Effects of Acute Digitalization on the Pulmonary Blood Volume in Patients with Heart Disease

By Gerald W. Murphy, M.D., Bernard F. Schreiner, Jr., M.D., and Paul N. Yu, M.D.

SUMMARY
Basic hemodynamic data and the pulmonary blood volume (PBV) were determined in 23 patients before and after intravenous administration of acetyl strophanthidin during right and left heart catheterization. These patients were divided into two groups depending upon whether or not digitalization produced a significant fall in left ventricular end-diastolic pressure (LVID). Group I consisted of 11 patients who manifested a significant decrease in LVID, while in group II no change was noted after digitalization. In both groups, a significant rise in LV stroke volume, stroke work, and maximal rate of rise of LV systolic pressure (dp/dt) was recorded. In group I, a significant decrease in the pulmonary vascular distending pressure (Pd) was accompanied by a decrease in PBV. In contrast, no change in Pd or PBV was noted in the patients in group II. Changes in pulmonary vascular resistance (PVR) were inconsistent. It is concluded that: (1) in patients of group I the concordant decrease in Pd and PBV represented a passive effect on the pulmonary vascular bed mediated by improved LV performance and decrease in LVID; (2) in patients of group II, despite evidence of significant positive inotropic effects on the left ventricle, the failure of LVID to fall prevented a decrease in Pd and PBV; (3) no evidence of active vasomotor effects of acetyl strophanthidin in the lung could be demonstrated. Changes in PVR were capricious and not apparently useful in assessment of the presence or absence of pulmonary vasomotor effects induced by digitalis. The results of this study differ from the findings of other investigators in cardiac patients and experimental animals. Some of the differences may be attributed to different experimental methods and to species variation in vascular reactivity.

Also, the findings in this report contrast with those previously reported for isoproterenol and aminophylline, agents that produce both positive inotropic effects on the heart and active vasomotion in the pulmonary circulation.

Additional Indexing Words:
Ventricular function Pulmonary vasomotor effects Mitral valve
Aortic valve

The effects of digitalis on the heart and systemic circulation in both normal and disease states have been extensively studied, but little information is available concerning its effects on the pulmonary...
vasculature and pressure-volume relationships within the pulmonary circulation. In a recent study an increase in pulmonary vascular resistance was noted after administration of ouabain to patients with mitral stenosis. This change was interpreted as evidence of a direct vasoconstricting effect of the drug on the pulmonary arteries.\(^1\)

Experimental evidence in animals suggests that digitalis preparations, acetylstrophanthidin in particular, produce pulmonary arteriolar constriction in the normal dog\(^2\) and in dogs with augmented pulmonary blood flow.\(^3\)

We undertook the present investigation in order to (a) explore further the possibility of a direct vasomotor action of acetylstrophanthidin on the pulmonary arterioles in man and (b) describe the changes in the pressure-volume relationships in the pulmonary vascular bed after acute digitalization of patients with heart disease. A summary of some of the data was included in a recent monograph from this laboratory.\(^4\)

Methods and Clinical Material

The effects of intravenous acetylstrophanthidin were studied in 23 patients at the time of combined right and transseptal left heart catheterization. All studies were conducted in the supine position following light sedation with pentobarbital and promethazine. No patient had received digitalis for at least 6 weeks prior to the study.

The average age of the 23 patients in this study was 40 years. Specific clinical diagnoses of each patient and his functional cardiac classification are listed in tables 1 and 2.

The central blood volume (CBV), which includes the blood volume in the lungs, left heart chambers, and the major portion of systemic arterial volume, was calculated as the product of cardiac index and the mean transit time from the pulmonary artery to the systemic arterial sampling site. The pulmonary blood volume (PBV), defined as that volume of blood between the main pulmonary artery and the left atrium, was estimated as the product of cardiac index and the mean transit time from the main pulmonary artery to the left atrium. Rapid sequential injections of indocyanine green dye were made into the main pulmonary artery and left atrium, and blood was sampled from a systemic artery for determination of cardiac index and the mean transit times. In an analysis of duplicate determinations of the PBV in our laboratory in 57 patients with various types of cardiac disease, the standard deviation for a single determination was 15.6 ml/m\(^2\).\(^5\) A detailed description of the methods used in our laboratory for the determination of pressure, rate of blood flow, CBV, and PBV have been reported elsewhere.\(^6,\)^\(^7\)

