Nontraumatic Determination of Left Ventricular Ejection Fraction by Radionuclide Angiocardiography

By Heinrich R. Schelbert, M.D., John W. Verba, Ph.D., Allen D. Johnson, M.D., Gary W. Brock, Naomi P. Alazraki, M.D., Frank J. Rose, M.D., and William L. Ashburn, M.D.

SUMMARY
Previous reports have suggested that left ventricular ejection fraction can be assessed by recording the passage of a peripherally administered radioactive bolus through the heart. The accuracy and validity of this technique were examined in 20 patients undergoing diagnostic cardiac catheterization. $^{99m}m$Te-human serum albumin was injected via a central venous catheter into the superior vena cava and precordial activity recorded with a gamma scintillation camera interfaced to a small digital computer. A computer program was designed to generate time-activity curves from the left ventricular blood pool and to calculate left ventricular ejection fractions from the cyclic fluctuations of the left ventricular time-activity curve which correspond to left ventricular volume changes during each cardiac cycle. The results correlated well with those obtained by biplane cineangiocardiography ($r = 0.94$) and indicated that the technique should allow accurate and reproducible determination of left ventricular ejection fraction. The findings, however, demonstrated that the time-activity curve must be generated from a region-of-interest which fits the left ventricular blood pool precisely and must be corrected for contributions arising from noncardiac background structures. This nontraumatic and potentially noninvasive technique appears particularly useful for serial evaluation of the acutely ill patient and for follow-up studies in nonhospitalized patients.

Additional Indexing Words:
Left ventricular time-activity curve
$^{99m}m$Te-human serum albumin
Ejection fraction

Computer analysis
Gamma scintillation camera
Radionuclide angiography

RADIONUCLIDE ANGIOCARDIOGRAPHY is now well recognized as a useful tool in studying left ventricular (LV) anatomy and function. Previous studies have shown that following the injection of a radioactive bolus, the LV cavity can be visualized by recording precordial activity with a wide-field gamma scintillation camera.1-3 The image data can be stored together with the ECG on magnetic tape and the LV displayed selectively at end-diastole and end-systole, thus permitting detection of regional myocardial dysfunction.5 From these images, LV end-diastolic and end-systolic volumes can be estimated by use of the area-length method6 and LV ejection fraction calculated.7-10

More recently, it has been suggested that ejection fraction can be obtained in a different manner by analysis of time-activity curves generated during the passage of the radionuclide bolus through the left ventricle.11-14 Assuming complete mixing of the radioactive tracer with the blood in the LV, changes in count rate originating from this chamber during any cardiac cycle reflect changes in its volume between systole and diastole. It follows that the fraction of end-diastolic blood volume ejected with each systolic contraction can be calculated from this data.

There is, however, only sparse information regarding the validity and accuracy of this method. Therefore, a study was undertaken to compare LV ejection fractions obtained by analysis of LV time-activity curves with those concurrently derived from biplane cine ventriculograms. Moreover, the method was examined for potential sources of error in obtaining accurate ejection fractions and a computer routine, which permits the use of the technique in clinical practice, was developed.

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Material and Methods
Twenty-six consecutive patients were studied while undergoing diagnostic cardiac catheterization. However, six patients with LV bivplane cineangiograms technically unsatisfactory for calculation of the LV ejection fraction were excluded from the comparison, leaving 20 patients with a mean age of 54 years (range 38 to 71 years) in the group (table 1). No patient was excluded as a result of technically unsatisfactory radionuclide angiograms. Informed consent was obtained in all patients participating in this study. LV bivplane cineangiograms were recorded on 35 mm film at 80 frames/sec in the frontal and lateral projections following intraventricular injection of 75% sodium diatrizoate (Hypaque 75, 1 ml/kg) over a 2- to 3-second period. LV cavity silhouettes were drawn from end-diastolic and end-systolic angiographic frames in both frontal and lateral projections; corresponding frontal and lateral end-diastolic and end-systolic frames were determined by analysis of the simultaneous electrocardiogram and markers for each frame exposure recorded during the cineangiogram. After correction for magnification and distortion by means of a grid composed of 1 cm squares embedded in lucite, volume estimates were made using the area-length method and ejection fractions were then calculated. All beats analyzed represented ventricular contractions originating from normal electrical depolarizations and none were preceded by extra systoles. Either prior to or approximately 45 min following completion of cineventriculography 8 mCi of $^{99m}$Tc, labeled to human serum albumin by the electrolytic method and dissolved in 0.5-1.0 normal saline solution, were rapidly introduced into the superior vena cava via a 7F catheter. Precordial activity was recorded during the first circulation through the heart, then intermittently for 10 min with a gamma scintillation camera (Searle Pharma/Gamma HP) equipped with a converging, low energy collimator in a 30° right anterior oblique position and stored in "real time" on magnetic tape (Searle Data Storage/Accessory). In these patients, the ECG was not recorded simultaneously on the magnetic tape.

