

DATA PROCESSING IN NUCLEAR CARDIOLOGY: MEASUREMENT OF VENTRICULAR FUNCTION

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Many interesting and innovative approaches have been employed in the processing of cardiac data. It is the purpose of this paper to present and discuss several of these. Rather than skim the entire field, several methods have been arbitrarily selected from among those felt to be the most interesting and promising. The disadvantages of bias in the selection are hopefully offset by the gain in time and space for a more thorough presentation. The paper is further narrowed by limiting the discussions to those methods attempting to describe left ventricular (LV) cardiac function, primarily from gated equilibrium measurements. Despite this restriction, it will be clear that many of the techniques presented are applicable to other forms of cardiac data, and even (in some cases) to other organ systems.

Measurement of Global Ventricular Function

Many data processing techniques are available which facilitate the analysis of global, as opposed to regional, ventricular function. Broadly, these can be divided into two categories: methods which attempt to quantitate certain well defined aspects of ventricular function (e.g. ejection fraction, etc.), and methods which attempt simply to differentiate normal function from abnormal function. In the former category belong those methods whose principle goal is the investigation of physiology; in the latter, methods whose goal is disease detection.

Quantitation of Function

Nearly all current methods for quantitation of global ventricular function use a curve of activity over the LV as a function of time (Fig. 1). Various parameters describing this time activity curve (TAC) can then be used to quantitate LV function. Ejection fraction and stroke volume are two commonly used indices of LV function. These systolic measures have been treated exhaustively in the literature and will not be discussed here. Recently there has been much interest in the diastolic portion of the LV time activity curve. There are many different parameters which could be employed to describe the diastolic behavior of an LV TAC. The maximal rate of LV filling and its time of occurrence are two such parameters

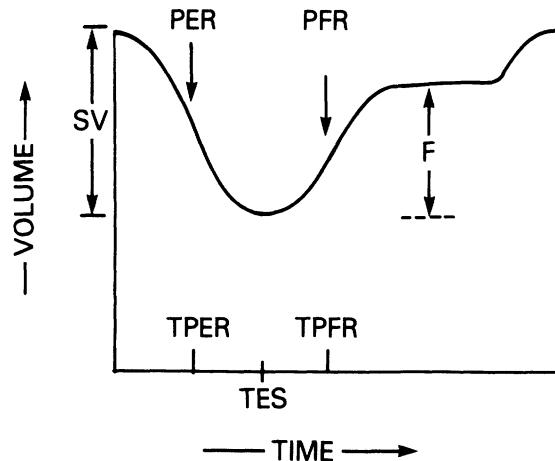


Figure 1. Idealized left ventricular time activity curve. SV= stroke volume; PER= peak ejection rate; TPER= time to PER; PFR= peak filling rate; TPFR= time to PFR; TES= time to end systole; F= fraction of filling in early diastole.

which have been shown to be of potential value (1-3). One method of calculating this maximal rate is to fit a limited portion of the LV TAC (Figure 2) to a third order polynomial (i.e. a cubic equation) of the form

$$A_0 + A_1*t + A_2*t^2 + A_3*t^3$$

It has been shown (4) that, with the LV counting statistics attainable in a typical resting gated equilibrium study (e.g. $6*10^{10}$ counts within a $15\text{cm} \times 15\text{cm}$ field of view), higher order terms do not contribute significantly to the information content available. A lower order polynomial (e.g. fitting a quadratic or a straight line to a narrower portion of the filling curve) results in significantly higher statistical fluctuations in the value of the peak filling rate, or (if too many

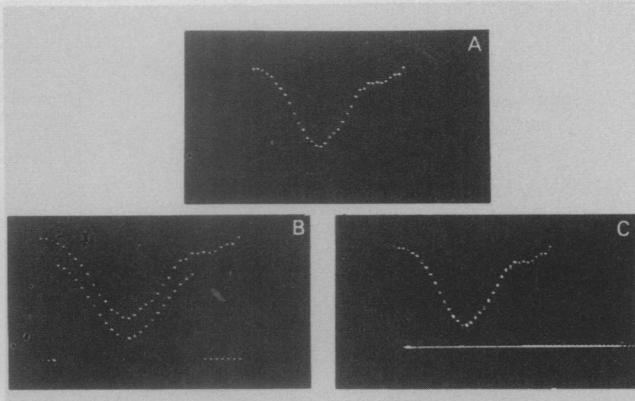


Figure 2. Cubic fits to ejection and filling periods of TAC. A: LV TAC. B: LV TAC + fit(offset). C: LV TAC + fit(overlayed).

points are fit), a function which does not adequately describe the data. If a fit to a third order polynomial is used, and if the errors in the coefficients are calculated (see reference 5 for a fortran program which accomplishes this) then one can easily show that

$$\text{peak slope} = A_1 - \frac{A_2^2}{3A_3}$$

and that the time of occurrence of this peak slope is

$$\text{TPFR} = -\frac{A_2}{3A_3}$$

Likewise, knowing the errors in the coefficient of the fit, σ_{A_n} , the variance in the slope is found to be:

$$\sigma_{sL}^2 = \sigma_{A_1}^2 + \frac{A_2^2}{3A_3} \left[\left(\frac{25A_2}{A_3} \right)^2 + \left(\frac{\sigma_{A_3}}{A_3} \right)^2 \right]$$

and the variance in the time of occurrence is:

$$\sigma_{TPFR} = \text{TPFR} \left[\left(\frac{\sigma_{A_2}}{A_2} \right)^2 + \left(\frac{\sigma_{A_3}}{A_3} \right)^2 \right]$$

Although tedious to include, the above errors are a very important part of the clinical data. Usually the clinician is interested in changes in filling rates or in comparing the value obtained to those obtained from a population of normal values. In either case it is necessary to know not just "is there a difference" but "is there a statistically significant difference." This latter question can be answered only by performing an appropriate error analysis.

The peak slopes are themselves not clinically useful, as they depend on the absolute value of count density achieved. To account for this, one can normalize the slopes using one of two different methods--either by dividing by the end diastolic

counts (properly background corrected) or by the stroke counts. Each method produces slightly different information. The practical advantage of normalization to stroke counts is that it is independent of background.

