Limitations in the current screening practice of assessing left ventricular ejection fraction for a primary prophylactic implantable defibrillator in southern Ontario

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BACKGROUND: Screening echocardiography (ECHO) is commonly performed to determine whether the patient's left ventricular ejection fraction (LVEF) is appropriate for primary prophylactic implantable cardiac defibrillator (ICD) referral. However, radionuclide ventriculography (RNA) is used by many implantation centres for decision making.

OBJECTIVE: To determine whether current screening ECHO techniques are effective in identifying patients suitable for primary prophylactic ICD referral.

METHODS: Correlation, sensitivity, specificity and likelihood ratios (LRs) of semiquantitative and numerical quantitative ECHO LVEFs were calculated for predicting RNA LVEFs that met implantation criteria (LVEF less than 30% and less than 35%).

RESULTS AND DISCUSSION: Among 193 patients, the LRs for a semiquantitative ECHO predicting an RNA LVEF of less than 30% (negative LR was 0.21 to 0.69 and positive LR was 1.22 to 2.83) or RNA LVEF of less than 35% (negative LR was 0.24 to 0.73 and positive LR was 1.33 to 3.46) demonstrated that current screening ECHO techniques are ineffective. However, the positive predictive value of grade 4 ECHO was 93.0%, suggesting that these patients may not require further LVEF investigation before implantation. Among 102 patients, current quantitative ECHO techniques did not improve the screening characteristics.

CONCLUSIONS: Current screening ECHO techniques may not be adequate for screening patients for consideration of a primary prophylactic ICD, but a grade 4 ECHO finding has a high positive predictive value in meeting implantation LVEF criteria. Improved screening standards should increase the number of patients referred with appropriate LVEF for primary prophylactic ICD implantation.

Key Words: ECHO; LVEF; Primary prophylactic ICD; RNA; Screening; Sudden cardiac death

Les limites des pratiques de dépistage actuelles pour évaluer la fraction d'éjection ventriculaire gauche en vue de l'installation prophylactique primaire d'un défibrillateur interne dans le sud de l'Ontario

HISTORIQUE : On procède souvent à une échocardiographie (ECHO) de dépistage pour déterminer si la fraction d'éjection ventriculaire gauche (FÉVG) du patient justifie un aiguillage en vue de l'installation d'un défibrillateur interne (DI). Cependant, de nombreux centres d'installation recourent à la scintigraphie ventriculaire (SGV) pour prendre leur décision.

OBJECTIF : Déterminer si les techniques actuelles d'ECHO de dépistage sont efficaces pour repérer les patients admissibles à un aiguillage en vue de l'installation prophylactique primaire d'un DI.

MÉTHODOLOGIE : Les auteurs ont calculé la corrélation, la sensibilité, la spécificité et les rapports de vraisemblance (RV) des FÉVG par ECHO semi-quantitative et quantitative numérique pour prédire les FÉVG par SGV qui respectent les critères d'installation (FÉVG inférieure à 30 % et inférieure à 35 %).

RÉSULTATS ET EXPOSÉ : Chez 193 patients, les RV pour une ECHO semi-quantitative prédisant une FÉVG par SGV inférieure à 30 % (le RV négatif était de 0,21 à 0,69 et le RV positif, de 1,22 à 2,83) ou une FÉVG par SGV inférieure à 35 % (le RV négatif était de 0,24 à 0,73 et le RV positif, de 1,33 à 3,46) démontraient l'inefficacité des techniques actuelles d'ECHO de dépistage. Cependant, la valeur prédictive positive de l'ECHO de niveau 4 s'élevait à 93,0 %, laissant supposer que ces patients n'ont pas besoin d'exploration supplémentaire de la FÉVG avant l'installation. Chez 102 patients, les techniques d'ECHO quantitatives courantes n'amélioraient pas la caractéristique de dépistage.

CONCLUSION : Les techniques actuelles d'ECHO de dépistage ne conviennent peut-être pas pour repérer les patients chez qui envisager l'installation primaire prophylactique d'un DI, mais une ECHO de niveau 4 a une valeur prédictive positive élevée pour respecter les critères de FÉVG en justifiant l'installation. L'amélioration des normes de dépistage devrait accroître le nombre de patients aiguillés en raison d'une FÉVG justifiant l'installation prophylactique primaire d'un DI.

