

Mean Pulmonary Transit Time in First-Pass Studies

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We studied the measurement reproducibility of mean pulmonary transit time in first-pass radionuclide angiography. Two bolus injections of ^{99m}Tc HDP were administered into each human subject approximately five minutes apart. Patients did not move between studies. The same regions of interest were used in both studies. Transit time measurement of the ^{99m}Tc from the right ventricle to the left ventricle was first approximated by the time difference between the maxima of the time-activity curves and was then computed by fitting the time-activity curves to exponential functions. Both methods have comparable reproducibilities. Better precision was obtained by using the ejection fraction and cardiac cycle to monitor patient condition stability. Measurement of transit time was reproducible to an average of 0.40 ± 0.35 sec.

First-pass (or first-transit) radionuclide angiography has been used to study ventricular function and to quantitate cardiovascular left-to-right shunts. Several investigations measuring other physiologic parameters of the pulmonary system also have been conducted. Using a multicrystal detector, Jones et al. (1) measured transit time of a [^{99m}Tc]pertechnetate bolus from right atrium to left ventricle as well as pulmonary mean transit time in a patient. These values were found to be sensitive to septal defects, shunts, and valvular stenosis and insufficiency. Fazio et al. (2) used detector probes to record the transits of ^{113m}In and H_2^{15}O through the lungs to measure extravascular lung water in humans. Critchley et al. (3) extended the technique of lung water measurement to involve the use of a scintillation camera and the use of dual tracers of ^{123}I antipyrine and ^{113m}In transferrin. Pillay et al. (4) used the first-pass of ^{99m}Tc methylene diphosphonate to study changes in the lungs after radiation therapy. The first transit of the radioactive bolus through the cardiopulmonary system has shown convenient utility in investigational applications.

Before the efficacy of pulmonary transit time (PTT) measurement can be established, its precision (reproducibility) should be determined. Upton et al. (5) and Dymond et al. (6) have studied this problem. Reproducibility of 0.65 ± 0.64 sec was reported by Upton et al. (5). Dymond et al. (6) found reproducibility to depend strongly on the quality of the bolus injection. However, these investigations did not correlate the differences in successive measurements with changes in the condition of subjects. With this in mind, we have performed

sequential studies on a number of patients and have analyzed the reproducibility of the right-to-left ventricle transit time. Intraobserver and interobserver variabilities were minimized to give values of reproducibility intrinsic to the physiology of patients.

METHODS

Twenty male patients referred for bone scans were used in this study. Their ages ranged from 45 to 75 yr old, with a mean of 62 ± 8 yr. All patients were in a clinically stable condition and were not known to have any cardiac abnormalities. Data were acquired with a large-field-of-view scintillation camera,* which was interfaced to a computer.† A 20% energy window centered at the 140 keV photopeak of ^{99m}Tc was used. A low-energy general-purpose collimator was used for all imaging, which was obtained from the anterior view.

The dose of ^{99m}Tc hydroxyethylidene diphosphonate (HDP) was given in two injections for the purpose of this investigation. List-mode data acquisition began with the injection of the radionuclide. The period of acquisition was 40 sec, with a time marker being recorded every 10 msec. Four min were allowed for the vascular clearance of the radioactive tracer, after which the second injection was given and data were recorded as before. Patients remained motionless between injections.

In 18 of the studies, a 19-gauge needle was used for injection. For the other two studies, a 21-gauge needle was used. Either the right or left antecubital vein was the site of injection. The Oldendorf technique was used, and compact bolus was injected as rapidly as possible by hand.

Bolus volume ranged from 0.15 to 0.65 ml, with a mean of 0.27 ± 0.13 ml. Each injection was flushed with saline of a volume ranging from 7 to 15 ml, with a mean of 10.08 ± 1.89 ml. The total amount of radionuclide administered ranged from 555 MBq to 1,014 MBq with a mean dose of 740 ± 74 MBq. Each prescribed dose was divided in a manner so that the first injection had less radioactivity than the second injection. The first injection consisted of a mean of 296 ± 82 MBq; the second injection had a mean of 444 ± 97 MBq.

