Non-invasive Estimation of the Human Pulmonary Blood Volume with Gamma Camera and RI-angiocardiography

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A new, non-invasive method for the estimation of the human pulmonary blood volume (PBV), existing between the pulmonary artery bifurcation (PAB) and the left atrium (LA), has been developed in this laboratory, in the form of \( \text{PBV} = \text{PPT} \times 0.77 \times \text{CO} \), equation (6), given in Appendix.

This was an extension of the classical Stewart-Hamilton method of indicator dilution, applied to radioisotope angiocardiography. Using a gamma-camera, the radio-isotope (99m Tc-albumin) dilution curves were recorded externally at the region of PAB, LA and LV (left ventricle), among other things, in human subjects in supine position. The mean transit time (MTT) was determined for each region, and the difference in MTT, e.g., \( \Delta \text{MTT}_{\text{PAB-LA}} \), was measured. We calculated PBV between PAB and LA as \( \text{PBV} = \Delta \text{MTT}_{\text{PAB-LA}} \times \text{CO} \), equation (1) given in Appendix.

Empirical time relations between \( \Delta \text{MTT}_{\text{PAB-LA}} \) and PPTRCG were examined in mechanical models and human subjects, through several steps represented by equations (2) to (5), given in Appendix, and our tentatively final formula was equation (6).

The values of PBV estimated in this way were in good agreement with those of PBV measured invasively in the past, using two injection sites (PA and LA) and one sampling site (artery).

The standard method for the measurement of pulmonary blood volume (PBV) is an invasive one, requiring two catheters, one for injecting the indicator substance into the pulmonary artery (PA) and the other (usually Brockenbrough catheter with tip penetrating the interatrial septum from the right-side) for injecting the same indicator substance into the left atrium (LA). The sampling site is usually an artery (A), for example, the brachial artery. The indicator dilution curves, recorded from the arterial blood, give two values of mean transit time (MTT), one for PA injection (\( \text{MTT}_{\text{PA-A}} \)) and the other for LA injection (\( \text{MTT}_{\text{LA-A}} \)), and, from these, one obtains \( \Delta \text{MTT}_{\text{PA-LA}} \). The volume of blood, existing between PA and LA, is then given by a formula, \( \text{PBV} = \Delta \text{MTT}_{\text{PA-LA}} \times \text{CO} \), where CO is the cardiac output. Unfortunately, this method of measuring PBV has not gained much popularity, because the catheterization of LA (usually by Brockenbrough catheter) is not always a safe procedure.

As to the non-invasive measurement of PBV, radioangiograms were analyzed, employing some simplifying assumptions and mathematical theories.

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Key words:
Pulmonary blood volume
Non-invasive measurements
Indicator dilution technique
RI-angiocardiography
Mean transit time

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With the advent of gamma-camera and radioisotope angiography (RI-angiography), it became possible to record, during the first pass, the time-activity curve at any spot over the chest walls, with nearly clear identification of what structure, of the cardiopulmonary system, is, being examined for RI-dilution curve.

For the last several years, we have been interested in the estimation of PBV, existing between PAB (pulmonary artery bifurcation) and LA, non-invasively with RI-angiography, using a single injection site (antecubital vein) and two “sampling” sites, i.e., regions of PAB and LA on the scintillation screen. According to our method, RI-dilution curves were recorded externally at the regions of PAB, LA and left ventricle (LV), among other things, during the first pass immediately after RI was injected as a bolus, into the antecubital vein. The MTT was determined for each region, and the difference in MTT, e.g., ΔMTTPAB–LA was determined. We calculated PBV, between PAB and LA, as PBV = ΔMTTPAB–LA × CO, equation (1) given in Appendix.

The purpose of this paper is to describe a series of empirical time relations which we found between ΔMTTPAB–LA (or ΔMTTPAB–LV) and PPTRCG (peak-to-peak time of radiocardiogram) which led to our tentative final expression, PBV = PPTRCG × 0.77 × CO, equation (6), given in Appendix.

METHODS

1) Model experiments

Mechanical models of the cardio-pulmonary circulation were constructed by acryl plastic bottles and connecting rubber tubings. The right and left “ventricles” were placed on magnetic stirrers, so that a nearly complete mixing was possible. The lungs were simulated simply by rubber tubings. We gave a steady and constant volume flow of water to this system, and 99mTc pertechnetate, in dose of 5 mCi, was injected into the “caval vein” by a technique similar to the abrupt cuff release. RI-angiography was performed by a gamma-camera (Pho Gamma Hp and LFOV, Cearle) and the data were stored in the video-tape recording system or in a computer.

