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VENTRICULAR FUNCTION

Comparison of Techniques for the Measurement of Left Ventricular Function Following Cardiac Transplantation

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ABSTRACT

Background: Assessment of graft function after cardiac transplantation is essential for patient management and clinical research. Previous studies have found that the left ventricular (LV) ejection fraction (EF) by echocardiography (echo), radionuclide ventriculography (RNV), and cardiovascular magnetic resonance (CMR) is discrepant in patients with heart failure.

Method: Twelve patients underwent LV EF assessment by echo, angiography (angio), RNV, and CMR one year following heart transplantation. The scans were analyzed independently in blinded fashion.

Results: The mean EF was 63 ± 6% by RNV, 66 ± 6% by CMR, 70 ± 12% by angio, and 74 ± 4% by echo. Significant differences were found between CMR and echo ($p < 0.001$), RNV and echo ($p < 0.001$), and RNV and angio ($p < 0.05$). The correlation between the techniques was poor ($r = 0.3–0.6$), and the scatter plots also suggested considerable variations between techniques. This was confirmed by the wide Bland–Altman limits of agreement (ranging from 22 to 45%). These were particularly wide for comparisons with angiography (43–45%).

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Conclusion: The EF measurement by echo, angio, RNV, and CMR are not interchangeable in patients following heart transplantation. The CMR and RNV provided the best agreement in EF and appear preferable for research studies. Echocardiography systematically overestimated LV EF and showed poor agreement with other techniques. Angiography overestimated LV function, and its routine use did not add to information gained from noninvasive studies.

Key Words: *Angiography; Echocardiography; Radionuclide ventriculography; Cardiovascular magnetic resonance*

BACKGROUND

Assessment of graft function after cardiac transplantation provides information about both acute and chronic rejection and is essential for patient management and clinical research (1–3). Echocardiographic (echo) methods can be used to diagnose acute rejection (4,5), and measurement of left ventricular (LV) function has prognostic significance in this population (6). Despite the availability of several different imaging techniques to assess LV function, the results of each method have not been compared in patients following heart transplantation.

We previously have found that the LV volumes and EF by echo, radionuclide ventriculography (RNV) and cardiovascular magnetic resonance (CMR) are not interchangeable in patients with heart failure (7,8). Factors contributing to this are the presence of regional wall motion abnormalities and regional shape deformation in dilated ventricles that do not conform to the geometric assumptions used by echo (9,10). In contrast, transplantation patients receive anatomically normal donor hearts that may undergo a remodeling process characterized by hypertrophy (11–13), thereby maintaining a normal geometric shape with no additional regional wall motion abnormality. In view of this, the ejection fraction (EF) by echo, invasive left ventriculography (angio), and RNV might be expected to be similar in this population.

It is important to know how comparable various measurements of LV function are in the transplant population, both to interpret the results of research studies and to use such measurements to guide patient management. We, therefore, aimed to compare EF assessment by echocardiography (echo), angiography (angio), RNV, and CMR in patients one year following orthotopic heart transplantation.

METHODS

Patients

Twelve patients underwent echo, angio, RNV, and CMR 365 ± 11 days following orthotopic heart transplantation as part of a routine one year postoperative evaluation. All were Caucasian, nine were male and the mean age was 51 ± 9 years. All patients were clinically well at the time of the study, and all had normal coronary arteries at angio. All the scans were completed within 4 ± 8 days of each other. No patient had evidence of rejection on cardiac biopsy at the time of scanning, and there was no change of medication or clinical condition between scans. Different investigators who were blinded to the results of the other techniques performed all acquisitions and analysis. Royal Brompton and Harefield Hospital Ethical Committee approved the protocol. All subjects gave written consent.

Echocardiography

Echo was performed using 2D guided M-mode echo in the left lateral decubitus position with the head of the bed elevated by 30°. The LV EF was calculated in accordance with the standard clinical formula (cube method), which assumes that the LV cavity approximates an elllipsoid whose volume can be calculated by cubing the minor axis dimension (14), where LV EF was equal to $(EDV - ESV)/EDV$ and $EDV = EDD^3$, $ESV = ESD^3$. All measurements were performed by an experienced cardiac sonographer.