Numerous clinical trials have demonstrated that impaired left ventricular ejection fraction (LVEF) is one of the most important criteria for risk-stratifying patients who may benefit from an implantable cardiac defibrillator (ICD). Different LVEF cut-off values (30%, 35% and 40%) have been used in the inclusion criteria of clinical trials (1-3). According to the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) (1), after at least one month post-myocardial infarct, patients benefitted from an ICD if their LVEF was less than 30%. The Sudden Cardiac Death in Heart Failure Trial

(SCD-HeFT) (2) demonstrated that patients with symptomatic heart failure (New York Heart Association [NYHA] class II or III) benefitted from an ICD if their LVEF was less than 35%. The Multicenter Unsustained Tachycardia Trial (MUSTT) (3) included patients with coronary artery disease, an LVEF of less than 40% and nonsustained ventricular tachycardia. The current Canadian guidelines (4) give a class I recommendation for primary prophylactic ICD implantation for postinfarction patients with an LVEF of less than 30%, and a class IIa indication for patients with an LVEF of 30% to 35%, ischemic heart

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disease and inducible ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study.

Although very specific about the LVEF cut-off value, these previous trials did not specify a particular technique for determining a patient's LVEF. Various modalities, including quantitative echocardiography (ECHO), semiquantitative ECHO, radionuclide ventriculography (RNA), methoxyisobutyl isonitrile scanning, angiography, computed tomography (CT), positron emission tomography and magnetic resonance imaging (MRI), exist for estimating LVEF (5-16). In clinical practice, ECHO is often used as the first-line test for screening patients for decreased LVEF (17).

In southern Ontario, a semiquantitative approach is often used for classifying LVEF into four discrete increments (grade 1 indicates a normal LVEF and grade 4 indicates the worst LVEF). Patients with a poor LVEF (grades 3 to 4) based on semiquantitative ECHO are frequently referred for a primary prophylactic defibrillator. As recommended by the current guidelines, many electrophysiological centres reassess the LVEF using their modality of choice as their final determination of LVEF to decide the patient's eligibility for ICD therapy (18). At St Michael's hospital (SMH) in Toronto, Ontario, RNA is used as the final LVEF determinate because RNA was shown to be one of the more reliable and reproducible (11) assessments of LVEF, and is broadly available. The present study attempted to determine whether the current screening techniques to identify patients who should receive a primary prophylactic ICD are useful.

METHODS

The present prospective cohort study collected clinical information from patients who were referred to a single academic centre (SMH) for consideration of primary prophylactic defibrillator implantation between January 1, 2003, and June 30, 2006. Patients were referred based on quantitative ECHO, semiquantitative ECHO or RNA (except for eight patients who were referred based on contrast ventriculography or MRI). If patients did not undergo an RNA on referral, they were sent prospectively, either locally or to SMH, for this investigation. The study was approved by the institutional research ethics board.

For each patient, clinical information was collected prospectively and any estimates of LVEF were recorded from available reports, noting the type of measurement and the study date.

ECHO measurements

ECHO measurements were performed in more than 20 referring centres; most were community cardiology offices or community hospitals, and only a few were academic centres. Various quantification techniques were performed, including Simpson's formula and modified Simpson's formula. However, the details of these techniques were often not reported. Similarly, information regarding whether the study was technically adequate was not always disclosed. Consequently, the present study relied on the expertise of the echocardiographer to determine what techniques should be performed and reflects the assortment of techniques that are currently used. Although there are specific Canadian guidelines regarding the method of LVEF measurement and how to report it, the guideline was published toward the end of the study period and there is no information regarding how closely those guidelines were followed (19). The semiquantitative approach has been used for 20 years, but has not been validated. The generally accepted LVEFs used in clinical practice for semiquantitative ECHO grades are LVEF of 60% or greater (grade 1), LVEF of 40% to 59% (grade 2), LVEF of 20% to 39% (grade 3) and LVEF of less than 20% (grade 4).

RNA

The RNA LVEF was prospectively measured in patients using electrocardiogram-gated equilibrium blood pool RNA. Patients were prepared by in vivo red blood cell labelling with 10 mg of stannous pyrophosphate injected intravenously, followed by an intravenous injection of 1000 MBq of sodium pertechnetate radioisotope 20 min later.