Data Processing
Since the method for estimating LV ejection fraction is based on the assumption that changes in count rate originating from the LV blood pool reflect changes in LV volume, care was taken to generate a time-activity curve based only on counts arising from the LV blood pool. This curve was obtained in the following manner: the raw data were transferred from the magnetic tape to a small dedicated digital computer (MED II, Nuclear Data, Palatine, Illinios) and stored in an event-by-event mode (list mode). In order to clearly identify the LV cavity, the first 40 seconds of precordial activity were summed and displayed in a 64 by 64 matrix on the computer oscilloscope showing an image of the bolus as it traveled through both the right

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Ejection fraction</th>
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<td>±0.04</td>
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</table>

Abbreviations: C and NC = time-activity curve corrected and not corrected for background activity; AS and AI = aortic stenosis and regurgitation; MS and MI = mitral stenosis and mitral regurgitation; IHSS = idiopathic hypertrophic subaortic stenosis; CAD = coronary artery disease; beats = number of cycles analyzed.

Table 1
Clinical Data and Ejection Fraction Measured by Biplane Cine and Radioisotope Angiography

Abbreviations: C and NC = time-activity curve corrected and not corrected for background activity; AS and AI = aortic stenosis and regurgitation; MS and MI = mitral stenosis and mitral regurgitation; IHSS = idiopathic hypertrophic subaortic stenosis; CAD = coronary artery disease; beats = number of cycles analyzed.
and left heart (fig. 1A). A region-of-interest (ROI) was then assigned roughly to the LV cavity with the computer light pen (fig. 1B) and a preliminary time-activity curve was generated (fig. 1C). From this curve, a 20 sec time period corresponding to the passage of the bolus through the LV (as identified on the time-activity curve by the second and larger peak) was selected to produce a new image, this time delineating clearly the LV blood pool without superimposed contributions from the right heart chambers. (fig. 1D). ROIs were fitted precisely to the LV cavity silhouette as well as to the immediately surrounding (background) noncardiac structures (fig. 1E). Within these 'sampling windows' counts were collected for 40 msec periods (i.e., 25 data samples/second) and two time-activity curves were produced. In order to correct for interference from noncardiac background structures, the curve obtained from the region-of-interest surrounding the LV cavity was normalized for area (i.e., comparable number of channels within both ROIs) and subtracted from the LV time activity curve to produce a ''corrected'' curve (fig. 1F).

**Computer Analysis**

On the left ventricular time-activity curve each peak was presumed to correspond to the LV volume at end-diastole and each valley to the volume at end-systole. Ejection fraction, therefore, could be computed by dividing the difference between count rates at end-diastole and at end-systole by the count rate at end-diastole. Assuming that the changes in ventricular volume, thus in count rate during the cardiac cycle, could be approximated by a sinusoidal function, an ''average'' curve was fit to the raw data. The deviations of the uncorrected data points from the average curve were determined and their root mean square (i.e., the square root of the mean of the squares of the deviations during a 2 sec time segment on the curve) was calculated (fig. 2). Standard sine wave analysis was employed which states that the amplitude of a sinusoidal variation is equal to the root mean square (RMS) times the square root of two. Thus, the average difference between count rates at end-diastole and end-systole could be expressed by twice the square root of two times the root mean square and reflects stroke volume (fig. 2). The end-diastolic count rate was derived from the amplitude of the sine wave, that is, the root mean square times the square root of two, plus the mean value of the ''average'' curve for that 2 sec time segment. Accordingly, ejection fractions were calculated in 2 second segments for the entire period that the bolus was in the LV. However, only the early, monoeponential portion of the descent of the time-activity curve (usually corresponding to the first two or three cardiac cycles following the point of maximum counting rate) was used for final analysis, since mixing of the tracer within the LV blood pool was assumed to be most complete during this period.