There are several potential technical difficulties which must be resolved in order to properly measure diastolic phenomena, such as peak filling rate. First, the temporal resolution of the data must be adequate. It has been shown (4,6) that at rest, 20 msec per point is adequate (i.e. a frame rate of 50 frames per second) to determine peak filling rate, while at exercise it may require 10 msec per point. At 20 msec per point a small but measurable drop in the measured value of peak rate occurs. It is possible that the magnitude of this drop is clinically insignificant. The second technical difficult concerns the drop in the LV TAC which occurs in late diastole due to the finite fluctuations in beat length. Such fluctuations occur even in normal individuals. Although this problem may be avoided by list mode acquisition, it is a difficulty present in most commercial nuclear medicine systems. Fortunately the R wave to R wave variations occurring in nearly all subjects (without electrical arrhythmias) are such as to simplify this problem. If a so called "beat length histogram" (i.e. number of beats versus R-R interval length) is accumulated during acquisition it is found that only rarely, if at all, does a subject have an R to R interval as short as the time to peak filling. Thus the maximum slope is not distorted by the R to R fluctuations (7). Such fluctuations will, however, influence the range of points surrounding TPFR which can be used for the cubic fit.

There are several other diastolic indices which, from a physiologic point of view, are thought to be of potential clinical significance. One of these is (Figure 1) the fraction of blood entering the ventricle during early filling (i.e. the relative height "F" in Figure 1 divided by the stroke volume). No one has yet devised a reliable way to determine this quantity. A second quantity of potential interest is the shape of the TAC immediately after its minimum. It has been noticed that in subjects with wall motion abnormalities the shape of the TAC around its minimum is no longer symmetric, but instead, often appears as a minimum followed by a period of only slightly increasing counts. There is reason to believe (as we shall see later) that regional contraction abnormalities may be responsible for this alteration in shape. As yet there have been no methods developed to quantitate these particular curve shape changes.

Most often the LV TAC is created from a series of gamma camera images spanning an average cardiac cycle. It is also possible, however, to use a non-imaging detector (8-11). Such a detector, when properly collimated and positioned over the left ventricle, can directly produce an LV TAC. Sufficient validation studies have been performed to indicate that these devices can usually be posi-

tioned over the subject's chest. A brief gated gamma camera acquisition was performed and the resulting cinegraphic display observed. The lead annulus was then moved until it precisely encircled the LV. The position of the annulus was marked on the subject's chest and the annulus removed. The probe could then be positioned, using the chest markings, at the same angulation as the gamma camera.

In Figure 3 many parameters were calculated from each single beat TAC, as shown in the accompanying legend. The topmost panel of this figure indicates the R to R interval length of each beat (i.e. the inverse of the heart rate) and the time to end systole. The subject (a normal volunteer) was supine. After about 30 beats (arrow A) he placed his feet up on bicycle pedals, but did not begin pedalling. As seen from Figure 3, the end diastolic counts (and hence ED volume) increased slightly as a result of this maneuver. After about 20 more beats, the subject began exercising, causing his R-R interval to drop (panel A) and both his ES and ED volumes began to fall (arrow B in Figure 3).

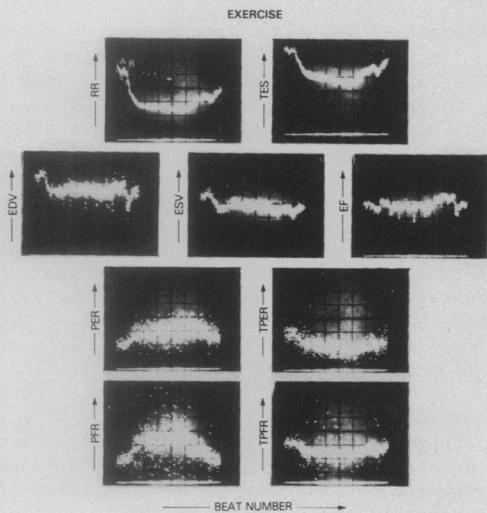


Figure 3. Plot of various single beat parameters as function of beat number, during exercise

The ability to monitor such phenomena on a beat-to-beat basis is proving valuable in physiologic studies: e.g. assessing the immediate effects of fast acting drugs (12); observing changes due to various external stimuli, etc.

Several collimator designs have been used in addition to the ultra high sensitivity parallel hole collimator described above. These other collimators are primarily of a single straight or tapered bore design. Devices with such collimators have been found to accurately measure changes (but not necessarily absolute values) of EF. No similar validations have been performed to assess the accuracy of other parameters derived from probe produced TACs. Although early measurements (8,9) have

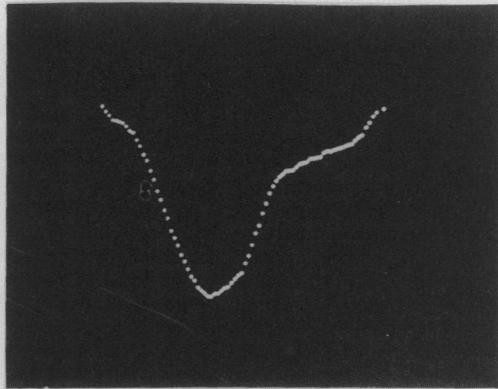


Figure 4. Gated TAC from high count rate probe. No smoothing or similar processing performed.

indicated the probe TAC appears quite similar in shape to the gamma camera TAC, further validation studies are necessary. This is especially true of the single hole collimator equipped devices, as they exhibit large variations in sensitivity with position.

These high efficiency probes also permit acquisition of high temporal resolution TAC's of unprecedented statistical reliability. This is achieved by gating (i.e. adding together) many single beat TACs together. Figure 4 illustrates such a TAC. The low statistical fluctuations present in such data allow detailed investigation of the details of the LV TAC curve shape.

Another innovative use to which these non-imaging devices are being put is in the creation of nearly real time pressure-volume loops. This is accomplished (invasively) in the catheterization laboratory by digitizing LV pressure from a catheter tip transducer simultaneously with TAC creation.