TABLE 1

Number of patients included and excluded from the study

Characteristics of tests	Patients, n
Total number of patients seen in clinic	405
Patients excluded:	
Only RNA	40
Only ECHO	24
Neither ECHO nor RNA	8
Patients excluded due to tests occurring more than 180 days apart	
Semiquantitative ECHO and RNA	67
Quantitative ECHO and RNA	33
Patients included with both:	
Semiquantitative ECHO and RNA	193
Quantitative ECHO and RNA	102
Locations of LVEF tests	
Semiquantitative ECHO at SMH	36
Semiquantitative ECHO at nonacademic sites	157
Quantitative ECHO at SMH	26
Quantitative ECHO at nonacademic sites	76
RNA at SMH	112
RNA at nonacademic sites	183

ECHO Echocardiography; LVEF Left ventricular ejection fraction; RNA Radionuclide ventriculography; SMH St Michael's Hospital (Toronto, Ontario)

RNA scans were acquired on an APEX-409 ECT gamma camera (Elsint Ltd, Israel) or equivalent, electrocardiogram-gated on R waves at 32 frames per R-R interval. Images contained 3.2 million counts in 64×64 pixel matrix size with a zoom factor of 2. Three gated images were acquired in the anterior, lateral and left anterior oblique views. Left ventricular activities were calculated from a region of interest manually drawn around the left ventricular perimeter at end-diastole. A 2 mL blood sample withdrawn during the gated left anterior oblique image acquisition was counted on the camera for volume calculation. Left ventricular time activity curves were generated after correction for decay and attenuation (20).

To determine how accurately the referral semiquantitative ECHO screened patients for a primary prophylactic ICD, the semiquantitative ECHO was compared with the RNA results and how well it identified patients using specific cut-off values of 30% and 35% by RNA. The referral ECHO obtained closest to the date the patient was seen at SMH for the RNA procedure was chosen for analysis. Any tests that were conducted more than 180 days apart were excluded.

To determine whether the quantification techniques currently performed on screening ECHOs are better than semiquantitative ECHOs for screening those who qualify for an ICD using specific RNA cut-off values, the LVEFs obtained in patients using referral quantitative ECHOs were compared with the RNA LVEF. Again, the quantitative ECHO obtained closest to the date the patient was seen at SMH was used for analysis and any tests conducted more than 180 days apart were excluded.

Statistical analysis

Sensitivity, specificity and likelihood ratio (LR) values were calculated using the specific cut-off LVEF values. Correlation coefficient and correlation line were derived for the comparison of ECHO and RNA results. Bland-Altman agreement was calculated and displayed by plotting the difference between the RNA and ECHO measurement against the average of the two. Kappa statistics were used to assess agreement between two modalities where appropriate.

RESULTS

Study population

Between January 1, 2003, and June 30, 2006, 405 patients were seen at SMH for consideration for a primary prophylactic defibrillator. As shown in Table 1, 64 of these patients were excluded from the study

TABLE 2
Characteristics of included patients (n=241)

Characteristic	%
Men	83.0
Cause of heart disease	
Ischemic heart disease	70.1
Dilated cardiomyopathy	8.7
Nonischemic dilated cardiomyopathy	15.8
Other	5.4
Angina and heart failure	
Canadian Cardiovascular Society class	
0	61.4
I or II	22.0
III or IV	3.3
New York Heart Association class	
I or II	64.7
III or IV	31.9
CABG or PCI	46.9
Previous myocardial infarction	68.9
Congestive heart failure for less than 12 months	35.3
Diabetes	33.6
Hyperlipidemia	66.4
Hypertension	54.8
Stroke/transient ischemic attack	10.8
Atrial fibrillation	25.3
Dialysis	0.8
Beta-blocker	85.1
ACE or ARB	94.2
Spironolactone	35.3
Loop diuretic	67.6
Anticoagulation	42.3
Digoxin	30.0
Amiodarone	20.8
Class 3 antiarrhythmic	0.0

ACE Angiotensin-converting enzyme; ARB Angiotensin receptor blocker; CABG Coronary artery bypass graft; PCI Percutaneous coronary intervention

because they did not receive both a referral ECHO and an RNA estimate of the LVEF. Sixty-seven semiquantitative ECHO and 33 quantitative ECHO results were excluded because the RNA was conducted more than 180 days from the ECHO.