Angiography

Angio was performed during retrograde left heart catheterization using a pigtail catheter. The ventricle was defined by a single injection of nonionic (Ultravist) angiographic contrast. The LV volumes were calculated at end diastole and end systole by the right anterior oblique single plane method described by Dodge et al. (15,16). The ventricular border was determined by visual inspection with the papillary muscles included in the outline. Any premature ventricular contraction and immediately following beats were excluded from the analysis. Software was provided by the GE Advantax System.

Radionuclide Ventriculography

In vivo labeling was performed using stannous pyrophosphate and 800 MBq Tc-99m pertechnetate, and data were acquired by a Trionics dual headed scanner in the left anterior oblique view with the patient in the supine position. Parameters included: electrocardiogram (ECG) gating with a 10% window, photopeak 140 KeV, 20% window with no offset, 64×64 matrix, 3–4 mm pixel size, 32 frames and acquisition to 5 million counts. The LV EF was calculated by dividing the background-corrected difference in end-systolic (minimum) and end-diastolic (maximum) counts by the end-diastolic counts. All patients were in sinus rhythm.

Cardiovascular Magnetic Resonance

Subjects were scanned on a Picker Edge 1.5 T scanner (Marconi, Cleveland, OH), using the body coil and ECG triggering (8). The cardiac short axis was positioned using three scout images: transverse, vertical, and horizontal long axis. The basal short-axis slice was positioned just forward of the atrio-ventricular ring from a diastolic breath-hold horizontal long-axis image, and all subsequent short-axis cines were acquired in 1-cm steps toward the apex. A segmented gradient-echo Turbo-FLASH sequence was used with acquisition during a single breath hold. Parameters were as follows: TE 3.8 msec, TR = RR interval, slice thickness 10 mm, field of view 35×35 cm, read matrix 128, phase matrix 128, frames 16, flip angle 35°, phase-encoded group 6–10. An average of 10 short-axis cines were needed to encompass the entire left ventricle. The average scanning time was 18 min.

Image analysis was performed on a personal computer using in-house-developed software (CMRtools© Imperial College). Short axis end-diastolic and end-systolic images were chosen as the maximal and minimal mid-ventricular cross-sectional areas in a cinematic display. End-diastolic and end-systolic endocardial borders for each slice were manually traced, with the summation representing the overall volumes. The difference in the summed end-diastolic and end-systolic volumes equalled the LV stroke volume. Ejection fraction (%) was calculated as LV stroke volume/LV end-diastolic volume. Papillary muscles were excluded from the volume (17).

Statistical Analysis

The mean differences in EF were calculated between each technique, and Student's *t*-test was used to determine statistical significance. A line of identity on a scattergram was drawn between each technique to allow a visual assessment of agreement. The correlation coefficient was then calculated to assess the strength of the relation. However, since correlation does not necessarily represent agreement (18,19), the Bland–Altman limits of agreement were also determined, with the difference in EF between techniques established for each subject along with the range of values within which 95% of the differences were expected to lie (20). Results are presented as mean ± standard deviation.

RESULTS

The mean EF for each technique is shown in Fig. 1. The EF was 63.0 ± 6% by RNV, 66.1 ± 6% by CMR, 70.1 ± 12% by angio, and 74.2 ± 4% by echo (Fig. 1).

When comparing the results of the different techniques, a number of significant differences were found (Table 1). The CMR and echo differed by a mean of 7.7 ± 5.9% ($p < 0.001$), RNV, and echo by 10.8 ± 4.6% ($p < 0.001$), and RNV and angio by 7.3 ± 11% ($p < 0.05$). Other differences were not significant.

The strength of the relationship between techniques was also assessed by calculating the correlation coefficient. The closest correlation was between echo and RNV, although this only reached 0.6. All other correlation was poor, with echo and CMR representing the worst at 0.3.

The individual differences in EF between techniques can be readily recognised from the scatter plots in Fig. 2, with wide scatter around the line of agreement.

