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Authors

Steele, Peter P
Dyke, Donald Van
Trow, Richard S
et al.

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would appreciate your comments.*

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A SIMPLE AND SAFE BED-SIDE METHOD FOR SERIAL
MEASUREMENT OF LEFT VENTRICULAR EJECTION FRACTION.
CARDIAC OUTPUT AND PULMONARY BLOOD VOLUME.

by

Peter P. Steele

Donald Van Dyke

Richard S. Trow

Hal Anger

Hywel Davies

From the Department of Medicine, Division of Cardiology, University of Colorado Medical Center, 4200 E 9th Ave., Denver, Colorado, Section of Cardiology, Denver Veterans Administration Hospital, Denver, Colorado, and the Donner Laboratories, University of California, Berkeley, California.

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ABSTRACT:

A simple, safe method for bedside measurement of left ventricular (LV) function and pulmonary blood volume (PBV) has been developed. A single scintillation probe positioned over the mid-LV records the passage of bolus of radioisotope (^{113m}In) injected into the superior vena cava, from which LV ejection fraction (EF) can be determined after proper background correction. ^{113m}In , half-life 1.7 hours, easily prepared from a commercial available, long-lived generator, rapidly binds to plasma protein (transferrin) and can be used to determine blood volume (BV) and cardiac output (CO). With CO and LVEF determined simultaneously, LV end-diastolic volume (EDV) can be calculated and PBV can be determined from pulmonary transit time.

With this method, we have demonstrated stable and changing LV function and PBV in a variety of clinical situations; e.g., myocardial infarction, pulmonary embolism, severe pulmonary parenchymal disease and following cardiac surgery. BV and CO correlate well with standard techniques. LVEF and LVEDV determined by this method correlate well with these measurements obtained at the same time from LV angiography over a wide range (EF 20-80%).

Loss of temporal separation between right ventricle (RV) and LV has been demonstrated in severe pulmonary vascular obstruction (embolism), in severe bronchial obstruction and as a result of

The ability repeatedly to quantitate left ventricular (LV) function at the bedside would be an important adjunct to care of the seriously ill patient. Not only would such information be of value in the management of the individual patient, but would provide the basis for evaluation of various forms of therapy. External monitoring of the passage of a bolus of radioactive tracer through the central circulation is a method which has been developed over the last 25 years (1) in an attempt to fulfill the need for safe, easily repeatable method of quantitating cardiac function. Earlier attempts to utilize simple scintillation probes and low frequency data for evaluation of the left ventricle following a right-sided injection failed because of the difficulties in analyzing the complicated functions resulting from passage of the bolus through the right heart chambers and lungs (2-7).

With the advent of scintillation cameras with high frequency recording, interfaced to data storage, acquisition and manipulation systems, a better understanding of the influence of ventricular function on the radioisotope concentration patterns has been obtained. What has been learned is that although the low frequency patterns in the left ventricle, following an injection on the right side, has not as yet provided clinically useful information about the left ventricle, high frequency recording when appropriately corrected for "cross talk" provides an accurate measure of LV ejection fraction (EF). To obtain LVEF one must have a high frequency recording of activity from within the confines of the LV,

ABSTRACT CONT.

massive RV dilatation in the presence of normal PBV. This method, which can be frequently performed, has proved useful in serial measurement of cardiac function at the bedside.

corrected by a recording of the activity in the immediately surrounding structures (cross talk) (5-7). This information, combined with the classic information obtainable from the low frequency part of the data (cardiac output and pulmonary blood volume), provides an abundance of clinically useful information.

Since locating the scintillation camera and its associated data storage system at the patient's bedside is not readily achieved, ~~the use of an~~ easily portable, properly collimated single probe ~~with direct strip chart recording~~ has been investigated. The technique requires pre-determining the area of interest (mid-point of the LV) from a chest film, the presence of a central venous catheter and simultaneous or subsequent (as in this case) recording from a "window" around the left ventricle. Results from the serial study of patients with stable or changing cardiac and pulmonary function are presented.

The high frequency single probe precordial radioisotope concentration curve consists of 11 essential parts, each of which provides evidence of central circulation function (Fig 1).

- Fig. 1:
- 1) Overall transit time through the central circulation (time from injection to peak of LV): prolonged in circulatory failure.
 - 2) Rate of appearance of label in RV (flow from SVC to RV); Prolonged in circulatory failure.
 - 3) ~~Downslope of RV washout curve:~~ slow in circulatory failure and in the presence of dilated right heart chambers.

- 4) Pulmonary transit time (PTT): decreased with decreased pulmonary blood volume and vice-versa; decreased in right-to-left shunt and increased in circulatory failure.
- 5) Temporal separation between RV and LV: obliterated with markedly decreased PBV or markedly dilated right heart chambers.
- 6) Area under the first pass of the indicator: when related to the concentration after mixing in the blood, #11, is inversely related to cardiac output.
- 7) Cross talk correction: provides the baseline against which EF is measured.
- 8) Ejection fraction (EF): related to #7.
- 9) Washout slope of LV: slow in failure, rapid with reduced PBV.
- 10) First re-circulation oscillation: function of total circulatory competence. Shortened in AV fistula and blunted in circulatory failure.
- 11) Concentration after complete mixing A-V: small (as compared to area under first pass, #6) in low cardiac output or exceptionally large BV.

METHODS: In order to measure blood volume (which is required for calculating cardiac output by the externally monitored radio-isotope method) one must inject agents such as ^{99m}Tc albumin (8) or ionic Indium 113m , which remain within the vascular compartment. When ^{113m}In -chloride (in gelatin solution) is injected intravenously, ^{113m}In binds to the plasma transferrin (9,10). Because no preparation time (pre-labeling) is required for the use of ^{113m}In and because its energy is suitable for use with the probe, this short-lived (1.7 hr.) radionuclide, which is obtained from a long-lived generator (118 days) has been used in the majority of the studies reported here.

We have estimated the radiation dose resulting from the administration of 1.5 mCi of ^{113m}In to be 320 mrad to the

blood and 30 mrad to the whole body.

Preparation of the patient for study requires inserting a catheter to the superior vena cava (SVC), taping a radio-opaque marker, such as a paper clip, to the skin over the estimated mid-point of the LV and then taking a portable roentgenogram in supine position. From the roentgenogram, the position of the catheter in the SVC and the mid-point of the LV relative to the marker can be confirmed. The correct position for the probe is then drawn on the chest with a felt pen to facilitate accurate re-positioning for serial studies.

A standard, commercially available, portable scintillation probe (see accompanying photograph) with a 2" by 2" sodium iodide crystal is used. This portable stand carries the high voltage power supply, count rate meter with 10 M cts./min. capacity and time constant of less than 0.1 sec. and high speed strip chart recorder. Linearity of the entire system is demonstrated by rotating an absorber wheel with 10 steps having from 0 to 100% absorption over a 1 mCi ^{113m}In source.

Collimation for obtaining the LV radioisotope concentration curve is as shown at the top of Fig. 2. A 1 3/8" circular port (in 1/2" Pb collimator) is positioned over the mid-point of the LV. A bolus of 1 mCi ^{113m}In is flushed through the central venous catheter and the activity over the LV recorded with the probe perpendicular to the chest wall. Recording is repeated from 5 min.

to obtain the concentration after mixing. A blood sample is taken at this time for determination of blood volume. From these two measurements, CO is determined.

