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Right-sided cardiac function in healthy volunteers measured by first-pass radionuclide ventriculography and gated blood-pool SPECT: comparison with cine MRI

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Summary

Background: Right ventricular (RV) function is of interest in an array of cardiopulmonary diseases. First-pass radionuclide ventriculography (FP), gated blood-pool single photon emission tomography (GBPS) and cardiac magnetic resonance imaging (MRI) are three currently used non-invasive methods for evaluation of right-sided cardiac function. The aim of our study was to compare the agreement between these methods when measuring right-sided cardiac function.

Methods: Twenty-four healthy volunteers were included. Mean age was 44 years (range: 25–60) and 29% were females. All participants had FP, GBPS and breath-hold cine MRI performed according to standard protocols.

Results: Normal ranges for RV ejection fraction (RVEF) defined as mean ± 2SD were 0·49–0·72, 0·44–0·66 and 0·40–0·69 when measured by MRI, FP and GBPS respectively. Bland–Altman analysis showed a mean difference (bias) between MRI and FP of 0·05 (95% CI: 0·03–0·08) and of 0·06 (95% CI: 0·02–0·10) between MRI and GBPS. No systematic bias was found between FP and GBPS. Normal values for RV end-diastolic volume index (RVEDVI) were 37–95 and 29–91 ml m^{-2} when measured by MRI and GBPS respectively. The mean difference between RVEDVI was 6 ml m^{-2} (95% CI: 0–11).

Conclusions: (i) Normal values of RVEF differ between MRI, FP and GBPS with wide limits of agreement, accordingly it is difficult to evaluate changes over time if measured by different methods, (ii) RV volumes are in the same range when measured by MRI or GBPS but with wide limits of agreement, and (iii) if MRI is considered gold standard then FP is more accurate than GBPS for RVEF measurements.

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Introduction

Assessment of the right ventricular (RV) function is of interest in an array of cardiopulmonary diseases (Oldershaw, 1992). In pulmonary hypertension the function of the right ventricle is an important prognostic factor (Rich *et al.*, 1987; D'Alonzo *et al.*, 1991) and in other chronic pulmonary diseases enlargement and dysfunction of the right ventricle is an important parameter from a clinical point of view. Also in many congenital heart diseases involvement of the right ventricle is of interest.

At present, three non-invasive methods are used for quantitative evaluation of RV function: first-pass radionuclide ventriculography (FP), gated blood-pool single photon emission tomography (GBPS) and cardiac magnetic resonance imaging (MRI). In addition, two-dimensional echocardiography is used for estimation of right-sided cardiac function but conceptually may not be very accurate or reproducible due to the complex geometry of the right ventricle which makes two-dimensional-based methods challenging. However, the recent development of commercially available three-dimensional echocardiography systems may change this.

With increased interest in quantitative assessment of RV function it becomes important to know the limits of normalcy for the methods used. Furthermore, it is important to know how the agreement is between the different methods. The aim of our study was therefore to compare the agreement between

measurements of right-sided cardiac function using each of the three currently used methods FP, GBPS and MRI.

Material and methods

Study subjects

Twenty-four healthy volunteers (Caucasians) with no history or symptoms of heart disease or other chronic disease were included. The study group had a very low likelihood of coronary artery disease (Diamond & Forrester, 1979). Mean age was 44 years (range: 25–60) and 29% were females. Mean body mass index was 25 kg m^{-2} (range: 19–32). The study was performed in accordance with the Helsinki declaration and was approved by the local scientific ethics committee. Written, informed consent was obtained from all participants.

Imaging methods

The nuclear medicine examinations and MRI study were performed within an interval of <1 month.

First-pass radionuclide ventriculography (FP)

FP is a count-based technique independent of RV geometry. Calculation of right ventricle ejection fraction (RVEF) is based on the assumption that there is proportionality between count rate and blood volume in the RV cavity in diastole and systole. FP was performed using a bolus of 700–900 MBq of ^{99m}Tc-labelled human serum albumin and a small field-of-view gamma camera (GE Starcam, General Electric, Milwaukee, WI, USA) positioned in RAO 30°. RVEF was calculated by commercially available software (eNTEGRA v. 1.5, GE Starcam). In brief, cardiac cycles representing right ventricle passage were manually selected and reframed with 16 frames per RR interval. Thereafter, separate end-diastolic and end-systolic regions of interest were manually drawn. FP does not allow for direct calculation of RV volumes or for calculation of RV mass.