The characteristics of the included 241 patients are shown in Table 2. The patients were predominately men, with the most common cause of heart disease being ischemia followed by nonischemic dilated cardiomyopathy. 'Other' heart disease included patients with valvular disease, hereditary arrhythmia, myocarditis, congenital heart block and sarcoidosis. Most of the patients were asymptomatic from angina and with respect to heart failure, they were equally distributed between NYHA classes I to III, with only a few patients as severe as NYHA class IV.

Semiquantitative ECHO for screening LVEF

One hundred ninety-three patients had both a semiquantitative ECHO and RNA performed with a median time delay between tests of 51 days (range zero to 180 days). Figure 1 plots the RNA LVEF for each of the semiquantitative ECHO categories. There was a trend toward patients with a grade 4 LVEF having a lower RNA LVEF estimate. Table 3 outlines the number of patients in each LVEF grade and the percentage of patients in that grade who had an RNA LVEF of less than 30% and less than 35%.

There is substantial overlap between the RNA LVEF values for each grade, as demonstrated in Figure 1. Table 4 quantifies the number of patients in each of the grade 4, grade 3 and grade 2 categories who

Figure 1 Semiquantitative echocardiography (ECHO) versus radionuclide ventriculography (RNA) left ventricular ejection fraction (LVEF) (n=193)**TABLE 3**
Patients with radionuclide ventriculography (RNA) left ventricular ejection fraction (LVEF) estimates of less than 30% or less than 35% for each semiquantitative echocardiographic category

	Patients, n	RNA LVEF, n (%)	
		<30%	<35%
Grade 4	57	45 (78.9)	53 (93.0)
Grade 3 to 4	36	19 (52.8)	28 (77.8)
Grade 3	77	41 (53.2)	61 (79.2)
Grade 2 to 3	11	4 (36.4)	6 (54.5)
Grade 2	9	1 (11.1)	4 (44.4)
Grade 1 to 2	2	0 (0.0)	1 (50.0)
Grade 1	1	0 (0.0)	0 (0.0)
All grades	193	110 (57.0)	153 (79.3)

had RNA LVEF values corresponding to the various ECHO grades. As can be seen, most of the patients had an LVEF in the grade 3 range and 79.2% of these patients had an RNA LVEF in the expected range. Only 35.1% of the grade 4 patients and 22.2% of the grade 2 patients were in the expected range.

Table 5 outlines the positive and negative LR for the various semiquantitative ECHO categories. Because previous data demonstrated that the various semiquantitative ECHO grades are not discrete sequential ranges of LVEF, but have a large overlap, the LR were not calculated for each grade independently. Rather, they were calculated using the grade as a cut-off. This approach is clinically logical because, ideally, a semiquantitative grade exists where everything worse should be referred.

If only grade 4 LVEF was considered for implantation using an RNA LVEF of less than 30%, the negative LR of 0.69 was close to 1.0. A negative LR of less than 0.1 is a sensitive test, good for ruling out a disease. A positive LR of greater than 10 is a specific test, good for ruling in a disease. Thus, the negative LR of 0.69, which is closer to 1.0 than to 0.1, means that the test is not very sensitive and there are many patients with an LVEF of less than 30% by RNA who have a semiquantitative ECHO grade better than grade 4. The positive predictive value for grade 4 ECHO (Table 3) is 93% for an LVEF of less than 35% and 78.9% for an LVEF of less than 30%. Consequently, patients with a grade 4 ECHO are very likely to have an LVEF that would qualify for an ICD when seen by an electrophysiologist, and should be referred.

TABLE 4

Semiquantitative echocardiography (ECHO) and the radionuclide ventriculography (RNA) left ventricular ejection fraction (LVEF)

ECHO grade	Total patients, n	Grade 4 (RNA LVEF <20%)		Grade 3 (RNA LVEF 20% to 39%)		Grade 2 (RNA LVEF 40% to 59%)		Grade 1 (RNA LVEF ≥60%)	
		Patients, n	%	Patients, n	%	Patients, n	%	Patients, n	%
Grade 4	57	20	35.1	36	63.2	1	1.8	0	0
Grade 3	77	6	7.8	61	79.2	10	13.0	0	0
Grade 2	9	0	0	6	66.7	2	22.2	1	11.1

TABLE 5

Sensitivity, specificity, likelihood ratios (LRs), positive predictive values (PPVs) and negative predictive values (NPVs) for various semiquantitative echocardiography (ECHO) grades