Of particular importance are the Bland–Altman limits of agreement, within which 95% of the differences were expected to lie. These limits are listed in Table 1 and shown in Fig. 2 and are wide for every comparison, with the smallest difference between techniques being 22% (echo and RNV). The Bland–Altman limits of agreement

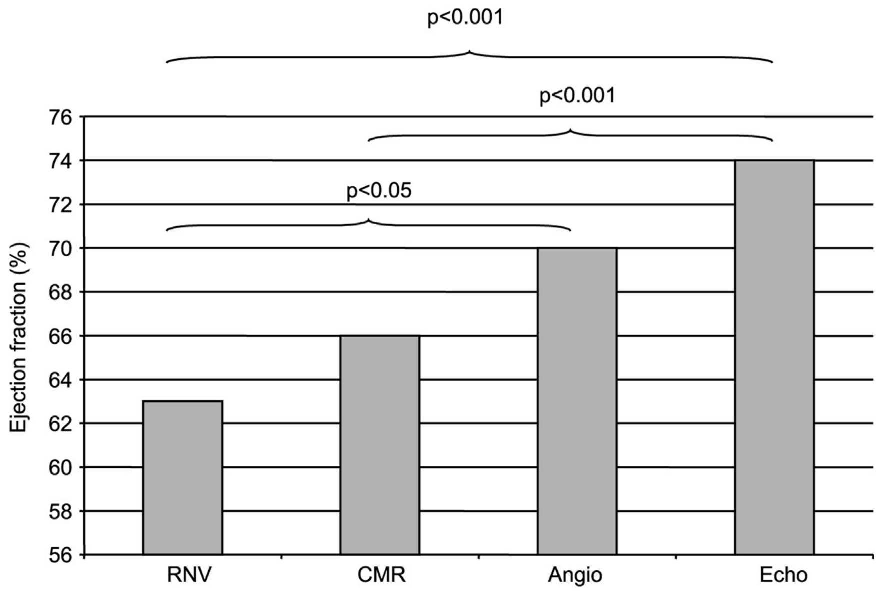

Figure 1. Mean EF by echo, angio, RNV, and CMR.

were particularly wide for comparisons with angio, ranging from 43 to 45%.

DISCUSSION

The main finding of this study was the systematic differences between the four methods for measuring LV function in heart transplant patients. Such differences confirm that results of differing modalities are not interchangeable.

It is not possible from this study to determine which of the modalities was more accurate as no "gold standard" was available. Nevertheless, CMR and RNV provided the best agreement in EF (no significant mean difference and reasonable Bland–Altman limits of agreement) and, therefore, appear preferable for research studies. The exposure to ionizing radiation required by RNV, together with previously published excellent reproducibility of CMR posttransplantation (17) studies would suggest, however, that of the two, CMR is the preferable technique for serial studies of patients.

Systematic differences arise between techniques for a number of reasons. CMR takes into account all the segments of the LV, while M-mode echo, as well as being operator and acoustic window dependent, only measures

Table 1

The Mean Differences and Standard Deviation (SD) for Ejection Fraction Between Each Technique, Together with the Student's t-test and Correlation Coefficient (The Bland–Altman Limits of Agreement Are Also Illustrated and Represent Absolute Ejection Fraction Units (%))

	Mean Difference ± SD (%)	*p*-value	Correlation	Bland–Altman Limits (%)	Range of Bland–Altman Limits (%)
Angio-RNV	7.3 ± 11	<0.05	0.4	−15–30	45
Echo-RNV	10.8 ± 4.6	<0.001	0.6	+2–20	22
CMR-RNV	3.1 ± 7.2	0.16	0.3	−11–17	28
Angio-Echo	−3.4 ± 11	0.3	0.5	−25–18	43
Angio-CMR	4.2 ± 11	0.2	0.5	−18–26	44
Echo-CMR	7.7 ± 5.9	<0.001	0.3	−4–20	24