Gated blood-pool SPET (GBPS)

GBPS is a volumetric technique based on visualization of the contour of the ^{99m}Tc-labelled blood pool in the RV cavity in diastole and systole. RVEF calculation is a mean of many cardiac cycles. GBPS was performed on a dual-headed, orbiting gamma camera (GE Millennium MG, General Electric) at equilibrium following the FP study. The number of frames was 16. RVEF, right ventricular end-diastolic volume (RVEDV) and right ventricular end-systolic volume (RVESV) were automatically calculated using GBPS software (Blood Pool Gated SPECT v. 1.0, Cedars-Sinai Medical Center, Los Angeles, CA, USA installed on an eNTEGRA workstation). Prior to the calculation, the images were manually reoriented and the reconstruction limits manually set. Right ventricular stroke volume (RVSV) was calculated as the difference between RVEDV and RVESV. Volumes, corrected for body surface area calculated from height and weight, are presented as RVEDV index (RVEDVI), RVESV index (RVESVI) and RVSV index (RVSVI). The method does not allow for calculation of RV mass.

Magnetic resonance imaging (MRI)

MRI is a volumetric technique based on visualization of the anatomy of the right ventricle that does not require injection of contrast agent. The technique gives precise anatomical information. MRI was performed on a 1·5 T whole-body scanner (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands) using a phased array cardiac coil (Synergy, Philips). Following localization of the long axis of the heart, contiguous true short-axis slices were acquired using breath-hold, ECG-triggered cine MRI. Each slice was obtained during one breath-hold of 20–30 s. Typically, the heart was covered by 10–15 slices of 10 mm. The number of phases obtained was 15–20 depending on heart rate. The temporal resolution was 46 ms. The field of view was 300 mm with a matrix of 256 × 256. A turbo field echo M2D cine MRI with breath hold was used (Gyroscan NT CompactPlus release 6.1.2). The sequence parameters were TR 9·6 ms, TE 4·5 ms and FA 25°. The endocardial and epicardial contours of the right ventricle were traced manually on all phases and slices using standard software (EasyVision, release 4.4, Philips). We took into consideration the shortening of the ventricle, i.e. we did not necessarily include the most basal and most apical slice in all phases. On the most basal slice we avoided the right atrium and the pulmonary artery. In all cases we started with viewing the slice dynamically in movie-mode to get an overall impression of movements including shortening and to visualize the functional separation of right ventricle and atrium. Following that, we draw our endo- and epicardial contours. We did not predefine end-systole and end-diastole but draw contours on all phases and defined end-systole and end-diastole as the phase with highest and lowest volume. In practice, this lead to phase one always being end-diastole. Right ventricle end-systole was not always the same as end-systole of the left ventricle but could be one phase apart. RVEF, RVEDV, RVESV and RVSV were then automatically calculated adding the volumes of each slice. RV myocardial mass (RVM) was also calculated using a density factor of 1·05 g ml^{-1} and the myocardial volume at end diastole. Volumes and mass were corrected for body surface area as described above. Using the described methodology the difference between RV and LV stroke volumes was <10% in all cases.

Data analyses

Comparison between values obtained by the different methods was performed using a paired *t*-test. Agreement between the methods was analysed by means of Bland–Altman plots where the central line (mean) indicates the bias and the outer lines (±2SD) indicates the limits of agreement (LoA) (Bland & Altman, 1986). The 95% confidence interval on bias was

calculated and the bias was considered significant if 0 was not embraced in the confidence interval. Data are presented as mean ± SD unless stated otherwise.

Results

The RVEF values measured by MRI, FP and GBPS are shown in Table 1. Both FP and GBPS measurements differed from MRI measurements ($P<0{\cdot}01$) whereas no significant difference was found between FP and GBPS. Normal values for RVEF defined as mean ± 2SD were 0·49–0·72, 0·44–0·66 and 0·40–0·69 when measured by MRI, FP and GBPS respectively. Bland–Altman plots of RVEF measured by MRI versus FP, MRI versus GBPS and FP versus GBPS are shown in Fig. 1. The mean difference (bias) between MRI and FP was 0·05 [95% CI on difference: 0·03–0·08; limits of agreement (LoA): −0·09–0·19], i.e. on average MRI values were 0·05 higher. The mean difference between MRI and GBPS was 0·06 (95% CI on difference: 0·02–0·10; LoA: −0·11–0·23) and 0·01 (95% CI on difference: −0·04–0·05; LoA: −0·19–0·21) between FP and GBPS.

