Comparison and Co-Relation of Invasive and Noninvasive Methods of Ejection Fraction Measurement

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Background: Accurate estimation of left ventricular ejection fraction (LVEF) has assumed great significance in the era of automatic implantable cardioverter defibrillators (AICDs), and a low EF may be one of the sole deciding factor in determining AICD implantation in certain patient populations.

Aim: There are various methods, invasive and noninvasive, which can help calculate EF. We sought to conduct a retrospective study comparing EF estimation by invasive (angiography) and noninvasive methods [MUGA (multiple-gated acquisition), echocardiography (echo), single-photon emission computed tomography (SPECT)] in 5,558 patients in our hospital from 1995–2004.

Methods and Results: EF was estimated by ≥1 method (angiography, MUGA, echo, SPECT) within a one-month period. Values for the four tests in 5,558 patients were as follows: angiography mean 46.2, range 20–75, standard deviation (SD) 13.1; MUGA mean 45.7, range 20–70, SD 11.6; echo mean 45.7, range 22–70, SD 11.2; and SPECT mean 54.4, range 30–75, SD 11.9. Excellent positive correlations were found among all four tests as follows: angiography and MUGA, correlation coefficient (r)=0.97, angiography and echo r=0.96, angiography and SPECT r=0.94, MUGA and echo r=0.97, MUGA and SPECT r=0.94, and echo and SPECT r=0.94. Values for SPECT were significantly higher than for angiography, echo and MUGA ($p<0.001$). The arithmetic difference between angiography and MUGA (mean 0.50, range -5.0–5.0) and the arithmetic difference between angiography and echo (mean 0.52, range -5.0–15.0) were similar ($p=0.59$). The arithmetic difference between SPECT and angiography (mean 8.2, range -15.0–20.0) was significantly larger than the arithmetic difference between angiography and echo ($p<0.001$).

Conclusions: All the four methods used to estimate EF co-relate well with each other. However, values estimated during stress testing by SPECT overestimate EF and are significantly higher as compared to MUGA, echo and angiography. Estimation of EF by MUGA, echo or angiography should be preferred over SPECT, especially when that patient warrants intervention. We conclude that the overestimation of EF by SPECT may deprive some deserving patients of the survival benefit afforded by ICD.

Key words: cardiovascular ■ imaging

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INTRODUCTION

Cardiovascular disorders account for increasing numbers of U.S. hospitalizations per year and are on the rise. With two-thirds of left ventricular (LV) dysfunction due to coronary artery disease, the total mortality rose by 148% during 1979–2000.[1,2] Low left ventricular ejection fraction (LVEF) may lead to ventricular arrhythmias and sudden cardiac death, which contributes to a large portion of the mortality. Keeping in mind the above possibility, many of these patients are recommended automatic implantable cardioverter defibrillator (AICD) devices as primary prevention based on ejection fraction (EF).[3-8] There are many modalities to estimate EF such as angiogram, echocardiography (echo), single-photon emission computed tomography (SPECT), multiple-gated acquisition (MUGA) and, more recently, magnetic resonance imaging (MRI)—some or all of which a patient may undergo as a part of his cardiac work-up. However, while qualifying these patients for AICD, there are very strict guidelines which consider the highest values of EF when evaluating a patient for AICD. This rule is laden with fallacies, as some patients who come for a stress test following angioplasty or bypass surgery may have EF estimation by SPECT, which may be falsely high and thus deprive a deserving patient of primary prevention from ventricular arrhythmias.[9-11]

While LV angiography is held as the gold standard[12-14] for consistent, reliable and reproducible LVEF, its side effects, common to all invasive procedures, makes it prudent not to use on a frequent basis, especially given the availability of noninvasive measurement like echo, MUGA scan and SPECT, as used in our study.

We performed a large-scale retrospective study of 5,558 charts of patients who underwent coronary angiogram for various indications and ≥1 of the above-mentioned tests other than angiogram, i.e., echo and/or MUGA and /or SPECT within a one-month timeframe, over a 10-year period (1994–2004). Using angiogram both independently and as a yardstick, we co-related the four tests with each other and performed correlation and comparison analysis, proving some meaningful results that will help shed some light on the elusive debate of finding a practically reliable noninvasive modality.

