Rapid Dextran Infusion in Essential Hypertension

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SUMMARY Hemodynamic parameters were studied before and after rapid dextran infusion in 34 men including 17 patients with sustained essential hypertension and 17 normotensive controls. In both groups of patients, dextran infusion induced a significant increase ($p < 0.001$) in central venous pressure (CVP), cardiac output (CO), and stroke volume. The percent change in stroke volume was significantly higher in hypertensives ($p < 0.001$) than in controls. Three indices of volume expansion were calculated: 1) the ratio between the change in CO and the change in volume, which was significantly higher in hypertensives ($p < 0.025$), 2) the ratio between the change in CO and the change in CVP, which was similar in both groups, and 3) the ratio between the change in volume and the change in CVP, which was significantly reduced in hypertensives ($p < 0.001$). In the overall population, the latter ratio was negatively correlated with the change in CO (or in stroke volume) induced by expansion ($r = -0.75$). The results provided evidence that: 1) the slope of the relationship between CO and blood volume was steeper in hypertensives than in normotensives, and 2) the steeper slope was due to a reduction in the effective compliance of the vascular bed, causing a greater elevation in CO per unit rise in volume. (Hypertension 1: 615-623, 1979)

KEY WORDS • essential hypertension • volume expansion • vascular compliance • cardiac output • dextran

The links between blood volume and cardiac output (CO) in hypertension remain controversial. At the onset of several types of experimental hypertension, both volume expansion and increased CO have been observed. The explanation for this volume-flow correlation is considered to be very simple: increased blood volume causes elevated venous pressure, and consequently increases venous return and CO. This is supported by the observation that increased venous pressure coincides with increased volume and flow in several of the experimental models studied.

However, such a simple relationship between fluid volumes and CO has not been observed in man. Usually, normal or increased values of CO are associated with normal or decreased values of intravascular volume. In a previous study, we showed that, in basal conditions, a strong positive relationship between blood volume and CO is found in human essential hypertensives but not in normotensives. This observation raised several problems. First, the result was obtained from the investigation of a wide range of subjects, by means of a new type of statistical evaluation, the smoothing technique. Such a methodology requires an experimental validation. Second, the cause of the close relationship between volume and flow in hypertensives was not explained. Changed performance of the heart might be involved. Reduced effective compliance of the total vascular bed has recently been shown in essential hypertension and could also modulate the volume-flow relationship.

In the present investigation, volume expansion by rapid dextran infusion has been performed in hypertensive patients in comparison with normotensive controls. With this methodology, the relationship between CO and blood volume has been studied in basal conditions and after volume changes. An
attempt has been made to determine the contribution of cardiac and vascular factors in the characteristics of the volume-flow relationship.

Material and Methods

Patients

The study group consisted of 34 men: 17 normotensive controls and 17 sustained essential hypertensives. All were untreated or had discontinued their therapy at least 4 weeks before the study. They were hospitalized for 6 days and placed on a 110 mEq/day sodium diet.

The subjects were considered to be normotensive controls if the reason for their admission was not a cardiovascular disease, and if after clinical and extensive laboratory investigations, they were strictly normal. Sustained hypertensives had a diastolic pressure constantly equal to or above 90 mm Hg on the third day of hospitalization. Extensive investigations included determination of blood and urinary electrolytes, urinary catecholamine levels, endogenous creatinine clearance, and timed intravenous urography. The 17 hypertensive subjects were listed as having essential hypertension. In all cases, the duration of hypertension was less than 3 years. Fundoscopy showed neither hemorrhages, exudates, nor papilledema. Mean creatinine clearance for the overall population was 130 ± 5 ml/min/1.73 m² (± 1 SEM). All hypertensive patients had a normal chest roentgenogram. Eleven patients had a normal electrocardiogram and six had only a left atrial abnormality, according to the criteria described by Frohlich et al. No patient had clinical renal, cardiac, or neurological involvement. Clinical characteristics did not differ between the two groups (table 1).

The protocol was approved by the Institut National de la Santé et de la Recherche Médicale (INSERM). Consent was obtained from the patients after a detailed description of the procedure.

Central Hemodynamics

On the third 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°C. No premedication was administered. Under local anesthesia, an antecubital vein and brachial artery were catheterized. Catheters were advanced into the right atrium and the aortic root immediately distal to the aortic valves. Mean right atrial pressure was used as an index of central venous pressure and 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 base line for the gauge. A large forearm vein was cannulated for infusion. With the subject in the supine position, CO was measured at least three times, using Waters’ 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 seconds. With a constant rate pump, blood was withdrawn from the arterial catheter through the densitometer. Blood was reinjected. The system was calibrated before each determination. Curves were measured planimetrically. Cardiac output was expressed in ml/min/m² after correction was made for body surface area. Arterial pressure and CVP 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.