ECHO grade	Sensitivity, %	Specificity, %	LR+	LR-	PPV, %	NPV, %
RNA <30%						
4	40.9	85.5	2.83	0.69	78.9	52.2
3 to 4 or worse	58.2	65.1	1.67	0.64	68.8	54.0
3 or worse	95.5	21.7	1.22	0.21	61.8	78.3
RNA <35%						
4	34.6	90.0	3.46	0.73	93.0	26.5
3 to 4 or worse	52.9	70.0	1.76	0.67	87.1	28.0
3 or worse	92.8	30.0	1.33	0.24	83.5	52.2

+ Positive; - Negative. RNA Radionuclide ventriculography

Figure 2) Quantitative echocardiography (ECHO) versus radionuclide ventriculography (RNA) left ventricular ejection fraction (LVEF) (n=102)

If patients in grades 3, 3 to 4 and 4 (grade 3 or worse) were considered, the negative LR decreased to 0.21, meaning that the test was much more sensitive, but the positive LR was only 1.22, meaning that the test was much less specific. Similar results were seen when examining the results for an RNA LVEF of less than 35%.

Quantitative ECHO for screening LVEF

One hundred two patients had both a quantitative ECHO and an RNA estimate of LVEF with a median time delay between tests of 52 days (range zero to 180 days). Figure 2 shows a plot of ECHO LVEF versus RNA LVEF with a linear regression and the correlation coefficient. The regression line had a positive slope of less than 1 (slope 0.67) and a Y intercept of 12.6, indicating that at a lower LVEF, the RNA estimate will tend to be higher than the ECHO

Figure 3) Bland-Altman graph of quantitative echocardiography (ECHO) and radionuclide ventriculography (n=102). LVEF Left ventricular ejection fraction; MUGA Multigated acquisition scan

TABLE 6

Frequency of patients with quantitative echocardiography (ECHO) and radionuclide ventriculography (RNA) left ventricular ejection fraction (LVEF) estimates below 30% and 35%, and estimates greater than or equal to 30% and 35%

ECHO LVEF	RNA LVEF <30%		LVEF RNA ≥30%	
	n	%	n	%
<30%	38	40.4	22	23.4
≥30%	7	7.5	27	28.7
Kappa = 0.39				
ECHO LVEF	RNA LVEF <35%		RNA LVEF ≥35%	
	n	%	n	%
<35%	63	64.3	14	14.3
≥35%	8	8.2	13	13.3

Kappa = 0.40

estimate but at higher ejection fractions, the RNA estimate will tend to be lower than the ECHO estimate. Figure 3 is a Bland-Altman graph of these same data with the mean and SD shown for the difference of RNA and ECHO LVEF. The two SD limits of the Bland-Altman agreement were wide, indicating that the difference between the LVEFs estimated by the referral screening ECHO and the RNA may be as high as 20%.

Table 6 outlines the number of patients with an LVEF of less than 30% and less than 35% on the referral ECHO and RNA obtained at SMH. Only fair agreement between the two measurement methods was observed with a kappa statistic of 0.39 for an LVEF of less than 30% and 0.40 for an LVEF of less than 35%. Table 7 shows the sensitivity and specificity of quantitative ECHO

TABLE 7
The sensitivity, specificity and corresponding likelihood ratios (LRs) for quantitative echocardiography (ECHO) for predicting a radionuclide ventriculography below 30% and below 35%

ECHO	Sensitivity, %	Specificity, %	LR+	LR–
<30%	84.4	55.1	1.88	0.28
<35%	88.7	48.2	1.71	0.23

+ Positive; – Negative

for detecting an RNA LVEF of less than 30% and less than 35%, as well as the corresponding LRs.

DISCUSSION

The questions addressed in the present paper are relevant for all cardiologists, internists and family doctors to consider. For referring physicians, it is important to have an easily accessible modality for determining who should be referred to an electrophysiologist for a primary prophylactic ICD based on cardiac conditions and LVEF.

The primary prophylactic ICD studies, among other modalities, all used ECHO, RNA and contrast ventriculography for patient selection. The current guidelines do not identify the modality of choice, but rather suggest to use the modality the implanting centre is most familiar with. This modality is RNA in many Canadian electrophysiology centres. Other methods, such as contrast ECHO, CT or MRI, may be equivalent or even better, but this remains unknown and for clinical practice, a standard was required. Previous Canadian studies have shown that it is cost effective to repeat the measurement of LVEF with RNA (21). SMH elected to use RNA as their final LVEF determinant because it was demonstrated to be reproducible, reliable and less dependent on the operator (11). RNA also has greater availability than some other techniques such as CT or MRI. However, the referring physicians seldom use RNA as their modality of choice to determine a patient's eligibility for a primary prophylactic defibrillator. Rather, the referring pattern suggests a variety of ECHO-based methods, frequently only a semiquantitative measurement of the LVEF.