The entire recording, storage, and processing system was tested for its frequency response. Scintillation camera recordings were made with 8 mCi of $^{99m}$Tc in a 12 ml syringe placed in front of the collimator. By rotating an eccentrically suspended lead wheel (4 mm thick) at varying speeds (1 to 6

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**Figure 1**

*Extraction of precordial time-activity curves from the left ventricular (LV) blood pool. A. Precordial activity is summed to produce a 40 sec image and displayed in a $64 \times 64$ matrix on the computer oscilloscope. A region-of-interest (ROI) is assigned roughly to the LV (B), and a preliminary time-activity curve (C) generated. The curve permits temporal separation of peak LV activity (second peak), which then is summed over 6 sec and displayed in D. ROIs are precisely assigned to the LV blood pool and the surrounding noncardiac structures (bkg). A time-activity curve for the left ventricle is generated (F) which must then be corrected for "background."*

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cycles/sec) between the radioactive source and the collimator, sinusoidal time-activity curves with frequencies from 1 to 6 cycles/sec (60–360 'beats' per minute) were obtained and analyzed.

The importance of assigning proper LV and background regions-of-interest was examined in a group of six patients in the following manner. Ejection fractions were determined from LV time-activity curves, generated from a ROI encompassing the LV cavity precisely in each case and corrected for background activity as obtained from ROIs which (a) encircled the LV cavity entirely including the aortic root or (b) surrounded the LV cavity but excluded the aorta. In addition, ejection fractions were measured from time-activity curves produced from ROIs assigned to the LV cavity which either (a) were too small, (b) fitted precisely, (c) were too large, or (d) extended into the aortic root.

Since the computerized curve analysis required active operator interaction, the reproducibility of the technique was determined in the same six patients by two additional relatively untrained observers. In order to ascertain that ejection fraction could be determined equally well when the radioactive bolus was administered through a peripheral vein instead of into the superior vena cava, an additional six patients were studied. In each patient, ejection fraction was measured first by injecting the radioactive bolus through a central venous catheter, and, on the following day, after injecting the bolus through a needle in the antecubital vein. For the intravenous injection a large medial vein was chosen and the radioactive bolus flushed in.

Student's t-test for paired data and standard regression analysis for calculating correlation coefficients were used for statistical analysis.  

**Results**

In each of the 20 patients ejection fractions were obtained by averaging the values calculated for a 2 to 4 sec time period (usually including two to five beats) following the maximum point of the LV time-activity curve. A typical time-activity curve obtained by sampling counts within the region-of-interest precisely fit to the LV blood pool along with the "average" curve as calculated by the computer is shown in figure 3. On the early monoequponential portion of the downslope, a 2 sec time period (indicated by the line a and including 2½ consecutive beats) was used for analysis yielding an ejection fraction of 0.51.

The results in the 20 patients are listed in table 1 and are compared to ejection fractions determined from biplane cineventriculogram (fig. 4). The methods correlated well (r = 0.94) and in only one instance (patient H.G.) did both techniques differ significantly. In this case an ejection fraction of 0.59 was calculated from the radionuclide angiographic data as compared to 0.82 by biplane cineangiography. If the time-activity curves were not corrected for contributions from noncardiac background structures, the agreement between the cineangiographic and radionuclide methods (see table 1 — not corrected)
Effects of contributions from noncardiac background structures on calculation of ejection fraction in a group of six patients. A) No correction for background activity. B) Correction for background utilizing a semiannular-shaped region of interest (ROI). C) ROI encircling the LV including the aorta. Each bar represents the corresponding average value and 1 SEM.

was less close \((r = 0.87)\), with the latter method underestimating ejection fractions by an average of 24%.