Prior to the hemodynamic study, total blood volume (TBV) and total plasma volume were measured by the isotopic dilution method, using radiiodinated albumin, as previously described. After withdrawal of a control sample, 3 μCi were injected. After 10 minutes, a single sample was taken for counting and volume estimations. In 20 of the 34 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 volume 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 volume was expressed in ml/kg. Mean hematocrit was 44 ± 1 vol % in normotensive controls and 45 ± 1 vol % in hypertensive subjects.

Peripheral venous compliance 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 and Eckstein. The cuff pressure was increased in 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 con-

| Table 1. Clinical Characteristics of the Two Groups of Patients* |
|-----------------------------|-----------------------------|
|                             | Normotensive Controls       | Hypertensive subjects |
| Number of patients          | 17                          | 17                        |
| Age (yr)                    | 30 ± 3                      | 35 ± 2                    |
| Weight (kg)                 | 71 ± 2                      | 76 ± 2                    |
| Body Surface Area (sq m)    | 1.87 ± 0.03                 | 1.92 ± 0.03               |
| Creatinine clearance (ml/min/1.73 sq m) | 121 ± 6                      | 139 ± 9                   |

* = 1 standard error of the mean.
secutively to 5, 10, 15, 20 and 25 mm Hg above the zero level. At each increase, pressure was kept con-
stant 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 compliance coefficient
— was expressed in ml/mm Hg/100 g tissue.

Blood Volume Expansion

Dextran was used for the blood volume expansion. To minimize secondary effects due to capillary fil-
tration and delayed compliance, the study was carried out in the shortest possible time. Within a 4-minute period, 500 ml of 6% dextran solution were infused using a Sogreath MP 66 pump. Cardiac and peripheral hemodynamics were performed before and immediately after the infusion. In nine normotensive and nine hypertensive patients, blood volume was measured before and after volume expansion, using radioiodinated albumin. At the second determination, 6 μCl of radioiodinated albumin were used for injection. The increases in blood volume were nearly the same in the two groups (528 ± 34 ml and 496 ± 21 ml, respectively). Central venous pressure was by

The linearity of the relationships between blood volume and CO, and CO and CVP, was verified as
an index of cardiac performance.

1. ΔCO/ΔTBV (/min) represents the ratio between the change in CO (ml/min) and the change in
blood volume (ml) during expansion. This ratio corresponds to the slope of the relationship
between CO and blood volume.

2. ΔCO/ΔCVP (ml/min/mm Hg) represents the ratio between the change in CO and the change in
CVP during expansion. As shown in figure 1B, this ratio corresponds to the slope of the relationship between CO and CVP and is used as an index of cardiac performance.

3. ΔTBV/ΔCVP (ml/mm Hg) represents the ratio between the change in blood volume and the change in CVP during expansion. This ratio is used as an index of effective vascular compliance of the system.

Systolic Time Intervals

Prior to the hemodynamic study, systolic time intervals were measured from simultaneous record-
ings of the electrocardiogram, phonocardiogram, and
carotid arterial pulse using a multichannel system, as previously described. Since mean heart rate was the same in hypertensives and normotensive controls, systolic time intervals were not corrected for heart rate (table 2).

Statistical analysis by classical methods (differences of means, paired t test, correlations, stepwise regressions) was performed on a HP 9815 A calculator.

Results

Hemodynamic Effects of Dextran Infusion

Basal hemodynamic parameters are indicated in table 3. In comparison with normotensive controls, hypertensives had similar values for cardiac index, stroke index, heart rate, CVP, right diastolic end ven-
tricular pressure, and a significant increase in total peripheral resistance (p < 0.001). Absolute values of total and cardiopulmonary blood volumes (ml) were the same in the two groups of patients. Weight-normalized blood volume was significantly reduced in hypertensives (67 ± 2 vs 81 ± 2 ml/kg; p < 0.001).

Hemodynamic changes after volume expansion (table 3) included in both groups: 1) no significant change in blood pressure and heart rate; and 2) significant increases in CVP, cardiac index and stroke index (p < 0.001). After expansion, CVP was significantly higher in hypertensives than in normotensives (p < 0.05). The change in cardiopulmonary blood volume was significantly higher in hypertensives than in normotensives (144 ± 15 vs 102 ± 9 ml; p < 0.02).

Figure 2 indicates that the same amount of dextran induced a higher increase in cardiac index and stroke index (p < 0.01) in hypertensives than in normotensives. The ratio between the change in CO and the change in cardiopulmonary blood volume was similar in both groups (11.2 ± 0.7 and 11.3 ± 0.7).

Basal peripheral compliance was lower in hypertensive than in normotensive subjects (6.5 ± 0.5 vs 9 ± 0.3 ml/mm Hg/100 g tissue; p < 0.001). No significant changes for hypertensives and normotensives were observed after dextran infusion (1.4 ± 5% and 1.5 ± 3%, respectively).