Figure 5 illustrates such a pressure-volume loop. The ability to easily produce such pressure-volume (P-V) relations in nearly real time, is proving quite useful (11,12). At present, however the analytic methods used to quantitate the P-V loops are quite rudimentary. As these data become more commonplace, more sophisticated methods must be developed.

Detection of Abnormalities Using Global TAC's

Frequently the objective of a cardiac study is not the quantitation of some particular aspect of the LV TAC but instead, is the determination of whether the TAC is "normal". By this is meant whether the LV TAC in question differs from TAC's obtained from subjects with normal cardiac function. Several processing methods are currently under investigation for this purpose.

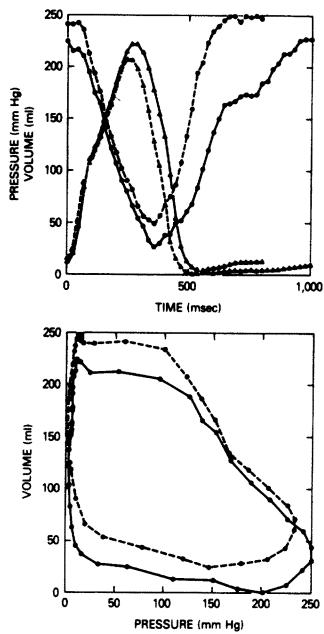


Figure 5. Top: two LV TAC's and LV pressure curves. Bottom: resultant PV loops.

Flow Volume Loops

In this method each LV TAC is operated upon to create a plot of counts (relative volume) versus relative flow (derivative of counts). The resulting curve is a closed curve, or loop, referred to as a "flow-volume loop." (13) Figure 6 illustrates how such a loop is created. Note the small secondary lobe resulting from atrial contraction. Quantitating the magnitude of atrial contraction, a difficult task using only the LV TAC, may be facilitated when the data is presented as a loop. Extracting data from the loop, instead of from the LV TAC itself, has other advantages. The loop inherently results in some normalization for R-R interval length. The long flat diastasis periods of a TAC map into a single point in the flow volume loop (the cusp in Figure 6). Thus, variations in the diastasis period do not cause appreciable variations in the loop shape. This allows TAC's produced from different subjects to be more easily intercompared.

The loop shown in Figure 6 is normalized in the following way, to aid in intercomparison of loops. The flow axis (vertical) is normalized to the peak flow, be it a positive or negative value. Thus, one can imagine the flow loop to be bounded by two horizontal lines (the horizontal lines of the box in Figure 6) and tangent to at least one of the horizontal lines--the upper if the flow is greater during systole, the lower if the flow is greater during diastole, or both if both flows have the same peak value (irrespective of sign). The volume (i.e. counts) axis is normalized to constant stroke volume, and so the loop will always be tangent to the vertical sides of the box on Figure 6. This normalization allows

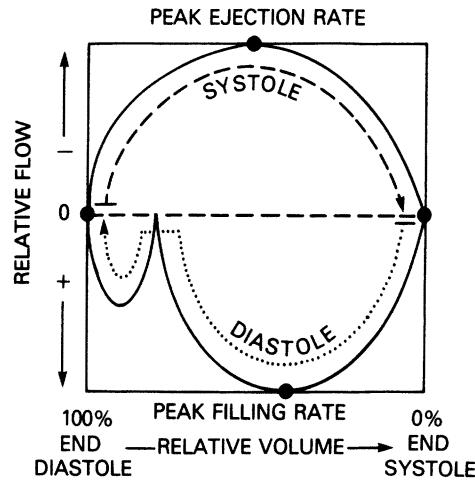


Figure 6. Illustrating creation of flow volume loops from an LV TAC.

comparison of LV TAC shape independent of stroke volume. In preliminary studies these loops have been able to distinguish normal subjects from abnormal ones. The loops are compared by superimposing the loop of a subject to be tested to those of the normal population. The difference in area between the two loops is then used as an index describing the TAC of the subject. The normalization scheme described above tends to emphasize differences in flow between systole and diastole. Other normalization schemes are also possible (but remain untested), as are other methods for comparing loops.

Phase and Amplitude Analysis of Global LV TACs

Cardiac abnormalities may produce a wide variety of changes in the LV TAC curve shape. Coronary artery disease, for example, may result not just in a decreased EF, but also in abnormalities of other aspects of the LV TAC. Delays in contraction, decreases in filling rate, increases in the magnitude of atrial contraction, delay in time to end systole, etc.--any of these, may be affected by the presence of cardiac disease. A measure of LV TAC shape which was influenced by many or all of these factors might prove useful in attempting to separate abnormal subjects from individuals with normal cardiac function. The parameter known as "Fourier phase" (14-20) is such a quantity. To understand the meaning of "phase" it is necessary to briefly recall the Fourier expansion theorem. This theorem simply states that any periodic function (such as an LV TAC) may be represented by the sum of a series of sine and cosine waves of varying frequencies. That is, considering the LV TAC to be a function of time t , then:

$$LV(t) = A_0 + \sum A_n * \sin \frac{2\pi t}{T} + B_n * \cos \frac{2\pi t}{T}, \quad (1)$$

where the A's are constants and T is the period of the cardiac cycle. For a periodic function, such as the LV TAC, the relationship is exact--that is, it is possible to perfectly reproduce an LV TAC using equation (1). It is easily shown that one can compute the coefficients A_n and B_n as follows:

$$A_n = \frac{2}{T} \int_{-T/2}^{T/2} LV(t) \cos \frac{2\pi t}{T} dt$$

$$B_n = \frac{2}{T} \int_{-T/2}^{T/2} LV(t) \sin \frac{2\pi t}{T} dt$$

This is quite easy to implement. One simply multiplies the first point on the LV TAC by the value of $\sin 2\pi(0)/T$ and adds it to the second point on the TAC multiplied by $\sin 2\pi(1)/T$ and likewise for all remaining points on the TAC. The difficulty in applying equation 1 arises because the sums specify an infinite number of terms must be used. In practice, however, it is found that very few terms are needed to at least visually reproduce the LV TAC. Figure 7 illustrates this finding. Panel A shows the actual LV TAC. Panel B is the result of equation 1 using only a sine and a cosine of a single frequency (i.e. 1 term, or "harmonic"); Panel C uses 2 sines and cosines (i.e. 2 harmonics) to represent the TAC so on. It is clear, that at least visually, 3 or 4 terms produce a quite satisfactory result.