Changes in left ventricular performance were evaluated by means of: (a) measurement of the maximum rate of rise of left ventricular systolic pressure (LV dp/dt), (b) calculation of LV stroke work index by use of a standard formula,\(^8\) and (c) measurement of changes in left ventricular end-diastolic pressure (LVP). In our laboratory, LV dp/dt is measured by means of an RC differentiating circuit connected to the output of the recording amplifier.\(^8,\)^\(^9\) This technique permits a semi-quantitative evaluation of directional changes in dp/dt, but the frequency response of the catheter-gauge system does not permit reliable calibration of the recordings in mm Hg/sec.

Changes in the relationship of the PBV and the mean pulmonary vascular distending pressure (P\(_p\)) were used as an aid in the distinction between active and passive effects of digitalization upon the pulmonary vasculature.\(^10\) The mean distending pressure is obtained by the averaging of the pulmonary artery and left atrial mean pressures, as described by Milnor et al.\(^11\)

After positioning the right and left heart catheters, we made control recordings of the electrocardiogram, of pulmonary arterial (PA), left ventricular (LV), and systemic arterial (SA) pressures, and of LV dp/dt. We used high gain recordings to facilitate accurate measurement of LVP. The transseptal catheter was then withdrawn to a position in mid-left atrium under fluoroscopic control, and left atrial (LA) pressure was recorded. Control period values for cardiac output, CBV, and PBV were then obtained as described. In three patients the left heart catheter remained in the LV during determinations of flow and volume. Thus, in these patients (S.B., D.T., and H.B.), the reported values for PBV include the left atrial volume as well.

After these observations, 0.5 mg of acetylstrophanthidin was administered intravenously over a 2-min interval, followed by increments of 0.1 mg/min until a total dose of 1.1–1.3 mg was given. The time required for infusion of the drug was 9–12 min. During this time the electrocardiogram and the LA and SA pressures were continuously monitored. Pulmonary artery pressure was also recorded after completion of the infusion.

Determinations of PBV and CBV were repeated between 12 and 15 min after completion of the drug infusion. The transseptal catheter, which was positioned in the mid-left atrium, was

