Cardiac Output and Central Volume as Determined by Dye Dilution Curves

Resting Values in Normal Subjects and Patients With Cardiovascular Disease

By Albert A. Kattus, M.D., Arthur U. Rivin, M.D., Aaron Cohen, M.D. and Gilbert S. Sofio, M.D.

Dye dilution curves determined by the method of Hamilton have been obtained from a series of normal subjects and from a group of patients with various types of cardiovascular disorders. Cardiac indices calculated from these curves revealed expected values. Central volume, believed to be an index of pulmonary blood volume, was calculated from the slopes of the down strokes of the curves. Central volume indices in normal subjects averaged 0.590 liters. Central volume in patients with heart disease was frequently normal or less than normal. Only cor pulmonale patients with high output had central volumes significantly greater than normal.

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OWLEDGE of the volume of blood in the lungs and the manner in which this volume is altered in various clinical and environmental conditions might be expected to aid in understanding the mechanisms of cardiac dyspnea, pulmonary edema and the redistribution of the blood volume which is believed to occur in congestive heart failure.

A new approach to the indirect determination of the pulmonary blood volume was suggested by Newman and his associates. In 1951, these investigators published a theoretical analysis of dye-dilution curves obtained by the Hamilton single injection technique. They showed that from the slope of the downstroke of the semilogarithmically plotted arterial dye concentration curve one could calculate the volume of the largest mixing chamber traversed by the dye as it traveled from the point of injection to the sampling point in a peripheral artery. Newman called the volume calculated from the slope, the “central volume,” and postulated that it was identical with or closely related to the pulmonary blood volume. Subsequently, Pearce, Newman, and their associates published supporting evidence for this contention derived from experiments on dogs.

Previous indirect methods for measuring pulmonary blood volume have employed the formula of Stewart which was subsequently modified by Hamilton. With this method, also based on the dye dilution technique, the intrathoracic blood volume is calculated by multiplying the cardiac output by the mean circulation time. Pulmonary blood volume is then obtained by subtracting assumed or calculated values for the volume of blood in the heart and great vessels from the intrathoracic blood volume.

Central volume, on the other hand, is an index of pulmonary blood volume, which is probably independent of the volume of blood in the heart and great vessels, provided that the volume of blood in the right or left chambers of the heart does not equal or exceed the pulmonary blood volume.

It seemed to us desirable to determine the central volume in normal subjects and in a series of patients with various cardiovascular abnormalities in order to ascertain the range of normal values and to note to what extent the abnormal subjects vary from the normal.

Resting, single-injection dye-dilution curves were, therefore, obtained from a group of normal subjects and patients with cardiovascular disease.
normal subjects and from a series of patients with a variety of cardiovascular abnormalities. Cardiac output was calculated from the areas of the curves. Central volume was calculated from the down-slopes of the curves and blood volume was determined from venous blood samples drawn 10 minutes after the dye injection. These values are reported together with certain relationships between them which may be of interest.

**Methods and Materials**

Normal subjects were healthy, young laboratory and professional personnel. There were only two females in this group. Patients were selected from the wards of the United States Veterans Administration Hospital, Los Angeles, California. All were classified as to functional capacity according to Nomenclature and Criteria for the Classification of Heart Disease of the New York Heart Association.

All subjects were studied in the supine position in the postabsorptive state in the morning after at least 30 minutes rest in the bed on which the test was done. Evans blue dye (T-1824) was injected into an antecubital vein as rapidly as possible through an 18-gauge needle. The time required for the injection was less than one second. The amount of dye injected ranged between six and nine mg. accurately determined by weighing the syringe before and after injection. Arterial samples were obtained through a 17-gauge needle inserted into a procainized brachial artery on the opposite side from the injection. The arterial blood was led through a 20 to 25 cm. length of plastic tubing (3 mm. internal diameter) to a rotating collecting device similar to the one illustrated in Newman's paper. The device was rotated at such speeds that samples were collected over a span of 1.5 to two seconds. Samples ranged in size between one and three ml.