The concepts of Fourier "phase" and "amplitude" as they are applied in nuclear medicine are a simplification of the Fourier expansion theorem. One attempts to describe the LV TAC by only the

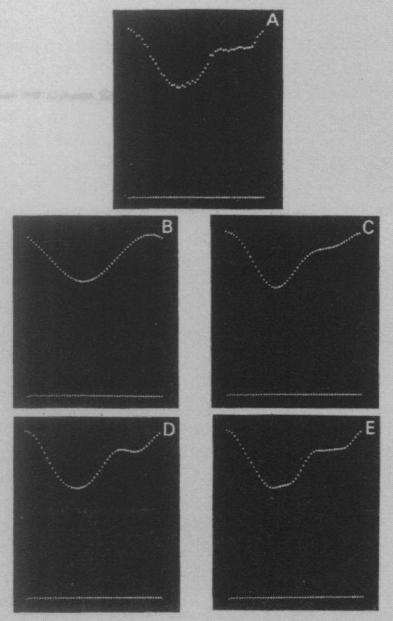


Figure 7. A: actual LV TAC from gamma camera. B: 1st harmonic fit. C: 2 harmonics. D: 3 harmonics. E: 5 harmonics.

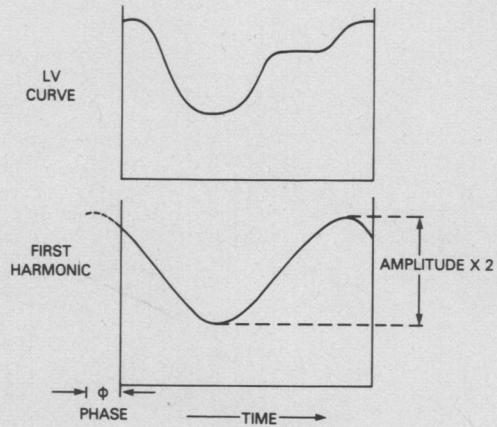


Figure 8. Illustrating definition of phase and amplitude.

first harmonic--that is by the sum of a single sine wave and cosine wave of frequency equal to one cycle per cardiac R to R interval. Obviously, from Figure 7, using a single harmonic produces only a crude representation of the LV TAC. Using basic trigonometry one can show that the sum of a sine and cosine of the same frequency is equal to a single cosine, displaced by an amount ϕ , as in Figure 8. This shift, ϕ , is the quantity we call "Fourier phase". (NB-this name is actually a misnomer since there exists, in mathematics, a much more complicated quantity with the same name). Amplitude is simply the height of this shifted cosine curve, as also illustrated in Figure 8. It should be clear from the above discussion that the "phase" of an LV TAC is not a very sophisticated measure. It simply describes how much one must shift a cosine in order to make it fit (as best as possible) the LV TAC. Clearly the "quality" of the fit will almost always be poor since LV TAC's are more complexly shaped than a cosine. Because phase is computed by fitting a cosine to the entire LV curve, it is influenced by the shape of the entire curve. Despite a growing literature of misuse, phase is not necessarily a measure of the time to onset of contraction of the ventricle. It is influenced by this quantity but so is it influenced by many other features of the LV curve shape. Figure 9 illustrates this dependence of phase on LV curve shape. At the top of this figure is an idealized LV TAC with a pre-ejection period T_1 , a time to end systole of T_2 , etc. By artificially adjusting each one of the parameters, T_1 , T_2 , etc. and holding the others constant, we can investigate the influence of each parameter separately on phase. We see from Figure 9 that although increases in time to onset of contraction (T_1) results in an increase in phase, so also do many other parameters. Note also that alterations in many of the timing parameters also cause changes in amplitude. Physically, one can think of phase as simply a measure of the symmetry of the LV TAC. Any alterations in curve shape which effect the symmetry will also effect the phase.

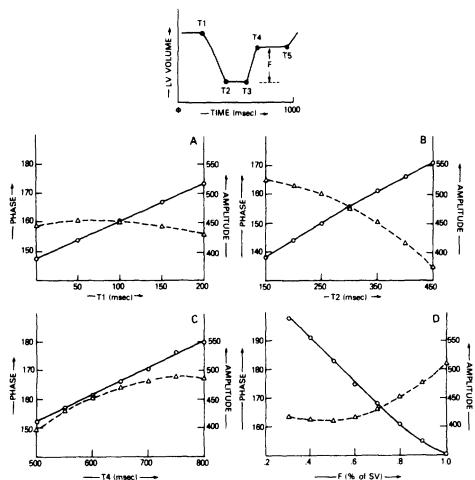


Figure 9. Dependence of phase(solid line) and amplitude(dashed line) as function of LV curve shape. (from ref. 20)

Measures of Regional Function

The global LV time activity curve gives us much useful information about the functioning of the ventricle. It is however, only an average quantity--an average over the many portions of the LV, each of which may be functioning differently from the rest. In a global TAC, the behavior of a small, poorly functioning portion of the ventricle may well be masked by the normally functioning remainder. If it is desired to examine each region of the LV separately, different techniques must be employed than those discussed above--techniques which can elucidate regional, as opposed to global, function. As with measures of global function, we can divide these regional measures into two categories. First, those measures which seek to quantitate a certain well defined aspect of LV function and second, those measures which seek primarily to differentiate between normal and abnormal function. The latter category of measures consists of parameters, like phase, which are influenced by many different aspects of ventricular function.