The intent of the present study was not to determine the superior modality of estimating LVEF for predicting primary ICD implantation, but to determine whether current screening techniques in a southern Ontarian community can effectively identify patients who are deemed to be appropriate for ICD implantation by a Canadian electrophysiology centre. Consequently, ECHO was examined as the screening technique and RNA was chosen as the standard for comparison.

The population and LVEF measurement modalities used in the present study are clinically relevant because they are representative of Canadian patients typically referred for consideration of a primary prophylactic ICD in southern Ontario. There were minimal exclusion criteria and because referrals were accepted from a range of centres, selection bias was minimized as much as possible given the clinically available data. The patients had the expected risk factors for cardiac disease and were typically treated pharmacologically according to guidelines. One limitation resulting from the broad inclusion criteria was that the number of patients in the different semiquantitative ECHO categories could not be controlled and consequently, some of the categories had limited numbers of patients.

Previous research has demonstrated that various modalities of LVEF measurement are not interchangeable (4-11) but the magnitude of the difference was larger in the present screening study than previously reported. It is understood that numerous factors, including medications, volume status, myocardial contractility, adrenergic stimulation and valvular disease, affect the LVEF. It is also accepted that these factors change over time and that a patient's LVEF is not static. Previous research has shown that a repeat LVEF measurement may vary by up to 8.5% (22), but our data indicated that when screening quantitative ECHO is performed by various operators, including academic and

community cardiologists, the difference may be as high as 20%. The data also indicated that this difference could exist at any LVEF and did not show a bias toward normal or very poor ejection fractions.

This is in contrast with the findings of Yu et al (20), who demonstrated that ECHO measurements of LVEF have very good correlation with RNA measurements when performed in a nearly simultaneous, standardized manner, and using enhancing techniques such as contrast ECHO when necessary. This indicates that a likely explanation for some of the difference between the screening LVEF and the RNA LVEF in our study could be due to the fact that the screening LVEF was obtained by multiple operators, in multiple laboratories, using different techniques, and with a significant time delay between the two measurements. Ideally, screening techniques and their clinical timing should be optimized to reasonably predict patients who will maintain an LVEF in the range considered appropriate for primary ICD implantation or at least within the variability of repeat LVEF measurement. In clinical practice, there will always be a delay between when patients are screened by a referring physician and when they are seen by an electrophysiologist. Consequently, the present study population, including the delay between screening and electrophysiological consultation, reflects clinical practice and demonstrates that current screening techniques could be improved.

Another novel finding of the present study was the quantification of the semiquantitative ECHO system used in southern Ontario. Despite its use in clinical practice, this semiquantitative ECHO method has not been described in previous studies and intra/interobserver studies are not available. Our data demonstrated that echocardiographers estimate LVEF with grade 4 being the worst LVEF and grade 1 being the best. There is, however, a more than 50% overlap between each of the grades. This demonstrates that semiquantitative ECHO techniques are useful for roughly quantifying ejection fraction, but the precision is not sufficient for all applications.

The data for semiquantitative ECHO demonstrates extensive overlap between ECHO grades and there is not a single semiquantitative ECHO grade cut-off that gives both a good sensitivity and specificity for predicting an RNA LVEF of less than 30% or 35%. As a screening tool, the specificity is not as important as the sensitivity; consequently, one may argue that using a grade 3 or worse cut-off may be acceptable. The difficulty with this is that the majority of the patients are in either grade 3 to 4, or grade 3, and in these grades, only 52.8% and 53.2% of the patients, respectively, had an RNA LVEF of less than 30%. This means that with a grade 3 cut-off, nearly one-half of patients who are referred will not qualify with an RNA of less than 30%, and patients with a grade 3 LVEF may require another test to determine their ejection fraction.

If one examines patients with grade 4 ECHO, the positive predictive value (Tables 3 and 5) is 93% for an LVEF of less than 35% and 78.9% for an LVEF of less than 30%. Consequently, patients with a grade 4 ECHO are very likely to have an LVEF that would qualify for an ICD when seen by an electrophysiologist and they should be referred. In fact, with the positive predictive value of semiquantitative ECHO being 93% for an LVEF of less than 35%, it is possible that electrophysiologists would not need to repeat the LVEF assessment in this group.

