Errors in the Determination of Left Ventricular Functional Parameters

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Gated blood-pool scans of the left ventricle are routinely employed for determination of the left ventricular ejection fraction. Recently, attempts have been made to evaluate other left ventricular functional parameters. These values include peak emptying rate (PER), time to peak emptying rate (TPER), peak filling rate (PFR), and time to peak filling rate (TPFR). In studying these parameters clinically, we identified many software errors and assumptions that impact on these values. These errors may also affect the determination of left ventricular ejection fraction (EF). We conclude that before any serious investigation of left ventricular functional parameters is undertaken, a detailed evaluation and standardization of the acquisition and edge detection algorithms must be performed.

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Almost 18 yr after the introduction of multi-gated blood-pool imaging (MUGA) the predominant use remains the determination of left ventricular ejection fraction (LVEF) (*1*). If properly performed, the left ventricular volume curve generated as part of the MUGA study contains much of the information that has traditionally been obtained by more invasive techniques (*2*).

As computer manufacturers and users attempt to extract this data, it becomes obvious that interinstitutional and intermanufacturer variables exist that may render the data unreproducible and therefore nearly useless. In this paper we will examine the sources of error that lead to this lack of reproducibility.

Recently, efforts have been made to derive left ventricular functional parameters from MUGA data, and correlate them with various clinico-pathologic states (*3–6*). Before attempting to correlate these values with pathologic states, we evaluated existing commercial software as well as our own left ventricular functional software for the derivation of left ventricular values beyond EF and identified some of the variations that occur between commercial packages.

We report below on our findings and the identified sources of error making the comparison of LV functional parameters between the various commercial software packages difficult. We will report separately on clinical applications of the LV parameters.

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MATERIALS AND METHODS

All patients studied were referred for clinically indicated gated blood-pool studies. No normal volunteers were employed. Each patient's red cells were labeled using an in vivo technique with 25 mCi of technetium-99m pertechnetate (*2*). All MUGA studies were acquired in a modified 45-degree LAO projection positioned to achieve the best ventricular separation (best septal view). Each study consisted of 32 frames with a minimum of 200k counts per frame. These were filtered temporally with a three point 1-2-1 filter, which is standard procedure at our institution. Left ventricular edges were determined by two commercially available software packages on different computer systems. In each case 32 independent ROIs were generated for each study. During this generation, a spatial nine point smooth was performed within the user defined area of interest. Variable region background correction systems were employed. The area for background correction was determined automatically.

The results were evaluated for the calculation of functional left ventricular values by processing patients on both systems and comparing the results. The patient studies were acquired on one system and then transferred for parallel processing to the other system. Initially there was a good correlation between the two systems for LVEF. We then developed our own postacquisition EF processing software for one system, and modified the available software on the other so that both yielded the same final ventricular function parameters calculated with the same algorithms. The functional parameters derived from the study were the peak ejection rate (PER),

peak filling rate (PFR), the time-to-peak ejection rate (TPER) and the time-to-peak filling rate (TPFR).

Eight patient studies were then processed four times on each system by the same operator to determine the precision of the two systems. Each ventricular parameter for each patient was averaged. A standard deviation was calculated for each ventricular parameter for each patient and expressed as a percent of the average. These percents were then averaged for a given software protocol to give an indication of the variability in calculating each value. This process was identical for both computer systems. The only difference in processing was the commercially supplied edge detection algorithm.

Methods of Edge Detection

System A (Siemens Microdelta/Maxdelta, Version 6.2). A zero crossing, second derivative edge tracking algorithm was used. Edge enhancement was with a spatial invariant second derivative Laplacian operator after application of a nine-point smoothing filter. Edges were searched radially outward from the center of the ventricle. A gradient threshold is applied, either low, medium, or high, which must be surpassed before an edge point is considered. The edge search is limited to within a rectangular region defined by the user.

