and may contribute further to lack of development of the RV as the patient grows. The absence of a hemodynamic explanation for ventricular hypoplasia makes the presence of a developmental factor such as marked inequality of the A-V valve to the ventricles probable and it may be that such a heart cannot be repaired by conventional techniques.

In conclusion, our volumetric studies show that the LV, and to a lesser extent the RV, are enlarged in most cases of uncomplicated CAVC but normal in most cases with right ventricular outflow obstruction or PVO. LV dysfunction is more frequent than RV in both groups. RV hypoplasia is rare in CAVC but does occur in both uncomplicated forms and forms with RV obstruction. Further ventricular volume studies are needed in CAVC to confirm these findings and document the occurrence of LV hypoplasia, which was not found in this study. Although data concerning surgery in CAVC with ventricular hypoplasia are scanty, there is reason to believe that the surgical approach to these patients may need to be modified.

Acknowledgment

We wish to thank Mr. Frank Domanszky and Ms. Audra Strokas for expert technical assistance and Ms. Bernice Senger and Anna Mae McNerney for assistance in preparation of the manuscript.

Total Effective Compliance, Cardiac Output and Fluid Volumes in Essential Hypertension

GERARD M. LONDON, M.D., MICHEL E. SAFAR, M.D., ALAIN CH. SIMON, M.D., JEAN M. ALEXANDRE, M.D., JAIME A. LEVENSON, AND YVES A. WEISS, M.D.

SUMMARY Total effective compliance, hemodynamic parameters, extracellular fluid volume, cardiopulmonary (CPBV) and total blood (TBV) volumes were determined in 32 men, including 14 normotensive controls and 18 sustained essential hypertensive patients. The effective compliance was calculated from the changes in central venous pressure recorded simultaneously with the changes in blood volume obtained after a rapid Dextran infusion. In normotensive controls, compliance was 2.08 ± 0.09 ml/mm Hg/kg and was positively correlated with plasma (r = 0.79) and extracellular fluid (r = 0.84) volumes. In hypertensives, compliance was significantly reduced (1.49 ± 0.06 ml/mm Hg/kg; P < 0.001) and was correlated negatively with the CPBV/TBV ratio (r = -0.75) and positively with the plasma volume/interstitial fluid volume ratio (r = 0.84). These results suggest that in normotensives, there is a regulatory mechanism between volume and compliance and that this contributes to maintaining filling pressure and cardiac output within normal ranges. In hypertensives, the reduced compliance could participate in the maintenance of normal values of cardiac output and extracellular fluid volume by influencing the partition of intravascular and extracellular fluid volumes.

REFERENCES


From the Hemodynamic Laboratory (Prof. Ag. Safar) of the Hypertension Research Center, Hopital Broussais, Paris, France.

Address for reprints: Prof. Ag. M. Safar, Hopital Broussais, 96 rue Didot, 75014 Paris, France.

Received July 25, 1977; revision accepted December 19, 1977.
expected, while cardiac output is nearly normal.\textsuperscript{12} A decreased compliance of the total venous bed could partly explain this fact.\textsuperscript{13, 14} A direct evaluation of total vascular compliance cannot be performed in man since the measurement requires sudden arrest of the heart and rapid redistribution of blood between the arteries and veins.\textsuperscript{15} However, when the heart is beating, a positive relationship between total blood volume and central venous pressure can be established, enabling the slope of the pressure-volume relationship to be calculated.\textsuperscript{16-18} In such a determination, the elastic properties of the vascular bed cannot entirely explain the pressure changes in the central veins. Secondary effects of blood volume changes on arterial hemodynamics and venous tone also contribute to variations in central venous pressure. In this case, the term "effective compliance" is used to describe the slope of the pressure-volume relationship.\textsuperscript{16-18}

The purpose of the present study is to determine the total effective compliance in sustained essential hypertensive patients and to evaluate the role of capacitance changes in the control of cardiac output and extracellular fluid volume in these subjects.

**Material and Methods**

**Patients**

The study was performed in 32 men: 14 normotensive controls and 18 sustained essential hypertensives. All patients were untreated or had discontinued their therapy at least four weeks before the study. They were hospitalized for six days and placed on a diet containing 110 mEq sodium per day.

In hypertensives, diastolic pressure was constantly equal to or above 90 mm Hg on the third day of hospitalization.