The blood samples were allowed to clot and the tubes were centrifuged. The serum was then transferred to micro cells and the optical density read at a wave length of 620 Å in a Beckman Model B spectrophotometer. The patients' undyed serum was used as the blank. Standard curves were made up in serum, but a fresh standard curve was not made for each patient since curves made up in numerous patients' sera at the beginning of the study showed no deviation from the original standard curve.

The dye concentration curve was then plotted against time on semilogarithmic paper. The straight line down-stroke established prior to the appearance of recirculating dye was extrapolated through at least one cycle of the graph paper. Cardiac output was calculated from the area under the curve as described by Hamilton, and central volume from the cardiac output and the slope of the down-stroke as described by Newman.

Ten minutes after the dye injection a sample of venous blood was drawn for the determination of the blood volume.

**Results**

The data are presented in table 1 and in graphic form in fig. 1. Cardiac output, central volume, and blood volume are expressed both as absolute values and as their respective indices, i.e., by dividing the actual values by the surface area of the subject in square meters.

The ratio \( \frac{\text{cardiac output}}{\text{blood volume}} \times 100 \), gives that per cent of the total blood volume which is pumped by the heart in one minute. Lewis and coworkers have recently shown that the normal resting individual has a cardiac output per minute about equal to his total blood volume.

Thus if \( \frac{CO}{BV} \times 100 \) were equal to 100 per cent this is what one would expect of a normal resting individual. If this value were significantly greater than 100 then one would suspect that the cardiac output had been increased over normal perhaps by anxiety or some abnormality of the circulation. Values significantly less than 100 would suggest low cardiac output such as might be seen in cardiac failure or some abnormal depression of the circulation.

The ratio \( \frac{\text{central volume}}{\text{blood volume}} \times 100 \) gives the per cent of the total blood volume which comprises the central volume.

Blood volume per kilogram of body weight is given because numerous other authors have used this method of reference.

**In Normal Subjects.** In normal subjects cardiac index averaged 3.48 liters per minute. Central volume averaged 1.133 liters with an index of 0.590 liters. It should be noted that the lowest values for central volume index, 0.374 liters and 0.291 liters were found in the only two females in the group. The central volume averaged 20.2 per cent of the total blood volume with a range of 13.5 per cent to 32.8 per cent.

**In Patients With Mitral Stenosis.** In this group all subjects had what appeared to be pure mitral stenosis without clinical evidence.
### TABLE 1.—Cardiac Output, Central Volume, Blood Volume and their Respective Indices Along with Some Interrelationships of Interest in 9 Normal Subjects and 45 Patients with Cardiac Disease.