Relationship Between Cardiac Output and Total Blood Volume

Table 4 shows the correlation coefficients of the relationship between CO and blood volume in normo-
tensive controls and in hypertensives. Before expansion, the relationship was significant in hypertensives (p < 0.001) and not in normotensive controls. Similar observations were made after expansion.

The results become obvious when, in each group, all the points of the relationship (before expansion plus after expansion) are plotted together (fig. 3). The cor-
relation coefficient is 0.60 in normotensive controls ($p < 0.01$) and 0.75 in hypertensives ($p < 0.001$). However, in comparison with the normotensive curve, the hypertensive curve is characterized by a steeper slope ($2.16 \pm 0.39$ vs $0.97 \pm 0.26; p < 0.01$) with no significant difference in the intercept.

Indices of Volume Expansion

Indices of volume expansion are indicated in table 5. In comparison with normotensive controls, the $\Delta CO/\Delta TBV$ ratio of hypertensives was increased ($p < 0.025$), while the $\Delta CO/\Delta CVP$ ratio was quite similar. The $\Delta TBV/\Delta CVP$ ratio was significantly reduced ($p < 0.001$) and was correlated positively with peripheral venous compliance ($r = +0.72; p < 0.001$) (fig. 4) and negatively with basal cardiac output ($r = -0.72; p < 0.001$).

The changes in $CO$ and in stroke volume were negatively correlated with the $\Delta TBV/\Delta CVP$ ratio ($r = -0.65$ and $-0.75; p < 0.001$) (fig. 5). These changes were not related to systolic time intervals. For instance, the correlation coefficients of the change in stroke volume with pre-ejection period (PEP) was $+0.26$, with left ventricular ejection time (LVET) was $-0.12$, and with PEP/LVET was 0.26.

Discussion

In the present investigation, rapid dextran infusion was performed in patients with essential hypertension and compared with normotensive controls. As previously shown, the hemodynamic consequences represent a volume effect rather than a response to dextran per se. Both groups of patients had the same basal value of blood volume (ml) and received the same amount of dextran. At the end of volume expansion, hypertensives had a more elevated CVP, with a higher increase in stroke volume and CO. Similar tendencies have been observed in previous reports, but the observed changes were less significant. The reasons for this discrepancy can be easily explained. In earlier studies, dextran infusion was performed over a long-term period, enabling delayed compliance and reflex adjustments to occur. In our

<table>
<thead>
<tr>
<th>Table 2. Basal Systolic Time Intervals*</th>
<th>Normotensive Controls</th>
<th>Hypertensive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (b/min)</td>
<td>78 ± 3</td>
<td>75 ± 2</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td>98 ± 4</td>
<td>103 ± 4</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>271 ± 6</td>
<td>280 ± 7</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.37 ± 0.02</td>
<td>0.38 ± 0.02</td>
</tr>
</tbody>
</table>

* = 1 standard error of the mean.

Abbreviations: HR = heart rate; PEP = pre-ejection period; and LVET = left ventricular ejection time.
Table 3. Hemodynamic Parameters Before and After Volume Expansion*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive controls</th>
<th>Hypertensive patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (1)</td>
<td>After (2)</td>
<td>Before (3)</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>135 ± 3</td>
<td>138 ± 2</td>
<td>180 ± 6</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>79 ± 2</td>
<td>81 ± 1</td>
<td>103 ± 1</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>4.4 ± 0.6</td>
<td>7.8 ± 0.5</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>4.6 ± 0.6</td>
<td>8.2 ± 0.3</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>CI (ml/min/m2)</td>
<td>3826 ± 112</td>
<td>4454 ± 110</td>
<td>3439 ± 115</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>50 ± 2</td>
<td>57 ± 2</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>78 ± 3</td>
<td>80 ± 3</td>
<td>75 ± 2</td>
</tr>
<tr>
<td>TPR (dynes · sec cm⁻² · m⁻²)</td>
<td>2119 ± 75</td>
<td>1886 ± 65</td>
<td>3018 ± 132</td>
</tr>
<tr>
<td>TBV (ml)</td>
<td>5576 ± 147</td>
<td>6076 ± 147</td>
<td>5191 ± 121</td>
</tr>
<tr>
<td>CPBV (ml)</td>
<td>1243 ± 42</td>
<td>1344 ± 41</td>
<td>1325 ± 63</td>
</tr>
</tbody>
</table>

* ± 1 standard error of the mean.

Abbreviations: SAP = systolic arterial pressure; DAP = diastolic arterial pressure; CVP = central venous pressure; RVEDP = right ventricular end-diastolic pressure; CI = cardiac index; SI = stroke index; HR = heart rate; TPR = total peripheral resistance; TBV = total blood volume; and CPBV = cardiopulmonary blood volume.