Extensive investigations included blood and urinary electrolytes, catecholamine determinations, endogenous creatinine clearance and timed intravenous urography. The 18 hypertensives were listed as essential hypertensives. Clinical characteristics are indicated in table 1. Mild to moderate left ventricular hypertrophy was observed in eight patients. None had cardiac or neurologic involvement. Mean creatinine clearance was 101 ± 6 ml/min/m\(^2\) (± 1 SEM).

The protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale). Consent for investigations was obtained from the patients after a detailed description of the procedure, which included determinations of fluid volumes, hemodynamic parameters and total effective compliance.

**Extracellular Fluid Volumes**

Patients were investigated on the third day of hospitalization, after overnight fasting. An antecubital vein of each arm was catheterized. Extracellular fluid volume was determined in the supine position, using the distribution volume of inulin. The inulin space was estimated by the single injection technique, according to Ladegaard-Pedersen.\textsuperscript{19} This method was derived from the theory of Meier and Zierler\textsuperscript{20} for flow and volume estimations using tracer injection techniques. Forty-five milliliters of a 10% inulin solution (4500 mg of inulin) were injected intravenously over 4½ minutes. Blood samples were taken prior to administration and repeated 5, 7, 10, 15, 30, 45, 60, 75, 90, 105, 120, 150 and 180 minutes after the start of the injection. Inulin was measured with photometric method by using the method of Roe.\textsuperscript{21} The plasma inulin concentration was plotted against time on a semi-logarithmic scale. A curvilinear curve was obtained and divided into two exponential functions according to the "peeling off" technique. Since the two-exponential model was demonstrated to be more valid than the mono-exponential one for calculation of the inulin space, the two exponential functions were used. The inulin distribution volume equals the product of the total clearance and the mean transit time calculated from classical equations.\textsuperscript{22} Inulin space and clearance were corrected for the plasma water content by a factor:

\[
p = (100 - 0.73 \text{ pp})/100
\]

where 0.73 is the volume of liquid displaced by 1 g of protein in 100 ml of plasma and pp is the plasma protein concentration in g/100 ml.\textsuperscript{22} The normal value of the inulin space was found to be 158 ± 5 ml/kg. It is known that inulin underestimates extracellular fluid volume,\textsuperscript{18} but this is also true for sucrose and radio-sulfate estimations. Conversely, it is well established that techniques using thiocyanate and bromide ions, which penetrate cells to a significant extent, overestimate the extracellular space.\textsuperscript{19} In six patients, inulin space was compared to the bromide space measured according to the method of Tarazi et al.\textsuperscript{23} Mean values were respectively 163 ± 5 and 210 ± 7 ml/kg. The correlation coefficient was 0.95.

At the same time as the extracellular fluid volume measurement, total blood and plasma volumes were measured by the isotopic dilution method, using radioiodinated albumin, as previously described.\textsuperscript{24} After withdrawal of a control sample, 3 \(\mu\text{Ci}\) were injected. Ten minutes later, a single sample was taken for counting and volume estimations. In 20 of the 32 patients, several consecutive blood samples were taken and activity was plotted against time. The volume was calculated from the extrapolated activity at zero time. The value was lower than that obtained from the single 10 minute sample, but the difference (5 ± 3%) was not significant, so the determination with the single 10 minute sample was used as an estimation of intravascular volume in all patients. Blood and plasma volumes were expressed in ml/kg. To evaluate the ratio between plasma volume (PV) and interstitial fluid volume (IF), plasma volume was cor-

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics</th>
<th>Normotensive controls</th>
<th>Hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33 ± 4(\dagger)</td>
<td>37 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 ± 2</td>
<td>76 ± 1(*)</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>1.75 ± 0.03</td>
<td>1.84 ± 0.02(\ast)</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>138 ± 3</td>
<td>187 ± 3(**)</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>77 ± 2</td>
<td>110 ± 3(**)</td>
</tr>
</tbody>
</table>

\(\dagger\) mean ± SEM.

\(\ast\) p <0.05.

\(\ast\) p <0.01.

\(\ast\) p <0.001.
rected for water content by the same factor used for inulin space.

Central Hemodynamics

On the fourth day of hospitalization, hemodynamic studies were performed after the patients had fasted overnight. Investigations were carried out with the patients in the supine position; the room temperature was between 23° and 25°. No premedication was administered. Under local anesthesia, an antecubital vein and brachial artery were catheterized and catheters advanced into the right atrium and the aortic root immediately distal to the aortic valves, respectively. Central venous pressure was measured with a Statham strain gauge. An imaginary line parallel to the examination table and at one-third the distance between the anterior chest wall and the table was used as baseline for the gauge. A large forearm vein was cannulated for infusion. With the subject in the supine position, cardiac output was measured at least three times, using Water’s Cuvette and densitometer as previously described. Indocyanine green (5 mg) was introduced into the central venous catheter and flushed into the circulation in less than 0.5 sec. With a constant rate pump, blood was withdrawn from the arterial catheter through the densitometer. Blood was reinfused. The system was calibrated before each determination. Curves were measured planimetrically. Cardiac output (CO) was expressed in ml/min/m² after correction for body surface area. Arterial pressure and central venous pressure were recorded with a Siemens apparatus.