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<td>4.17</td>
<td>2.20</td>
<td>43.6</td>
<td>1.500</td>
<td>.773</td>
<td>15.3</td>
<td>9.80</td>
<td>5.05</td>
<td>116.0</td>
<td>IV: Aneurysm pulmon. art., asymptomatic</td>
</tr>
<tr>
<td>G. W.</td>
<td>63</td>
<td>2.54</td>
<td>1.31</td>
<td>46.2</td>
<td>.630</td>
<td>.325</td>
<td>11.4</td>
<td>5.50</td>
<td>2.84</td>
<td>69.2</td>
<td>III: Complete heart block, pulse 27.</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>4.36</td>
<td>2.36</td>
<td>67.7</td>
<td>.952</td>
<td>.508</td>
<td>14.0</td>
<td>6.74</td>
<td>3.61</td>
<td>90.1</td>
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</tr>
<tr>
<td>A. McC.</td>
<td>65</td>
<td>6.28</td>
<td>3.41</td>
<td>117.4</td>
<td>1.18</td>
<td>.641</td>
<td>22.1</td>
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<td>2.91</td>
<td>72.7</td>
<td>III: Arteriosclerotic Heart Disease</td>
</tr>
<tr>
<td>W. D.</td>
<td>56</td>
<td>3.47</td>
<td>1.99</td>
<td>91.3</td>
<td>1.18</td>
<td>.678</td>
<td>31.1</td>
<td>3.80</td>
<td>2.18</td>
<td>57.1</td>
<td>III: Mitral insuf.</td>
</tr>
<tr>
<td>M. T.</td>
<td>57</td>
<td>3.60</td>
<td>1.81</td>
<td>40.0</td>
<td>1.68</td>
<td>.850</td>
<td>18.7</td>
<td>9.00</td>
<td>4.55</td>
<td>115.0</td>
<td>IV: Complete heart block, pulse 42.</td>
</tr>
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<td>Mean</td>
<td></td>
<td>4.45</td>
<td>2.40</td>
<td>82.9</td>
<td>1.35</td>
<td>.723</td>
<td>24.0</td>
<td>6.05</td>
<td>3.21</td>
<td>81.6</td>
<td></td>
</tr>
<tr>
<td>F. M.</td>
<td>68</td>
<td>6.35</td>
<td>2.95</td>
<td>152.0</td>
<td>.830</td>
<td>.386</td>
<td>19.8</td>
<td>4.17</td>
<td>1.94</td>
<td>43.5</td>
<td>III: Luetic Aortic Insufficiency</td>
</tr>
<tr>
<td>R. B.</td>
<td>58</td>
<td>3.70</td>
<td>2.15</td>
<td>88.3</td>
<td>.683</td>
<td>.397</td>
<td>16.3</td>
<td>4.19</td>
<td>2.44</td>
<td>68.2</td>
<td>III: Complete heart block, pulse 42.</td>
</tr>
<tr>
<td>Mean</td>
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<td>5.02</td>
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<td>.391</td>
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<td>2.19</td>
<td>55.8</td>
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<tr>
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<td>2.11</td>
<td>75.3</td>
<td>.713</td>
<td>.405</td>
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<td>4.94</td>
<td>2.81</td>
<td>87</td>
<td>IV: Complete heart block, pulse 27.</td>
</tr>
<tr>
<td>T. W.</td>
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<td>3.88</td>
<td>1.92</td>
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<td>1.850</td>
<td>.915</td>
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<tr>
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<td>1.660</td>
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<td>23.8</td>
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</tr>
<tr>
<td>H. W.</td>
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<td>5.70</td>
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<td>1.360</td>
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<td>8.20</td>
<td>3.96</td>
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<td>A. P.</td>
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<td>2.63</td>
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<td>.476</td>
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<td>54.9</td>
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<td>58</td>
<td>5.15</td>
<td>2.49</td>
<td>69.6</td>
<td>1.415</td>
<td>.684</td>
<td>19.1</td>
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<td>3.57</td>
<td>78.3</td>
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<td>57</td>
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<td>2.46</td>
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<tr>
<td>T. G.</td>
<td>47</td>
<td>3.36</td>
<td>1.93</td>
<td>81.0</td>
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<td>.268</td>
<td>11.2</td>
<td>4.15</td>
<td>2.38</td>
<td>52.8</td>
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</tr>
</tbody>
</table>

| CO         | = Cardiac output, liters per minute. |
| CI         | = Cardiac index, liters per minute per square meters, body surface area. |
| CV         | = Central volume, liters.           |
| CVI        | = Central volume index, liters per square meters, body surface area. |
| BV         | = Blood volume, liters.             |
| BVI        | = Blood volume index, liters per square meters, body surface area. |
| BV\_Kg     | = Blood volume in cc. per Kg. body weight. |

CO = Cardiac output, liters per minute.  
CI = Cardiac index, liters per minute per square meters, body surface area.  
CV = Central volume, liters.  
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BV = Blood volume, liters.  
BVI = Blood volume index, liters per square meters, body surface area.  
BV\_Kg = Blood volume in cc. per Kg. body weight.
of significant mitral insufficiency. All but three of them eventually had mitral commissurotomies. Patients M. C. and R. W. were studied only postoperatively three weeks after mitral commissurotomy. At the time of study, rumbling presystolic apical murmurs could still be heard in both of them. Patients R. B. and T. R. were not subjected to operation because of age, and N. D. refused surgery.