METHODS

Patient Population and Inclusion and Exclusion Criteria

Patients were selected from the database of a community center in southern Brooklyn over 10 years from 1994–2004. Nine-thousand, eight-hundred-sixty consecutive patients who underwent diagnostic coronary angiography for various indications were included in the study. After this, retrospective chart analysis was done to see how many of the selected patients had other tests (echo, MUGA, SPECT) for EF quantification within one month of the angiogram. Patients who had interval myocardial infarction; recurrent exacerbations of heart failure; had echo, SPECT or MUGA done after interval revascularization; or those who had the studies beyond the one-month period were excluded from the study. This left us with 5,558 patients who had ≥1 study other than angiogram and did fit into the above criteria.

Calculation of Ejection Fraction Based on Various Modalities

EF was estimated by two independent reviewers after scanning all the studies. For echocardiography, Simpson's two-dimensional methodology was utilized for deriving LVEF. Radionuclide determination of EF by MUGA was performed with a single dose of technetium-99m Sestamibi (Cardiolite). EF by SPECT was estimated using automated volumes provided by Quantitative Gated SPECT (QGS) software. LV angiography was acquired by the single-plane method. The endocardial borders of the LV were traced manually by carefully outlining the ventricular silhouette and then converting to area.

Statistical Analyses

Arithmetic differences were calculated among values for angiography, MUGA, echo and SPECT. Two-tailed Pearson product-moment correlation coefficients were done to determine the extent of correlation among angiography, MUGA, echo and SPECT. Per published guidelines, correlations were considered poor if r was <0.25, fair if r was between 0.25–0.50, moderate to good if r was between 0.50–0.75, and good to excellent if r was >0.75. Paired, two-tailed t tests were done to determine if significant differences were found between values for these four tests. Alpha was set at p<0.05.

RESULTS

In reviewing the values for the four tests—angiogram, MUGA, echo and SPECT—in our 5,558 patients, there were apparent discrepancies as well as strong correlations to be made.

Tables 1A–B highlight the main initial findings of our study before further comparative analysis. Of the tests, echo showed the lowest mean value of 45.657 [range 22–70, standard deviation (SD) 11.186] and SPECT the highest of 54.393 (range 30–75, SD 11.9), with MUGA 45.68 (range 20–75, SD 11.56) and angiography 46.18 (range 20–75, SD 13.12). The strongest correlation was between MUGA and echo (r=0.97)

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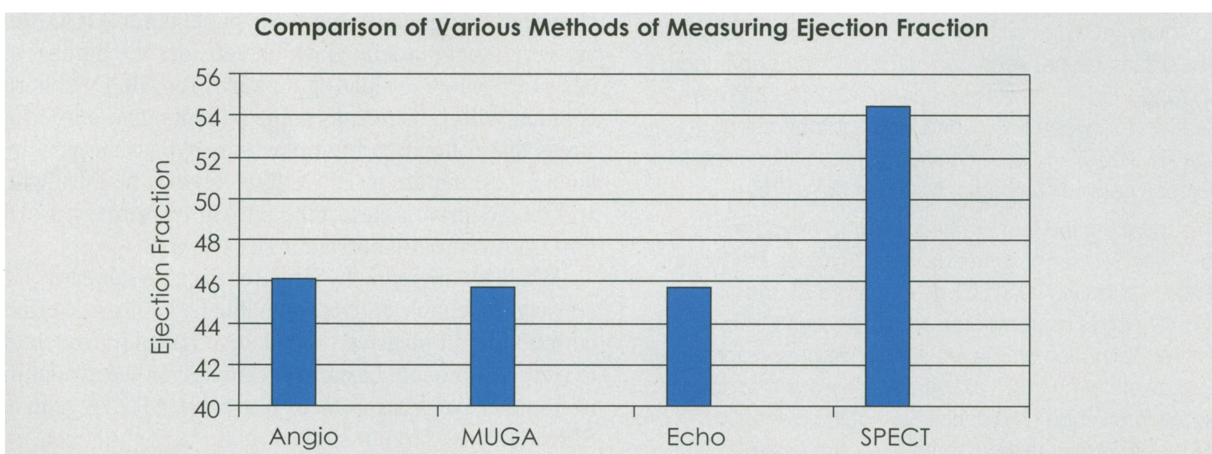
Figure 1. Bar diagram clearly depicting overestimation of ejection fraction by SPECT



Mean LVEF from all four methods obtained yielded a cluster of two values from MUGA and ECHO of 45.7 and 45.7, respectively, significantly below the angiographic average of 46.17 (p < 0.001), while SPECT was significantly higher than all three at 54.4 (p<0.001).

