Current perspectives

Quantitation of left ventricular mass and function: balancing evidence with dreams

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Key words:
Diastolic function; Echo-Doppler; Hypertrophy; Left ventricular mass.

The quantitative evaluation of the echocardiographic geometry and function for non-ischemic, symmetrically contracting left ventricles is increasingly requested, even when the request is not clinically fully justified and does not take into account the feasibility and reliability of measurements. The general opinion is that, despite a number of technical limitations, the overall information gained from left ventricular (LV) quantitation has a crucial importance for risk stratification, mainly due to the prognostic impact of echocardiographically evaluated LV hypertrophy. This trend tends to automatically transfer epidemiological evidence into clinical application, without consideration of the consequences of the transition of standard errors into single cases. Two recent studies, though differently designed, have demonstrated that the test-retest intraobserver variability of LV mass performs well enough to allow, in most circumstances, the identification of patients with LV hypertrophy. In contrast, the variability of nominal, individual values is high. Tables are available to weigh the probability of true biological change when comparing values in the same patient. To a lesser extent, the same conclusions as for LV mass can be applied to measures of systolic function. The technical reliability for measures of diastolic filling is generally good or very good, but the intrapatient variability is probably higher than with measures of LV geometry and systolic function. Moreover, the utility in clinical practice of measures of diastolic filling should be proven. In general, the accurate quantitation of LV geometry and function implies reliable methods and appropriate learning procedures in every echo lab, according to the procedures and the achievements recommended in the current literature. The development of new echocardiographic techniques and the adoption of the procedure of off-line revision of echocardiographic studies might further reduce the variability in the quantitation of measures of LV geometry and function.

(Ital Heart J 2002; 3 (10): 562-570)

Received July 16, 2002;
accepted July 29, 2002.

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There is an increasing demand for the quantitative evaluation of echocardiographic left ventricular (LV) geometry and function. From a clinical standpoint this is sometimes unjustified[1]. The increasing pressure on echocardiography laboratories often influences the organization, procedures and waiting list, but this trend substantially parallels the increasing familiarity of general practitioners, cardiologists and patients with both the feasibility of the echocardiographic examination and the reliability of the information that can be obtained from LV quantitative evaluation. This common behavior tends to uncritically merge findings from epidemiological studies with needs for clinical practice, assuming that the magnitude of measurements performed (and the variability found) in an epidemiological scale can be legitimately applied to the examination of individual patients. The increasing demand for LV quantitative evaluation is even clearer in countries where public health is regulated by government interventions and the economic burden of relatively expensive procedures does not directly affect the citizen's income[2]. As compared with the strict guidelines of American institutions[1], in Italy and other European countries the indications for echocardiography are in general more flexible and, consequently, a high number of patients with at least doubtful indications overcrowd echocardiography laboratories, indirectly increasing the waiting list and thus rendering a disservice to patients for whom a class I or IIa indication[1] would be indisputable.

Due to the widely available evidence of the importance of the LV mass as the most potent indicator of a high cardiovascular risk[3-5], which attains especially to arterial hypertension, family doctors and cardiologists have years ago began to ask for echocardiography almost for every patient with arterial hypertension. This spontaneous extension of the primary work-up for arterial hypertension, which in Italy dou-

bles the cost of required lab exams, has been legitimated by the 1999 guidelines of ANMCO-SIC-SIIA[6], which explicitly suggest the quantification of LV geometry and function in almost all hypertensive patients. Applying the suggested ANMCO-SIC-SIIA criteria to the cohort of the PIUMA study, we found that 97% of patients would require an echo exam[7]. Although performing echocardiograms in all hypertensive patients would be theoretically ideal, this suggestion does not take into account the technical problems, the need for evidence-based decision-making, and the consequent economic compatibility[7-10].

This review deals with the applications of the quantitative evaluation of LV geometry and function in patients with symmetrically contracting left ventricles, coping with the feasibility, utility, and limitations of the main procedures.