a single segment and assumes that this is representative of the entire LV. Echo is also operator and acoustic window dependent, and the volumes and mass are calculated from formulae based on geometric assumptions. These assumptions do not hold true in the presence of regional abnormalities. Furthermore, as the LV volume increases, the LV becomes more spherical and the relation between length and diameter is altered. As a result, as the LV diameter increases, the 95% confidence interval of prediction of LV volume from the diameter rapidly increases (21). Two-dimensional echo overcomes some of these problems but still extrapolates data from limited views, which are dependent on correct angulation of the probe, gain-dependent edge identification, and good endocardial border definition. As a consequence, this study found that the EF by echo was significantly greater than that of both CMR and RNV. Systematic differences between angio and other techniques have also been described (21) due to the geometric assumptions of angio, together with differences introduced by the use of contrast volume load and vasodilator effects. The RNV is based on projection of an image and is affected by varying attenuation between anterior and posterior walls, as well as errors from overlapping structures. It is also subject to background subtraction errors and systematic bias in the placement of the regions of interest. As a result, RNV measurements are generally center dependent (22) and in this study underestimated the EF when compared to angio and echo, with a trend to underestimation with CMR.

The CMR provides high resolution images in any desired plane without the need for ionizing radiation. As a consequence, a stack of contiguous short-axis slices that encompass the entire left ventricle can be acquired and the precise volumes, mass, and function calculated without the need for geometric assumptions. This results in measurements that are not only accurate (23–27) but highly reproducible (28–32). Furthermore, the current fast sequences allow this to be achieved in a shorter imaging time than many of the other techniques (8).

The RNV has been reported previously as a precise measure of EF, and the results in this study were similar to that of CMR but significantly different to echo ($p < 0.001$) and angio ($p < 0.05$). In clinical practice, echo is perhaps the most valuable technique readily available, time efficient, and cost effective, but the results are less precise and subject to the problems already mentioned. The RNV is widely available but requires ionizing radiation, longer imaging times, and is generally less acceptable to patients (8). Angio is the most variable, being dependent on the physiological state that is itself altered by the procedure and the use of contrast agent.

Although the direct comparison of these techniques has not been previously described in the transplant population, studies have been performed in different settings. For example, studies in heart failure have demonstrated wide limits of agreement and systematic bias in volume estimation between techniques (7). Indeed, Naik et al. found that a patient with an EF of 40% by echo could have an EF of between 20 and 60% by RNV (33). Similar findings have been described in patients following myocardial infarction (34–36). Patients in this study did not suffer the same degree of dilatation and regional wall motion abnormality that limits the agreement in patients with heart failure. Nevertheless, the agreement between techniques remained poor. Interestingly, the systematic bias in this study reflected studies in heart failure, with RNV giving the smallest estimation of EF, echo the greatest, and CMR lying between the two (7).

Study Limitations

The study population was selected consisting of patients who were clinically well and free of angiographic coronary disease and who did not have regional wall motion abnormalities. The results might be expected to show greater differences if patients with wall motion abnormalities were included. The aim of this study was to evaluate the imaging techniques currently used in clinical practice. Quantitative two-dimensional echo is not routinely used at our center in transplant patients and was not, therefore, evaluated. It may, however, offer a realistic alternative to M-mode assessment where CMR is not available. Nevertheless, 2D echo still extrapolates data from a limited sampling of the LV and is highly dependent on good endocardial border definition. Similarly, gated SPECT was not used in this study, although other studies have shown a reasonable correlation with EF from CMR, but with wide limits of agreement and evidence of systematic bias (37). A further limitation was that all the scans were not completed on the same day, although the interval between scans was limited.

CONCLUSION

The EF measurement by echo, angio, RNV, and CMR are not interchangeable in patients following heart transplantation. Ideally, patients should undergo serial