In the group of six patients used for examining the effects of background interference and improper assignment of the ROI upon the accuracy of the technique, ejection fractions determined cineangio-graphically served as the control and averaged 0.59 ± 0.10 SEM (ranging from 0.15 to 0.86; fig. 5). Using the radionuclide data, ejection fractions consistently were too low and averaged 0.45 ± 0.06 \((P < 0.02)\), when the LV time-activity curve was produced from an ROI which fit the LV cavity precisely but was not corrected for background interference. Correction for background activity as determined within a semiannular ROI (2 to 3 matrix points in width and surrounding the LV blood pool with a separation of 1 matrix point) resulted in an average value of 0.58 ± 0.08 and correlated best with the angiographic results. Significantly higher values were obtained (avg. 0.90 ± 0.14; \(P < 0.005)\) when background activity was measured within a ring-shaped ROI encircling the LV blood pool entirely, thus including a portion of the aortic arch.

Based on the results, a semiannular ROI was used for assessing background activity, while site and extent of the LV ROI were altered in the same six patients (fig. 6). Ejection fractions tended to be too high (averaging 0.67 ± 0.11) when the LV ROI was too small. They were significantly lower than the control values when the ROI extended beyond the LV cavity silhouette (avg. 0.55 ± 0.04; \(P < 0.05)\) and decreased even further as the ROI extended into the aortic root (avg. 0.45 ± 0.05; \(P < 0.05)\).

Ejection fractions obtained by the three different observers in the same six patients are compared graphically with the values determined by cineventriculography in figure 7. There was good agreement among the three observers and in no instance did the results differ significantly from the values calculated from the cineangiograms. The average difference between ejection fractions as determined in each

\[ \text{Ejection fraction} = \frac{\text{Volume of blood ejected}}{\text{Volume of blood in LV}} \]

**Figure 5**

**Figure 6**

**Figure 7**

*Ejection fraction in a group of six patients derived from precordial time-activity curves by three different observers as compared to the values obtained from biplane cineangiograms.*
patient by the three observers was 5.4%.

In the six additional patients in whom ejection fraction was determined by the radioisotopic method following administration of the bolus into the superior vena cava and on the following day after injection of the bolus through a needle in the antecubital vein, the results of both measurements correlated well and are listed in table 2.

Recording, processing, and analysis of sinusoidal "time-activity curves" of increasing frequencies, as generated with the lead wheel rotating eccentrically over a radioactive source showed no significant decrease in peak to valley ratios when the rate varied from 1 to 6 cycles per second (100% at 1 cps, 96% at 6 cps).

**Discussion**

The results of the present study demonstrate that LV ejection fraction can be determined accurately from analysis of the time-activity curves recorded precordially during the passage of a radioactive bolus (e.g., 99mTc-pertechnetate or labeled albumin) through the heart with a scintillation camera interfaced to a small dedicated digital computer. The results correlated well with those derived from biplane cineventriculograms and thus are in agreement with previous reports.\(^\text{11, 12, 13}\) Among the 20 patients studied, the methods differed significantly in only one instance. It is possible, of course, that the method is less accurate in patients with extremely low ejection fractions (e.g., patient O.W., whose ejection fraction was 0.15 by cineangiography as compared to 0.22 by the radionuclide method). This discrepancy might be due to low counting statistics and high background noise as pointed out previously by Van Dyke and coworkers.\(^\text{11}\)

**Table 2**

**Comparison of LV Ejection Fractions Obtained after Injecting the Radioactive Bolus into the Superior Vena Cava and Through a Peripheral Vein**

<table>
<thead>
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<tr>
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<td>AI</td>
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<tr>
<td>C.D.</td>
<td>Cardiomyopathy</td>
<td>0.41</td>
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<tr>
<td>C.A.</td>
<td>CAD</td>
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<td>Avg</td>
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<tr>
<td>SEM</td>
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**Abbreviations:** SVC = injection through superior vena cava; IV = injection through large medial antecubital vein; other abbreviations see table 1.