Technical variability in the assessment of the left ventricular mass

In opposition to the argument that, due to its very high technical variability, the echocardiographic assessment of LV mass cannot be used for the clinical follow-up of individual hypertensive (or valve) patients there is a more optimistic opinion that, despite a number of technical limitations, the overall information obtainable from LV quantitation has a crucial importance for risk stratification, due to the prognostic impact of LV hypertrophy, recently also supported by the evidence of the beneficial effect of its regression[11,12]. The present prevalent trend is to take into consideration the utility of the echocardiogram in the work-up for risk stratification[13,14]. However, such an approach still leaves a number of unresolved questions. In an attempt to meet the increasing demand for elucidations, two studies have been implemented[15,16] to try to answer two simple questions: a) is quantitative echocardiography reliable for risk stratification in individual patients, or does its variability blunt the clinical application of epidemiological findings? b) is quantitative echocardiography precise enough to detect a biologically significant change in individual LV geometry and could such a change be used as a monitor for the cardiovascular system?

There are important differences between these studies. In the first one[15], 183 hypertensive patients (≥ 50 years) with echocardiographically diagnosed LV hypertrophy were enrolled in a multicenter controlled clinical trial, the PRESERVE study[17]. In the PRESERVE trial, sonographers from all centers participating in the study received extensive training, including written material and, afterwards, didactic and hands-on training directly at the Reading Center in New York. The procedure of data acquisition was, therefore, tentatively standardized. The standardized protocol required recording of ≥ 10 cycles of two-dimensional parasternal long- and short-axis LV views and ≥ 10 cycles of M-mode views with an optimal cursor beam orientation in each view[18]. The same observer compared two echocardiograms obtained during screening and during randomization, 45 ± 25 days apart. Most of the primary measures of LV wall thickness and chamber diameter were derived from the two-dimensional long-axis view[19] using electronic calipers, due to the orientation of the ultrasound beam which permitted the taking of these measures from the M-mode strip-chart tracings only in a minority of cases. The LV mass was calculated using the common American Society of Echocardiography-corrected formula[20,21].

In the RES trial[16], 16 Italian Hypertension Units served by echocardiography laboratories were asked to participate in the trial. A single meeting among sonographers established that a high parasternal long-axis view had to be first recorded in order to verify whether the direction of ultrasound beam was perpendicular to the septum and LV posterior wall. M-mode tracings had to be obtained from a short-axis view at the level of the mitral chordae. A recording of M-mode tracing was a requirement for the study and all measurements were performed on strip-chart paper. No further attempt was made to standardize the procedure of acquisition. Every center participating in the study was required to take the primary measures of the LV wall thickness and chamber dimensions on each M-mode tracing (2 sets of recordings for each day), with the participation of two different readers (a junior and a senior reader). Thus, in addition to the intraobserver variability also studied in the PRESERVE trial, the RES trial offered the possibility of evaluating even the interobserver variability and intraexam variability (as the true variability due to reader).

But the most important difference between the RES and the PRESERVE protocols lay in the decision of promoting peripheral reading in each echo lab, instead of using a core lab. Thus, while the PRESERVE trial gave a measure of the medium term variability assessed by a worldwide leader in this field, which can be assumed to be the best test-retest intraobserver variability obtainable, the RES trial represents the reality, as each lab assessed its internal consistency and sent the raw data to the analysis center for elaboration.

Despite the difference in the designs, the test-retest intraobserver variability for the calculation of the LV mass between the PRESERVE (an average of 15% compared to the first measurement) and the RES trial (18%) was very consistent and so was the reliability measure performed in both studies using the intraclass correlation. Even more positive, the RES trial demonstrated that the degree of test-retest intraobserver concordance for the classification of patients with clear-cut LV hypertrophy was good enough (87%) to suggest that quantitative echocardiography can be used, in most circumstances, to identify those patients with LV hypertrophy and improve the classification of cardiovascular risk, as requested by recent guidelines[13,14]. This

result, however, is achieved by the categorization of LV mass, but when the nominal value is required, for instance when comparing two values in a single patient, the variability due to chance, error, or unweighted biological changes[2,22,23] is too high to be ignored. If a LV mass of 200 g is measured initially in a single patient, at the distance a repeated value comprised between 164 and 236 g falls within the 90% confidence limit of the error and should be evaluated very carefully in terms of its biological reliability. In other words, if we are looking for a probability of 90% that the reduction in LV mass is due to a true biological effect of our therapy, for a 200 g left ventricle, we need to expect a value < 164 g. Although when biological changes are taken into account this error is reduced, the magnitude of the crude expected difference is very high and substantially limits (albeit in our opinion it does not blunt completely) the possibility of a clinical use[24].