The mean 'within-method' difference (inter-observer difference) was −0·02 (95% CI on difference: −0·05–0·01; LoA: −0·10–0·06) for MRI, 0·00 (95% CI on difference: −0·03–0·02; LoA: −0·07–0·06) for FP, and −0·02 (95% CI on difference: −0·05–0·01; LoA: −0·10–0·06) for GBPS.

The RVEDVI, RVESVI and RVSVI values measured by MRI and GBPS are shown in Table 2. RVEDVI and RVSVI measured by GBPS differed from the MRI measurements ($P<0{\cdot}05$) whereas RVESVI did not. The normal values defined as mean ± 2SD for RVEDVI were 37–95 and 29–91 when measured by MRI and GBPS respectively. Measured values and normal values for RVEDVI, RVESVI and RVSVI are summarized in Table 2. Figure 2 shows Bland–Altman plots of RVEDVI, RVESVI and RVSVI measured by MRI versus GBPS. The mean differences between MRI and GPBS were: RVEDVI, 6 ml m^{-2} (95% CI on difference: 0–11; LoA: −21–33); RVESVI, −2 ml m^{-2} (95% CI on difference: −5–1; LoA: −12–27); and RVSVI, 8 ml m^{-2} (95% CI on difference: 4–12; LoA: −12–27).

The mean 'within-method' differences (inter-observer difference) for MRI were: RVEDVI, 1 ml m^{-2} (95% CI on difference: 0–3; LoA: −5–7); RVESVI, 2 ml m^{-2} (95% CI on difference: 0–4; LoA: −5–9); and RVSVI, −1 ml m^{-2} (95% CI on difference: −2–1; LoA: −6–5). For GBPS the mean 'within-method' differences (inter-observer difference) were: RVEDVI, −1 ml m^{-2} (95% CI on difference: −7–4; LoA: −18–16); RVESVI, 1 ml m^{-2} (95% CI on difference: −2–3; LoA: −7–8); and RVSVI, −2 ml m^{-2} (95% CI on difference: −6–3; LoA: −14–11).

Right ventricular myocardial mass index (RVMI) measured by MRI was 25 ± 7 g m^{-2} (range: 14–43). The normal values defined as mean ± 2SD for RVMI were 10–40 g m^{-2}.

Table 1 RVEF measured by magnetic resonance and two different nuclear medicine techniques in 24 healthy volunteers.

RVEF	MRI	FP	GBPS
Mean ± SD	0·60 ± 0·06	0·55 ± 0·05**	0·54 ± 0·07**
Range (min–max)	0·50–0·72	0·46–0·69	0·46–0·69
Range (mean ± 2SD)	0·49–0·72	0·44–0·66	0·40–0·69

RVEF, right ventricular ejection fraction; MRI, magnetic resonance imaging; FP, first-pass radionuclide ventriculography; GBPS, gated blood-pool SPECT.