Regions of interest (ROI) were placed, externally, in various parts of cardio-pulmonary system, i.e., right ventricle (RV), pulmonary artery bifurcation (PAB), left atrium (LA) and left ventricle (LV), and the time-activity curves were recorded at these regions. Mean transit time (MTT) was calculated from the indicator-dilution curves according to the method of Hamilton, i.e., $MTT = \int_0^t f(t) \cdot t \cdot dt / \int_0^t f(t) \cdot dt$, giving MTTPAB, MTTLA and so on. The difference in MTT between two ROI was calculated, for instance, ΔMTTPAB–LA from MTTPAB and MTTLA.

At the “same” time, ROI was set over an area just large enough to cover the entire silhouette of the heart. The time-activity curve recorded from such a large area, i.e., radiocardiogram (RCG), had two peaks, and the peak-to-peak time (PPTRCG) was determined.

2) Clinical studies on empirical time relations

We examined a total of 46 patients, consisting of 5 patients without heart disease and 41
patients with heart diseases. A gamma camera was placed in the second oblique projection, and 10–15 mCi of $^{99m}$Tc-albumin was injected into the right antecubital vein, either with abrupt cuff release method or with flushing with 10 ml of 20% glucose solution. In this RI-angiography, ROI were placed over the areas of RV, PAB, LA and LV, and time-activity curves were recorded from these regions. Mean transit time (MTT) was calculated for each region, just as in the mechanical model experiments, giving ΔMTT between two regions (Fig. 1).

3) Animal experiments

Eleven mongrel dogs were used to test, in parts, the validity of our empirical time relation of equation (5), given in Appendix. In adult dogs, weighing from 12 to 22 Kg, anesthetized with pentobarbital, chest-opened, and under artificial respiration, a NIH catheter (8F) was advanced through the right jugular vein until the tip was located in the right atrium; a similar catheter was advanced through the left jugular vein until the tip was located in the pulmonary artery (PA); the 3rd catheter was advanced, through the appendage of the left atrium, into the left atrium (LA). The 4th catheter (Courand-cathether, 8F) was advanced, through the left femoral artery, until the tip was located immediately above the aortic valves (Ao). Indicator dilution was performed by injecting indocyanine-green dye, in dose of 1.25 mg (0.5 ml), into PA and, separate from this, into LA, with saline flushing (3 ml), and withdrawing blood from Ao at a constant rate of 30 ml per minute. A well calibrated densitometer (Gilford, type IN-80) was used to record the dye dilution curves from Ao. A pair of injection, into PA and LA, was repeated three times, and we collected data from two pairs where the values of cardiac output were closely similar.

In this way, we measured $\text{MTT}_{PA}$ and $\text{MTT}_{LA}$ and, from these, $\Delta\text{MTT}_{PA-LA}$. At the “same” time, radiocardiograms (RCG) were recorded with a detector, housing a single NaI crystal (φ1½ inch), in the left anterior oblique (LAO) projection, and with injection of $^{99m}$Tc-per-technetate into the right atrium. The recorded RCG were examined for $\text{PPT}_{RCG}$.

RESULTS

1) Model experiments

In a preliminary series of experiments, using mechanical models, we examined the validity of calculating the volume of water, existing between two points of the mechanical cardiopulmonary model, as a product of $\Delta\text{MTT}$ and volume flow. In a total of 132 pairs of comparison, between the actual and calculated volume, the percentage difference averaged $-0.7 \pm 6.4\%$ (mean ±SD).

With regard to the agreement between $\Delta\text{MTT}$ and $\text{PPT}_{RCG}$, we found that $\Delta\text{MTT}_{PA-LV}$ best agreed with $\text{PPT}_{RCG}$, with coefficient of variation of ±7.6%. Thus, we may write $\text{PPT}_{RCG} = \Delta\text{MTT}_{PA-LV}$ which is equation (2), of Appendix.


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which is equation (4), of Appendix. The last term (0.05) was small enough to be neglected. From equation (3) and (4), we may write

$$\Delta \text{MTTPAB-LA} = \text{PPTRCG} \times 0.77$$

$$r = 0.85, \quad p < 0.01$$

which is equation (5), given in Appendix.

From equation (1) and (5), we may write

$$\text{PBV} = \text{PPTRCG} \times 0.77 \times \text{CO}$$

which is equation (6), of Appendix.