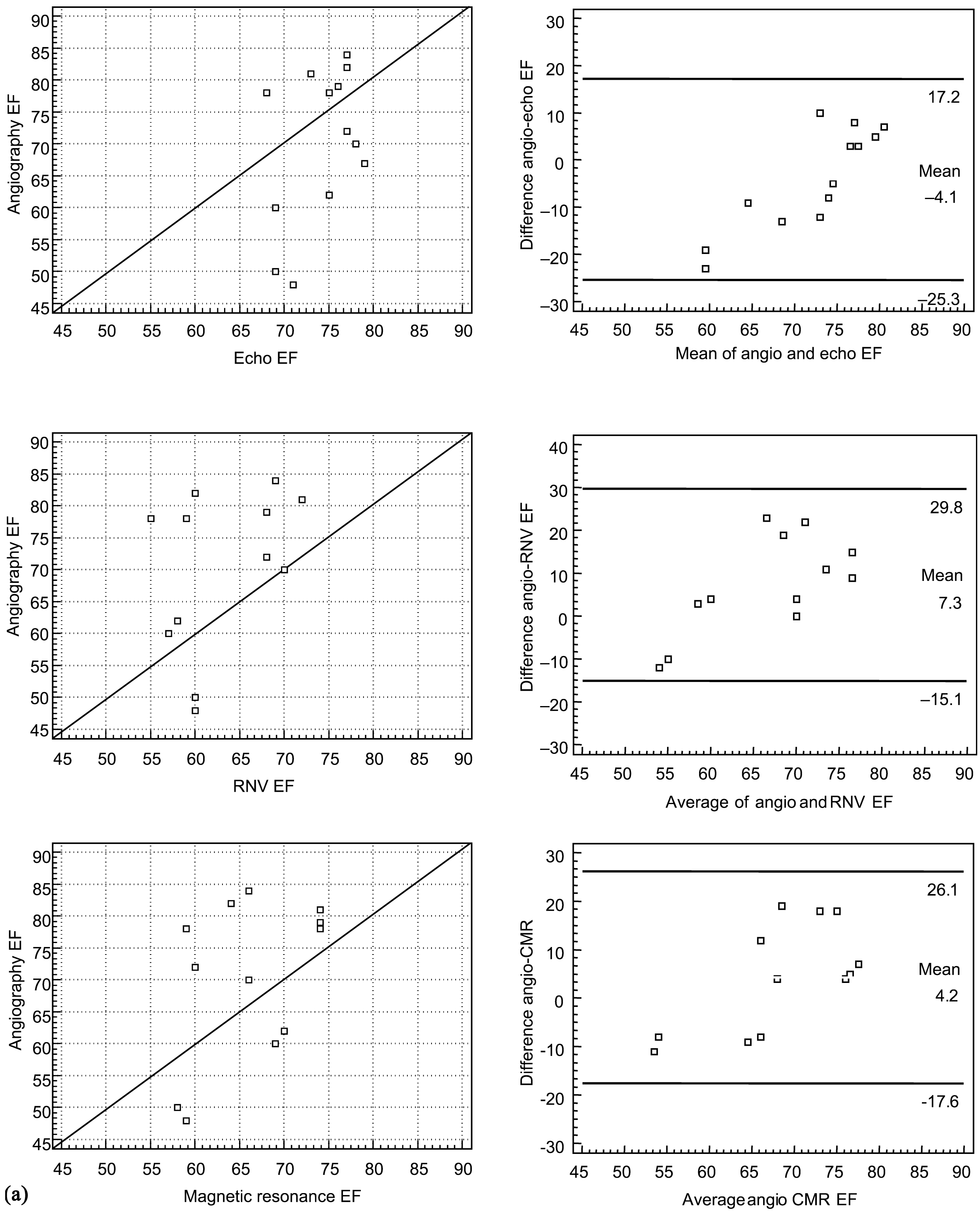

Figure 2. (a) and (b) Scatter plots with line of agreement and Bland–Altman plots for comparisons between techniques.