**Potential Sources of Error**

The present investigation demonstrates that great care must be taken when the time-activity curves are extracted from the precordial image data. In particular, proper display of the LV blood pool was needed for precise assignment of the ROI. This was achieved with the aid of the computer routine which allowed the observer to select only that brief period during which the bolus passed through the LV. Subsequent integration of the raw data recorded during this time produced a new image, clearly delineating the LV blood pool without superimposed contributions from the right heart. Accurate values for ejection fractions were obtained only after the ROI (or sampling window) was fit to the LV cavity silhouette precisely but also included the surrounding scatter zone. On the other hand, extending the sampling window well beyond the LV blood pool or even into the aortic root caused an upward bias in the time-activity curve and resulted in values which were consistently too low. The results were even less accurate when the ROI was too small. In this case, the LV cavity exceeded the sampling window at the time of end-diastole and disproportionately fewer counts were collected at this phase. One would anticipate that a small window might encompass only portions of the LV blood pool (e.g., excluding a dyskinetic apical region) which would yield falsely high ejection fractions due to an apparent greater degree of systolic emptying. These findings also suggest that it is desirable to select a projection which permits best separation between the left atrium, aortic root, and the LV cavity. Both the left lateral or the right anterior oblique view appeared suitable. The latter was used in this study since the design of our catheterization table precluded satisfactory recordings in the left lateral projection. On the other hand, recording in the left anterior projection with the collimator closer to the left ventricle would yield better counting statistics. This projection however does not permit clear separation between left ventricle and left atrium and therefore was not used in the current investigation.

In order to obtain high countrates and images of good spatial resolution all recordings were made with a converging collimator. Although this collimator distorts actual measurements, ejection fraction by this technique was calculated solely from countrates and no true measurements were necessary. Theoretically, a parallel hole collimator (e.g., high resolution type) should allow sufficient spatial resolution and is currently used in our institution.

In addition to a precise fit of the LV ROI, our results confirm previous observations that the LV time-activity curve must be corrected for activity aris
ing from noncardiac background structures such as aorta, lungs, as well as LA and other cardiac chambers. Background activity was overestimated when the ROI encircled the LV blood pool completely, and in addition, included the aortic root. The temporal distribution of "background activity" obtained in this fashion resembled closely that of the LV activity, while in theory one might expect the opposite, i.e., true background activity (as distinct from scatter from the LV) to be low during the time the bolus was predominantly in the LV cavity but not including LV scatter or the aortic root. Correcting the LV time-activity curve for background activity estimated from an ROI defined in this manner produced ejection fractions which were nearly identical to those obtained from cineangiograms.

It is important to note that ejection fractions could be derived accurately from only the early monoexponential portion of the downslope (i.e., the first few cardiac cycles following the maximum point of the LV time-activity curve). During this period mixing of the radioactive tracer with the LV blood pool would appear to have been most complete. When using the entire curve for analysis, values calculated for each sequential 2 sec period varied considerably and yielded an average ejection fraction which was consistently too high.

Since the computer analysis of these data requires operator interaction, the calculation of ejection fraction by the method described herein is not entirely operator independent. However, the results were easily reproduced by two additional inexperienced operators (J.V. and N.A.). While improper assignment of ROI initially presented minor difficulties for the operators, their results matched closely those obtained by cineventriculography after each had become familiar with the cardiovascular anatomy as displayed on the computer oscilloscope. Excellent agreement was obtained when each operator assigned the LV ROI precisely to the LV blood pool and consistently flagged the background with a semimunlar ROI which was two to three matrix points in width (equal to approximately 8-12 mm) and separated from the LV ROI by one unassigned matrix point (equal to approximately 4 mm). Although this semimunlar ROI for background correction was selected empirically, it is consistent with the equally empiric background ROI described by other investigators.