System B (Medical Data Systems A3 with MIPS Software). This system used a zero crossing, second derivative edge tracking algorithm with an outward radial as described above. An edge point may satisfy one of two conditions; either of zero crossing, or when the pixel count level falls below a user selected threshold within one of four quadrants placed over the ventricular region. The zero crossing takes precedence, and the threshold point is used if a zero crossing cannot be identified. Again, a gradient threshold, low, medium, or high can be selected.

Calculation of the Derivative Curve

Once the points of systole and diastole are identified and a left ventricular volume curve generated, the derivative curve may be created. This curve will identify the areas of peak ejection and peak filling and the times to their occurrence. To better represent continuous curves, both the ventricular volume and derivative curves were interpolated by a factor of two.

Interpolation and differentiation were obtained utilizing a Fourier transform technique (*7*). To obtain interpolation, the Fourier transform of the ventricular volume curve was extended in frequency to the Nyquist frequency of the desired sampling interval, followed by inverse Fourier transformation at the new sampling interval. The cutoff frequency beyond which the Fourier transform is zero is determined by the signal-to-noise ratio at the dominant frequency as prescribed by Bacharach et al. (*8*). For interpolation by two, the sampling interval is halved and the Nyquist frequency is doubled. The derivative of the volume curve is obtained by multiplying the Fourier transform of the ventricular volume curve by a frequency ramp filter scaled by 2*pi*i, where i is the imaginary number defined by the square root of −1, followed by inverse Fourier transformation. The ventricular volume curve was first replicated to three full cardiac cycles before Fourier transformation.

Finding PER, TPER, PFR, and TPFR

Once the derivative curve was generated, the peak ejection rate (PER) and peak filling rates (PFR) were identified by searching for the greatest slope. The search for peak ejection and peak filling was restricted to their portion of the left ventricular volume curve. Once these points were identified, the time-to-peak ejection rate (TPER) and time-to-peak filling rate (TPFR) were obtained by knowing the number of frames between events and the time per frame.

RESULTS AND DISCUSSION

There were considerable differences in the reproducibility of the calculation of left ventricular ejection fraction (LVEF), peak ejection rate (PER), time-to-peak ejection rate (TPER), peak filling rate (PFR) and time-to-peak filling rate (TPFR) between the two systems. As can be seen in Figure 1, each of the values determined on system A had greater variability than on system B. The greatest variations were in the calculation of TPER in both systems. The smallest variations were in determination of PER in system B and of the EF in system B. In both cases the PER was more precise than the PFR. Similarly, the TPFR was more precise than the TPER.

In order to better understand the errors that may occur, a brief review of electrical and mechanical cardiac events is necessary. Figure 2 shows the cardiac volume curve superimposed on the ECG. The first event is electrical depolarization of the left ventricle. The ventricles immediately begin to contract and the A-V valves close. Approximately 20–30 msec is required for the intraventricular pressure to increase to the level required to open the aortic valve. This is the period of isovolumetric contraction. Once the intraventricular pressure exceeds the aortic pressure, the aortic valve opens and the blood is propelled into the systemic circulation. Ejection is initially rapid and continues despite the initiation of ventricular relaxation. Repolarization begins and can be seen as the T-wave on the ECG.

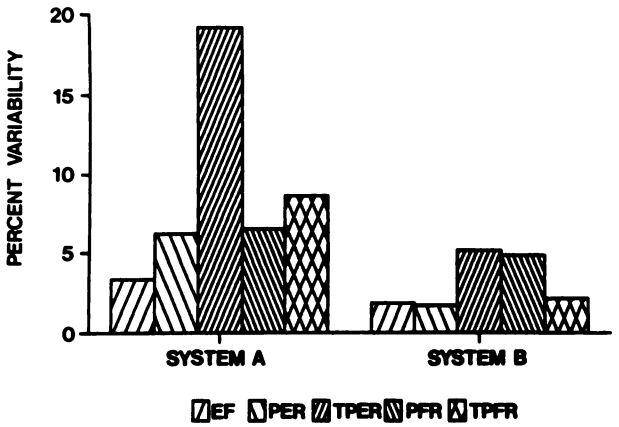

FIGURE 1
A graphic representation of the percent variability when generating the diastolic parameters on two systems.