Each 0.1 sec of list-mode data was reformatted to a frame of 128×128 matrix. From these frames a time-to-peak image was constructed. The shades of gray corresponded to the times when pixels reached the maximum count. The approximate centers of superior vena cava, right ventricle, right lung, left lung, and left ventricle were marked on the computer display with a light pen. The shades of gray then were translated to

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peak times of the arrival of the bolus. To enhance the visibility of the lungs for region of interest (ROI) definition, pixels within ± 1 sec of peak time in lungs were highlighted.

List-mode data within two seconds of the time of maximum count rate in the right ventricle were summed in a 128×128 image to represent the right ventricular phase. Similarly, two-second data were used to form the pulmonary phase image, and five-second data formed the left ventricular phase image.

The right ventricular phase image was smoothed once. A rectangular ROI was defined on the superior vena cava to monitor the bolus quality. The right ventricular phase image was edge enhanced by Laplacian transform[†]. A light pen was used to trace the enhanced edge of the right ventricle, defining its ROI. To make the left ventricle more conspicuous, background from the lungs was removed by subtracting the pulmonary phase image from the left ventricular phase image. The resulting image was smoothed and edge enhanced. The left ventricle also was manually traced using a light pen. Comparisons with unmodified images showed that the ventricles were contained entirely within these ROIs. Finally, the time-to-peak image with highlighted lungs was smoothed twice and edge enhanced. A light pen was used to define ROIs on the left and right lungs; vascular areas were avoided as much as possible.

The patient was absolutely still between studies, and the elapsed time was short. Therefore, for each subject, we applied the ROIs defined with the data of the first injection to the data acquired from the second injection.

Time-activity curves were generated with the ROIs. Total count rate within the full field of view and the known dead-time of the scintillation camera were used to correct for deadtime loss. Data acquired from the second injection contained residual activity from the first injection. To remove this background, we subtracted the respective count rates prior to the entrance of the bolus into the field of view from the respective time-activity curves.

The time-activity curves from the left lungs were filtered with a Butterworth algorithm. Each point in the time-activity curve represents 0.1 sec. Any activity in the ROI of the left ventricle before phasic fluctuation should be considered as background (7-9). If this background came from the lung, the magnitude would decrease at the rate of the washout curves of the lungs. Left ventricular time-activity curves were thus corrected by the left lung washout curves.

ANALYSES AND RESULTS

The full-width-at-half-maximum (FWHM) of the time-activity curve of the superior vena cava was measured to describe the quality of the bolus. Results have been tallied in Table 1. The right ventricular time-activity curve was fitted by a gamma-variate function, $kt^\alpha e^{-t/\beta}$ (Fig. 1A). For an extremely good bolus, the time-activity curve could not fit a gamma-variate function; instead, a simple exponential function, $ke^{-t/\beta}$, would be more appropriate (Fig. 1B).

Left ventricular time-activity curves, after correction by the left lung washout curve, were fitted to a gamma variate

TABLE 1. Full Width at Half Maximum of Time-Activity Curves at Superior Vena Cava to Indicate Bolus Quality

FWHM (sec)	Number*
0-1.0	12 (8)
1.0-2.0	11 (6)
2.0-3.0	3 (1)
>3.0	6 (1)

* Corresponding number of studies is presented. Values for stable subjects are in parentheses.

function (Fig. 2). The number of cardiac cycles employed for the fit was 6 to 15, with an average of 9.25.

The left ventricular time-activity curves, corrected by the left lung washout curve, were filtered by the Butterworth algorithm. From these filtered curves, occurrences of end-diastole points, in 7 to 13 cardiac cycles with a mean of 9.5 cycles, were used to compute cardiac periods. The ejection fraction was computed from the end-diastolic and end-systolic values of five cardiac cycles, starting either from the maximum of the time-activity curve or from one cycle before the maximum (10).