However, not necessarily, in every circumstance, the difference between two values of LV mass should be expected to give a 90% probability of true biological variation. Table I shows that if a 25% chance of error is believed to be acceptable, variations of 10% may also be worthy of consideration. Thus, depending on a number of considerations, a reduction in LV mass ranging from 200 to 180 g may also be considered clinically relevant.

The possibility of using the test-retest information, even if considering a higher probability of error, substantially depends on both the ability of echo labs to minimize their technical variability as well as on the degree of confidence that physicians have with their reference echo lab. Methodical errors can be further reduced by increasing the number of cardiac cycles to be measured (from 3 to 6 cycles)[16], but this increases the time allotted for evaluation.

The development of new echocardiographic techniques will certainly lead to a further reduction in this variability. The use of harmonic imaging coupled with other tools enhancing the identification of interfaces (for instance contrast echo), helps to define structures even in otherwise suboptimal examinations. The digital elaboration of the ultrasound signal allows M-mode evaluation even in conditions of inappropriate ultrasound alignment and, perhaps more important, it allows a good temporal resolution using a frame-rate lower than in traditional M-mode[25]. This method might reduce the mirror-effect due to saturation of the highly reflecting posterior pericardium[26], without the need to reduce the gain at a level that affects the possibility of precisely identifying the endocardial surface. The improvement in the reliability of these new tools should be quantified in appropriate studies.

Technical variability of measures of "systolic function"

The assessment of systolic function in symmetrically contracting left ventricles is performed by calculating the systolic fractional shortening at the level of the endocardium, or even at the midwall, using the same primary measures used to assess the LV mass. The technical variability, however, is lower than with the LV mass because the parameters resulting from the primary measures of the LV diameter and wall thickness (for midwall shortening) are not subjected to the cube function as for the computation of the LV mass[27].

A subtler question concerns the method of measurement of stroke volume. It is widely held that the gold standard for the ultrasound evaluation of stroke volume is the Doppler interrogation of LV outflow tract matched together with the cross-sectional area of the aortic annulus at the valve leaflets[28]. We still prefer to use imaging methods, namely M-mode derived measures, when the mitral valve is continent. The reason is that there is evidence that the technical variability of the time-velocity integral and of the aortic cross-sectional

Table I. Probability of true biological variation assessed using the percentiles of test-retest differences in two sequences of 6 cardiac cycles.

Percentiles	Day 1-day 2 intrareader 1 % difference	Day 1-day 2 intrareader 2 % difference	Probability of true biological variation for greater changes (%)
5	-14.92	-13.22	90
10	-11.72	-8.73	80
12.5	-9.95	-7.76	75
15	-8.57	-6.44	70
20	-6.51	-5.65	60
25	-5.06	-3.83	50
75	5.70	5.22	50
80	7.22	6.55	60
85	8.92	7.82	70
87.5	10.24	9.07	75
90	11.71	10.35	80
95	16.28	14.20	90

area are substantially higher than the direct measures of the LV chamber size[29,30] and that the use of a more recent method to derive LV volumes from linear measures, allows the evaluation of stroke volume even in case of dilated left ventricles[30]. In addition to the above considerations, another pitfall of Doppler evaluation has recently been proved with the demonstration of the systematic difference in the evaluation of LV outflow tract velocity integral in relation to the view of examination (i.e. apical 3- or 5-chamber) that should therefore be accounted for[31].

Technical variability of measures of "diastolic function"

While the same considerations outlined for the LV mass might also hold for simple measures of systolic function, what is usually termed "diastolic function" needs different considerations.