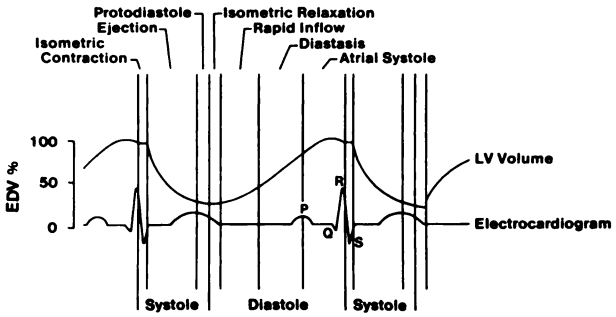

FIGURE 2
The LV volume curve and ECG superimposed on significant events in the cardiac cycle.

The majority of the stroke volume is ejected during the first ¾ of systole. The last ¼ is termed protodiastole. During this phase, there is still a small amount of blood that leaves the ventricle. During protodiastole, the ventricular pressure rapidly decreases, yet the musculature remains contracted. The systemic back pressure then forces the aortic valve closed and the ventricular muscle relaxes. This heralds the onset of isovolumetric relaxation which lasts another 30 to 60 msec after which the mitral valve opens and diastole begins. The A-V valves are normally very large and offer almost no resistance to blood flow. Most of the filling occurs during the first third of diastole, termed the rapid inflow phase. The second third of diastole, known as diastasis, sees only small amounts of blood entering the ventricles. The third and final portion of ventricular diastole is atrial systole which may be seen on the ECG as the P wave. This may account for up to 30% of the filling of the ventricle (*9*).

Since all of the LV function software employed was developed to derive the functional parameters using identical algorithms, the only change in the processing procedure between the systems was in the left ventricular edge detection. As expected, it was the first derivative parameters of the LV volume curve that consistently had a larger variability. The peak ejection rate as determined on system B was the only result that had a smaller variability than the determination of the ejection fraction. The PER was observed in both cases to be less variable than the PFR.

The ejection phase of the curve is more linear and shorter than the diastolic phase. It is therefore more difficult to place the exact point of peak ejection for the same reason. This made the time-to-peak ejection more variable than the time-to-peak filling.

Sources of Error in Calculation

The determination of EF, PER, TPER, PFR, and TPFR requires accurate representation of cardiac physiology and adherence to the appropriate cardiac intervals. Deviations in timing or approximations of frame length will seriously affect the accuracy of results. If the edge detector includes some of the right ventricle or excludes some of the left ventricle, the values will also be erroneous. For the edge detector to work properly, the operator must be able to position the patient such that a good separation of the ventricles is obtained (best septal view).

The background correction is often automatically determined by the software. Since rules that do not take into account anatomy are used to determine this area, this area may be anatomically incorrect in a number of cases. If the background correction region lies over the aorta or other high count structure, the ejection fraction will be artificially elevated (Figure 3).

Error can also be introduced by using too much magnification during the acquisition of the study. The information density per pixel in this case is not high enough for the edge detector to operate reliably. A magnification of 1.5:1 should be the maximum allowable for a 15 in. camera. None may be required for a 10 in. camera.

The most precise calculations are those of the EF. This calculation is based only on the counts in the systolic and diastolic frames. The calculation is simple and is shown below in Equation 1A.

$$EF = \frac{(\text{END DIAST. COUNTS} - \text{BKG}) - (\text{END SYST. COUNTS} - \text{BKG})}{(\text{END DIASTOLIC COUNTS} - \text{BKG})} \quad (1A)$$

On the other hand, determination of ventricular ejection and filling rates are more prone to error. This is because the rates and times are calculated using the first derivative curve which places more emphasis on the subtle changes in counts (slope) that occur between frames in the region of interest. Even small differences in determining the edges will cause substantial variability in the calculation of rates and times. This is apparent by comparing the reproducibility results from the two systems. Below are errors in calculation that have been identified and proposed standard methods of determination.