Collimation of the probe is then modified to the configuration shown at the bottom of Fig. 2 for recording activity immediately surrounding the LV. The LV is eclipsed by a $2 \frac{3}{16}$ " circular shield placed $1 \frac{3}{8}$ " out from the probe face ($4 \frac{3}{8}$ " from the sodium iodide crystal) and maintained in position by a styrofoam cone. For this recording a second bolus of 500 μCi $^{113\text{m}}\text{In}$ is given. The record is matched in amplitude to the record from within the LV area of interest to provide the "cross talk" correction or correct baseline from which ejection fraction (EF) is calculated. The rationale and method for this "cross talk" correction have been presented in detail elsewhere (5).

The pulmonary blood volume (PBV) is obtained from the product of the cardiac output and pulmonary transit time (PTT) using a modification of the formulation, $\text{PBV} = (\text{CO} \cdot \text{PTT})$, of Giuntini et al (12). The PTT is estimated as the interval from the time of ejection of label from the right ventricle to the time of peak count rate in the left heart. The basis of the modification used in this study is described below under low frequency events.

RESULTS

Normal precordial curves: Figs. 1 and 2 show characteristics radioisotope content curves from the mid LV precordial position in normal cardiac function. The first peak represents passage of the bolus through the RV, the first valley, its passage out of the field of view of the probe into the pulmonary circulation, and the second peak the left ventricular portion of the curve with the ejection pattern superimposed. The corrected base line or "cross-talk" correction, from which EF is measured is shown as a smooth curve under the LV washout portion, drawn as previously described.

Low frequency events: An important qualitative aspect of the record is overall transit time through the central circulation, which is most easily represented by the time elapsed between injection into the SVC and peak activity in the LV as illustrated in Figs 3 and 4. Fig. 3 shows a grossly abnormal pattern obtained shortly before death in a patient with a massive myocardial infarct. The possibility of his sudden onset of respiratory distress being due to pulmonary embolus could not be ruled out in the usual clinical grounds. The radioisotope record was clearly that of myocardial dysfunction rather than massive pulmonary embolism (see below).

Fig. 4 shows representative patterns from 21 serial studies ~~done over a 7-day period in the recipient of a heart transplant.~~ LV dysfunction is apparent in the markedly prolonged transit time in the record obtained three hours after completion of the surgical procedure. Dependency of the newly-transplanted heart on isoproterenol is apparent in the 4 subsequent records.

Cardiac arrest occurred shortly after the 4th record was obtained. Following resuscitation and re-initiation of a dose of 10 ug/min. of isoproterenol an entirely normal pattern with EF - 69% and overall transit time of 7 sec. was recorded. From the 2nd to the 7th day, when cardiac arrest and death secondary to immunologic rejection occurred, deterioration was progressive (overall transit time of 16 sec. on day 7).

Transit time through the central circulation is related to cardiac output and volume of blood in the various compartments of the central circulation, as discussed later in reference to pulmonary transit time.

Normally, between the RV and LV peaks in the radiocardiogram there is a valley during which the label is in the lungs. This results in temporal separation of RV and LV (Fig. 5).

The record from a patient in severe respiratory distress from multiple pulmonary thromboemboli is shown in Fig. 6. Part A of the figure shows complete loss of temporal separation between RV and LV. Introduction of the label into the pulmonary artery (shaded curve of part B) resulted in prompt labeling of the LV. Note similarity between Fig. 6 and the right part of Fig. 5. Fig. 7 shows the gradual emergency of temporal separation with time in the same patient. The method of Giuntini et al, (12) for calculation of PBV uses the value of 37% of the RV peak count as representative

mean time spent in the RV. Our studies have shown unequivocally that this figure is not universally applicable, for it would result in the RV registration occurring after that of the LV in Fig. 7 for example - clearly unacceptable. A reasonable minimal value (100-200 ml) for PBV was obtained in this case only by using the figure of 70 or 80% instead of the 37% of Giuntini.

It would therefore appear to be reasonable that the figure of 75% rather than 37% should be employed for this calculation in all cases, since in normal subjects the fall of RV activity is so rapid that it makes little practical difference which of these values is adopted.

Fig. 8 shows a series of studies from another patient with initial loss and gradual re-appearance of temporal separation between RV and LV. This patient had severe respiratory distress due to widespread bronchial carcinoma complicated by pneumonia.

Fig. 9 illustrates another mechanism by which temporal separation between RV and LV may be obliterated. On first examination (by pattern recognition alone) it might appear that this patient had a markedly reduced PBV. However, the PTT was found to be 5.3 sec., or the equivalent of 7.1 stroke volumes, ~~giving a normal (520 ml) PBV.~~ Introduction of the label into the pulmonary artery suggested a normal PTT (lower curve in Fig. 9), in contradistinction to Fig. 6. Scintillation camera pictures

taken during the passage of a bolus of ^{99m}Tc through the right heart, demonstrated an extremely large right atrium and right ventricle. Thus, dilatation of the right heart chambers to volumes approaching the PBV will result in obliteration of the pulmonary "valley" in the record, but not loss of temporal separation between RV and LV.

High frequency events (ejection fraction):

Ejection fraction is important for its intrinsic value as an indicator of LV function (14) and as the basis for the calculation of LV end-diastolic volume (net stroke volume/EF). Changes in EF with changing LV function as illustrated in Figs. 3 and 4. A series of studies in a patient with congestive heart failure during alcoholic detoxification are shown in Fig. 10. As can be seen, the low frequency pattern and cardiac output were not abnormal, but EF was markedly depressed with only slight improvement over the 6 days during which the patient was studied. The combination of normal CO and HR and small EF signifies a large EDV (300 ml. average value for the 5 studies) interpreted as depressed myocardial function secondary to alcoholic cardiomyopathy (15).

Fig. 11 shows the striking effect of sublingual isosorbide dinitrate on EF and EDV in a patient with coronary artery disease. Administration of the drug produced transient, but significant changes in all parameters measured.

DISCUSSION

It is vital to appreciate that the high-frequency part of the recording is an expression of content rather than concentration in the cardiac chambers. It is apparent as these studies progressed that in viewing sequential recordings it is possible to recognize improvement or deterioration of cardiac function from pattern recognition alone. Measurements of EF and transit times provide an easy method of quantitation which adds significantly to the value of the data, but rarely changes the impression gained from first viewing the strip chart recording of the bolus passage (Fig. 9 was an exception). Thus, the method has the singular advantage of almost immediate information transfer as compared to considerable delay when a scintillation camera with data store, retrieval and manipulation capability is used.

If in a given case information is required on cardiac output, left ventricular end-diastolic volume and pulmonary blood volume, such information can be obtained using the single probe and ^{99m}Tc -albumin or ionic ^{113m}In . This greater information is obtained at the cost of greater complexity (preparation of the labeled albumin or elution of the In generator, blood samples, preparation of a standard, sample counting and computation time).

Experience with more elaborate systems (5-7) indicated that a single-probe study would be useful provided a satisfactory baseline

TABLE I

PATIENT	DIAGNOSIS	ISOTOPE	CONTRAST
Z	Rheumatic heart disease	<20	31
L	Coronary artery disease	42	41
W	IHSS	66	71
K	Chronic pulmonary disease	64	59
S	Normal	80	78
F	Coronary artery disease	60	79
	Average	55.3	59.6

correction could be achieved. Could a fixed circular window (eclipse mask of the LV) serve to provide the proper correction for all subjects in all situations? Although many more direct comparisons with standard contrast angiography are needed to answer this question, the fixed "window" used in these studies appears to be surprisingly satisfactory over a wide range of EF when compared to standard angiography (Table I.).