Cardiopulmonary blood volume (CPBV) was defined as the volume between the right atrium and the tip of the arterial catheter. It was calculated by the Stewart Hamilton method as follows: CPBV (ml/kg) = CO (ml/sec/kg) × MTT, where MTT is the mean transit time in seconds from the right atrium to the tip of the arterial catheter. The correction for the sampling system was subtracted from the observed time in calculating MTT.

Before the hemodynamic study, total blood volume (TBV) was remeasured, as already described. Because of the preceding determination, 6 μCi of radio-iodinated albumin were used for injection. The partition of the intravascular volume was expressed as the CPBV/TBV ratio.

Effective Vascular Compliance

After the determination of the central hemodynamics, total effective compliance was measured. The procedure was a modification of that described by Echt et al. Effective compliance was determined during blood volume expansion using a Dextran infusion. In order to minimize secondary effects due to capillary filtration and delayed compliance, the study was carried out in the shortest possible time. Five hundred ml of 6% Dextran solution were infused within four minutes using a Sogreath MP 66 pump. Cardiac hemodynamics were performed before and immediately after the Dextran infusion. Central venous pressure was recorded during expansion and plotted against the volume changes. The pressure-volume relationship was practically linear (fig. 1). Elasticity coefficient (E) of the total vascular bed was calculated as the slope of the relationship. Vascular compliance (1/E) was estimated and standardized to body weight. The reproducibility of the method was tested in five patients three days later. The mean variation was 6.3%. In three other patients, the volume expansion was followed by the withdrawal of the same amount of blood. As in the Echt et al. report, the slope of the pressure-volume relationship was practically identical during expansion and hemorrhage.

In addition to the 32 studied patients, blood volume and venous tone were measured before and after Dextran infusion in seven normotensive and seven hypertensive patients. The increases in blood volume were nearly the same in the two groups (respectively, 537 ± 38 and 491 ± 28 ml). Venous tone was estimated by plethysmography applied to the right leg. Leg volume was measured with a mercury strain gauge and the venous distensibility was determined according to the method of Wood. The cuff pressure was increased by little steps of 1–2 mm Hg until the volume started to increase. The pressure just below that value was considered as the zero level of effective venous pressure. The cuff pressure was then increased consecutively to 5, 10, 15, 20 and 25 mm Hg above the zero level. At each increase, pressure was kept constant until the leg volume reached its maximum value. The plateau was then recorded. In each patient, the volume-pressure relationship was calculated and the slope of the curve — the venous elasticity coefficient — was used as an index of venous tone. As previously described, venous tone was higher in hypertensives than in normotensives (16.7 ± 1.2 vs 12.0 ± 0.7 mm Hg/ml/100 g tissue; P < 0.01). No significant changes (–1.2 ± 6.2% and 1.7 ± 4.1% for hypertensives and normotensives, respectively) were observed after Dextran infusion.

Statistical analysis by classical methods (differences of means, correlations, stepwise regressions) was performed on a HP 9805 A calculator. Only r values superior or equal to 0.75 were considered significant.

Results

Basal Hemodynamic Parameters (table 2)

In comparison with the normotensive controls, hypertensives had (1) similar values for cardiac index, extracellular fluid volume, cardiopulmonary blood volume and CPBV/TBV ratio, and (2) a significant decrease in total

![Figure 1. An example of the relationship between blood volume changes and central venous pressure. Total effective compliance is the inverse of the slope of the curve.](image-url)
blood and plasma volumes (P < 0.001) and in the PV/IF ratio (P < 0.05).

**Determinaton of Total Effective Compliance**

Table 3 indicates that normotensives and hypertensives received the same percent amount of Dextran and had similar changes in cardiac index and heart rate.

Total effective compliance was significantly reduced (P < 0.001) in hypertensives (1.49 ± 0.06 vs 2.08 ± 0.09 ml/mm Hg/kg in controls).