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### Table 1

**Hemodynamic Data before and after Digitalization in Patients of Group I**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>BSA(m²)</th>
<th>Class</th>
<th>Diagnosis</th>
<th>Condition</th>
<th>Blood flow</th>
<th>Pressures (mm Hg)</th>
<th>Volumes (ml/m²)</th>
<th>Resistance (dyne-sec cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.B.</td>
<td>50</td>
<td>2.07</td>
<td>M</td>
<td>IHD</td>
<td>C NSR</td>
<td>1.99</td>
<td>16 14 15 16 113</td>
<td>581 298</td>
<td>39 2185</td>
</tr>
<tr>
<td>M</td>
<td>3 III</td>
<td>2.52</td>
<td>D</td>
<td>CM</td>
<td>C NSR</td>
<td>2.00</td>
<td>12 8 10 10 108</td>
<td>51 273</td>
<td>77 2087</td>
</tr>
<tr>
<td>D.T.</td>
<td>45</td>
<td>2.13</td>
<td>D</td>
<td>CM</td>
<td>C NSR</td>
<td>1.85</td>
<td>17 – – 18 110</td>
<td>574 360</td>
<td>– 1640</td>
</tr>
<tr>
<td>H.B.</td>
<td>45</td>
<td>1.94</td>
<td>D</td>
<td>IHD</td>
<td>C NSR</td>
<td>3.82</td>
<td>19 – – 12 125</td>
<td>579 331</td>
<td>– 1350</td>
</tr>
<tr>
<td>R.F.</td>
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<td>1.80</td>
<td>D</td>
<td>CM</td>
<td>C NSR</td>
<td>2.14</td>
<td>13 5 9 4 112</td>
<td>619 316</td>
<td>129 1811</td>
</tr>
<tr>
<td>M</td>
<td>IV</td>
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<td>D</td>
<td>CM</td>
<td>C NSR</td>
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<td>42 28 35 25 80</td>
<td>853 363</td>
<td>253 1444</td>
</tr>
<tr>
<td>M</td>
<td>III</td>
<td>1.80</td>
<td>D</td>
<td>AS</td>
<td>C NSR</td>
<td>3.10</td>
<td>21 17 19.0 23</td>
<td>574 186</td>
<td>57 1290</td>
</tr>
<tr>
<td>M</td>
<td>III</td>
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<td>D</td>
<td>AR</td>
<td>C NSR</td>
<td>2.50</td>
<td>28 25 25.5 30</td>
<td>673 254</td>
<td>77 2429</td>
</tr>
<tr>
<td>M</td>
<td>IV</td>
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<td>D</td>
<td>AR</td>
<td>C NSR</td>
<td>2.66</td>
<td>29 23 26.0 32</td>
<td>640 278</td>
<td>112 1680</td>
</tr>
<tr>
<td>C.W.</td>
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<td>1.70</td>
<td>D</td>
<td>AR</td>
<td>C NSR</td>
<td>2.46</td>
<td>32 25 28.5 40</td>
<td>860 238</td>
<td>119 1947</td>
</tr>
<tr>
<td>S.E.</td>
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<td>1.83</td>
<td>D</td>
<td>AR; MS</td>
<td>AF</td>
<td>1.08</td>
<td>32 20 22.0 10</td>
<td>588 330</td>
<td>104 2156</td>
</tr>
<tr>
<td>S.M.</td>
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<td>1.59</td>
<td>D</td>
<td>MS</td>
<td>AF</td>
<td>2.52</td>
<td>38 29 33.5 – 82</td>
<td>724 474</td>
<td>180 1640</td>
</tr>
</tbody>
</table>

*Includes left atrial volume.

Abbreviations: M = male; F = female; BSA(m²) = body surface area in square meters; CI = cardiac index (liters/min/m²); HR = heart rate, beats/min; SI = stroke index (ml/min/m²); PAM = pulmonary artery mean pressure; LAM = left atrial mean pressure; SAM = systemic artery mean pressure; Pa = pulmonary vascular distending pressure; LVd = left ventricular end-diastolic pressure; LVSW = left ventricular stroke work in g-m/m²; CBV = central blood volume; PBV = pulmonary blood volume; PVR = pulmonary vascular resistance; TSR = total systemic resistance; C = control; D = after acetyl strophanthin; IHD = ischemic heart disease; CM = cardiomyopathy; AS = aortic stenosis; AR = aortic regurgitation; AVP = aortic valve prosthesis; MS = mitral stenosis; NSR = normal sinus rhythm; AF = atrial fibrillation; S.E. = standard error of the mean.
### Table 2