The average absolute difference between the ejection fractions from the two injections was $8.0\% \pm 6.0\%$. The absolute difference between the cardiac cycle periods from the two injections had a mean of 0.038 ± 0.037 sec. There was no systemic change in the ejection fraction or cardiac cycle period from the first study to the second.

The measurements of these physiologic parameters were affected adversely by the limited amounts of radionuclide and the coarse framing rate in our protocol. Therefore, these results would not be accurate enough to describe the pathophysiology. However, these parameters could be used to select a subsample of patients in a more stable condition.

For four patients, one of the two injections gave a left ventricular time-activity curve having a secondary maximum. This could be the result of a fragmented bolus. Therefore, these studies were excluded from further analysis. For the remaining 16 patients, we selected eight "stable" subject studies who had (a) no hint of fragmentation in bolus curve at the superior vena cava, (b) a change in ejection fraction of $<14\%$ (mean plus one standard deviation) in the repeated study, and (c) a change of cardiac period of <0.075 sec.

The first method for computing transit time in the subset of eight subjects was to visually pick out the maxima on the time-activity curves of the right and left ventricles. The difference between these maxima was the transit time. For each subject, the second study was compared to the first. For all subjects the difference of the transit times was 1.06 ± 0.80 sec. For the "stable" subjects, reproducibility was improved to 0.74 ± 0.63 sec (Fig. 3).

In the second method, the gamma-variate function, which was fitted to the time-activity curve of the right or left ventricle, had the convenient form of $\beta(\alpha + 1)$ for transit time (11). For the few right ventricular time-activity curves fitted by

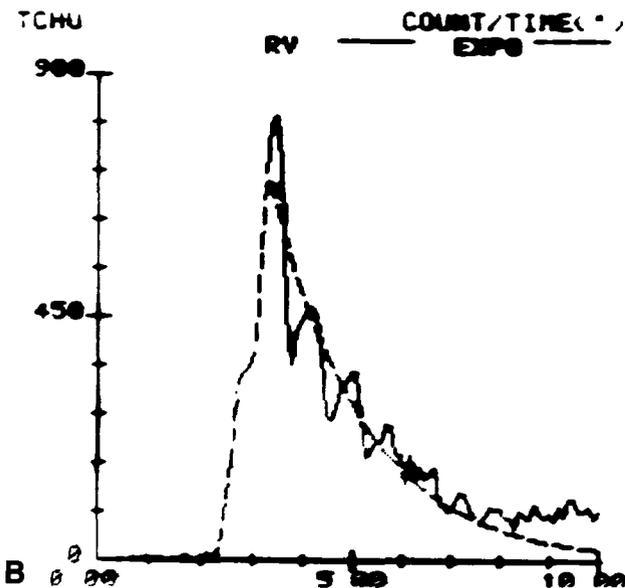
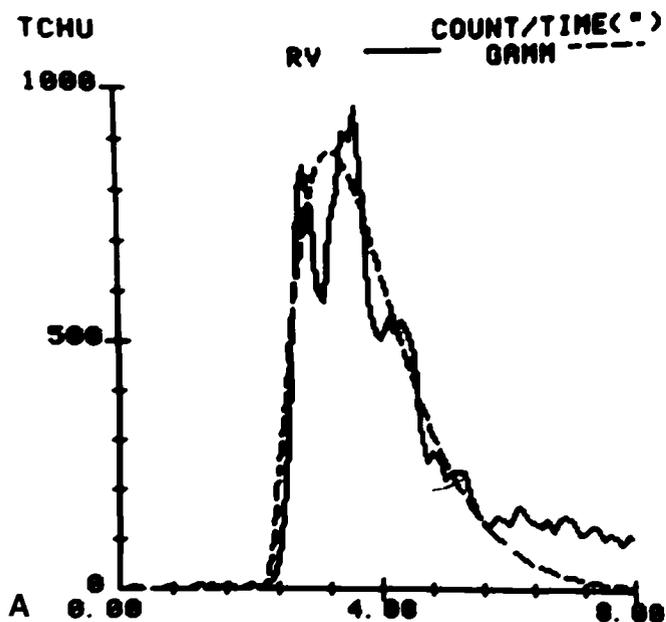


FIG. 1. Example of right ventricular time-activity curve with (A) gamma-variate fit and (B) simple exponential function.

simple exponential functions, transit times were computed from the mean times (β 's). The transit time from right ventricle to left ventricle will be the difference between the transit times of the two ventricles. For each subject, the transit time from the right ventricle to the left ventricle in the second study was compared to the first. For all subjects, the mean of the difference was 0.98 ± 0.94 sec. For the "stable" subjects, reproducibility was 0.40 ± 0.35 sec (Fig. 3).