3) Animal experiments

Empirical time relation between PPTRCG and \(\Delta \text{MTTPAB-LA}\) was examined in eleven mongrel dogs, and we found the average time relation of

$$\Delta \text{MTTPAB-LA} = \text{PPTRCG} \times 0.68 + 0.75$$

$$r = 0.81, \quad p < 0.01 \quad n = 11$$

This equation may look different substantially from the time relation of \(\Delta \text{MTTPAB-LA} = \text{PPTRCG} \times 0.77\), equation (5), but this is not so. As is evident from Fig. 3, the data from dogs, represented by an equation of \(\Delta \text{MTTPAB-LA} = \text{PPTRCG} \times 0.68 + 0.75\), appear to fall around the regression line of equation (5), i.e., \(\Delta \text{MTTPAB-LA} = \text{PPTRCG} \times 0.77\). This fact indicates that the empirical time relation in human, of equation (5), approximately holds good also for dogs.

4) Pulmonary blood volume in heart diseases

Pulmonary blood volume, existing between PAB and LA, was measured, either with a gamma-camera and RI-angiocardiology according to equation (1) or (6), of Appendix, or with a detector housing a single NaI crystal and radio-

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**TABLE I** COMPARISON OF THE VALUES OF PBV ESTIMATED BY OUR NON-INVASIVE METHOD AND THOSE OF PBV MEASURED INVASIVELY IN THE PAST, USING TWO INJECTION SITES (PA AND LA) AND ONE SAMPLING SITE (ARTERY)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cases</th>
<th>PBV/M² (ml/M²) (mean) ± (SD)</th>
<th>Authors</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>( 4)</td>
<td>246 ± 22</td>
<td>Dock, D.S.</td>
<td>(1961)</td>
</tr>
<tr>
<td>Normal</td>
<td>( 5)</td>
<td>266 ± 46</td>
<td>Yu, P.N.</td>
<td>(1967)</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>(44)</td>
<td>273 ± 62</td>
<td>Gotoh, K. et al.</td>
<td>(1980)</td>
</tr>
<tr>
<td>MS</td>
<td>(16)</td>
<td>360 ± 35</td>
<td>Fujimoto, K.</td>
<td>(1960)</td>
</tr>
<tr>
<td>MS</td>
<td>(15)</td>
<td>335 ± 117</td>
<td>Dock, D.S.</td>
<td>(1961)</td>
</tr>
<tr>
<td>MS</td>
<td>( 8)</td>
<td>316 ± 53</td>
<td>Yu, P.N.</td>
<td>(1967)</td>
</tr>
<tr>
<td>MS</td>
<td>(15)</td>
<td>351 ± 77</td>
<td>Russell, C.</td>
<td>(1971)</td>
</tr>
<tr>
<td>MS</td>
<td>(39)</td>
<td>340 ± 55</td>
<td>Gotoh, K. et al.</td>
<td>(1980)</td>
</tr>
</tbody>
</table>

**MS:** Mitral Stenosis

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cardiography (RCG), using R^{131} IS, according to (6) of Appendix. A total of 83 cases, consisting of 44 non-cardiac cases and 39 cases of mitral stenosis were studied. This series of patients included some of the 46 patients used for the clinical studies on empirical time relations, but consisted mostly of the patients who were not subjected to the clinical studies on empirical time relations.

As shown in Table I, the values of PBV estimated by our non-invasive method were in good agreement with those of PBV measured invasively in the past, using two injection sites (PA and LA) and one sampling site (artery).

**DISCUSSION**

For the estimation of PBV, existing between PAB and LA, we started out with a direct application of Stewart-Hamilton method of indicator dilution to the RI-angiocardiology, i.e., equation (1), given in Appendix. We examined the empirical time relation between $\Delta MTTPA-LA$ and $\Delta PPRCG$ through several steps of investigation, represented by equations (2) to (5), using mechanical models and clinical RI-angiocardiological studies, culminating in our tentatively final equation of $PBV = PPRCG \times 0.77 \times CO$.

Validity of this method of estimating PBV, existing between PAB and LA, was tested, at least, in two ways. First, we examined 11 mongrel dogs, anesthetized, chest opened and maintained on artificial respiration, for the time relation between $\Delta MTTPA-LA$ (indocyanine green dye, with sampling at the root of aorta) and $\Delta PPRCG$. The average time relation, $\Delta MTTPA-LA = PPRCG \times 0.68 + 0.75$, was not substantially different from the relation, in human, of $\Delta MTTPAB-LA = PPRCG \times 0.77$, as shown in Fig. 3.