In every meeting, seminar or grand-round based on the pathophysiology of LV hypertrophy, most cardiologists and physicians at some point raise questions about the "diastolic function". The topic is hot and to date it is recognized that Doppler ultrasound represents a unique method for the non-invasive monitoring of LV filling. Generally, the ratio between the E and A transmitral flow velocities is taken into consideration when defining the different degrees of abnormalities in LV filling, and it has been very recently shown to independently predict the cardiovascular outcome in arterial hypertension[32]. However, it is also clear that other measures of Doppler velocities and times might be even more important, since the E/A ratio is highly influenced by preload variations and possibly generates confusion when attempting to distinguish a normal and "pseudonormal" or "restrictive" diastolic filling pattern without more information[33]. Just as for M-mode measurements, the attention for the diastolic time intervals is conceptually justified by the fact that Doppler signals are viewed at a very high temporal resolution which allows accurate determinations.

On these grounds, in order to generate adequate conditions for a useful clinical applicability of notions from large-scale surveys, the reproducibility of the Doppler parameters of diastolic filling has been assessed in several studies.

The intraobserver variability of the Doppler measures of diastolic filling is very low. This warrants an excellent reproducibility. As far back as in 1988, Spirito et al.[34] reported minimal reader-variability for the Doppler indices of LV relaxation (isovolumic relaxation time, duration of the early peak flow velocity, rate of decrease of the early peak flow velocity, maximal early flow velocity), while the reproducibility was lower for the indexes assessing late diastolic events (maximal atrial flow velocity and E/A ratio) in 12 normal subjects. Other investigations also reported similar results in limited numbers of normal subjects in clinical settings[35,36], indicating that both the image acquisition and quantitation as well as the subject variability contribute to the total variability in echocardiographic and Doppler indices, suggesting that sequential follow-up studies should be interpreted by the same readers using the same sonographers. Of interest, in an ancillary assessment of the interobserver reproducibility performed in 20 subjects using the most conservative Bland-Altman interval of agreement, we found that the error is smaller for measurements of the isovolumic relaxation time than for the deceleration time of the E velocity (a parameter often used as a surrogate index of early LV relaxation)[37].

Finally, the Framingham Heart Study proposed the only available intra- and interobserver reproducibility analysis, performed in a large epidemiological setting[38]. The study population included 92 randomly selected patients (12 with atrial fibrillation). A very high reproducibility was found for measurements of the peak velocities and time-velocity integrals while the variability was greater for acceleration and deceleration measurements.

Biological variability

There is a variability which is perhaps more important than the technical variability, that is actually common to each biological variable: the "temporal (or day-to-day) variability". This type of variability depends on the interaction of the variable of interest with other influencing variables that might or might not confound our evaluation.

While depending on variation of biological variables a relatively long time is necessary for any appreciable changes in LV geometry, the LV chamber systolic function and diastolic properties might be sensitive to biological variations occurring in the medium or even short run. When assessing LV geometry or function using a single temporal gate in a patient, one should be aware of the stability of the evaluated measures over time.

A substantial proportion of the LV mass longitudinal variability is explained by variations of body size and cardiac workload over time[2]. Even on cross-sectional evaluation, the between-subject variability in the evaluation of LV mass can be substantially explained (up to 82% of variance) by gender, body size (height) and loading conditions (stroke work), even in the absence of a large variability in blood pressure and body weight values[22,23]. An appealing possibility to overcome the problems related to this type of biological variability, would be the consideration of values of LV mass, weighted for demographic and hemodynamic determinants, by using the percent deviation of the observed magnitude from the ideal value predicted on the basis of sex, body size and stroke work[39,40].

Even more complex is the greatest biological variability occurring in the parameters of diastolic filling[34,36,41,42], because it involves variations that might occur in the short run.

Pozzoli et al.[42] checked the reproducibility of Doppler indices in patients with severe heart failure. The authors found a low variability over a few hours of observation, i.e. within 10% of the mean value, for most Doppler-derived indices, but much greater variation on a day-to-day basis. Besides depending on age[43,44], which is a stable factor, the Doppler-derived indices of diastolic filling are also sensitive to the heart rate[45,46] and respiration phase (more for right ventricular interrogation)[47]. Yet, the Doppler parameters of diastolic filling are also sensitive to variations in loading conditions[37,48-51], body weight[52], atrioventricular conduction[46], and even to hematocrit variability[53].