**$P<0{\cdot}01$ versus MRI by paired *t*-test. There was no significant difference between FP and GBPS.

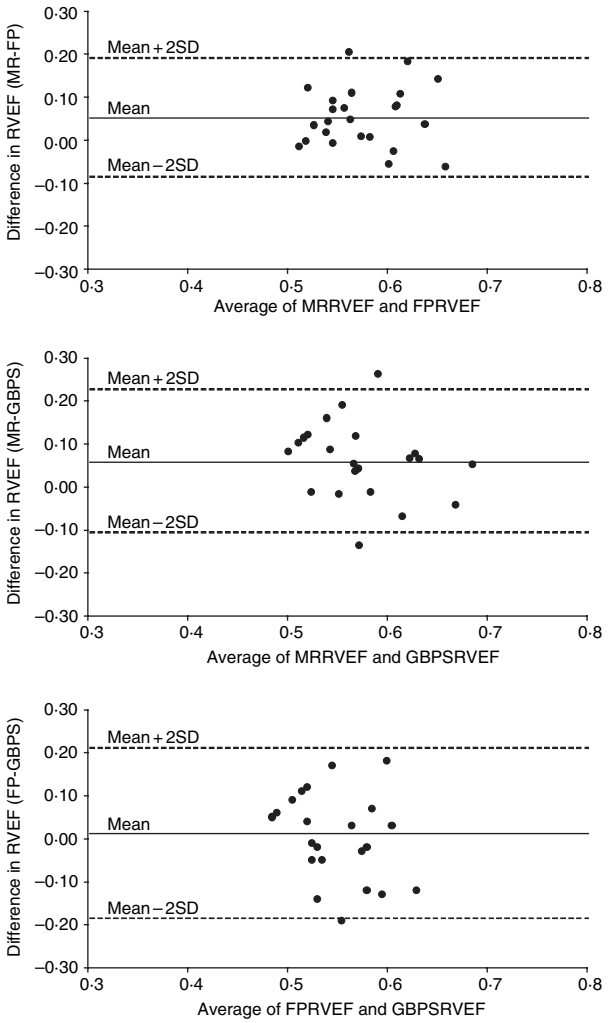

Figure 1 Bland–Altman plots comparing three methods for measurement of right ventricular ejection fraction (RVEF) in healthy volunteers. MRRVEF: RVEF measured by magnetic resonance, FPRVEF: RVEF measured by first-pass radionuclide ventriculography and GBPSRVEF: RVEF measured by gated blood-pool SPECT. The central line (mean) indicates the bias and the outer lines (±2SD) indicate the limits of agreement.

Discussion

Measurement of RV function is important in many cardiopulmonary diseases that affect the function and geometry of the

Table 2 Right ventricular volumes measured by magnetic resonance imaging (MRI) and gated blood-pool SPECT (GBPS) in 24 healthy volunteers.

	MRI	GBPS
RVEDVI (ml m^{-2})		
Mean ± SD	66 ± 15	60 ± 15*
Range (min–max)	36–100	19–89
Range (mean ± 2SD)	37–95	29–91
RVESVI (ml m^{-2})		
Mean ± SD	26 ± 7	28 ± 9
Range (min–max)	10–42	6–44
Range (mean ± 2SD)	11–41	10–46
RVSVI (ml m^{-2})		
Mean ± SD	40 ± 9	32 ± 9***
Range (min–max)	23–58	13–52
Range (mean ± 2SD)	22–57	14–50

RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVSVI, right ventricular stroke volume index.
*P<0·05, ***P<0·001 versus MRI by paired *t*-test.

right side of the heart (Oldershaw, 1992). Monitoring in connection with diseases such as chronic obstructive pulmonary disease and pulmonary hypertension may be clinically relevant in order to detect cardiac involvement at an early stage in order to prevent overt heart failure. Although many methods have been evaluated and compared with respect to function and volume of the left ventricle the data on performance of the different methods with respect to RV function is sparser.

Currently, the three most used methods for quantitative evaluation of the right ventricle are FP, GBPS and MRI, which we all included in our study. We did not include two-dimensional echocardiography as we believe it is generally not considered a quantitative method with regard to the right ventricle. Planar equilibrium multiple ECG-gated isotope ventriculography is not useful for RVEF as it is not possible to separate the right ventricle and its results show a very high variability (Marving *et al.*, 1985).

Using these methods we found that the normal values of RVEF differed between the methods. Of clinical interest is probably the lower threshold of the normal range of RVEF, which was 0·49, 0·44 and 0·40 for MRI, FP and GBPS respectively. The value for lower normal RVEF measured with breath-hold cine MRI has in previous studies been found to be in the range of 0·45–0·57 with most of the studies around 0·45–0·49 (Boxt *et al.*, 1992; Lorenz *et al.*, 1999; Rominger *et al.*, 1999; Sandstede *et al.*, 2000). When using FP technique the lower normal value of RVEF was found to be significantly lower, namely 0·44. Previous studies of using methodology similar to our have found the lower normal value to be 0·39–0·54 (Marving *et al.*, 1985; Schulman, 1996). When comparing the values of RVEF measured by MRI and FP in the same subject a systematic bias was present as MRI values were on average 0·05 higher. Furthermore, the LoA are wide which should be kept in mind when comparing data obtained with the two modalities.