Second, the values of PBV measured in this way in our series of patients ($n = 83$) were quite similar to those reported, for similar series of patients, in the literature$^{1,3,11,12}$ (Table I). We have another indirect evidence supporting the validity of our non-invasive estimation of PBV, existing between PAB and LA. We examined a series of patients, 19 cases in total, different from the afore-mentioned series of patients, for PBV and its change with passive elevation of both legs. For this examination, RI angiocardiology was performed in supine position, and PBV was measured according to our method, either by equation (1) or by equation (6), given in Appendix. Next, the gamma-camera was brought over the right anterior chest and ROI was set at an area distant from the heart and liver. After assuring that the radio-activity from this ROI became stable, we had the patient elevate both legs passively at an angle of 30–40°. This produced a distinct and highly reproducible rise in the radio-activity from the ROI ("lung" field), suggesting that the volume of blood in the lungs increases when both legs are elevated passively. From the percentage increment in the radio-activity and the initial value of PBV, we calculated the increment in PBV ($\Delta PBV$), after corrections for 2 sources of errors, one, radio-activity from the anterior and posterior chest walls, and, two, absorption of radio-active beams within the lung and anterior chest wall. By definition, the increment of blood volume in the pulmonary "venous" system ($\Delta V^V^V^V^V$) was $\Delta V^V^V^V^V = 0.8 \times \Delta PBV$. Mean pulmonary artery wedge (PAW) pressure was measured by Swan-Ganz catheter, in supine position and during passive leg elevation. From the increment in mean PAW pressure ($\Delta PAW$), we calculated the compliance ($\Delta V/\Delta P$) of the human pulmonary "venous" system as $\Delta V/\Delta P = \Delta V^V^V^V^V/\Delta PAW$$^{13,14}$.

At the same time and in the same human subjects, $\Delta V/\Delta P$ of the pulmonary "venous" system was estimated by an entirely different method, previously developed by Hirakawa and his colleagues in this laboratory, employing PAW pressure tracings, with a formula $\Delta V/\Delta P = 0.4k^{**}S/(v-d)$, where $k^{**} = 0.075 \times PAW + 0.9015$. We found, in 19 patients, that the values of $\Delta V/\Delta P$, calculated from PBV measurements and passive elevation of the legs (X), were close to the values of $\Delta V/\Delta P$, estimated from PAW pressure tracings (Y), in the form of $Y = 0.73X + 3.5$ ($r = 0.70$, $p < 0.01$)$^{13,14}$.

**APPENDIX**

A new, non-invasive method for the estimation of the human pulmonary blood volume (PBV), existing between the pulmonary artery bifurcation (PAB) and the left atrium (LA), has been developed, over several years, by Hirakawa and his colleagues in this laboratory$^{7-10,14}$. Derivation of our formulas, described in this paper, may be profitably presented here in a compact way.

First, using a gamma-camera, the radio-
isotope ($^{99m}$Tc albumin) dilution curves were recorded externally at the regions of PAB and LA and LV (left ventricle), among other things, and the mean transit time (MTT) was determined at PAB, LA and LV, among other things, in human subjects in supine position. From the difference in MTT ($= \Delta \text{MTT}_{\text{PAB-LA}}$) and cardiac output (CO), PBV between PAB and LA was given by:

\[ \text{PBV} = \Delta \text{MTT}_{\text{PAB-LA}} \times \text{CO} \]  

(1)

At the same time and in the same human subjects, we recorded the peak-to-peak time of radioactivity curve (PPTRCG), time-activity curve obtainable by placing a large region of interest (ROI) of a gamma camera exactly over the cardiac silhouette.

In mechanical cardiopulmonary models, there was an approximate empirical time relation

\[ \text{PPTRCG} = \Delta \text{MTT}_{\text{PAB-LV}} \]  

(2)

In 46 patients with or without heart diseases, there was an approximate empirical time relation

\[ \text{PPTRCG} = \Delta \text{MTT}_{\text{PAB-LV}} \]  

(3)

Furthermore, in 24 patients, there was an approximate empirical time relation

\[ \Delta \text{MTT}_{\text{PAB-LA}} = \Delta \text{MTT}_{\text{PAB-LV}} \times 0.77 + 0.55 \]  

(4)

where the last term (0.05) was small enough to be neglected.

From equations (3) and (4), we may write, for human,

\[ \Delta \text{MTT}_{\text{PAB-LA}} = \text{PPTRCG} \times 0.77 \]  

(5)

From equations (1) and (5), we may write

\[ \text{PBV} = \text{PPTRCG} \times 0.77 \times \text{CO} \]  

(6)

which is our tentative final equation.\(^\text{10}\)

Validity of our empirical time relation of equation (5) was tested in dogs, as described in this paper. Briefly, in 11 mongrel dogs, anesthetized and chest-opened, we examined MTT PAB-LA by injecting indocyanine green dye, as a bolus, into the pulmonary artery and separate from this, into the left atrium. Dye dilution curves were recorded at the root of aorta. PPTRCG was recorded over the exposed hearts, using $^{99m}$Tc-pertechnetate. The plots of MTT PAB-LA against PPTRCG appeared to fall around the regression line of equation (5), indicating that the empirical time relation, in human, of equation (5) approximately holds good also for dogs.

REFERENCES


