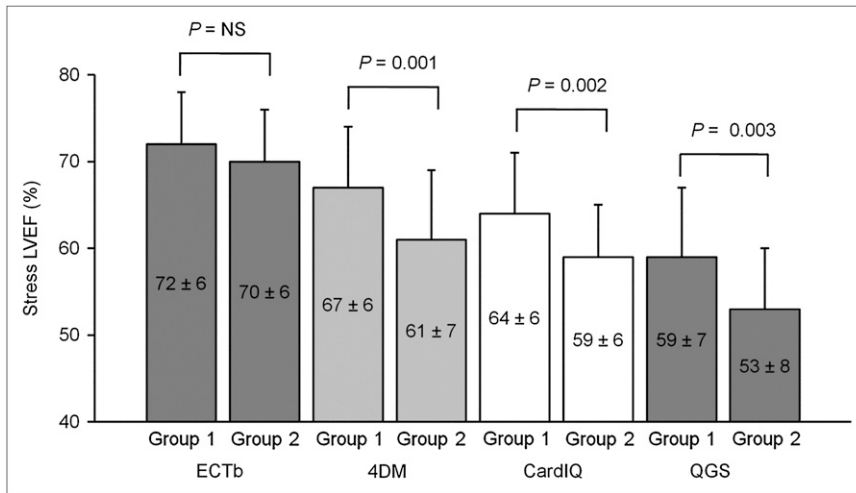
One of the unique features of gated ^{82}Rb PET is that stress imaging, in contrast to SPECT, is conducted at a time close to peak vasodilator action. The dipyridamole-induced change of the LVEF is considered a marker of the severity of ischemia and extent of flow-limiting disease (*12,13*). The change was explained by an increase in EDV and mild decrease in ESV during vasodilator stress in our healthy subjects. Interestingly, the magnitude of the response of LVEF to vasodilator stress in our population was rather comparable among software packages, ranging from 5.9% ± 5.3% (ECTb) to 8.1% ± 5.4% (4DM). In contrast to absolute LVEF values, the LVEF response to vasodilation may thus be used independently of the software package, although the observed range is large and the value as an independent parameter requires further validation.

Finally, another interesting aspect of our study was that the definition of healthy subjects by a low pretest probability of CAD (subgroup 1) versus normal coronary CTA findings (subgroup 2) yielded slightly different functional results. Twenty of 28 individuals in subgroup 2, compared with subgroup 1, were prepared with β-blockers before CTA, and this difference may potentially explain borderline differences in the baseline and peak heart rate during vasodilator stress. Nevertheless, no significant differences were observed in LVEF within subgroup 2 between subjects who received β-blockers versus those who did not (data not shown). And other prior studies used CTA to define the validity of LVEF measurements, which did not differ from reference methods in which β-blockade was not used (*24–27*).

Because both subgroups had comparable baseline characteristics except for age, the reasons for the LVEF difference are not obvious. The definition of an individual having a low pretest probability of CAD is an entirely clinical assumption, which is based on the patient's age, sex, and chest pain

FIGURE 3. Comparison of mean LVEF at rest between subjects with low pretest probability of CAD (subgroup 1) and normal coronary CTA results (subgroup 2). NS = not significant.

FIGURE 4. Comparison of mean LVEF at stress between subjects with low pretest probability of CAD (subgroup 1) and normal coronary CTA results (subgroup 2). NS = not significant.

characteristics as first described by Diamond and Forrester (*18*). Therefore, individuals with a low pretest probability of CAD are likely a good standard for the definition of healthy subjects, although no imaging test is available to confirm the absence of disease. In individuals with normal angiography results, on the other hand, the absence of disease is confirmed but the patients usually have symptoms or other factors that prompt the angiogram. Although not clearly identified by our analysis, the reason for the differences between both subgroups may lie in unknown factors that prompt the angiogram. It has been discussed controversially whether one group should be preferred over the other for the definition of a reference database (*17*). Because we were not able to identify a clear reason to disqualify either group, we decided to combine both for definition of the reference ranges reported in our study.