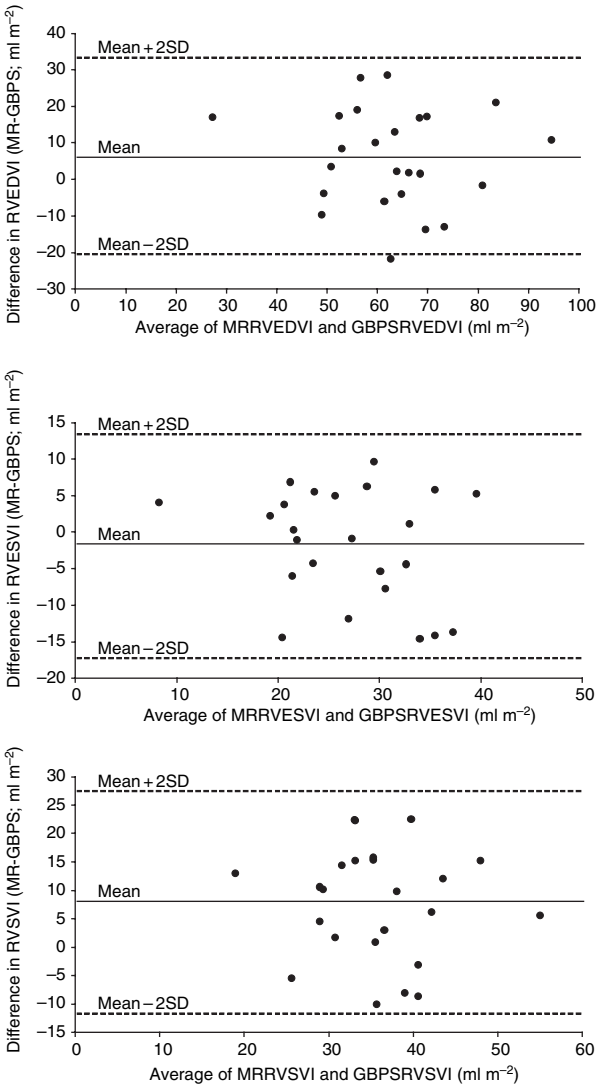

Figure 2 Bland–Altman plots comparing magnetic resonance (MR) and gated blood-pool SPECT (GBPS) for measurement of right ventricular volumes in healthy volunteers. Right ventricular end-diastolic volume index (RVEDVI; upper panel), right ventricular end-systolic volume index (RVESVI; middle panel) and right ventricular stroke volume index (RVSVI; lower panel). The central line (mean) indicates the bias and the outer lines (±2SD) indicate the limits of agreement.

Accordingly, it is difficult to evaluate changes in RVEF over time if measured by different methods at different time points. We and others (Hoilund-Carlsen *et al.*, 1987; Pattynama *et al.*, 1995) found that the LoA between repeated RVEF measurements with the same technique were lower both for FP and MRI. When measured by GBPS technique, the lower normal value of RVEF was even lower namely 0·40. Compared with MRI values, RVEF measured by GBPS have a systematic bias as GBPS values are on average 0·06 lower. LoA between MRI and GBPS were even wider than was the case between MRI and FP. No systematic bias was present between RVEF measured by FP and GBPS but wide LoA were present (risk of statistical type II error in our study around 20%). The systematic bias found between some of the

methods seem not just to be caused by low reproducibility and measurement errors as a bias was not found within any of the methods and the LoA were much narrower. The reproducibility of the three methods for RVEF measurements was similar. Thus, the degree of automation in calculations did not seem to influence the variability. It should, however, be noted that none of the methods were fully automated. Which method should be considered the gold standard for RVEF? We found a very good agreement between left ventricular stroke volume and RV stroke volume ($R = 0{\cdot}98$) using MRI. Therefore, we consider MRI of RVEF and RV volumes are the gold standard, as MRI is widely accepted as the gold standard for left ventricle evaluation. If MRI is considered the gold standard, FP seems to be more accurate than GBPS for determination of RVEF.

If RV volumes are to be measured only MRI and GBPS are capable of doing this directly. Normal values for RVEDVI were slightly higher when measured by MRI than by GBPS ($P = 0{\cdot}044$). However, the mean difference of 6 ml m^{-2} only represents a relative difference of 11%. Thus for most purposes the values are within the same range. Furthermore, upper normal limits, which are the most important measure from a clinical point of view, were found to be 95 and 91 ml m^{-2} using MRI and GBPS respectively. RVESVI did not differ between the two methods. Accordingly, RVSVI was higher when measured by MRI compared with GBPS. However, although the different normal values of RV volumes were in the same range when measured by MRI and GBPS and the values on average were quite similar the LoA still were rather wide. In general, our values of MRI volumes were in the same range as found by others (Lorenz *et al.*, 1999; Rominger *et al.*, 1999; Sandstede *et al.*, 2000; Alfakih *et al.*, 2002).