Functional Maps

A common technique employed to assess regional function is the technique of functional

imaging (21). A functional image (often called a functional map) is simply an image in which each pixel represents not counts, but some descriptor of function. Functional images are usually produced (in the case of dynamic imaging) by forming a TAC from each single pixel in the region of interest. The intensity of each pixel in the functional image is set equal to the value of the parameter of interest extracted from the single pixel TAC. In practice, the single pixel TAC's may not actually be created but rather the para-

meter of interest extracted by direct calculation, on a pixel by pixel basis, from the dynamic images. Whether physically created or only conceptually created, we will find it useful in what follows to speak of the single pixel TACs as though they actually existed.

A second method of producing functional images is to divide the ventricle up into roughly pie shaped pieces, called sectors. The center of gravity (with respect to counts) might perhaps be taken as the "pie" center. Time activity curves can be created (either conceptually or in fact) from each sector, and then analyzed for the parameter of interest (EF, phase, etc.). As the image is a square matrix of pixels, it is necessary to decide upon a scheme for apportioning counts from "partial" pixels into one sector or another. The polar coordinate system, inherent in the use of sectors, is especially useful in cardiology for two reasons. First, it is anatomically convenient to divide the LV up in this way. Second, although the entire surface of the image carries information, it is frequently edge bordered defects which dominate. The polar coordinate system tends to emphasize edge bordered regions, as more pixels from the LV edges are included in each sector than are pixels from the center of the LV.

Quantitating Functional Maps

Functional images offer a convenient method for presenting the hundreds of values of a parameter which one has extracted from each pixel of a cardiac image sequence. Rather than having to inspect a list of hundreds of values of EF (for example), each of which has been obtained from a single pixel TAC, one can simply observe the image created by setting the intensity of each pixel to the value of EF. This is a very useful method of processing and displaying data. Although the functional image is quantitative in nature, it is usually evaluated subjectively-by visual inspection of the image. Two methods which permit quantitative (and hence objective) evaluation of functional images are discussed below. We first give a brief description of ejection fraction functional images so that we may have an example to use in discussing these quantitative techniques. Later we will describe other, more interesting, functional images.

EF and Stroke Volume Maps

Two widely used functional maps in nuclear cardiology are the ejection fraction image and the stroke volume (counts) image. The latter is formed by subtracting the end systolic image from the end diastolic image, pixel by pixel. The end systolic image ideally is defined as the image coinciding with aortic valve closure. In practice it is usually defined as the minimum of the global LV TAC. Usually one sets negative values in the map to zero. In so doing, however, it must be remembered that a slight systematic error will be introduced into all calculations which use the stroke counts image. Figure 10C illustrates a typical stroke counts image in which negatives have been set to zero.

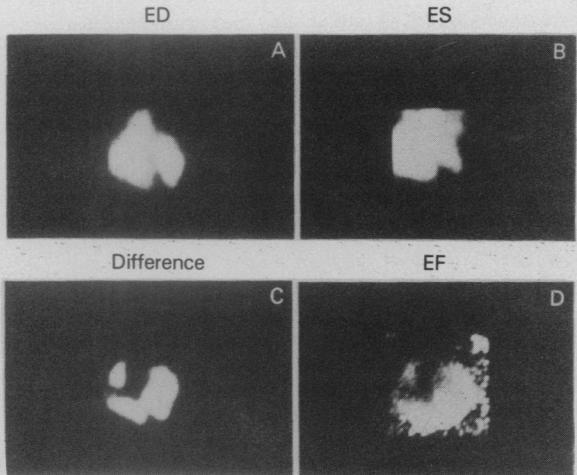


Figure 10. A: ED image. B: ES image. C: stroke count map. D: EF map.

The EF image is just a normalized version of the stroke counts image, formed by dividing (pixel by pixel) the stroke counts image by the ED image. Figure 10D illustrates such an image, formed from the ED & ES images in 10A, B. Figure 10D also illustrates one of the major difficulties encountered in functional imaging--namely, that the functional value is calculated everywhere in the image--even at locations in which it is a poorly defined quantity. For the stroke count image this is not a significant problem. For the EF image it is. In the EF image even regions outside the LV possess EF values--values which may range from 0 to 1 due to the large statistical uncertainty in dividing a small (and statistically unreliable) value of stroke counts by an equally small (and almost as unreliable) ED count. One method for overcoming this problem is to mask out (i.e. set to zero) all but the structures of interest. Unfortunately there exists no method of edge detection reliable enough for this purpose. The calculation of most global parameters is relatively insensitive to precise LV edge delineation. The appearance (and quantitation) of functional maps is frequently exquisitely sensitive to the borders of the ROI used--it is at the edges that the statistical fluctuations in EF are the greatest. Later a technique will be described which minimizes this difficulty.

Sector Analysis

One method to quantitatively describe functional images is to use the method of sectors, as discussed previously. Instead of computing a TAC from each sector, however, the functional map itself may be divided up into "pie" shaped pieces. If one applies this technique to the EF map, a value of EF can be assigned to each pie shaped wedge by averaging the single pixel (or partial pixel) values of EF in the map. This is very different than actually applying the sectors to the original (counts) image sequence

in the manner described earlier. Averaging the individual single pixel EF values treats all pixels equally. Pixels toward the edges of the LV (which have low counts) are weighted equally with pixels in the center of the LV (which have many counts). Thus this procedure emphasizes edge pixels more strongly than does applying the sectoring to the original (counts) image sequence. Again the difficulty in determining the LV borders becomes important. Values of EF outside the LV region of interest may cover the whole range of 0 to 1 or may even be negative. One is tempted to weight each pixel with the ED image to compensate for this effect. It is immediately clear, however, that doing so simply gives the stroke volume image.

Once the sector values of the parameter of interest (in this example, EF) have been calculated, they can be used to quantitate function. Frequently, it is not the absolute values of the sector parameter which are important, but rather how the values vary over the 360° of the "pie". If this is the case, the sector values are often normalized to the overall global value of the same parameter. One interesting approach to assessing the changes in the functional parameter, from one section to another, makes use of the periodic nature of the sector values (Dino Vitale, Private Communication). That is, as one goes around the sectors, one returns again to the starting sector. A plot of the sector value versus angle in either polar or linear coordinates can be made. To assess the magnitude of the deviations in this plot it is possible to expand the function in a one (or possibly two) harmonic Fourier series. The Fourier amplitude can then be used as an index of the magnitude of the deviations in regional values (due perhaps to regional LV functional abnormalities). It should be pointed out that there is no need to always strive for a single index (e.g. the Fourier amplitude) to serve as a descriptor of regional function, even from a single sector map of a single parameter. It is quite possible that a multivariate analysis of several parameters describing the variation of the values from sector to sector in the map would be optimum. A single descriptor is merely one simple way to first approach the problem of quantitating regional function.