In these patients LV angiograms were filmed using standard techniques in the 40° RAO position and LV volumes were obtained by area length. Computation with correction for magnification.

Note that in the last 3 records of the series shown in Fig.4, EF could not be estimated. This was due to the fact that as rejection and LV dysfunction progressed, both LV and background configurations resulted in similar patterns during the LV phase of the record because of marked dilatation of the LV (central port and circular window seeing the same information). However, before this becomes a problem, transit time has become markedly prolonged and EF has fallen below clearly recognizable amplitude, so that the need for a baseline against which to judge EF has disappeared.

Except for its use in transit time analysis and in cases where ~~gross abnormality imposes itself on the record~~ (Figs. 6 and 9) no attempt has been made to quantitate the right ventricle in these studies. Previous studies (1-7,16) have demonstrated that determination

of RVEF and EDV will depend on adequate correction of the precordial record for mixing, streaming and "cross talk". Whether the eclipse mask technique applied in these studies to the LV would be equally applicable to the RV is under investigation.

The time required for the study as well as the dose of radioisotope to the patient could be reduced if the LV and circular window recordings could be made simultaneously. A mosaic probe with multiple photomultiplier tubes, dual count rate meters and dual channel pen recorder is being build for this purpose.

DESCRIPTION OF FIGURES

Fig. 1. See text.

Fig. 2 shows the collimation for obtaining the LV radio-isotope concentration curve (top) and eclipse collimation for obtaining "cross talk" correction (bottom). The auxiliary collimators are made of 1/2" Pb.

Fig. 3 shows a grossly abnormal pattern (prolonged transit time and loss of EF) obtained shortly before death from a massive myocardial infarct.

Fig. 4 shows representative patterns from 21 serial studies done over a 7 day period in the recipient of a heart transplant. The records demonstrate the effects of surgical trauma (top), drugs (middle) and immunologic rejection (bottom).

Fig. 5 left: a semilogarithmic graph of time concentration curves of an indicator injected into the proximal chamber of a two-chamber system. The components of which are of equal size and perfused by the same flow.

Right: illustration of the displacement of the concentration curve of the second chamber by the interposition of a labyrinth of transit sections between the two chambers. From Giutini, et al (12), (reproduced by permission of the authors and J Clin Invest).

Fig. 6: Part A of the figure shows an abnormal pattern obtained when the probe was positioned over the LV of a patient subsequently shown to have multiple pulmonary emboli. The reduced pulmonary blood volume (PBV) obscured temporal separation of right and left ventricle. Part B is the pattern obtained with the probe over the RV after an SVC injection superimposed on the pattern of LV following injection into the pulmonary artery by means of a flow directed catheter.

Fig. 7 shows the gradual emergency of temporal separation between RV and LV with time in the same patient illustrated in Fig. 7.

Fig. 8 shows a series of studies from a patient with initial loss and gradual re-appearance of temporal separation between RV and LV. This patient had severe respiratory distress due to widespread bronchial carcinoma complicated by pneumonia.

~~Fig. 9 illustrates one of the mechanisms by which temporal separation between RV and LV may be obliterated.~~ In this case the PTT was normal and loss of temporal separation was due to massive dilatation of right heart chambers. The shaded portion (bottom) of the figure shows the pattern obtained over the LV when the radioisotope was introduced into the pulmonary artery, bypassing the dilated RA and RV.

Fig. 10 shows a series of studies done during alcoholic detoxification with congestive failure. This series illustrates the stability of the PBV measurement in a patient whose difficulties resulted from ventricular dysfunction (loss of normal EF and increased EDV).

Fig. 11 shows a striking effect of isosorbide dinitrate on EF and EDV in a patient with coronary artery disease.

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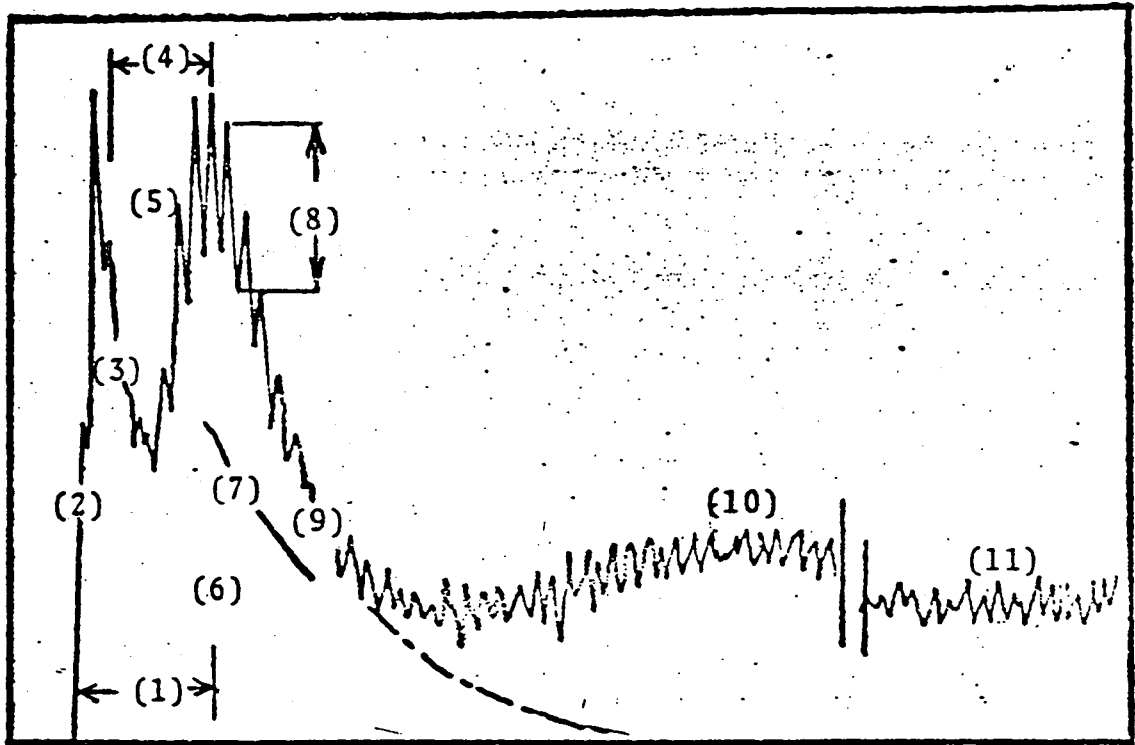