Cardiac outputs and indices in this group were generally lower than in the normal subjects, as might be expected. However, some patients did have cardiac indices within normal limits. Central volumes and indices tended to be considerably smaller than normal particularly in patients in class II. The larger central volumes seemed to be in patients in class III. However, F. M. is an exception and did not appear to be different clinically from L. W. who had a small central volume. In the two postoperative patients there were widely divergent central volume indices, 0.257 liters in M. C. and 0.612 liters in R. W. Patient M. C. had had long standing congestive failure prior to surgery and had been greatly relieved by the operation. R. W. had had comparatively mild symptoms and had been able to carry on his work as a school teacher.

In Patients With Aortic Stenosis. In this group cardiac indices were generally low except for W. G. who had a high cardiac output, and G. M. whose output was normal. Central volumes were strikingly small except for A. L. who was in congestive heart failure, and therefore in class III. The other class III patient, A. O., was disabled by angina pectoris but not by congestive failure. In this small series the central volume averaged only 13.9 per cent of the total blood volume.

In Patients With Cor Pulmonale. There were two patients with high cardiac indices in this group and both of these had large central volumes. Two patients had normal cardiac indices and both of these had central volumes in the normal range. One patient had low cardiac index, and his central volume was low. This is the only group in which central volume appeared to be directly related to cardiac output.
In Patients With Pulmonary Fibrosis. The only patient in this group, a 22 year old man, developed cyanosis and clubbing of the fingers following an attack of "virus pneumonia" two years prior to his study. Chest x-ray films showed a diffuse reticular pattern, and lung biopsy revealed marked interstitial fibrosis. Pulmonary ventilation was only mildly reduced. The cardiac index was high and the central volume was 0.277 liters, the smallest central volume found in the entire series of patients.

In Thyrocardiac Patients. Four of these five patients had the circulatory pattern expected in congestive failure due to thyrotoxicosis. The features were high cardiac index and large blood volume. The central volumes were remarkably uniform in this group, falling in the normal range. Because of the expanded blood volumes in this series, central volume comprised a smaller than normal percentage of the total blood volume. Although patient A. J. was mildly thyrotoxic by the usual clinical tests, he did not have the circulatory manifestations of this disease.

In Patients With Congestive Heart Failure. All of the patients in this group had congestive heart failure and were, therefore, in class III or class IV. All of them had clinical edema and all required digitalis, low salt diets, and regular administration of mercurial diuretic drugs. The group is divided into four subgroups; patients with hypertensive heart disease, arteriosclerotic heart disease, syphilitic aortic insufficiency, and a miscellaneous group comprised of: W. H., a man of 65 with coarctation of the aorta, T. W., a 45 year old man with idiopathic myocarditis, and M. L., a man 51 years old, with very marked mitral insufficiency due to ruptured chordae tendineae.

In Congestive Heart Failure Due to Hypertensive Heart Disease. Patients in this group had cardiac indices ranging from normal to very low. Central volumes were in the range of normal in three of the subjects and small in two of them. Central volume did not appear to be related to the cardiac output or to the blood volume.

In Congestive Heart Failure Due to Arteriosclerotic Heart Disease. These three patients all had large central volumes despite low cardiac indices in two and normal cardiac index in one. Blood volumes varied from small to large.

In Congestive Heart Failure Due to Syphilitic Aortic Insufficiency. These two patients had almost identical central volumes despite rather wide variations in cardiac index and blood volume.

In Miscellaneous Congestive Heart Failure. All three of these had very low cardiac indices. The patient with the coarctation had a small central volume while the one with myocarditis and the other with mitral insufficiency had large central volumes.