Frequency Distribution Functions

A straight forward way to quantitatively describe a functional image is to create from it a frequency distribution function of values. By this is meant a tabulation of the fraction of pixels possessing a certain value as a function of that value. This tabulation, which is most often plotted as a histogram, tells how frequently a certain functional value occurs in the image. Figure 11 illustrates such a frequency distribution for an ejection fraction image which has been masked by an LV region of interest. The distribution function is peaked at a value of about 50, indicating that this is the most probable value of EF for a pixel to have. This distribution function has been obtained from the ejection fraction image of a normal subject.

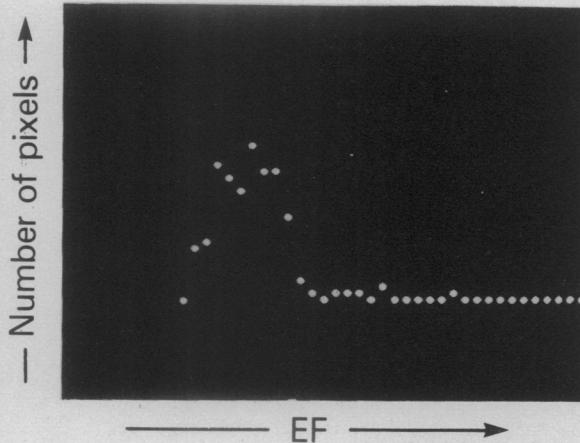


Figure 11. Frequency distribution function of EF values in the LV.

It is relatively symmetric. If a subject possessed a regional wall motion defect which in turn caused a regional depression in ejection fraction, then the distribution function might not appear as symmetric. Instead, since a group of pixels within the LV would have a depressed value of EF, these pixels would cause a bump on the low side of the distribution function. It is possible that analysis of distribution functions from EF functional maps may be of clinical use, but no one has yet thoroughly investigated this hypothesis. Analysis (often simply visual) of distribution functions produced from other functional maps has been reported in the literature (17-19, 21, 22).

There are several disadvantages in using frequency distribution functions to describe a functional image. First, the shapes of frequency functions are often quite sensitive to the precise borders selected for the region of interest. Imagine, for example, a distribution function created from the stroke counts image of Figure 10. After drawing an LV region of interest, the distribution function could be produced. If the LV ROI were increased in size and a second distribution function created, it would be considerably different from the first. The larger ROI would include many more pixels with small values of stroke volume, because the larger ROI includes more pixels from the periphery of the ventricle. The situation is even worse for distribution functions created from ejection fraction maps, as can be seen from Figure 10.

A second disadvantage of using frequency distribution functions to describe a functional map is that by doing so, all spatial information is lost. That is, there is no information in the frequency distribution function (DF) as to where in the ventricle a particular functional value came from. In cardiac studies this is important. For example, one characteristic of coronary

artery disease is the presence of regional wall motion abnormalities which may manifest themselves as abnormalities in the functional parameter being used to describe the regional TAC's. The fact that these abnormalities are regional is not contained in the frequency distribution function.

Methods exist which can (at least partially) circumvent the aforementioned difficulties. One of these methods (22) involves creation of an "error" map to complement the functional map. This error map is simply an image in which the value of each pixel is an estimate of the error (one standard deviation) of the corresponding functional parameter. The computation of the error may be based on the standard error propagation relations or can be empirically determined. For example, the calculation necessary to produce an error map corresponding to an ejection fraction map is:

$$\sigma_{EF}^2 = \frac{1}{ED-B} * \left\{ (1-EF) \sigma_{ED}^2 + \sigma_{ES}^2 + EF \sigma_B^2 \right\}$$

where

B = Background counts

Typically the values in an error map are small inside the LV, RV, and atria, and are large elsewhere (where the statistical precision is poor). Once an error map has been created, it can be used as an aid in quantitating the frequency distribution function. For example, variance and skew are two parameters which could be used to describe the frequency distribution. Usually they are calculated as:

$$\text{Skew} = \frac{M_r}{M_2^{1.5}} \quad \text{Variance} = M_2$$

$$\text{where } M_r = \frac{1}{N} \sum (x_i - \bar{x})^r f_i$$

and f_i = # of pixels at i^{th} point in DF

where the sums are over all pixels within the ROI, \bar{x} is the average value of the parameter of interest (e.g. ejection fraction) and $P(x, y)$ the value of the parameter at pixel (x, y) . The variance, of course, tells us how variable the values in the functional image are, and the skew tells us how symmetrically they are distributed about the mean. Just as the distribution function is strongly influenced by the exact boundaries of the ROI, so too are the variance and skew. This effect can be minimized by weighting the calculations with the estimates of error obtained in the error maps.

Weighted variance: Weighted skew:

As above with

$$M_r = \frac{\sum \frac{1}{\sigma_i^2} (x_i - \bar{x})^r}{\sum \frac{1}{\sigma_i^2}}$$

and all other terms are defined as before.

This error weighting allows only terms which are statistically significant to contribute to the calculation of variance and skew. In our example of EF, the error is in general, high outside the ventricle, and hence, even if the ROI is slightly too large, pixels outside the LV will not be counted heavily.

Another approach which has been reported (22) is to take the error map into account when making the distribution function itself. This can be achieved by treating each pixel in the functional image as though it were a gaussian distribution of values, with width given by the standard deviation obtained from the error map. Thus the frequency distribution function becomes a sum of gaussians:

Error weighted
Frequency distribution function (3)

$$DF(p) = \frac{1}{\sqrt{2\pi}} \sum_{x,y} (1/E_{x,y}) \exp[-(P - P_{meas})^2 / 2 * E_{x,y}^2]$$

where P_{meas} = measured value of parameter P , all else defined below.