**Hemodynamic Data before and after Digitalization in Patients of Group II**

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>BSA(m²)</th>
<th>Class</th>
<th>Diagnosis</th>
<th>Condition</th>
<th>Rhythm</th>
<th>Blood flow</th>
<th>Pressures (mm Hg)</th>
<th>Volumes (ml/m²)</th>
<th>Resistance (dyne-sec cm⁻²)</th>
</tr>
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<td>C</td>
<td>NSR</td>
<td></td>
<td>2.94</td>
<td>77</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>53</td>
<td>M</td>
<td>2.00</td>
<td>IHD</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>2.79</td>
<td>70</td>
<td>40</td>
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<tr>
<td>W.O'B.</td>
<td>57</td>
<td>M</td>
<td>1.92</td>
<td>CM</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>1.38</td>
<td>100</td>
<td>14</td>
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</tr>
<tr>
<td>J.W.</td>
<td>17</td>
<td>F</td>
<td>1.53</td>
<td>AS</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>3.04</td>
<td>100</td>
<td>30</td>
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</tr>
<tr>
<td>L.Z.</td>
<td>52</td>
<td>M</td>
<td>1.88</td>
<td>AS</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>2.46</td>
<td>85</td>
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<tr>
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<td>NSR</td>
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<td>3.12</td>
<td>82</td>
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<td></td>
</tr>
<tr>
<td>R.C.</td>
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<td>M</td>
<td>1.84</td>
<td>AS</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>3.80</td>
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<td>47</td>
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<tr>
<td>S.L.</td>
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<td>2.00</td>
<td>AR</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>2.30</td>
<td>100</td>
<td>23</td>
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</tr>
<tr>
<td>S.C.</td>
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<td>1.68</td>
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<td>NSR</td>
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<tr>
<td>T.V.</td>
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<td>M</td>
<td>1.45</td>
<td>MS</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>2.40</td>
<td>75</td>
<td>32</td>
<td></td>
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<tr>
<td>P.S.</td>
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<td>M</td>
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<td>MS</td>
<td>C</td>
<td>NSR</td>
<td></td>
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<td>48</td>
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<td>M</td>
<td>2.05</td>
<td>Normal</td>
<td>C</td>
<td>NSR</td>
<td></td>
<td>3.00</td>
<td>96</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- **Blood flow:** CI (Cardiac Index), HR (Heart Rate), SI (Stroke Index)
- **Pressures:** PAm (Atrial Pressure), LAm (Left Atrial Pressure), Pa (Aortic Pressure), LVP (Left Ventricular Pressure), SAm (Systemic Arterial Pressure), LVSW (Left Ventricular Stroke Work)
- **Volumes:** CBV (Cerebral Blood Volume), PBV (Peripheral Blood Volume)
- **Resistance:** PVR (Peripheral Vascular Resistance)

**Abbreviations:** Same as for table 1.
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then again advanced into the LV, and all pressure recordings and measurements of LV dp/dt were repeated. No evidence of digitalis intoxication was noted in any of the patients during this procedure.

Statistical analysis of the results was carried out by means of a paired sample comparison of control values with those obtained after acetyl strophanthidin infusion. For purposes of this analysis, the 23 patients were first divided into two groups (see Results).

Results

Preliminary examination of the data led to the hypothesis that the changes in the PBV and \( P_d \) observed in some of the patients were largely passive, induced by the extrapulmonary effects of digitalization on LV performance, and were not evidence of direct effects in the lung. One of the prominent manifestations of digitalization that might be expected to have an effect on the intravascular pressures in the lung was the observed reduction in \( LVD \) in some of the patients. In order to test this possibility, we divided the patients into two groups dependent on whether or not a significant decrease in \( LVD \) occurred after digitalization. The changes in PBV and \( P_d \) in these two groups were then analyzed.

Group I consisted of 11 patients in whom acute digitalization resulted in a decrease in \( LVD \) of 5 mm Hg or more. The average age of these patients was 42 years. Five patients had either ischemic heart disease or idiopathic nonobstructive cardiomyopathy. The remaining six patients had valvular heart disease. Of these, one patient had an aortic valve prosthesis, two patients had predominant aortic stenosis, two others had predominant aortic incompetence, and the remaining patient had mitral stenosis. At the time of cardiac catheterization, all patients were in normal sinus rhythm, but during the study two (S.E. and S.M.) developed atrial fibrillation. Although all of these patients had various degrees of fatigue and dyspnea with physical activity, only two (J. McE. and R.F.) had physical signs of pulmonary congestion and peripheral edema at the time of cardiac catheterization. The data obtained from the patients in group I are summarized in table 1, and are illustrated graphically in figure 1. All but two (H.B. and S.E.) of the patients in this group had initially elevated \( LVD \) or \( LAm \) during the control period. Acute digitalization resulted in a significant decrease in heart rate and in increases in stroke index and stroke work index. The average cardiac index rose slightly, with the most marked increases tending to occur in patients with low initial values and markedly elevated \( LVD \) (L.W., R.F., and J. McE.). Highly significant decreases in PA mean pressure (PAm), \( LAm \), as well as in \( LVD \) were noted, but no change in SA mean pressure (SAm) was produced. Although the pulmonary vascular resistance (PVR) did not change, the total systemic resistance (TSR) fell significantly after digitalization. The CBV and PBV fell in all patients, and the changes were highly significant.