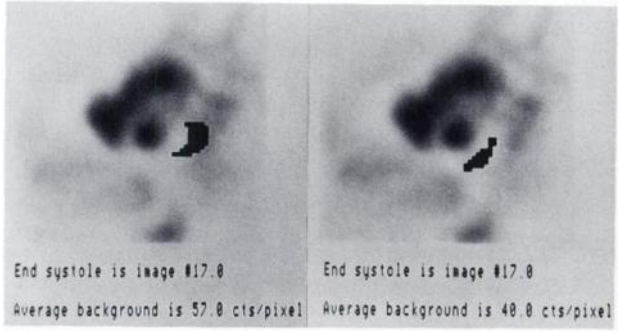

FIGURE 3
An example of improper placement of the region for background correction (left) and its correct position (right).

Errors in Determination of Heart Rate and Frame Length

When a study is acquired, the time per frame is determined from the preacquisition heart rate and this is used throughout the study, despite any variations in the heart rate. It was anticipated that this information would be stored by the computer. In both systems evaluated, this parameter was not available retrospectively. It is this time per frame value that is essential in the accurate calculation for PER, PFR, TPER, and TPFR.

The frame length is an essential part of the calculation of ventricular parameters as can be seen from the Eq. (2) through (5) below.

$$\text{PER} = \text{Max}\left[\frac{-dV}{dt}\right] \quad (2)$$

$$\text{PFR} = \text{Max}\left[\frac{dV}{dt}\right] \quad (3)$$

$$\text{TPER} = (\#\text{ of Frames between End Diast. and PER}) (\text{Time/Frame}) \quad (4)$$

$$\text{TPFR} = (\#\text{ of Frames between End Syst. and PFR}) (\text{Time/Frame}) \quad (5)$$

The simplest method to assure accuracy of frame length data is to store it at the time the study is acquired. If this is not possible, the original heart rate and the true number of frames can be used to calculate it.

$$\text{Time/Frame} = \frac{1}{(\text{HR})(\#\text{ of Frames per R} - \text{R interval})} \quad (6)$$

This gives the result in minutes per frame. To get more usable numbers, multiply by 60 sec per minute to get sec/frame.

The display of the regularity of the heartbeat and the user defined windows of acceptable beats is an important piece of data for both study quality control and computations. This R-R histogram is also an essential component of the LV analysis package. It may also be possible to determine an average heart rate from this data if the initial heart rate was not stored.

One error identified was that the use of all heartbeats to calculate the average heart rate may be erroneous and does not correspond to that represented by the image data. Premature ventricular contractions will greatly affect this average. This problem is more evident in the face of an arrythmia. To calculate an average heart rate, we suggest using two standard deviations from the mean of the obtained heart rate to calculate the average heart rate. This insures that the average heart rate is as accurate as possible.

If the original heart rate or the time per frame is not stored, any calculation of frame length will be in error. An average heart beat derived from the histogram as described above should not be used to calculate the frame length since millisecond differences from the actual frame length will cause the introduction of substantial error.

Errors in Detection of Systole

MUGA studies are acquired by gating the frame acquisition to the R wave of the QRS complex on the ECG. The assumption is made that systole begins with the first frame after detection of the R wave. There is in fact a lag of 20 to 30 msec between depolarization and onset of ejection as can be seen in Figure 2. This is, as noted above, the period of isovolumetric contraction. This may be prolonged in states where there is a conduction defect.

For greatest reliability, the software should search for the highest count obtained in the first 60% of the study rather than assume that the first frame of the study is the onset of systole. This will eliminate the isovolumetric contraction phase, and give a more accurate impression of the time of contraction.

The other assumption is that the acquisition begins instantaneously with the R wave. Depending on the hardware, this may not be true. A further time lag may occur between the sensing of the R wave and the beginning of the first frames acquisition due to hardware-software interaction. A long lag in starting acquisition may result in missing end diastole altogether. Knowledge of the precise onset of systole is necessary to calculate ejection fraction and the times to end systole and peak ejection rate. If the gating is delayed, the identification of end diastole may be erroneous and the ejection fraction may be several ejection fraction units lower than the actual as can be seen in Figure 4.