To see the effect that this procedure has, consider a single pixel in the functional map. This pixel has a value $P(x,y)$ corresponding to the value of the parameter being measured at point x,y (e.g. EF, stroke counts or whatever). The usual distribution function is simply a plot of the number of pixels having a value "P" versus P . Let this distribution function be called:

$D(P)$ = number of pixels in image possessing a value "P"

In the usual method for creating the distribution function our single pixel would contribute "one" to the number of pixels having value P . Using equation 3, however, the single pixel can be thought of as being divided up--most of the pixel having a value "P", but some parts of the pixel having values greater than P and some parts having values less than P , according to the gaussian expression of Eq. 3. The width of the gaussian in Eq. 3 is given by $E(x,y)$ --the value of the error map at (x,y) . If the error is small the gaussian is narrow, if the error is large, the pixel is thought of as being spread out over many values. If the error approaches 0, then the whole of the pixel has value P .

Distribution functions created with the above approach are smooth curves and are weighted for possible errors in the functional parameter. Thus, in an EF map, pixels outside the ventricles and atria might have a large error and hence contribute very little to any single point in the distribution function.

As was mentioned previously, a distribution function contains no information concerning the spatial distribution of the parameter of inter-

est in a functional map. There are several methods by which one could attempt to restore some spatial information to the distribution function. One of these is to use a technique known as "cluster" analysis. Cluster analysis involves examining all pixels which have the same value within a functional image. If these pixels are grouped closely together (i.e. clustered) this value should be counted more heavily in the distribution function. For example, consider an LV ejection fraction map containing normal values of EF everywhere except for a small group of pixels, all located at the apex, with an EF of .2. Because these pixels are grouped closely together, we may wish them to contribute more heavily to the distribution function than if the same pixels were scattered randomly over the LV (Figure 12). This could be accomplished by computing how "spread out" groups of pixels with similar values are. An obvious measure of the degree of "spread" is the spatial variance. One could examine an EF map, for example, and complete the spatial variance of all pixels with EF between 0 and .1, between .1 and .2, and so on. The distribution function for each interval of EF could then be weighted with the inverse of this spatial variance:

$$D^*(P) = DF(P) / SV(P)$$

where $SV(P)$ is the spatial variance of pixels with value P . This increases the contribution to the distribution from pixels with similar EF's which are located nearby each other in the LV.

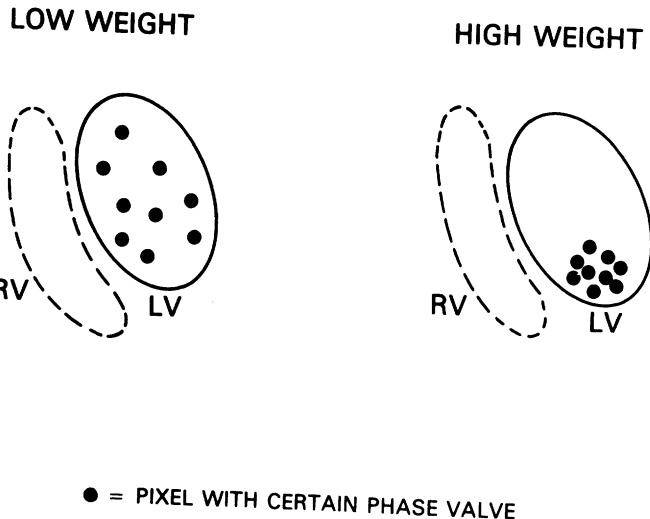


Figure 12. Illustrating concept of "cluster" weighting.

Some Examples

We have discussed several general methods for

displaying and analyzing regional cardiac function. We now present a few specific examples of these methods applied to ventricles with both normal and abnormal function.

"Time to Minimum" Imaging

There is evidence (24) that myocardial ischemia can produce localized delays in the pattern of myocardial contraction. These delays can result in different regions of the ventricle reaching minimum local volume at different times (e.g. an ischemic apex perhaps still contracting for many 10's of milliseconds after the rest of the ventricle has reached minimum volume--perhaps even after the aortic valve has closed). Such effects are easily observed by creating, from ECG-gated scintigraphic images, a functional map of time to minimum counts. Such a map is illustrated in the left panel of Figure 13 for the ventricle of a dog whose apex was rendered ischemic (surgically). The intensity of each pixel represents the time of occurrence of minimum counts in the corresponding single pixel TAC. Note the relatively non-uniform intensity of the LV, indicating a non-homogeneous time to minimum. The ventricle has been masked by a manually drawn ROI supposedly encompassing the LV. In order to quantitate this functional image a distribution function, over pixels within the ROI, has been created using the error map. The distribution function obtained by the gaussian error weighted scheme of equation 3. Similar images from a normal dog produce a more uniform map and a single peaked distribution function, while in the abnormal distribution function, two peaks are obvious.

It is not at all clear what the proper method for computing the time to minimum counts is. Should each, unprocessed (and therefore noisy), single pixel TAC be examined for the time of its minimum? Should spatial and/or temporal smoothing be performed first? The answers to many rather fundamental questions remain obscure, even for so simple a map as this. One technique which may prove worthwhile is to describe the TAC by an empirically determined function (e.g. a parabola in the neighborhood of the minimum) or to expand the TAC in a truncated Fourier series. This latter approach is of course identical to temporally filtering the TAC with a sharp cutoff, low pass filter. Using global TACs of high statistical reliability one finds that the time to minimum can be adequately described by a Fourier expansion with very few harmonics.