It should be noted that the PBV as calculated for patients S.B., D.T., and H.B. in group I also includes left atrial volume. A discordant change in the "true" PBV and the PBV including the left atrial volume seems highly unlikely. Thus, the "true" PBV in these three patients also apparently decreased. In

![Figure 1](http://circ.ahajournals.org/)

Changes in \( P_d \) are plotted against changes in PBV after administration of acetyl strophanthidin in the 11 patients in group I. The PBV included LA volume in the three patients indicated by circular symbols. In two of these (△), \( P_d \) was estimated by averaging of PAm and \( LVD \), since LAm was not recorded (see text).
two of these patients (D.T. and H.B.), LAm was not recorded at the time of determination of PBV. However, since LV_D and PAm declined after digitalization and neither patient had mitral valve obstruction, LAm and thus also P_d must have decreased in these cases.

Group II consisted of 12 patients in whom the changes in LV_D after acute digitalization did not exceed ±1 mm Hg. The average age in this group was 39 years. Three patients had ischemic heart disease or nonobstructive cardiomyopathy. Four patients had predominant aortic incompetence, and two had predominant mitral stenosis. The remaining patient (J.M.) had normal hemodynamics. Eleven of the 12 patients had cardiac symptomatology, but only one (W.O'B.) was in functional class IV.

The data obtained in group II is summarized in table 2 and figure 2. In contrast to the patients of group I, LV_D was elevated in only

![Figure 2](image-url)

Changes in P_d are plotted against changes in PBV after administration of acetyl strophanthidin in the 12 patients in group II. For better visualization, the scale of this figure has been expanded relative to that of figure 1.
three of the 12 patients in this group, and did not fall significantly in any patients after acute digitalization. The directional changes in average heart rate, cardiac index, stroke index, and stroke work index were similar to those noted in group I. However, only minor changes were observed in PAm, LAm, and LVd.

Although a decrease in Pa of borderline significance was noted in this group, the change in this parameter in group I exceeded that of group II by a factor of greater than tenfold. Systemic arterial pressure, PVR, and TSR failed to change. In distinct contrast to group I, the CBV and PBV in group II did not change significantly.

Table 3 compares the changes observed for each parameter for both groups I and II.

An increase in LV dp/dt was noted after administration of acetyl strophanthidin in every patient where satisfactory measurements were obtained, and the presence of this finding appeared to be unrelated to any other combination of hemodynamic changes during the procedure. The range of this increase varied from +20 to +85% of the control value prior to digitalization, and there was no significant difference in the response of groups I and II. Further attempts at calibration of this measurement were not made.

Transient increases in systemic arterial pressure were commonly noted during the infusion of acetyl strophanthidin, but ordinarily this change had dissipated by the time the hemodynamic measurements were made.

**Discussion**

As we have reported elsewhere, the use of this experimental protocol in a series of eight patients undergoing a sham intervention consisting of the infusion of 20 ml of physiologic saline failed to produce any significant hemodynamic alterations. Thus, the changes we observed in this study in both ventricular performance and the pressure-volume relationships in the pulmonary circulation after acute digitalization cannot be attributed to the effects of time or to chance alone.

The positive inotropic effect of acetyl strophanthidin on the myocardium was manifest in both groups I and II. The most consistently observed evidence of this effect was an increase in LV dp/dt, and this was frequently accompanied by an increase in stroke work index and a decrease in LVd. Also common to both groups was a significant slowing of heart rate and rise in stroke index.

Measurement of the PBV and pulmonary vascular distending pressure has been used as an aid in the interpretation of hemodynamic changes in the pulmonary circulation. A concordant rise or fall in Pa and the PBV is consistent with passive dilation or collapse of the pulmonary vascular bed, whereas discordant changes in Pa and the PBV suggest predominantly active vasoconstriction (rise in Pd, fall in PBV) or vasodilation (fall in Pd, rise in PBV). This interpretative scheme helps us avoid some of the pitfalls inherent in the use of pulmonary vascular resistance as an index of vasomotor activity in the pulmonary circulation.