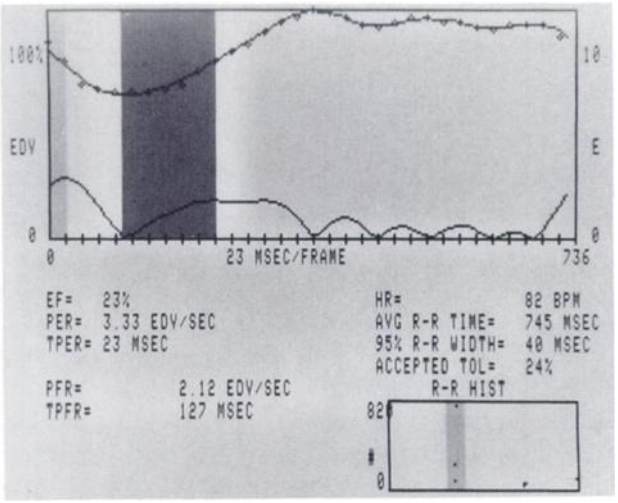

FIGURE 4
Delayed gating will shift the curve to the left and the determination of the onset of systole will be in error.

Errors in Detection of Diastole

The onset of diastole is the point at which the left ventricular volume is smallest. The search for the smallest number of counts (end systolic frame) must be restricted to the first 75% of the cardiac cycle. If later frames are included in the calculations, the onset of diastole may erroneously be determined to be one of the lower count terminal frames due to gating errors. This will result in an erroneous ejection fraction. To circumvent this problem it is advisable to include in the display of the ejection fraction curve, a shaded area or line as in Figure 5 indicating where systole and diastole began. This will ensure the interpreter that the correct assumptions were made for systole and diastole.

Proposed Methods for Determination of LV Parameters

The most consistent edge detection was performed using system B in combination with the variable background placement and filtering as described above. The detection of the onset of systole is the frame with the largest number of counts in the region of interest. End systole is the frame with the least number of counts. Frame length should be recorded at the time of acquisition. After the derivative curve is calculated by the above method, the peak emptying and filling rates are identified. From these points, the times-to-peak ejection and filling can be calculated.

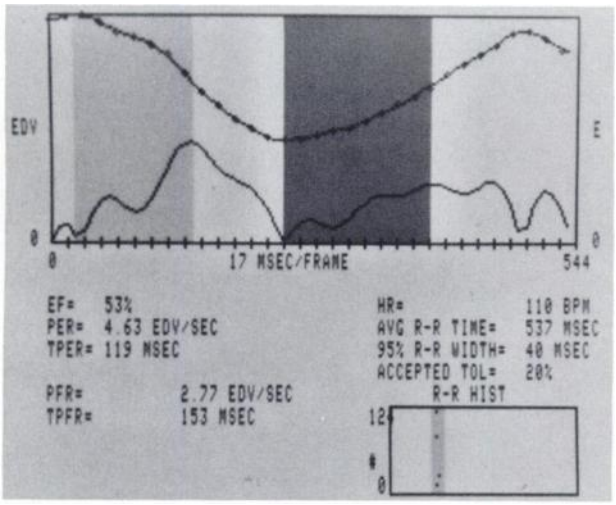

FIGURE 5
A normal ejection fraction curve with shaded areas depicting onset of systole-to-peak ejection rate (lt. gray) and onset of diastole-to-peak filling rate (dk. gray).

CONCLUSION

The calculation of ventricular parameters other than ejection fraction is becoming more useful as these parameters are identified and related to various disease states. The importance of the method of their calculation lies in the fact that such great variation can occur as to render these values nonreproducible and therefore clinically useless if done without close attention to detail. It is imperative that research done on these values be preceded by an evaluation of software design. Without a consistent standard by which to judge, it will be impossible to reproduce results among institutions or in a given patient.

NOTE

Since this study has been completed, System A's software (Version 87A) has been modified to be similar to that of System B.

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