DISCUSSION

Our choice of correction for lung background has been demonstrated by Gal et al. (12) to be the most accurate. However, the assumption of nonoverlap of bolus in right and left ventricle cannot be entirely correct. Dymond et al. (13) have shown that Compton scatter could be substantial. These

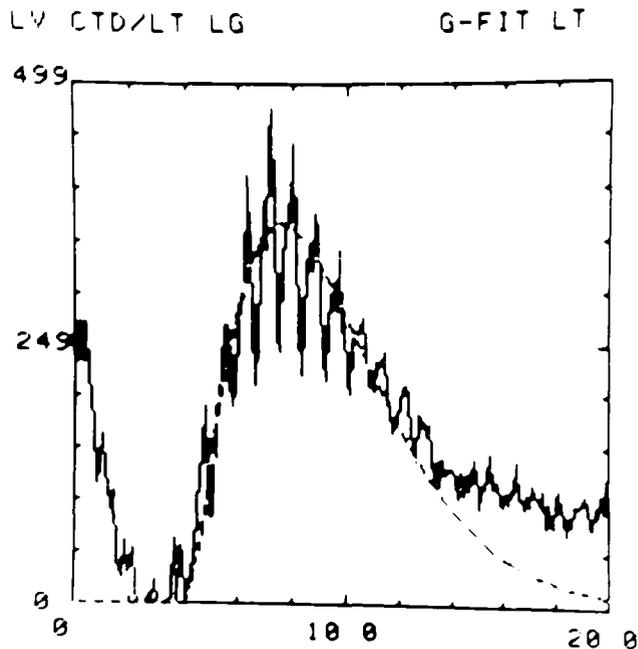


FIG. 2. Left ventricular time-activity curve fitted by a gamma variate function.

effects are expected to depend on the bolus quality as well as on anatomy. We have not yet conceived of a method of correction for the overlap. However, since these background contributions are likely to affect both studies in the same patient in a similar manner, the comparison of repeated measurements of transit time is therefore expected to be unaffected.

The computation technique for transit time of a cardiac chamber in other investigations (1,6) has consisted of the identification of the phasic maxima and assumption of a monoexponential tracer washout from each chamber. In our analysis, we used the gamma-variate function to describe the left ventricular time-activity curves. This formula has been shown by others (11,14,15) to describe the time-activity curves appropriately. The use of a gamma-variate function is also supported by mathematical model of flow studies (16, 17).

Upton et al. (5) performed first-pass angiograms on Day 1 and Day 3. Dymond et al. (6) studied each subject on two consecutive days in addition to performing sequential measurements carried out 15 min apart. There was little control in the repositioning of the subjects. We tried to minimize physiologic changes and irreproducibility of patient positioning by performing sequential studies five minutes apart. Furthermore, our data analysis differed from the other investigations by using the same ROIs for both studies in each subject.

All except one of the selected stable studies had FWHMs of bolus less than three seconds. However, in the selection of stable subjects, many studies with good bolus were excluded (Table 1). Therefore, injection quality does not appear to be a sufficient condition for reproducible measurement. We conclude that stability of physiologic conditions is essential to precise measurements.