In patients of group I, the marked decrease in LVd, LAm, PAm, and Pa was associated with a reduction in the PBV. This observation is consistent with the hypothesis that the fall in both Pa and PBV was a passive effect secondary to the decrease in LVd produced by digitalization.

As would be predicted on the basis of this same hypothesis, in the patients of group II, in whom LVd failed to decrease after drug infusion, both Pa and PBV remained essentially unchanged.

We have previously reported that the clinical syndrome of "pulmonary vascular congestion" in cardiac patients appears to be dependent on an abnormal elevation of the pulmonary transmural pressure and does not necessarily require for its presence an absolute elevation of the PBV. In a patient with left ventricular decompensation associated with an elevated Pa and either a normal or augmented PBV, a fall in Pa may be produced by either a reduction in LVp or a decrease in PBV, or both. The present study suggests that in patients of group I, the fall in Pa is

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mediated by a significant improvement in left ventricular performance and a reduction in ventricular filling pressure. The changes in LVD and subsequent decline in PBV thus seem most likely a consequence of improved left ventricular emptying. The reduction in PBV was observed regardless of whether or not the initial level was abnormally elevated. Furthermore, the magnitude of the reduction in the PBV required to produce a significant decrease in Pa may be relatively small. This is probably a reflection of structural disease in the lung parenchyma and the resultant abnormally low pulmonary vascular compliance previously noted in patients with chronic congestive heart failure.15

It is recognized that this study considers only the total response of the pulmonary vascular bed. Limitations of the method employed do not permit further subdivision of the vascular bed into arterial, capillary, and venous compartments. It seems likely that local differences in the pressure-volume response in the pulmonary vascular bed could be influenced greatly by the underlying pathologic changes.15

Digitalis glycosides, and particularly acetyl strophanthinidin, have a well-recognized direct vasoconstrictor action on systemic arterioles.16, 17 Such an effect is difficult to demonstrate convincingly with respect to the pulmonary arterioles. Recently, in a study of the effects of ouabain on patients with mitral stenosis, an increase in pulmonary vascular resistance was interpreted as evidence in support of a direct vasoconstrictor effect on these vessels.1 Our patients in group II resemble those observed in this study in that important changes in cardiac index and LAm did not occur after digitalization. However, we did not find any tendency for increase in pulmonary vascular resistance. Moreover, if digitalization had provoked significant vasoconstriction in the pulmonary circulation, a rise in Pa and a fall in PBV would have been expected. Neither was observed. This contrasts with experiments conducted in animals.2, 8 Thus, on the basis of our findings, a direct action of acetyl strophanthinidin on the pulmonary blood vessels is not apparent in these patients. We cannot explain the differences between these observations and those made in animals, but wide variation in experimental conditions and species differences in vascular reactivity in the pulmonary bed, as well as the effects of anesthesia, may be determining factors. However, we find it difficult to exclude the possibility of a weak vascular action that was transient and perhaps masked by the other more apparent effects of the drug or by the timing of the observations. It is of interest to us to compare and contrast the effects of digitalization on Pa and the PBV with those of isoproterenol and aminophylline, two agents that also have positive inotropic effects on the heart and additional known pharmacologic effects in the lung. Whenever an infusion of isoproterenol or aminophylline results in a fall in Pa, the PBV tends to rise.12, 18 This change suggests a vasodilating action on the pulmonary vasculature, possibly caused by a direct vascular effect or perhaps mechanically mediated by the prominent bronchomotor effects of these agents.19 Acetyl strophanthinidin, however, failed to produce any changes in the pressure-volume relationships in the pulmonary circulation that could be construed as evidence of a direct pharmacologic effect in the lung.

Acknowledgment

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4. YU PN: Pulmonary Blood Volume in Health and Circulation, Volume XLIII, January 1971
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