Computerized Data Analysis

In previous reports, the LV time-activity curves were analyzed manually, whereas in the present investigation a computer technique was employed for calculation of ejection fractions. While in theory it appears possible to obtain ejection fraction from the instantaneous count rates at end-diastole and end-systole alone (i.e., single high and low points on the curve), this could be expected to introduce significant errors since the count rate is subject to large statistical fluctuations, especially at the relatively low counting rates observed in this study (50 to 150 counts per each 40 msec curve point). In order to put less reliance on single curve points, the count rate changes during the cardiac cycle were fit with a sinusoidal function and its amplitude used to determine the end-diastolic and end-systolic values. One recognizes that LV volume changes during the cardiac cycle do not, in fact, follow a truly sinusoidal pattern, but rather a complex function composed of sine waves, triangular shaped waves and square waves. Indeed, if the cyclic fluctuations of the time-activity curve were pure square waves, but approximated with a sinusoidal function, ejection fraction would be greatly overestimated. Conversely, approximating a pure triangular shaped wave form with a sinusoidal function would be expected to greatly underestimate ejection fraction. Therefore, since on the LV time-activity curve the changes in count rate over time resemble more or less a sinusoidal function, any error in calculation of ejection fraction based on the use of this function would appear to be insignificant.

No corrections for dead-time losses of the camera/computer system (approximately 12 μsec) were made in the present study. Count rates within the entire field of detector view as the bolus passed through the LV never exceeded 15,000 counts/sec. While, indeed, at these count rates a significant dead-time loss occurred, the variation in count rates for the entire camera field of view and thus in dead-time loss over two to three cardiac cycles was small and the difference in calculated ejection fractions was less than 1%.

Analysis of sinusoidal time-activity curves of frequencies up to six cycles/sec obtained with the lead wheel rotating over a radioactive source demonstrated that "ejection fractions" would be expected to be calculated reliably over a wide range of physiologically occurring "heart rates."

Radionuclide angiography has been employed in a number of laboratories including our own to determine LV ejection fraction. In addition to analysis of the characteristics of the LV time-activity curve (sometimes referred to as "high frequency" analysis) as presented herein, many reports have described ECG gating techniques which are analogous to single or biplane end-systolic and end-diastolic area-length methods commonly used in cineangiography. While no such comparison was made in the 20 patients in this series, we have preliminary experience with both techniques in over 50 patients with acute
myocardial infarction examined in the intensive coronary care unit. Our results when comparing the ECG gating/area-length method with the LV high frequency curve analysis technique using the same patient data following the first circulation of a $^{99m}$Tc pertechnetate bolus injected intravenously suggests that analysis of the LV time-activity curve is preferable and that the results of this method are more consistent with other hemodynamic and clinical parameters. Considerable variance in the ability to determine the "true" LV outline at end-diastole (and end-systole) probably contributed most often to what appeared to be less reliable ejection fraction results with the area-length radionuclide method. In addition, since the method described herein is primarily based upon continuous recording of count rates originating from the LV, its accuracy appears to depend less on an intact LV geometry, which is often lacking in patients with extensive wall motion abnormalities. It should be pointed out, however, that this technique does not preclude standard ECG-gated blood pool imaging to visualize left ventricular wall motion abnormalities.

Based on the data obtained in the 20 patients reported in the foregoing, we conclude that it is possible to obtain reliable measurements of left ventricular ejection fraction by the ("high frequency") analysis of the LV time-activity curve following the injection of a bolus of a physiologically inert substance such as $^{99m}$Tc albumin or pertechnetate. Although the 20 patients in this series received injections into the superior vena cava, studies in six additional patients indicate that equally accurate results can be obtained using a peripheral vein as the site of injection. Despite possible day-to-day variations in the patients' cardiovascular state the results of both measurements agreed closely and substantiate the reproducibility of the technique. The safety and relative simplicity of the method should lend itself well to the study of LV function in acutely ill patients as well as in the serial evaluation of patients with ischemic heart disease on an outpatient basis without resorting to more invasive techniques such as contrast cineangiography.

Acknowledgments

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Nontraumatic determination of left ventricular ejection fraction by radionuclide angiocardiography.
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