Although obtained in a cross-sectional survey, the recent attempt of the PIUMA study[32] to generate an equation where the observed E/A ratio is adjusted for an individual's age (years) and heart rate (b/min) might be useful to remove at least two of the numerous confounders bearing on the evaluation of diastolic filling on a clinical basis[24].

Minimizing technical errors

As may be clearly deduced, while a chance of error of 10% for the calculation of LV mass can be clinically acceptable, a chance of error of 18% is not. However, a chance of error of 10% merges an overall accuracy of "only" 75%, which in many circumstances when there is no demonstrated ability of the echocardiography laboratory to produce reliable measures might be not sufficient. Gottdiener[54] showed an interesting simulation in a textbook of echocardiography, demonstrating that an erroneous ultrasound beam orientation is sufficient to change the quantification of the LV mass from a correct value of 277 g to a value of 448 g. Thus, the ability of the laboratory in performing accurate measurements of LV mass is a crucial factor. Results from the RES trial suggest that the probability of error is substantially dependent on the ability of the laboratory. The ability of laboratories participating in the RES trial was not systematically assessed, although a wide range of test-retest differences could be observed among them. Figure 1 shows that only two laboratories could exhibit a test-retest interobserver variability (i.e. the difference between two studies read by different readers in the same laboratory) that was within the 90% confidence limit of the study population. Three laboratories had a very high interobserver variability, and to different degrees 11 exceeded the lower or upper confidence limit. The performance of the test-retest variability when the procedure was performed by the same reader was much better (Fig. 2). There are a number of considerations that apply to these findings.

Most echocardiography laboratories are excellently equipped for diagnostic imaging and semiquantitative evaluation. The quantitative evaluation of LV geometry and function is rarely implemented with the same accuracy as other procedures. Thus, even laboratories that are reference centers for diagnosis might be unable to accurately evaluate LV geometry unless a reliable method and an appropriate learning procedure have been implemented. If we assume that this is the reality, requesting the evaluation of LV mass everywhere to every echo lab for every patient does not make a lot of sense.

There are numerous requests that echocardiography laboratories develop the ability to quantitatively measure LV geometry and suggestions for physicians to optimize the reliability of the information derivable from the quantification of LV geometry. The following "rules" might be summarized:

• every laboratory deciding to perform the quantitative evaluation of LV geometry should implement test-

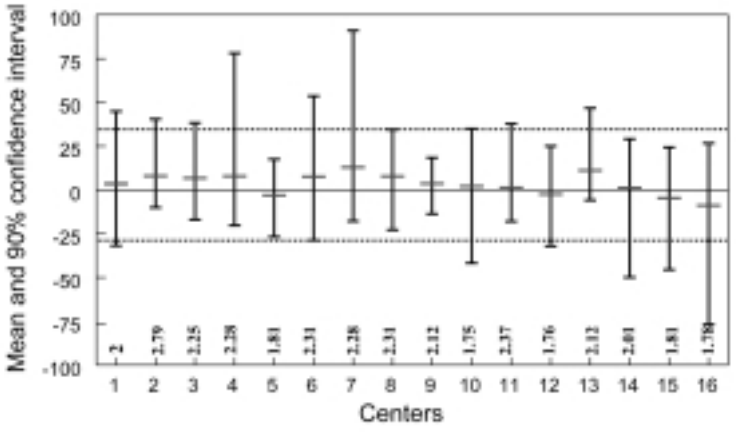

Figure 1. *Mean test-retest interobserver difference in left ventricular mass evaluation ± 90% confidence interval in each center participating in the RES trial[16]. The* dotted lines *represent the 90% confidence interval of the test-retest interobserver variability in the entire study population. Numbers* in bold at the bottom of the frame *are the average quality score in each center (1 = poor; 2 = sufficient; 3 = optimal).*