Fig. 1

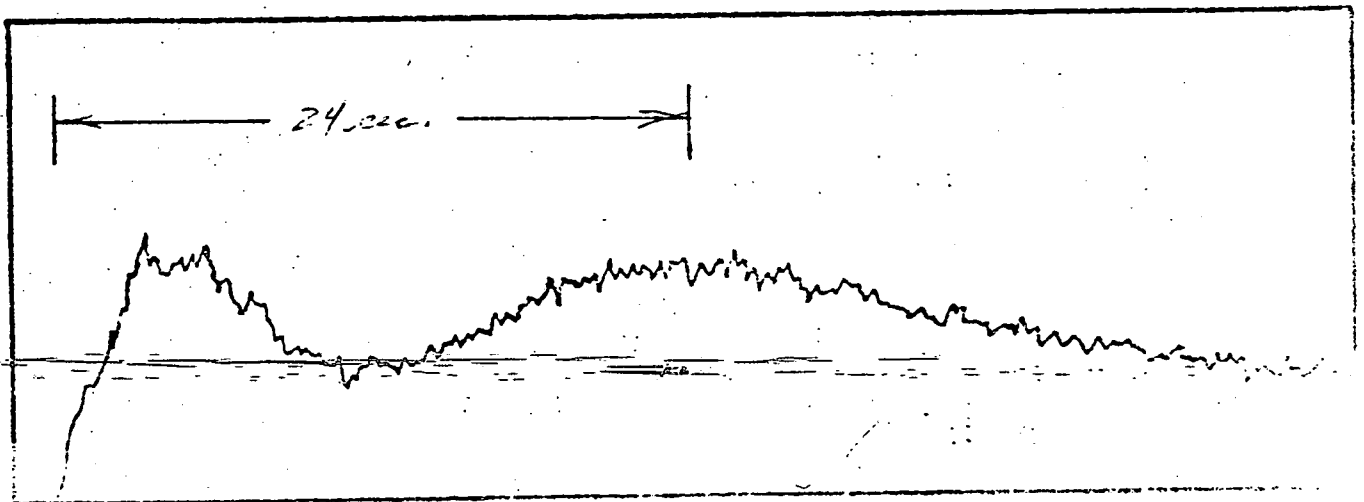


Fig. 3

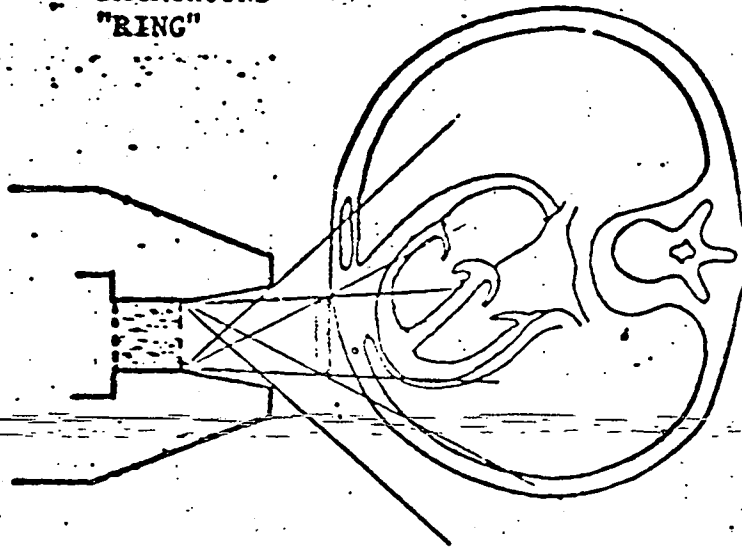
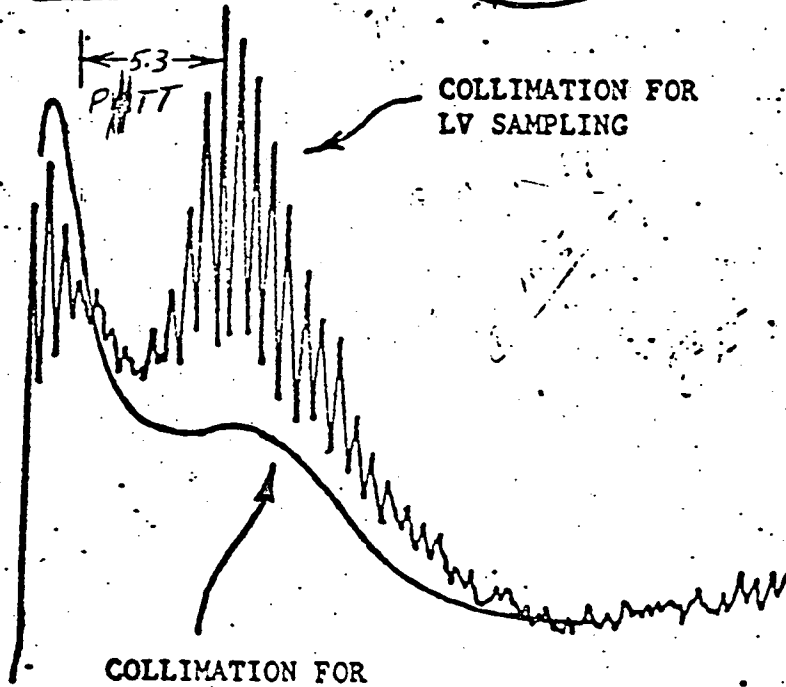
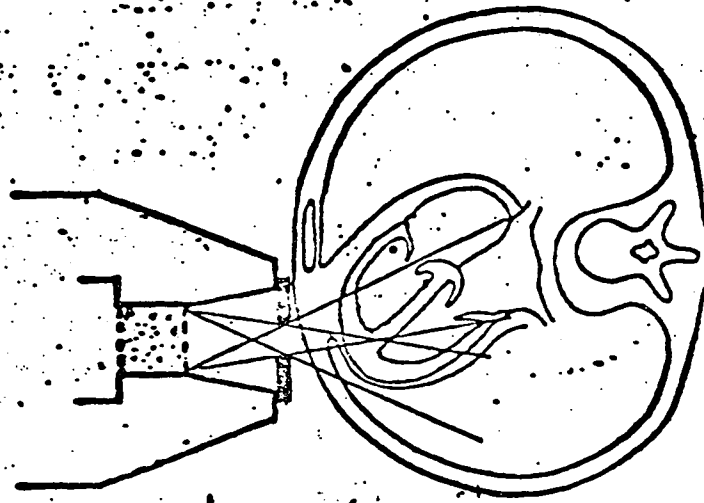