Measurement of the volume of the myocardium and thereby mass is possible by MRI but not by FP or GBPS. The normal values for RVMI of 10–40 g m^{-2} found by us is in accordance with several previous studies (Doherty *et al.*, 1992; Katz *et al.*, 1993; Lorenz *et al.*, 1999; Sandstede *et al.*, 2000).

Which method should then be used for RV evaluation? Based on the very close agreement of right and left ventricular stroke volumes found by us, MRI is probably to be considered the gold standard. However, we found good agreement between MRI and FP RVEF and between MRI and GBPS RV volumes. Thus, different useful methods are available and factors like cost, availability of equipment and the measures needed may influence the final choice. Whereas, MRI is able to measure function, volumes and mass, and this may also be the most expensive and laborious of the methods. The patient has to be cooperative if a breath-hold technique is used and should not be claustrophobic the latter being a problem in 4–5% of patients (Francis & Pennell, 2000). Furthermore, and probably most important, to our knowledge no reliable automatic contouring for the right ventricle exists at present. Therefore, endocardium and epicardium must be contoured by hand and on all phases. This is rather laborious and limits the use for routine purposes. However, MRI is a real non-invasive method without use of contrast media or radioactive isotopes. Further, MRI is a powerful technique as it – within less than half an hour of scanner time – offers the opportunity to evaluate volumes and ejection fraction of both ventricles, myocardial mass of both ventricles as well as quantification of forward and backward flow in relation to valves and large vessels. This integrated information of functional and anatomical nature is of importance in a variety of clinical settings, e.g. congenital cardiac diseases prior to surgery. With GBPS function and volumes are measured. The technique requires an orbiting gamma camera. Claustrophobia is normally no problem and the patient does not have to cooperate apart from quiet supine resting for 20–30 min. Calculations are performed automatically by commercially available software. When MRI is considered gold standard, GBPS is quite reliable with respect to RV volumes but somewhat less reliable with respect to RVEF. With FP it is only possible to measure RVEF. However, in many instances this is sufficient as major dilatation will almost always be accompanied by a reduced RVEF, i.e. a normal RVEF is indicative of normal right-sided function and volumes. Compared with MRI, FP RVEF correlates better than RVEF measured by GBPS. Compared with MRI of RV, FP is a more simple method requiring only a non-orbiting gamma camera with a small field of view and may be regarded as a low-cost procedure. Calculations, which are performed semi-manually with commercially available software, are quite fast (<5 min). If wanted, FP and GBPS may be combined as the bolus injected for the FP study may be used for a subsequent GBPS study. Based on the above-mentioned argument, at present for routine purposes we use FP if only RVEF is requested. If RVEF and volumes are requested we perform FP for RVEF measurement and immediately thereafter GBPS for volumes using the same dose of radionuclide. We use MRI if more information than RVEF and RV volumes is needed or if very accurate measurements are needed as, e.g. in research projects. However, comparative studies in patients with severe reduction of RVEF are needed to establish concordance between the different modalities also in a diseased population. At present, only few comparative studies have been undertaken in patients (Chin *et al.*, 1997; Bartlett *et al.*, 2001; Nichols *et al.*, 2002). In general, these studied found good or fair agreement between the modalities. Although several routine methods are available for measurement of RVEF and RV volumes the exact role and impact in clinical practice still has to be established.

In summary, we found that (i) values of RVEF differ significantly between MRI and FP or GBPS, respectively, (ii) the LoA between the methods are wide, (iii) when MRI is considered gold standard, FP is more accurate than GBPS for RVEF measurements, and (iv) RV volumes in general are in the same range when measured by MRI or GBPS. We conclude that if MRI is not used for assessment of RV function FP should be preferred for RVEF and GBPS may be used for volumes. The final choice of method depends on measures needed, availability of equipment and costs. However, it should be kept in mind that values obtained by the different methods are not directly comparable and separate reference values are needed for each method.

Study limitations

The normal ranges reported by us were for comparison between methods. Normal values are influenced by age and gender and should be established locally at each centre using large populations. Furthermore, the present study was performed in normal subjects only. Therefore, the conclusions drawn are based on RVEF and RV volumes in the normal range.

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