In Patients With Various Forms of Heart Disease But Without Heart Failure. In this group it is interesting to note that four of the patients had central volume indices ranging from 0.648 liters to 0.688 liters, values which are in the range of most of our normal males. These patients all felt well and had no limitation of their activities. One of these, H. Sp., had constricitive pericarditis which had produced enlargement of the liver and mild ankle edema but had not interfered greatly with his vigorous life. None of these four patients had dyspnea.

A comparison of the patient with constrictive pericarditis and the patient with pericardial effusion (A. P.) reveals that they had similar cardiac indices and similar blood volumes. Both had markedly elevated venous pressures. Yet, the central volumes showed marked differences, the pericardial effusion patient having a central volume index of 0.476 liters as opposed to the constricitive pericarditis patient with a central volume index of 0.657 liters. Both patients with complete heart block had small central volumes. The patient with malignant hypertension died of a cerebral hemorrhage a few days after our test.

Discussion

Early efforts to measure the pulmonary blood volume directly were summarized by Drinker, Churchill and Ferry in 1926. They cite the work of Spehl and his associates dating back to 1881. These investigators abruptly ligated the vessels leading into and out of the
heart in rabbits during various phases of respiration both at sea level and at 3,000 meters altitude. They found that the rabbit lungs contained 8 to 9 per cent of the total blood volume at the end of inspiration, 5 to 6 per cent of the total blood volume at the end of expiration. At high altitude the lungs contained slightly more blood. Similar experiments were performed on dogs by Plumier who found pulmonary blood volume to be about 10 per cent of the total blood volume.

Kuno employed the dog heart-lung preparation ligating both lung hilae simultaneously. He found values of pulmonary blood volume ranging from 9 per cent to 20 per cent of the total blood volume. In this series the pulmonary blood volume increased as the cardiac output increased. In two dogs in which pulmonary edema was induced the amount of blood in the lungs was 26.2 per cent and 23.4 per cent of the total blood volume.

Indirect methods for measurement of pulmonary blood volume were introduced by Stewart in 1921 when he published his formula for calculating pulmonary blood volume by multiplying cardiac output by the mean circulation time through the lungs. He believed that one could obtain the mean pulmonary circulation time by making minor corrections in the observed circulation time. He believed that at least in small animals the major part of the circulation time was spent in traversing the lungs. Employing his method in dogs he obtained pulmonary blood volumes of about 20 per cent of the total blood volume.

Stewart's method was subsequently modified by Hamilton and his associates who first employed a single rapid injection of dye and calculated cardiac output from the extrapolated curves of the dye concentration during its first circulation. Hamilton pointed out that in the human the volume calculated from the cardiac output multiplied by the mean circulation time really includes the blood in the heart, lungs, and great vessels leading to and from the heart.

A number of investigators in recent years have employed the Stewart-Hamilton formula to obtain the intrathoracic blood volume. Among these have been Ebert, Borden, Wells and Wilson, Lagerlöf, Werko, Bucht and Holmgren; Kopelman and Lee; and Doyle, Wilson, Lepine and Warren; all of whom injected the dye through a catheter into the right heart or pulmonary artery.

The data from the Ebert group are almost identical with ours for the normal subjects. However, they found slightly higher than normal values for intrathoracic blood volume in mitral stenosis and considerably higher values in left ventricular failure. Kopelman and Lee found higher values for intrathoracic blood volume when dye was injected through an antecubital vein than they did when injection was made through a catheter. Their average normal values were considerably higher than ours. In mitral stenosis they found that intrathoracic blood volume was not significantly increased and there was very little difference between the values in compensated and decompensated individuals. In left ventricular failure intrathoracic blood volume was considerably increased over normal and with compensation it decreased.