Fig 3 H

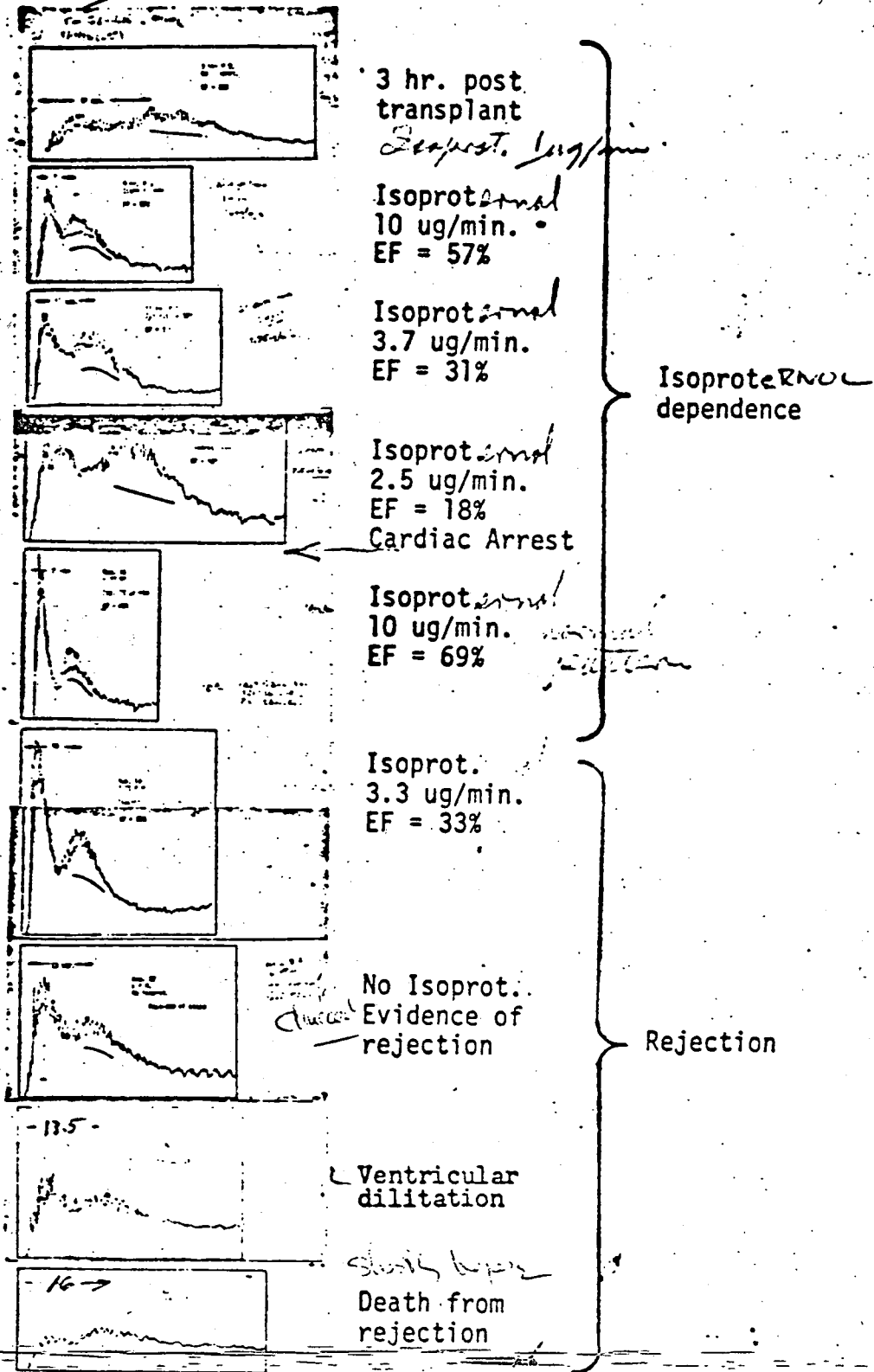
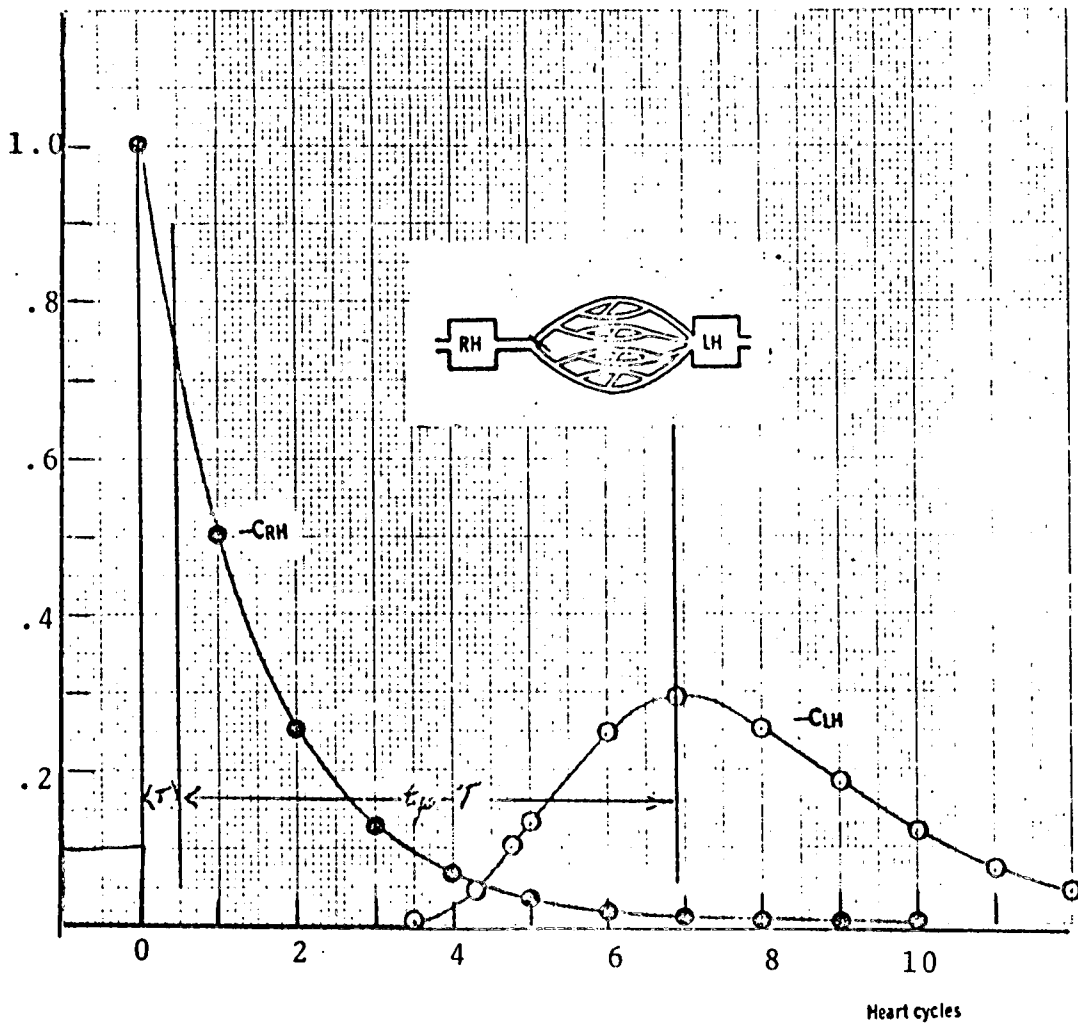
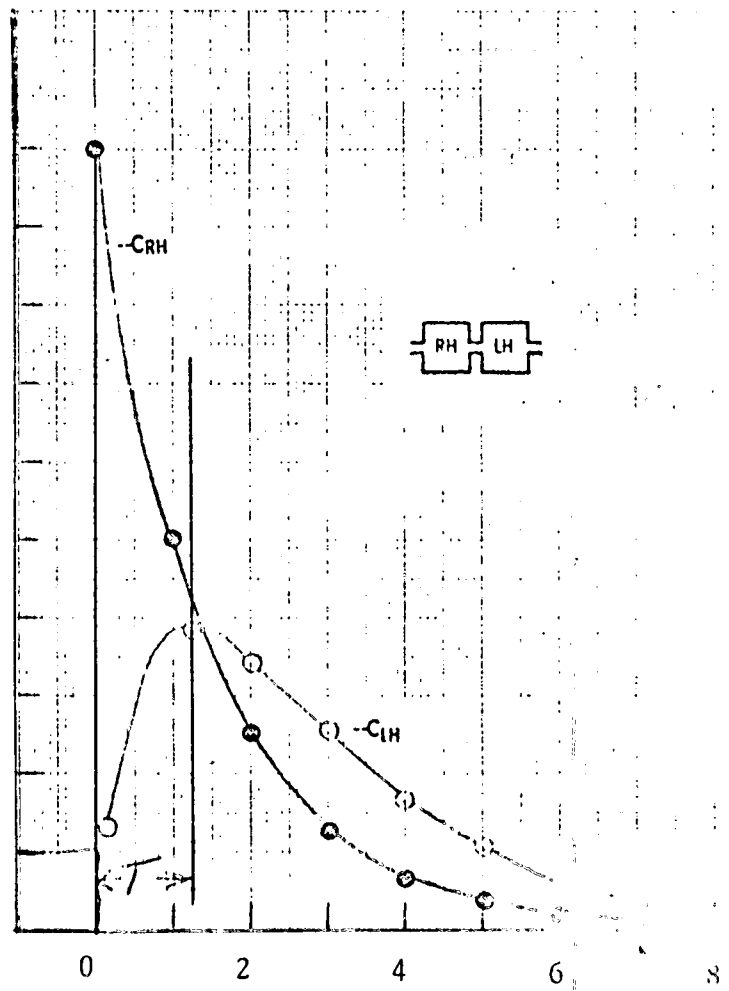