**Correlation Study (table 4)**

**Normotensive Controls**

Figure 2 shows a strong positive correlation (r = 0.79) between total effective compliance and plasma volume. Similar relationships were observed between compliance and the extracellular fluid volume (r = 0.84) (fig. 2), the interstitial fluid volume (r = 0.71) and the cardiopulmonary blood volume (r = 0.65). No significant correlations were observed with the CPBV/TBV and PV/IF ratios.

**Hypertensive Patients**

No significant correlation was observed between compliance and fluid volumes. Compliance was correlated negatively with cardiac index (r = -0.65), the CPBV/TBV ratio (r = -0.76) (fig. 3), and positively with the PV/IF ratio (r = 0.84) (fig. 3). The latter correlation existed even for a constant diastolic pressure (partial correlation). A weak negative relationship was observed between the PV/IF ratio and the diastolic pressure (r = 0.59). The relationship became weaker for a constant compliance (r = 0.32).

**Discussion**

In comparison with normotensive controls, hypertensives had similar values for cardiac output and extracellular fluid volume but a significant decrease in total effective compliance. These results suggest that the control of cardiac output and fluid volumes was different in these two groups of patients.

**Total Effective Compliance in Normotensive Controls**

The value of effective compliance in normotensive controls was 2.08 ± 0.09 ml/mm Hg/kg, in agreement with previous reports. An underestimation of the value could result from a slight capillary inward filtration due to the colloid osmotic pressure of the dextran, causing an underestimation of the blood volume changes. As shown by the blood volume determinations before and after expansion (see methods), this possibility does not seem to influence the result.

Since the arterial system is an insignificant fraction of the total compliance, the value of effective compliance is mainly determined by the properties of the low-pressure system which holds 80-85% of the total blood volume. The pressures in this system, and especially the filling pressure of the heart, depend largely on the blood volume and the dissensibility of the capacitance vessels. In normal conditions, concomitant variations in volume and compliance enable the filling pressure of the heart to be kept constant. In the present study, the strong positive relationship between compliance and plasma or total blood volume is consistent with such a control mechanism.

As demonstrated by animal experiments and by immersion in man, the filling pressure of the heart is monitored through cardiac mechano-receptors controlling renal function, extracellular fluid volume and thirst via the autonomic nervous system. Thus, reduction in compliance could cause an elevation of the filling pressure with activation of the mechano-receptors and neuro-humoral mechanisms of volume control. The result of the activation of the system would be water and sodium diuresis with a reduction of all the components of the extracellular fluid compartment.

In the present study, the strong positive relationships between compliance and cardiopulmonary, interstitial and extracellular fluid volumes, could reflect this possibility. In normally hydrated subjects, such a mechanism would act without any change in the partition of fluid volumes.

**Total Effective Compliance in Hypertensives**

In permanent hypertensives, total effective compliance is significantly reduced. In these patients, an overestimation of the value could result from two possibilities: (1) an increased

---

**Table 2. Basal Hemodynamic Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normotensive controls</th>
<th>Hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (ml/min/m²)</td>
<td>3668 ± 130</td>
<td>3413 ± 105</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>4.3 ± 0.6</td>
<td>5.3 ± 0.6</td>
</tr>
<tr>
<td>EFV (ml/kg)</td>
<td>14.8 ± 3</td>
<td>15.0 ± 6</td>
</tr>
<tr>
<td>TBV (ml)</td>
<td>245 ± 37</td>
<td>3197 ± 24</td>
</tr>
<tr>
<td>TTV (ml/kg)</td>
<td>81 ± 2</td>
<td>68 ± 1**</td>
</tr>
<tr>
<td>PV (ml/kg)</td>
<td>41 ± 1</td>
<td>35 ± 1**</td>
</tr>
<tr>
<td>CPBV (ml/kg)</td>
<td>17 ± 1</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>PV/IF ratio (%)</td>
<td>37 ± 1</td>
<td>31 ± 2*</td>
</tr>
<tr>
<td>CPBV/TBV ratio (%)</td>
<td>23 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>EVC (ml/mm Hg/kg)</td>
<td>2.08 ± 0.09</td>
<td>1.49 ± 0.06**</td>
</tr>
</tbody>
</table>

***P < 0.05; **P < 0.001.

Abbreviations: CI = cardiac index; CVP = central venous pressure; EFV = extracellular fluid volume; TBV = total blood volume; PV = plasma volume; CPBV = cardiopulmonary blood volume; IF = interstitial fluid volume; EVC = effective vascular compliance.