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and the weakest echo and SPECT (r=0.93), yet with all with excellent correlations. Among paired sample tests, echo-SPECT had the greatest discrepancy in mean value [-8.74, SD 4.16, standard error (SE) 0.055] with MUGA-echo with the least (0.02, SD 2.67, SE 0.036).

On the whole, the mean LVEF obtained yielded a cluster of two values from MUGA and echo of 45.68 and 45.66, respectively, slightly below the angiographic average of 46.17 (p=0.5), while SPECT was significantly higher than all three at 54.39 (p<0.001), as illustrated in Figure 1. When comparing the difference between the mean values against the mean LVEF obtained from SPECT, angiogram was the closest at -8.22 (with SD 13.1 and SE 0.176) and echo the furthest at -8.7361 (with SD 11.1 and SE 0.15). Values for MUGA and echo were not significantly different (p=0.59).

Excellent positive correlations were found among all four tests. When charting the Pearson correlations among the tests individually, as show in Table 2, MUGA demonstrated the overall greatest number of strongest correlations with each individual technique, with the strongest relative association between MUGA-echo at r=0.97, followed by MUGA-angiography at r=0.96 and by MUGA-SPECT at r=0.94. SPECT, by contrast, illustrated the overall greatest number of weakest correlations with each individual test, with its strongest correlation being with SPECT-MUGA at r=0.94, followed by SPECT-angiography at r=0.93 and SPECT-echo at r=0.92. Angiography showed the overall greatest number of medium correlations with each individual method, with strongest-to-weakest correlations being angiography-MUGA at r=0.97, angiography-echo at r=0.96, followed by angiography-SPECT at r=0.94. Echo, on the other hand, showed the greatest range and variation of correlation from r=0.93 between echo-SPECT and r=0.97 between echo-MUGA, while echo-angiography has r=0.95.

When grouping and comparing all the individual strongest and weakest correlations, overall, the strongest is between MUGA and echo (r=0.97), and the weakest is between echo and SPECT (r=0.93). Interestingly, and independently, a similar trend is seen when comparing the mean LVEF values. The least difference in the mean LVEF between two-paired tests is seen with MUGA and echo, differing only by 0.19, while the greatest difference in the mean LVEF is seen with echo and SPECT, by as much as 8.74.

In comparing paired differences among the three closest resembling tests in terms of mean LVEF (angiogram, echo, MUGA), differences between angiography-echo (mean difference 0.52) and echo-MUGA (mean difference 0.019) (pair 2) showed the greatest discrepancy from each another with resulting mean of 0.54, SD 5.72, SE 0.08, with lower and upper 95% confidence intervals (CIs) equaling 0.38 and 0.68, respectively. This is contrasted with paired angiography-MUGA and angiography-echo differences (pair 1) which has the least discrepancy from each other with mean of -0.02, SD 2.67, SE 0.04, with lower and upper 95% CIs of -0.0893 and 0.05, respectively. Pair 1 analysis also showed the strongest correlation of r=0.75, while pair 2's correlation is r=-0.47.