Some limitations of this study should be considered. First, it has a retrospective design and suffers from all the limitations of similar studies. Likewise, the findings may be limited by the relatively few patients and not be representative of the general population at any other site. Our healthy group consisted of a large fraction of female and obese individuals, which is an inherent bias in our referral population for PET myocardial perfusion evaluation. This bias is partly because PET, with its higher spatial resolution and attenuation correction, is considered superior to SPECT for the evaluation of obese individuals (*9,28*). Obese individuals may have higher LV volumes than healthy subjects; however, the LVEF is not adversely affected, even with severe degrees of obesity as previously reported by Dorbala et al. (*29*). Similar findings have been described using echocardiography (*30*).

Finally, multiple studies have shown that women have smaller EDV and ESV values and higher LVEFs than men (*15,29,31,32*), as agrees with our findings despite the fact we included a limited number of men. Some advocate an

TABLE 4. Mean LVEF and LV Volume Index Between Men and Women

Index	Men (*n* = 9) vs. Women (*n* = 53)	Software package			
		CardIQ Physio	ECTb	QGS	4DM
Rest LVEF (%)	M	49 ± 6	63 ± 7	46 ± 7	50 ± 9
	F	55 ± 7*	66 ± 6	50 ± 8	57 ± 7*
Stress LVEF (%)	M	61 ± 6	69 ± 3	53 ± 9	61 ± 5
	F	62 ± 7	72 ± 6	57 ± 7	65 ± 7
Rest ESVi (mL/m²)	M	17 ± 5	20 ± 6	25 ± 6	26 ± 5
	F	14 ± 5	15 ± 6*	21 ± 8	21 ± 8*
Stress ESVi (mL/m²)	M	16 ± 6	18 ± 6	25 ± 9	22 ± 5
	F	14 ± 5	14 ± 6*	20 ± 7	18 ± 7
Rest EDVi (mL/m²)	M	33 ± 10	51 ± 14	46 ± 9	53 ± 10
	F	31 ± 9	45 ± 12	41 ± 11	47 ± 12
Stress EDVi (mL/m²)	M	40 ± 11	51 ± 17	51 ± 11	55 ± 11
	F	36 ± 9	48 ± 12	44 ± 10	49 ± 11

*$P < 0.05$ vs. men.
ESVi = ESV index; EDVi = EDV index.
Data are mean ± SD.

TABLE 5. Intra- and Interobserver Agreement for Mean LVEF, ESV, and EDV

Software package (n = 24)	Intraobserver mean stress	Interobserver mean stress	Intraobserver mean rest	Interobserver mean rest
LVEF				
CardIQ Physio	0.92	0.82	0.88	0.88
ECTb	0.87	0.93	0.83	0.68
QGS	0.99	0.90	0.98	0.89
4DM-SPECT	0.95	0.93	0.93	0.87
ESV				
CardIQ Physio	0.99	0.96	0.97	0.91
ECTb	0.87	0.94	0.97	0.83
QGS	0.99	0.93	0.99	0.93
4DM-SPECT	0.98	0.97	0.97	0.96
EDV				
CardIQ Physio	0.97	0.92	0.99	0.95
ECTb	0.95	0.93	0.94	0.92
QGS	0.99	0.96	0.99	0.96
4DM-SPECT	1.00	0.99	0.99	0.98

Data are correlation coefficients.

overestimation of LVEF in women, because, in general, women have a smaller ventricular chamber than men (15,32). Others have hypothesized that women have a higher stroke volume for any given EDV, translating into a higher LVEF (31). In either case, it is clear that sex-specific differences exist and additional studies that include a higher number of men are necessary. The results of our study nevertheless support the notion that individual reference values should be established for gated ^{82}Rb PET/CT.

CONCLUSION

There are significant differences in the reference range of the functional parameters LVEF, ESD, and EDV from gated ^{82}Rb PET/CT among most of the currently commercially available software applications. These differences have implications for the interpretation of, definition of abnormality on, and interchangeable use of quantitative results from gated ^{82}Rb PET/CT.

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