The limitation for screening is that only 29.5% (57 of 193) of patients had a grade 4 ECHO.

Because the semiquantitative ECHO does not provide a single cut-off grade to adequately separate patients to determine whether their RNA will support an indication for a primary prophylactic ICD implantation, do the quantitative ECHO techniques currently being used for screening improve the results? Examining the LRs from the quantitative data, the results were similarly disappointing. A quantitative ECHO cut-off of 30% resulted in a positive and negative LR similar to having a grade between grades 3 to 4 and grade 3. Examining a quantitative ECHO cut-off of 35%, the positive LRs are actually worse than having a grade 3 to 4 ECHO and the negative LR is similar to a grade 3 or worse semiquantitative assessment. A major limitation of the current

quantification techniques is that many ECHO reports do not give the reader sufficient information to know what techniques were used and how well they were performed. Consequently, there may be considerable variability among centres. In a similar manner to semiquantitative ECHO, the current quantitative techniques used for screening do not improve the ability of a referring physician to consistently know who should be sent for consideration of a primary prophylactic ICD.

Similar to semiquantitative ECHO, it is possible that selecting a quantitative LVEF cut-off that is less than 30% may give a good positive predictive value. However, the limitation is similar in that only a minority of the patients will fall into this group.

ECHO techniques are inherently useful for screening LVEF due to accessibility and, as demonstrated, certain values have a good positive predictive value. The limitations in the current screening techniques may relate to the assortment of readers and the variety of quantification techniques used in interpreting LVEF. Previous research has demonstrated that with contrast ECHO, the correlation with RNA LVEF can be very good ($r=0.95$) (20). Perhaps if primary prophylactic ICD screening guidelines were established, referrals to electrophysiology would be better targeted to patients with LVEF considered appropriate by Canadian electrophysiology centres. Issues that could be addressed include the timing of the screening test, standardized LVEF quantification techniques, recommendations on the use of contrast agents and the need for repeat LVEF estimates for borderline cases. Standardized reporting, as outlined in the guidelines of the Canadian Cardiovascular Society/Canadian Society of Echocardiography (19), would allow the referring physician to know whether the quality of the imaging was adequate and what quantification techniques were used. This may help to avoid relying on results derived from suboptimal images or methods.

Limitations

The present study has several limitations. One of the most important limitations is that RNA was used as a gold standard when clinical trials did not specify the modality for estimating LVEF. The purpose of the present paper was to determine whether current screening techniques can effectively identify patients who are deemed to be appropriate for ICD implantation by a Canadian electrophysiology centre. Because

the standard modality of LVEF assessment for such purposes is RNA at SMH, RNA was chosen as the standard for comparison.

The referring LVEF assessment was performed in multiple laboratories by multiple echocardiographers using various hardware, software and techniques, which certainly accounts for at least some, if not most, of the disagreement with the RNA measurements.

Other limitations of the present study result from the broad selection criteria used. The number of patients in the different semiquantitative ECHO categories could not be controlled; consequently, some of the categories had limited numbers of patients.

Finally, we were only able to examine patients who were referred for ICD consideration and, therefore, a selection bias was introduced. The present study did not include patients who may have been screened and were not referred because their LVEF was close to normal. Regardless of this bias, the results of the present study remain relevant to the population that is referred for ICD consideration; however, the negative predictive values may be underestimated.

CONCLUSION

This clinically applicable population is consistent with previous research demonstrating that ECHO and RNA are not equivalent modalities to measure LVEF when the measurements are performed in multiple centres using multiple methods. Current semiquantitative ECHO techniques may not be a useful modality for screening patients for consideration of a primary prophylactic ICD, but patients found to have a grade 4 ECHO should be referred to an electrophysiologist given the high positive predictive value in this group. Similarly, current quantitative ECHO techniques using a cut-off value of 30% or 35% to predict an RNA LVEF of 30% or 35% are also not sensitive or specific enough for screening. The limitations in the current screening techniques may relate to the assortment of readers and the variety of quantification techniques used in estimating LVEF. Guidelines should be established to standardize screening techniques or the referring physicians should estimate the LVEF in the same manner used by their local electrophysiology centre.

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