When comparing angiography-echo, which has the greatest difference in the mean LVEF of 0.52 among the three closest tests, with SPECT-angiography (with mean difference 8.2), results show a relatively weaker correlation of r=-0.53 with mean 7.70, SD 7.37, SE 0.09, with 95% CIs -7.90 and -7.50.The arithmetic difference

Table 1. Showing mean LVEF of all the patients included in the study according to the method used to estimate ejection fraction (EF)

A. Mean LVEF Descriptive Statistics

	Mean	Range	Standard Deviation	N
EF ANGIO	46.18	20.00–75.00	13.12	5,558
EF MUGA	45.68	20.00–70.00	11.56	1,568
EF ECHO	45.66	22.00–70.00	11.19	5,000
EF SPECT	54.40	30.00–75.00	11.90	2,758

B. Correlation among Sampled Tests

Test	Correlation
EF Angiography and EF Echo	0.96
EF Angiography and EF MUGA	0.97
EF SPECT and EF angiography	0.94
EF MUGA and EF SPECT	0.94
EF ECHO and EF SPECT	0.93
EF MUGA and EF ECHO	0.97

between angiography and MUGA (mean 0.50, range -5.0–5.0) and the arithmetic difference between angiography and echo (mean 0.52, range -5.0–15.0) were similar ($p=0.59$). The arithmetic difference between SPECT and angiography, on the other hand, (mean 8.2, range -15.0–20.0) was significantly larger than the arithmetic difference between angiography and echo ($p<0.001$).

DISCUSSION

Recent data suggest that patients with heart failure and EFs <50% have mortality of almost twice the amount compared to those with an EF >50%, whose risk of mortality is 25% at five years.[13] Many patients who undergo angioplasty or bypass surgery have to undergo assessment of EF 90 days after revascularization to make a decision on whether they qualify for an AICD, and many times stress test doubles up to not only assess status of cardiac ischemia postprocedure but also to check for EF by SPECT. However, this may lead to falsely high values of EF and deprive appropriate patients of primary prevention from ventricular arrhythmias.

Similarities and Differences with Previous Studies

While consistent with previous studies noting that noninvasive techniques produced values lower than invasive methods to assess LVEF, our study complimented the findings,[14-18] with SPECT being the exception to the rule.

In comparing among noninvasive techniques, some findings place SPECT on par with echo in terms of reproducible LVEF[19,20] and showed that all gated SPECT parameters correlated with echo values.[21,22] Studies further reciprocate the findings with SPECT and echo values being lower than angiogram, with SPECT, if anything, actually being of lower value than echo, contrary to our study.[12] Similarly, investigators sought to study how LVEF by MUGA and SPECT correlated. As follows from above, the noninvasive methods showed consistency between LVEF values. In particular, the best relationships where found with 32-frame gated SPECT,[23] corresponding well with using MUGA as a standard.[24] Other studies found good correlation between the LVEF values[25] of the two tests, with such significant findings as $r=0.941$, $P<0.0001$ with SE of the estimate = 6.3% and mean difference -1.3%.[26]

Possible Explanations of Underestimation of Noninvasive Tests

Overestimation of actual ventricular volumes by standard angiographic models are postulated due to greater outflow tract amounts,[16,27] while other investigators have made noninvasive techniques the culprits by acknowledging the possibility of underestimating ventricular volumes due to inability to properly visualize and delineate correct borders, and accounting for distortion that occurs with SPECT due to temporal undersampling. Others have provided further evidence that significantly lower LVEF and end diastolic volume by gated SPECT was similarly due to greater outflow in angiography.[18] The reasoning continues that as myocyte concentration decreases rapidly at the ventricular base, it is likely that most gated SPECT methods will produce endocardial borders encompassing less of the outflow tract than do angiographic outlines. To compensate for these inherent discrepancies, some researchers have postulated using a regression equation to balance value to baseline angiography.[28]

Overestimation by SPECT

The above consideration, apparently, is not valid in all circumstances. Contrasted, studies postulated the exception of overestimation by SPECT, as in our study, could be explained partially by patients with small hearts because of reduced end systolic volume compared to end diastolic volume caused by noise filtering on edge-detection algorithms.[29,30]

Hambye et al. have postulated that the variations may not be due to SPECT but rather the implemented analysis algorithms. Comparing the most commonly used Cedars-Sinai Quantitative Gated SPECT (QGS),[31] as used in our study, with Emory Cardiac Toolbox (ECT) and the Standard University (SU) algorithms concludes that despite good correlation among each program in computing the same gated SPECT data,[32] it is not recommended for interchangeability or use of consecutive versions for follow-up in individual patients[33-35] due to specific characteristics of each algorithm.