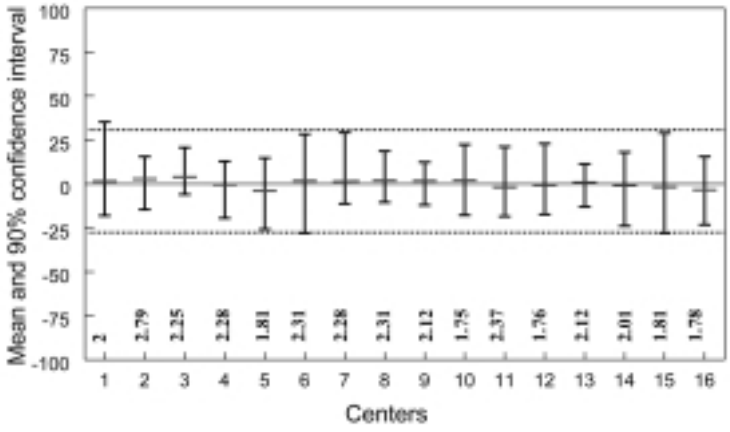

Figure 2. *Mean test-retest interobserver difference in left ventricular mass evaluation ± 90% confidence interval in each center. The* dotted lines *represent the 90% confidence interval of the test-retest intraobserver variability in the entire study population. Numbers* in bold at the bottom of the frame *are the average quality score in each center (1 = poor; 2 = sufficient; 3 = optimal).*

retest reproducibility analyses and generate learning curves. The suggested objective would be to reach a test-retest intraobserver variability of no more than 15-18%, according to results of the PRESERVE and RES studies. Referring physicians should request reliability analyses before deciding to refer patients to an echo lab. This, especially if their therapeutic approach to the patient may depend on the results of the echocardiographic exam;

• once a profitable relationship with an echo lab is established, referring physicians should, if possible, avoid changing laboratory. The variability between echocardiography laboratories can be enormous. This, due to different quality hardware, different technical skill, a different interpretation of the endocardial interfaces and to the variability in gain control and the different impact of the temporal drift;

• even using the same laboratory for all controls in the same patients, referring physicians should check whether the repeated study is performed and evaluated by the same observer and the same machine as the baseline echocardiogram. Ideally, echocardiography laboratories should identify one principal reader, responsible for all quantitative analyses and identify the machine which was used to perform the exam on the report sheet.

The same rules should be applied when the evaluation of diastolic filling is considered necessary for clinical decision-making. Recent technical suggestions should be carefully applied when acquiring Doppler signals[33].

If necessary, the quantitative evaluation of LV geometry and function should be performed off-line. This is a crucial aspect which offers many different topics for discussion. In countries where sonographer technicians perform the examination, the clinical evaluation of echocardiograms must be carried out off-line. In countries where cardiologists directly acquire the imaging, the time of acquisition often coincides with the clinical evaluation and no off-line re-reading is usually necessary. However, there are considerations suggesting that the attention paid to the correct visualization of structures and to an adequate representation of anatomical relationships may sometimes result in an inadequate interpretation of signals and that a systematic off-line re-evaluation of echocardiographic studies might minimize the possibility of clinical errors.

Off-line revision: it's time to start discussing

In our laboratory, off-line revision of clinical examinations is routinely performed for both teaching purposes and quality improvement. The process of acquisition is standardized in a way that every fellow performs the same procedures using the same approach, position of the patient, machine setting and recording criteria. During examination, fellows perform direct measurements of LV walls and diameters (M-mode parasternal short axis, when possible, or two-dimensional parasternal long axis), as well as of the mitral inflow and aortic outflow Doppler signals, using on-line electronic calipers and tape-recording the whole procedure. Every fellow must fill a preliminary report form that is thereafter examined during the revision session.