Fig 4



LEFT: ILLUSTRATION OF THE DISPLACEMENT OF THE CONCENTRATION CURVE OF THE SECOND CHAMBER BY THE INTRODUCTION OF A LABYRINTH OF CHANNELS BETWEEN THE TWO CHAMBERS. The transit times through the labyrinth have been simulated with a normal distribution (mean, 5 heart cycles; SD, 1 heart cycle); $t_p - T$ is 5.4 heart cycles.



RIGHT: GRAPH OF TIME CONCENTRATION CURVES OF AN INDICATOR INJECTED INTO THE PROXIMAL CHAMBER OF A TWO-CHAMBER SYSTEM, THE COMPONENTS OF WHICH ARE OF EQUAL SIZE AND PREPARED FOR IDEAL FLOW. C_{RH} = concentration in the first chamber (RH); C_{LH} = concentration in the second chamber (LH); T = turnover time of each chamber.

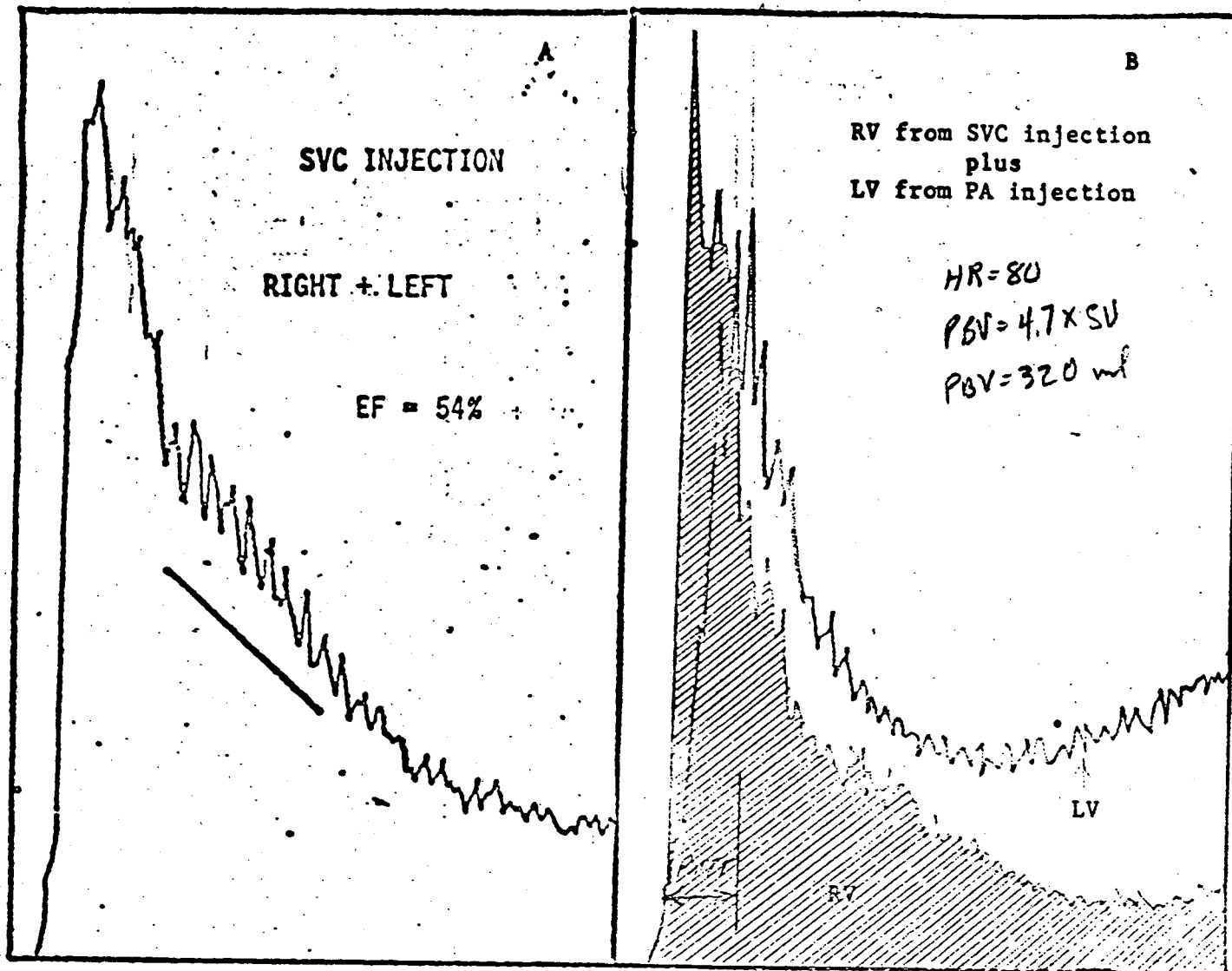


Fig. Part A of the figure shows an abnormal pattern obtained when the probe was positioned over the LV of a patient subsequently shown to have multiple pulmonary emboli. The reduced pulmonary blood volume (PBV) obscured temporal separation of right and left ventricle. Part B is the pattern obtained with the probe over the RV after an SVC injection superimposed on the pattern of LV following injection into pulmonary artery by means of a flow directed (Swan Ganz) catheter.