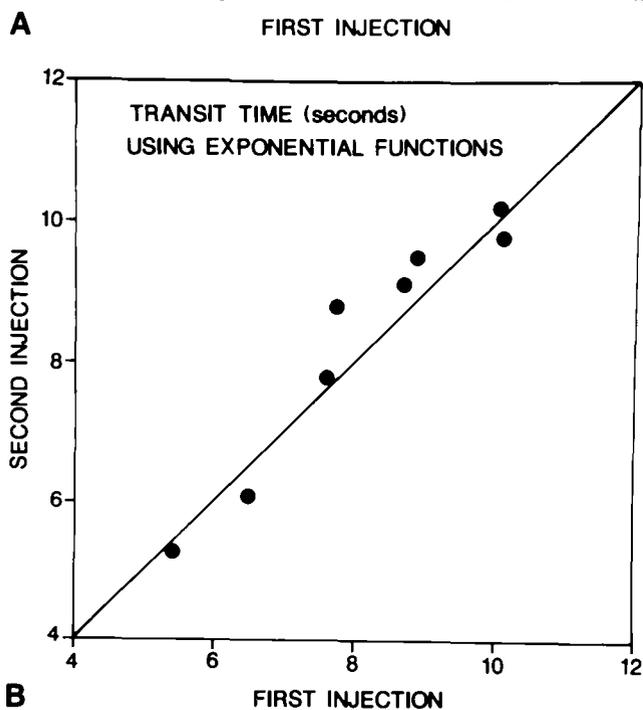
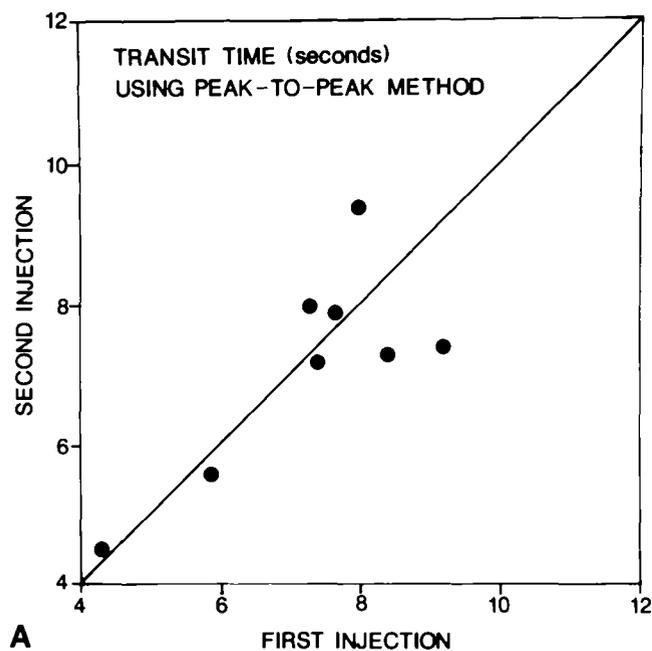


FIG 3. Comparing transit times from sequential studies on stable subject. The solid line represents an identical relationship (A) using peak-to-peak method and (B) using exponential functions.

Upton et al. (5) cited interobserver variability in transit time to be 0.35 ± 0.39 sec. Dymond et al. (6) found the measurement of PTT reproducible to a mean of 0.60 ± 0.21 sec for good quality bolus and a mean of 1.55 ± 0.86 sec for inferior boluses. Our measurement of transit time was reproducible to a mean of 0.40 ± 0.35 sec. This is in agreement with other investigations (5,6).

For a normal subject, the PTT is approximately nine seconds (1,18), and for an abnormal subject it could be much longer (1). The difference in transit times of dual tracers employed by Critchley et al. (3) in edematous subjects is 6.5

± 0.8 sec. Pillay et al. (4) showed an average increase of 1.6 sec in pulmonary mean transit time after radiation therapy.

We have shown that measurements of transit time can have a precision of better than one second. Hence, normal and edematous subjects can be distinguished whereas changes after radiation therapy cannot be measured with confidence.

We have determined the reproducibility of mean pulmonary transit time measurements. In the computation of transit time, the use of exponential functions gave more consistent results than the peak-to-peak method.

NOTES

* 400 AT, General Electric, Milwaukee, WI.

† System II, ADAC, Milpitas, CA.

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