The revision session is performed on videotapes using off-line working stations equipped with frame-grabbers and appropriate software for the quantitative measurements of the imaging and Doppler signals. The session is guided by a senior cardiologist in the presence of fellows participating in the acquisition sessions. The senior cardiologist checks the electronic marks identifying interfaces, and every other quantitative measurement taken on-line, discuss discrepancies in the interpretation of interfaces, velocities or times, and correct, when necessary, the errors, by using new off-line markers or tracers. Figure 3 shows the percent of off-line corrections needed over a 4-year period, in the

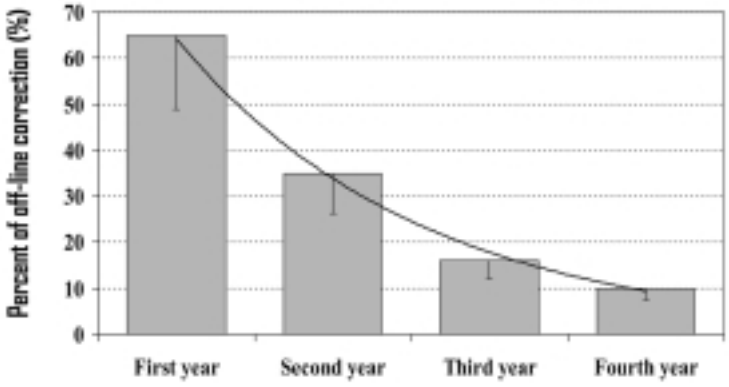

Figure 3. *Percent of total corrections done by senior readers (> 20 000 echocardiograms evaluated) on preliminary reports prepared by fellows during the on-line evaluation of patients. The rate of disagreement with the senior reader evaluation is 65% during the first year and drops down to < 10% after 4 years of collegial off-line evaluation.*

measures taken on-line and reported on the preliminary report form by the same fellow. The learning curve is exponential and shows an improvement in the performance of the overall quantitative measurements (also including Doppler mapping) dropping from 65 to 10% of errors (i.e. disagreement with the senior cardiologist).

The improvement in the learning curve is not the sole effect of the off-line evaluation. When considering the entire echocardiographic examination, other preliminary conclusions might be changed, including the evaluation of wall motion, wall thickness, and LV diameter. Most on-line preliminary evaluations are corrected by the same fellows participating in the reading sessions, without the need of the intervention of the senior cardiologist. We have calculated that expert fellows autonomously adjust up to 83% of the incorrect measures of LV wall thickness and diameter or of wall motion abnormalities taken on-line, with the approval of the senior cardiologist.

Although these data should be considered only as the consequence of an empirical experience, there is enough to believe that some systematic study should be conducted in order to verify whether or not off-line revision of echocardiograms can improve the quality of the service offered to citizens, thus counterbalancing the unavoidable increased costs of the procedure. By using last generation echocardiographic machines, a better alternative to videotape revision could be the off-line review of the imaging memorized in digital format. This kind of revision could be less time-consuming and has many advantages in terms of storage and classification.

Conclusive remarks

The quantitation of the parameters of LV geometry and function represents an important application of echocardiography that might help decision-making. However, most measures detectable on imaging or Doppler present a quite high degree of inaccuracy, when used on single individuals. Whilst, on the one hand, the error applied on an epidemiological scale is minimized because it is divided by the square root of the number of observations, on the other in the single observation its effect is maximized. Physicians should keep the high variability of the quantitation of LV geometry and function in mind when referring patients for echocardiographic evaluation, by paying due attention to the reliability that laboratories can offer. There is no possibility of establishing clear-cut margins of the possibility of error, because this depends on the quality control and experience of the echocardiography laboratory. Together with the availability of measures of test-retest reproducibility, the style of the report[55], the amount of technical information and a clear signature identifying the cardiologist who clinically evaluated the examination are markers of quality. If these conditions are not met, the information on LV geometry and function cannot be confidently used in every clinical circumstance. The technical improvements in last generation ultrasound machines, in particular the stable use of harmonic imaging, could further minimize the technical variability.

Some Doppler measures of diastolic LV filling are likely to be less sensitive to technical variability than parameters of LV anatomy, but in terms of biological variability they are probably less stable. In addition, their utility for clinical decision-making needs to be proven and there is no evidence that reporting on the E/A ratio, the deceleration time of the E-velocity, the isovolumic relaxation time or the pulmonary vein flow can change the management of patients[56].

Acknowledgments

We would like to thank the Italian Society of Hypertension and all participants who supported the RES study for the contribution given in designing the project, collecting data, and preparing the final manuscript.

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