Fig. 106

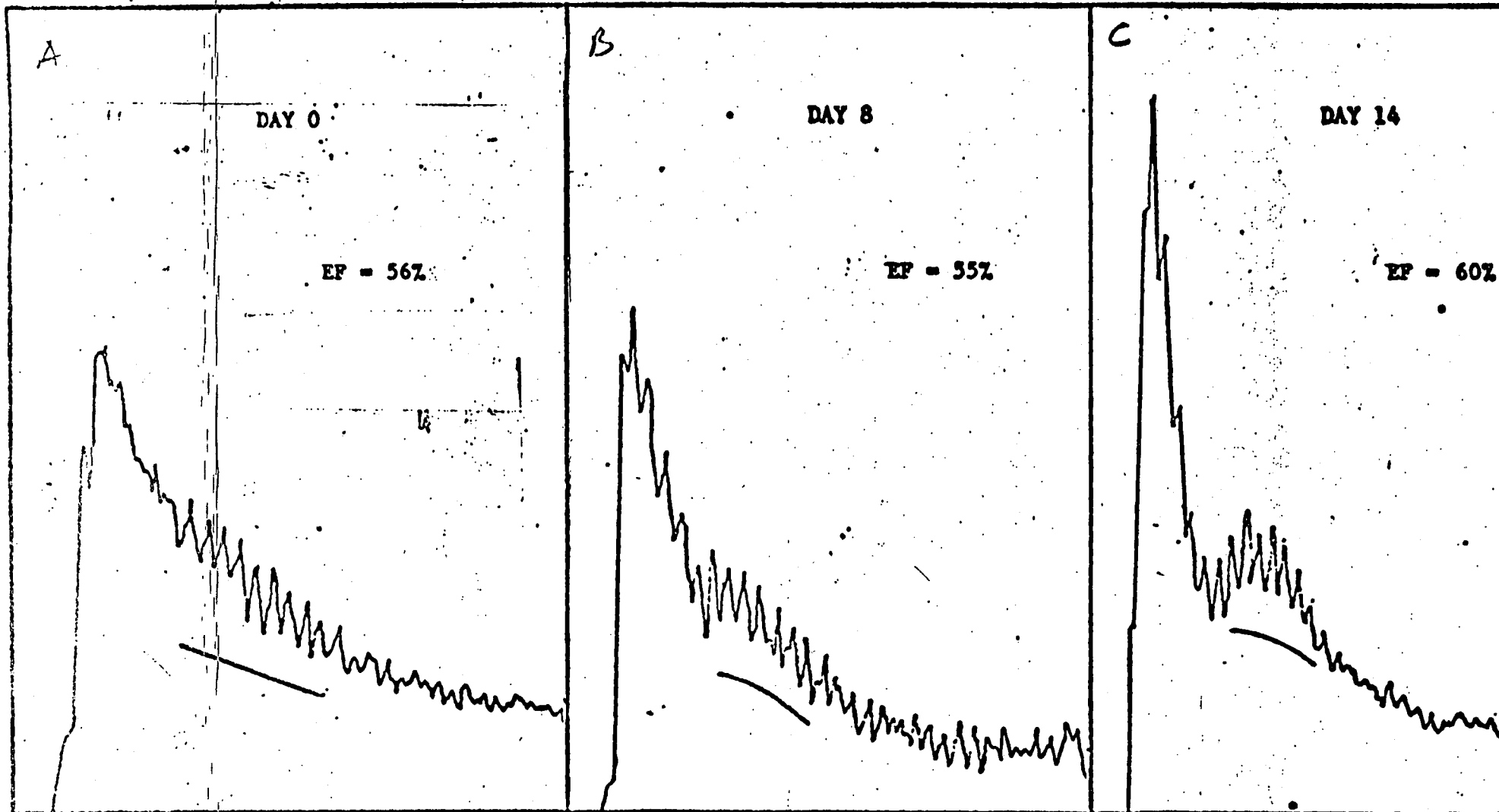
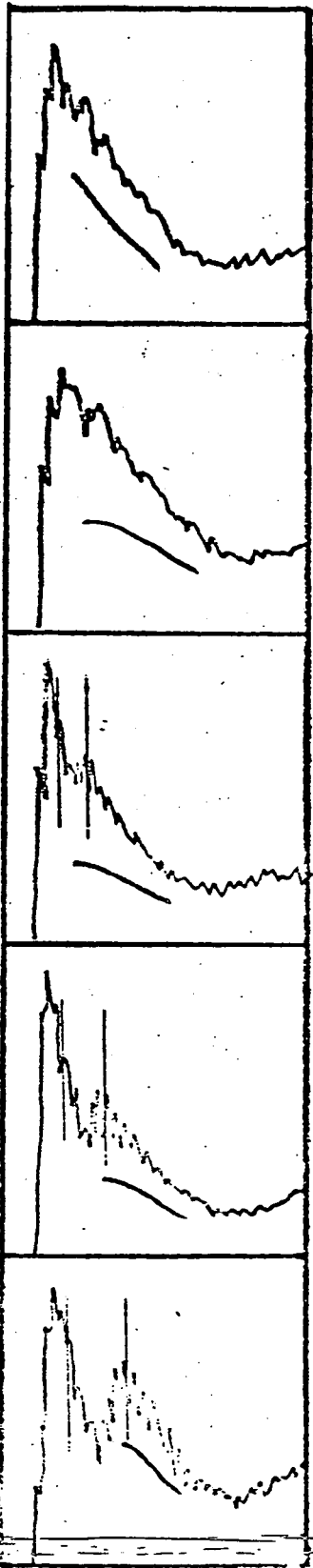


Fig # 7



DAY 0

DAY 1

DAY 2

DAY 3

DAY 7

CO = 5.36 L/min.
 HR = 124
 SV = 43 ml.
 EF = 20%
 EDV = 216 ml
 PBV - BELOW
 MEASURABLE

BV = 5.12 L
 CO = 6.6 L/min.
 HR = 145
 SV = 46 ml.
 EF = 20%
 EDV = 230 ml
 PBV = 140 ml

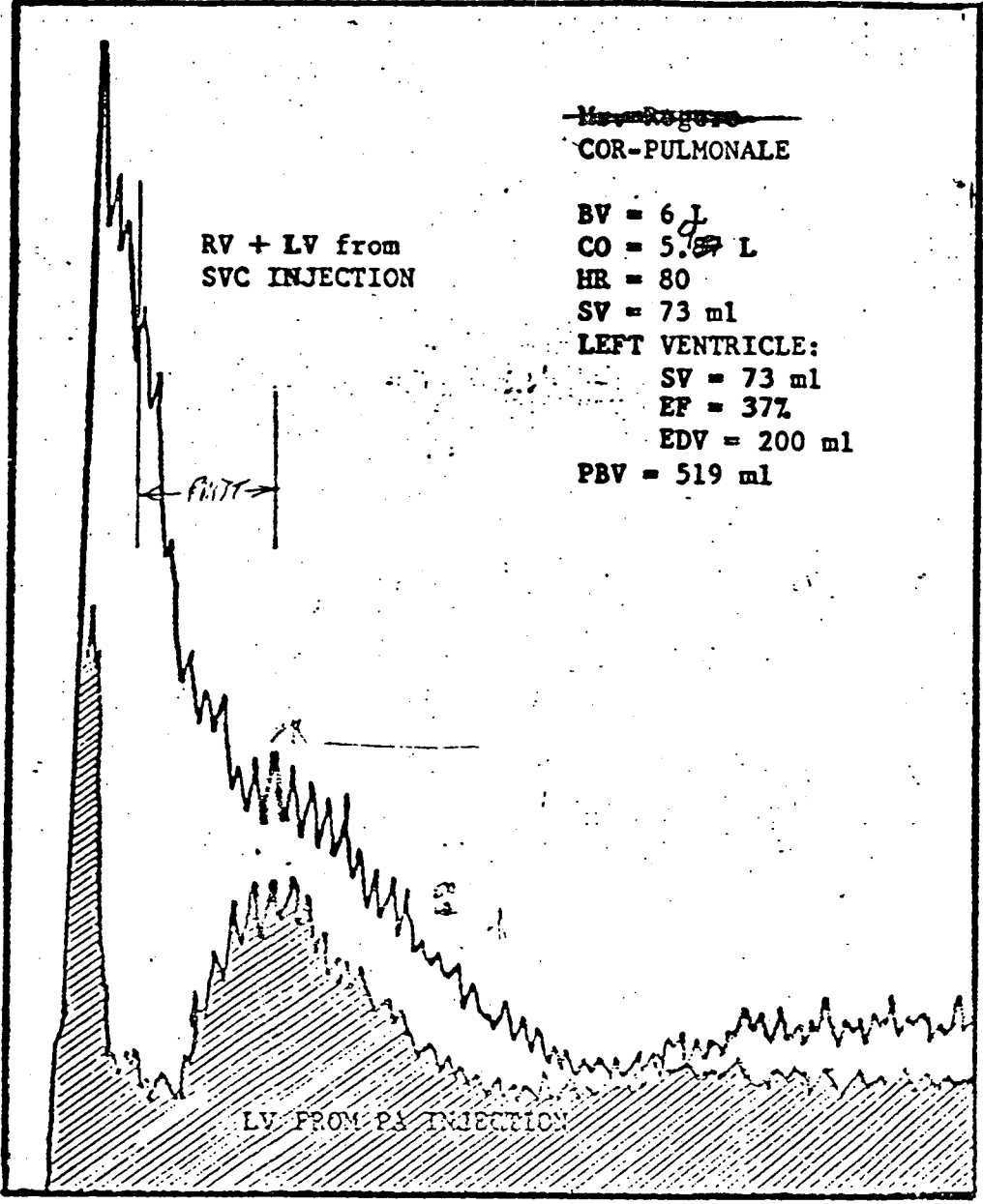
BV = 4.9 L
 CO = 6.5 L/min.
 HR = 120
 SV = 54 ml.
 EF = 34%
 EDV = 157 ml.
 PBV = 240 ml.