Phase and Amplitude Maps

Figure 14 illustrates a typical Fourier phase map and its corresponding amplitude map. These have been obtained by applying the previously described equations to each of the single pixel TAC's in the image. The amplitude map is similar in appearance to an ED-ES difference map, except that the amplitude map is bright wherever counts change greatly over the cardiac cycle, regardless of when the change occurred in the cycle. Thus, the atria, as well as the ventricles, have large

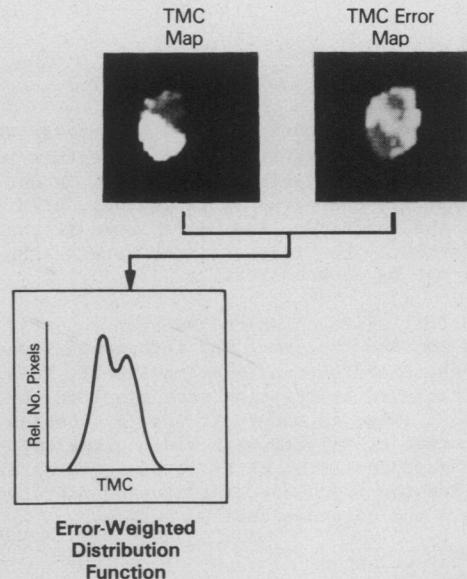


Figure 13. Upper: time to minimum counts image and associated error image. Lower: distribution function (error map weighted) of TMC. From ref. 24.

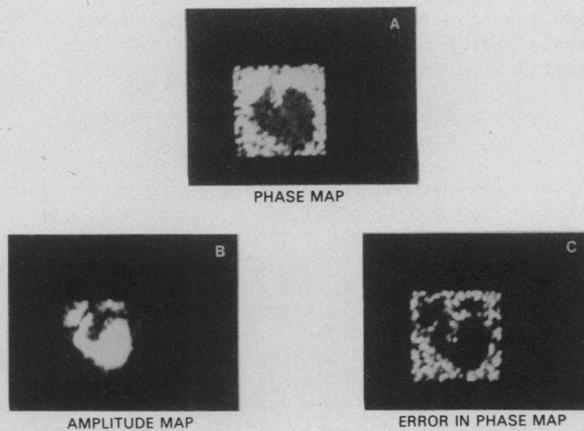


Figure 14. A: Fourier phase map. B: Fourier amplitude map. C: map of error in phase.

values in the amplitude map, as would regions of the LV that reached minimum counts at times other than end systole. The amplitude map, as it is defined here (and as it is currently used in a nuclear medicine today) is the amplitude of the first harmonic only. As such, it is influenced not only by local stroke counts, but also by how well the single pixel TAC's are described by a cosine curve. If the TAC's in a certain region of

the LV are not fit well by a cosine, the amplitude in that region will be reduced. If one wishes to produce a map descriptive of the magnitude of the blood volume change occurring over the LV, the (single harmonic) Fourier amplitude map is not satisfactory. One instead could use more harmonics in the Fourier expansion describing the TAC's or (more simply) one could calculate a "maximum difference" image. This latter image is formed by subtracting a minimum counts image (in which each pixel is the pixel of lowest counts throughout the cardiac cycle) from the maximum counts image (in which each pixel is the pixel of maximum counts). The advantage of this latter procedure is its simplicity; the disadvantage, its systematic errors due to counting statistics.

The phase map shown in Figure 14 illustrates many of the previously described difficulties encountered when analyzing functional maps. The most obvious of these is the fact that phase is calculated everywhere over the image, even over regions where counts are supposedly stationary with time. Precise definition of the edges of the ventricle then becomes quite important, either in computing a distribution function or in calculating other parameters from the functional image. One approach which has been suggested is to weight the phase values by their amplitude, using the amplitude map. This is reasonable, as a curve with zero

amplitude does not have a meaningful value of phase. The difficulty with this procedure is that while a low amplitude is a necessary condition for a non-reliable phase value, it is not a sufficient condition. For example, a ventricle with a hypokinetic apex may have a very low Fourier (1st harmonic) amplitude, yet, due to the high counting statistics which may be present over the apex, produce a statistically reliable value of phase. It is statistical reliability, then, which is the key. As mentioned previously, weighting the phase map with its associated error map allows the statistical reliable to be included in any calculations. Figure 15 (top left) shows the distribution function obtained with and without the error map weighting. In Figure 15 we illustrate the inclusion of spatial information into the distribution function. Figure 15 (top right) shows the distribution function before and after "cluster" weighting (as described previously) the phase map of a normal individual, while 15 (bottom left and right) illustrates the cluster weighting applied to a subject with a localized, regional abnormality in his phase map. In all of Figure 15 the distributions have been modified using the error map.

Statistical Considerations

Many of the methods for describing global and regional LV function are strongly influenced by counting statistics. We have already mentioned, for example, how strongly the "maximum difference" image is affected. In fact, there are many parameters (e.g. peak filling rate) describing regional function for which maps are not produced, simply because of the limited statistical reliability of single pixel TAC's. One solution to this difficult

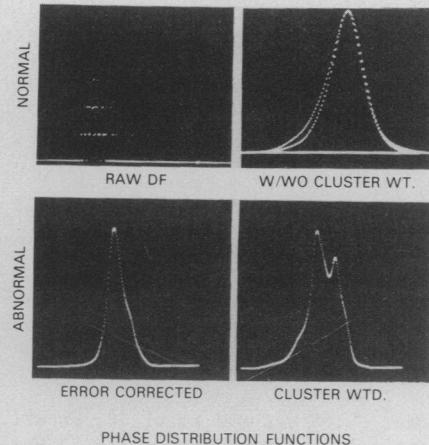


Figure 15. Phase distribution functions.

is to assume the single pixel LV TAC's can be described by an algebraic expression (e.g. a polynomial, or a finite Fourier series). One can then fit the LV TAC's to this algebraic expression and calculate the parameters not directly from the noisy LV TAC but from the perfectly defined algebraic expression. The obvious disadvantage of this procedure is that one must make some *a-priori* assumption about the functional form of the TAC (i.e. one must assume that the algebraic expression adequately describes the TAC). Nonetheless, much progress has been made along these lines--especially by describing the TAC by a finite Fourier series. After deciding upon the meaningful frequency content present in the TAC (6,25) one eliminates all greater frequencies from the Fourier expansion (Fig. 7). Any parameter of interest (e.g. peak filling rate, ejection rate, etc.) is easily calculated from the resultant smooth curve. As long as one remembers to keep in mind the fact that high frequency data has been discarded, this and similar procedures hold promise for the future.

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