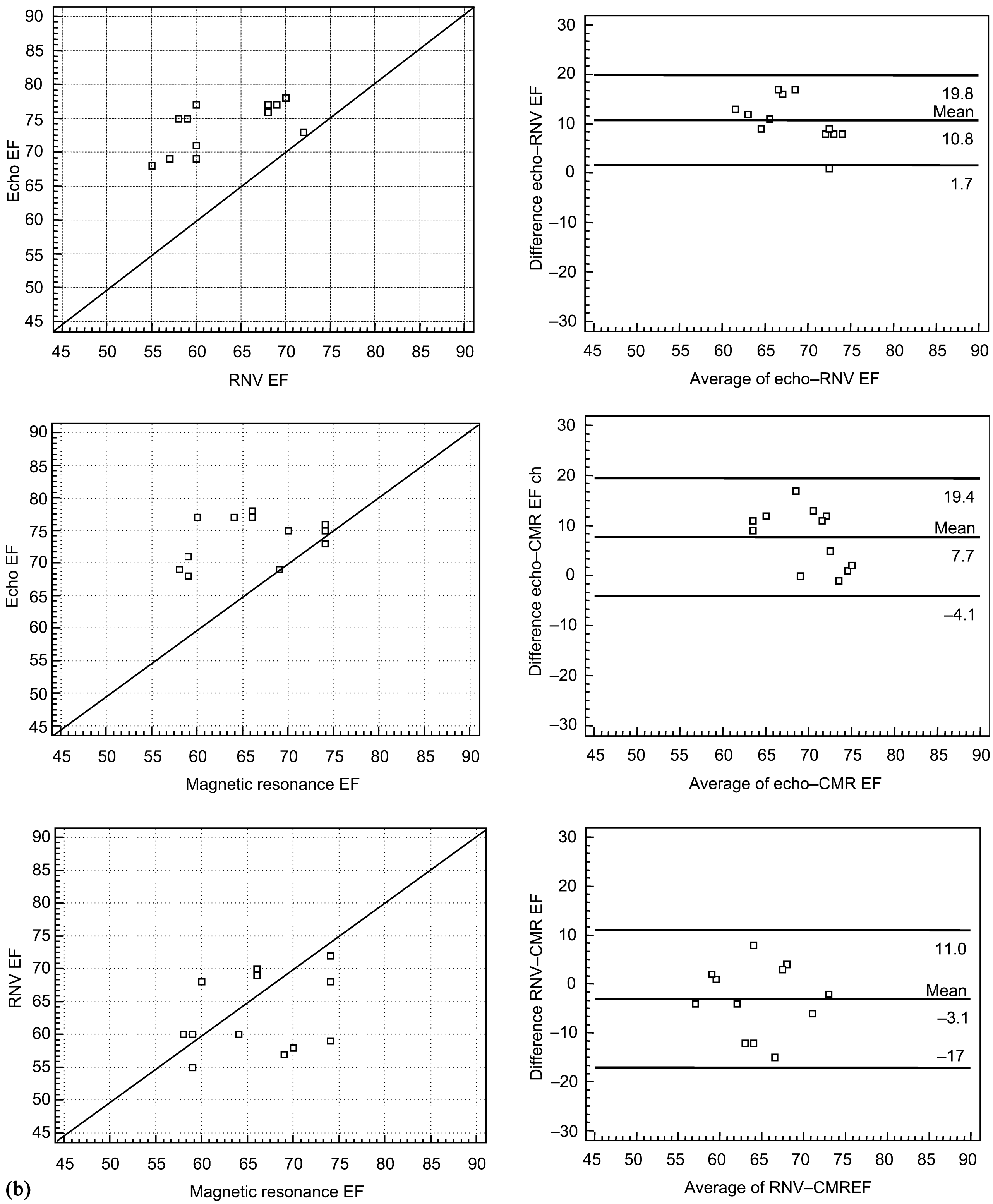

Figure 2. Continued.

assessment using one technique with high interstudy reproducibility, and the results of published research should also be considered in the context of the technique used. In this study, CMR and RNV provided the best agreement in EF (no significant mean difference and reasonable Bland–Altman limits of agreement) and appear preferable for research studies. The RNV slightly underestimated EF in comparison to CMR but the difference was not clinically significant. Studies using RNV, however, do require repeated doses of ionising radiation. Echo systematically overestimated LV EF and showed poor agreement with other techniques. Echo is readily available and easily repeatable and is, therefore, frequently used to monitor the progress of individual patients. For this purpose, the systematic error is unimportant, but the limited agreement with other techniques must be borne in mind when interpreting the results. Angio overestimated LV function and had wide limits of agreement with other techniques. Its routine use did not add to information gained from noninvasive studies. Eliminating routine ventriculography will reduce the risk of contrast nephropathy in this population (38).

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