CO = 4.9 L
 HR = 96
 SV = 51 ml.
 EF = 62%
 EDV = 83 ml.
 PBV = 245 ml.

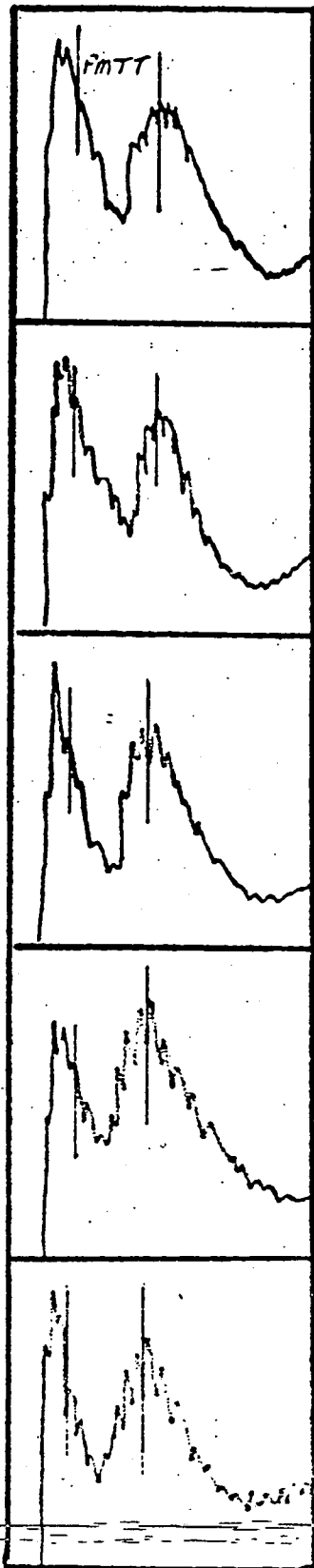
~~Mr. Rogers~~
COR-PULMONALE

RV + LV from
SVC INJECTION

BV = 6 L
CO = 5.5 L
HR = 80
SV = 73 ml
LEFT VENTRICLE:
SV = 73 ml
EF = 37%
EDV = 200 ml
PBV = 519 ml



LV FROM PA INJECTION



DAY 0

BV = 7.5 L
 CO = 6.4 L/min.
 HR = 100
 SV = 64 ml.
 EF = 25%
 EDV = 256 ml.
 PBV = 640 ml.

DAY 1

BV = 6.84 L
 CO = 7.75 L/min.
 HR = 88
 SV = 88 ml.
 EF = 25%
 EDV = 350 ml.
 PBV = 640 ml.

AM

DAY 1

BV = 6.84 L
 CO = 9 L/min.
 HR = 96
 SV = 94 ml.
 EF = 25%
 EDV = 377 ml.
 PBV = 660 ml.

PM

DAY 3

CO = 7.9 L
 HR = 88
 SV = 90 ml.
 EF = 34%
 EDV = 260 ml.
 PBV = 585 ml.

DAY 5

CO = 7.4 L
 HR = 84
 SV = 88 ml.
 EF = 33%
 EDV = 270 ml.
 PBV = 660 ml.

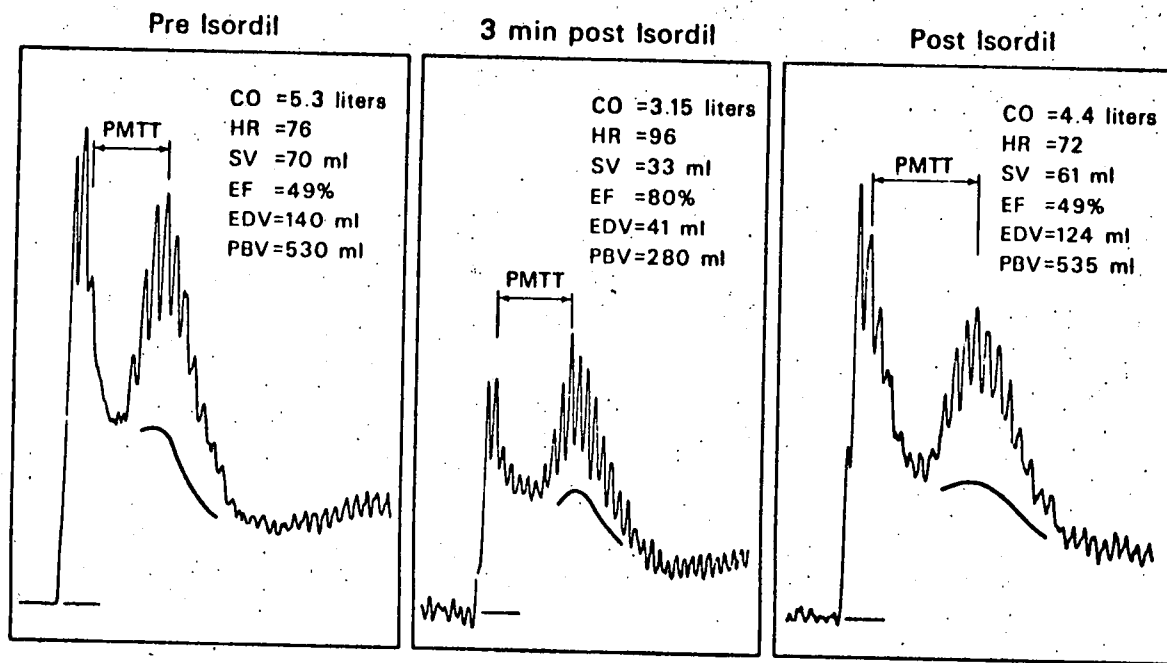


Fig. 11