Lagerlöf and his coworkers estimated the volume of blood in the heart from the size of the x-ray film silhouette and, using an estimated volume of blood in the aorta and large arteries, subtracted these from the intrathoracic blood volume to obtain the pulmonary blood volume. With this method the mean pulmonary blood volume index in seven normal subjects was 597 cc. Patients with hypertension, mitral stenosis and pulmonary disease had pulmonary blood volumes which were not significantly different from normal nor was there any significant difference between compensated and uncompensated cardiac patients.

In the study of Doyle and associates mean intrathoracic blood volume index was 634 cc. in normal subjects and 892 cc. in patients with congestive heart failure. These investigators found a significant difference between patients with mitral stenosis whose intrathoracic blood volumes averaged 28 per cent of the total blood volume and patients with tricuspid insufficiency whose intrathoracic blood volumes averaged 19 per cent of the total blood volume.

Nylin and Celander used radioactive phosphorus labeled red blood cells to obtain dilution
intrathoracic blood volumes in congestive heart failure, Lagerlöf and his co-workers found no significant increase in pulmonary blood volume in patients with heart failure. Most of our patients with congestive failure had central volumes within the normal range. However, those with arteriosclerotic heart disease tended to have higher volumes than those with hypertensive or with valvular disease.

Patients with high cardiac output or pulmonary had the highest central volumes in this series, while the patient with pulmonary fibrosis and no cardiac failure had the smallest central volume in the series.

The thyrocardiace, despite the high cardiac outputs, had central volumes within the range of normal. No consistent pattern could be discovered among those patients in the miscellaneous group who were studied.

That the size of the central volume is not related to the cardiac output is illustrated in the scatter graph (fig. 2) which plots central volume index against cardiac index.

Thus the pulmonary blood volume as estimated from the slope of the dye-dilution wash-out curves seems to vary considerably among normal subjects and patients with a variety of cardiovascular diseases with no sharp distinctions between clinical categories. It may be the size of this volume is governed by factors as yet undiscovered.

**Summary**

1. Single injection dye-dilution curves have been obtained on a series of nine normal subjects and 45 patients with a variety of cardiovascular abnormalities.

2. Cardiac indices were determined from the areas of the curves and central volume indices from the slopes of the semilogarithmically plotted downstrokes of the curves. Central volume is believed to be identical with or closely related to pulmonary blood volume.

3. Cardiac indices in this series revealed expected values.

4. Central volume indices in normal subjects averaged 0.590 liters.

5. Central volume indices in patients with valvular heart disease and hypertensive con-
gestive heart failure may be smaller than normal.

6. Central volume indices in numerous pa-
tients with cardiovascular abnormalities were
within the range of normal values.

7. The largest central volume indices were
found in patients with high cardiac output cor
pulmonale while the smallest central volume
index was in a patient with pulmonary fibrosis.

**Summario in Interlingua**

1. Curvas del dilution de colorantes post
non-repetite injectiones esseva obtenite ab un
serie de nove subjectos normal e de 45 patientes
con un varietate de anormalitates cardio-
vascular.

2. Indices cardiac esseva determinate super
le base del area del curvas. Indices de volu-
mine central esseva determinate super le base
del descenditas del curvas in presentation semi-
logarithmic. Nos ha rationes a credere que le
volumine central es identico, o strictemente
relatatone, con le volumine de sanguine pul-
monar.

3. In le serie hic presentate le indices cardiac
esseva conforme al valores expectate.

4. In individuos normal le valor median del
volumine central esseva 0,590 litros.

5. In patientes con morbos cardiac valvular
e hypertensive insufficientia congestive del
corde le indices del volumine central pote esser
infra le norma.

6. In multe patientes con anormalitates cardio-
vascular le indices del volumine central
esseva infra le limites normal.

7. Le plus alte indices del volumine central
esseva trovate in patientes con corde pulmonar
a alte rendimento cardiac. Le plus basse indice
de volumine central esseva illo de un paciente
con fibrosis pulmonar.

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