The study validates QGS as having the limitation of producing falsely elevated LVEF, with increased routine use in small hearts, while a version of the ECT consistently overestimated LVEF by >10%.[36,37] QGS, in addition, had marked variations in LVEF and end systolic volume

Table 2. Pearson correlation among four tests (angiography, MUGA, echo, SPECT)

	Angiography	MUGA	Echo	SPECT
Angiography	–	0.97** strongest	0.96** medium	0.94** weakest
MUGA	0.97** medium	–	0.97** strongest	0.94** weakest
Echo	0.96** medium	0.97** strongest	–	0.94** weakest
SPECT	0.94** medium	0.94** strongest	0.94** weakest	–

** Significant to 0.001

based on modifications to algorithm, filter cut-off frequency and population-specific, matrix size depending on version used. By adjusting for pixel size, zoom and filter from a smoother 0.4 cycles/cm to a sharper 0.6 cycles/cm, the investigators were able to significantly reduce LVEF, with resulting higher volumes in particular for patients with end diastolic volume equal to 60 mL.[38-40]

Using phantom models to determine LVEF by SPECT using QGS has lead to similar observations with the program's abilities to properly represent contracting myocardium edge,[35] filtering during reconstruction[36] and inaccurate determination of the inner boundary at the apex on the end systolic images.[37]

Other factors to consider for possible variations in SPECT LVEF value include whether images where acquired using eight-frame gating or 16-frame gating. Though it requires more processing time and room for data storage, 16-frame can provide more accurate estimates of LVEF, especially due to better diastolic functional assessment. The type of radionuclide used, Tl-201 versus Tc-99m sestamibi or tetrofosmin, can also lead to "blurring" and increased scatter translating into exaggerated LVEF.[38] In addition, using 2D versus 3D SPECT modalities to measure LVEF has been shown to overestimate values in patients with dyssynchronous septal wall motion.[39] Certain types of arrthymias—in particular premature ventricular contractions—though controlled with lidocaine, are known to compromise the quality of images.[40]

Implications

It is possible that not all SPECT machine values are incorrectly over- or underestimating true LVEF. Given the multitude of studies with varying results, it remains imperative, however, that each institution collaborate to determine if their values are producing consistent, reliable results and make appropriate corrections to ensure patients' proper prognostic and treatment options.

One important implication of obtaining proper LVEF, especially if it wrongly overestimates signaling a normal value, is the placement of the cardioverter-defibrillator. The Multicenter Automatic Defibrillatory Implantation Trial (MADIT) showed for the first time, in 1996, that in patients with risk of sudden death, mortality benefit of AICD therapy surpassed medications alone.[41] The MADIT II study, published in 2002, which extended these results to any patient with ischemic heart failure with depressed function, requires the inclusion criteria of a previous myocardial infarction with an EF <30%[42] to be considered a candidate for procedure. This simple measure reduces the mortality risk by approximately 31% in the following two years.

A recent review of published quantitative algorithms for gated perfusion SPECT references >75 validations of LVEF with other modalities.[43] The review discusses potential explanations for possible overestimation and need for corrective measures in order to ensure proper patient management, as those patients wrongly denied defibrillator placement by Medicare/Medicaid due to erroneously inflated LVEF values by SPECT.

Drawbacks of Our Study

Our study had a few drawbacks. Firstly, it is a retrospective study and, hence, the available data could not be designed in the manner and discipline of a prospective study. Secondly, we were not able to take into account factors such as very large and small body surface area of patients and what impact it may have on outcomes. Thirdly, we have tried to account for interobserver error by allowing two physicians to interpret all the data; however, advancements of machines and software, especially for echocardiography and nuclear imaging, over a 10-year period and their influence on accuracy of estimating EF has not been accounted in our study. And lastly, 3D echo and MRI may provide a better estimation of EF but are not routinely used at this point for EF estimation largely due to availability and cost.

CONCLUSION

All four methods used to estimate EF co-relate well with each other. However, values estimated during stress testing by SPECT overestimate EF and are significantly higher as compared to MUGA, echo and angiography. Estimation of EF by MUGA, echo or angiography should be preferred over SPECT especially when that patient warrants intervention. We conclude that the overestimation of EF by SPECT may deprive some deserving patients of the survival benefit afforded by ICD.

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