**Table 3. Hemodynamic Effects of Dextran Infusion**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normotensive controls</th>
<th>Hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume</td>
<td>9.39 ± 0.43</td>
<td>9.77 ± 0.23</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>22.4 ± 2.9</td>
<td>24.1 ± 1.7</td>
</tr>
<tr>
<td>Heart rate</td>
<td>2.7 ± 2.3</td>
<td>4.9 ± 2.1</td>
</tr>
</tbody>
</table>

---

**Table 4. Relationship of Total Effective Compliance with the Basal Hemodynamic Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>r value in normotensive controls</th>
<th>r value in hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.15</td>
<td>-0.29</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.17</td>
<td>-0.11</td>
</tr>
<tr>
<td>EFV</td>
<td>+0.85</td>
<td>-0.48</td>
</tr>
<tr>
<td>TBV</td>
<td>+0.64</td>
<td>+0.41</td>
</tr>
<tr>
<td>PV</td>
<td>+0.79</td>
<td>+0.40</td>
</tr>
<tr>
<td>IF</td>
<td>+0.71</td>
<td>-0.53</td>
</tr>
<tr>
<td>CPBV</td>
<td>+0.65</td>
<td>-0.52</td>
</tr>
<tr>
<td>PV/IF</td>
<td>-0.21</td>
<td>+0.84</td>
</tr>
<tr>
<td>CPBV/TBV</td>
<td>+0.30</td>
<td>-0.76</td>
</tr>
<tr>
<td>CI</td>
<td>+0.34</td>
<td>-0.65</td>
</tr>
</tbody>
</table>
transcapillary escape of dextran causing an overestimation of the blood volume changes, and (2) differences in reflex adjustments in comparison with controls. The determinations of blood volume before and after expansion do not fit with the first possibility. In agreement with Echt et al., the insignificant changes in heart rate and venous tone do not suggest that reflex adjustments could influence the validity of the determination to a significant extent.

In such conditions, the changes in right atrial pressure following fluid loading in hypertensives could be caused by two different factors: (1) the compliance of the peripheral vasculature (especially the veins), and (2) the ability of the heart to respond to the increased volume. In the present study, an altered pumping ability of the heart did not seem to be involved:2 congestive heart failure was not observed; central venous pressure was within normal ranges; the increase in cardiac output after dextran infusion was in the same magnitude in hypertensives and in controls. Furthermore, if the reduced compliance was mainly due to a decreased compliance and contractility of the left ventricle, a positive correlation or a lack of correlation would be expected between cardiac output and effective compliance. Since the two parameters were negatively correlated (table 4), the result minimizes the contribution of the heart in the observed decreased compliance. The possibility remains that the reduced vascular compliance in hypertensives was due to a disturbance in the pressure-volume relationship of the venous bed. This observation points to the existence of a reduced systemic venous distensibility in hypertensives, as previously observed in experimental hypertension and in spontaneous hypertension in rats.

Some results of the present study emphasize the consequences of the reduced compliance on the overall circulation of hypertensives. In contrast with normotensive controls, compliance was not correlated with fluid volumes but only with the indexes of partition, such as the CPBV/TBV and the PV/IF ratios. It is well established that decreased systemic venous compliance produces a redistribution of blood volume, resulting in a shift of blood to the central circulation, with a consequent increase in filling pressure and cardiac output. In the present study, the strong negative relationship between the total effective compliance and the CPBV/TBV ratio is in favor of this mechanism. Another consequence of the reduced total compliance could be the decreased PV/IF ratio. As previously reported, the altered partition within the extracellular fluid compartments in hypertensives is due to a displacement of plasma from the intravascular to the extravascular space. This shift has been assumed to reflect an elevated capillary filtering pressure resulting from abnormalities in the precapillary sphincters or in venular distensibility. The weak inverse relationship between diastolic pressure and the PV/IF ratio does not
fit with the former possibility. In contrast, the strong positive correlation between compliance and the PV/1F ratio suggests the role of a reduction in venous distensibility and compliance in the disturbed partition of extracellular fluid volume.

Several hypotheses, including functional or structural alterations of veins, 5, 24 26 and changed compliance of the interstitial space, 37 have been proposed to explain the decreased venous distensibility and compliance in hypertensives. This problem has not been investigated in the present report and requires further study.

Acknowledgment

We thank Mrs. Chantal Pillet and Miss Anne Mangin for their invaluable assistance.

References

Total effective compliance, cardiac output and fluid volumes in essential hypertension.

Circulation. 1978;57:995-1000
doi: 10.1161/01.CIR.57.5.995
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/57/5/995

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/