In addition, no significant changes in heart and peripheral venous tone were observed in either group of patients. Thus, the observed hemodynamic variations depended mainly on the mechanical properties of the system, i.e. the cardiac pump and the distensibility of the vascular compartment.

Figure 2. Changes in total blood volume (TBV), diastolic arterial pressure (DAP), cardiac index (CI), stroke index (SI) and heart rate (HR) during expansion.
The present data confirm our previous observations concerning the relationship between CO and blood volume in normotensive and hypertensive patients. A significant correlation was observed in hypertensives, but not in normotensives. This was true both in basal conditions and after volume expansion. When the overall points of the investigation were plotted together, the results became obvious: the volume-flow curve was significantly steeper in hypertensives than in normotensives. Moreover, the use of volume expansion provided the possibility to determine an index of the volume-flow connection in each individual patient. This index was the $\Delta CO/\Delta TBV$ ratio, which was elevated in hypertensives. Since normotensives and hypertensives received the same amount of dextran, the $\Delta CO$ value (or the change in stroke volume) also constituted an index of the relationship between CO and blood volume in individuals. Thus, the problem is to explain the mechanism of the cardiac hyperresponsiveness to acute volume expansion in hypertensive patients.

During volume expansion, hypertensives had a greater elevation in CVP than normotensives. In contrast, the variations in blood pressure and total peripheral resistance were nearly the same in normotensive and hypertensive patients. Thus, the changes in right atrial pressure following loading in hypertensives could be mainly caused by two different factors: 1) the compliance of the peripheral vascular system, and 2) the ability of the heart to respond to the increased volume. The latter point is discussed below.

In the present study, normotensives and hypertensives had the same basal values of CO and CVP. In addition, the $\Delta CO/\Delta CVP$ values were identical in the two groups of patients. Thus, within the limits of the investigation, hypertensive and normotensive subjects had the same cardiac output-central venous pressure curves. Two other observations confirm this result: 1) the change in cardiopulmonary blood volume was significantly higher in hypertensives, and 2) systolic
TABLE 5. Indices of Volume Expansion in Hypertensive Patients and Normotensive Controls

<table>
<thead>
<tr>
<th></th>
<th>Normotensive Controls</th>
<th>Hypertensive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta CO/\Delta TBV$ (ml/min)</td>
<td>$2.28 \pm 0.20$</td>
<td>$3.26 \pm 0.32^\dagger$</td>
</tr>
<tr>
<td>(ml/min/mm Hg)</td>
<td>$353 \pm 35$</td>
<td>$371 \pm 41$</td>
</tr>
<tr>
<td>$\Delta TBV/\Delta CVP$ (ml/mm Hg)</td>
<td>$148 \pm 6$</td>
<td>$118 \pm 6^\ddagger$</td>
</tr>
<tr>
<td>(ml/mm Hg/kg)</td>
<td>$2.16 \pm 0.09$</td>
<td>$1.56 \pm 0.07^\dagger$</td>
</tr>
</tbody>
</table>

* = 1 standard error of the mean.
† $p < 0.025$.
‡ $p < 0.001$.

Abbreviations: $\Delta CO/\Delta TBV = \text{ratio between the change in cardiac output and the change in blood volume; } \Delta CO/\Delta CVP = \text{ratio between the change in cardiac output and the change in central venous pressure; } \Delta TBV/\Delta CVP = \text{ratio between the change in blood volume and the change in central venous pressure (effective vascular compliance).}$

Time intervals were similar in the two groups and were not correlated with $\Delta TBV/\Delta CVP$ in hypertensives. However, left ventricular filling pressure and volume were not directly measured in the present study. Thus, a subtle alteration of cardiac compliance in hypertensives cannot be excluded. Since cardiac hypertrophy is a characteristic of sustained hypertensives, the problem is not really to affirm decreased cardiac compliance in these patients, but rather to evaluate its quantitative contribution to the decreased $\Delta TBV/\Delta CVP$ ratio. As previously shown by others, the normal value of left ventricular compliance is about 5.6 ml/mm Hg. Thus, a decreased left ventricular compliance cannot explain the 30 ml/mm Hg decrease in the $\Delta TBV/\Delta CVP$ ratio observed in hypertensives (see table 5). Furthermore, if the reduced compliance was mainly due to a decreased compliance of ventricle, a positive or lack of correlation would be expected between CO and effective compliance. Since the two parameters were negatively correlated, the result minimizes the contribution of the heart in the explanation of the observed decreased $\Delta TBV/\Delta CVP$ ratio.

The possibility remains that the increased right atrial pressure in hypertensives could be due to a reduced compliance of the vascular system. The $\Delta TBV/\Delta CVP$ ratio has been shown to be an adequate index of the effective compliance of the vascular bed in hypertensives. Since the arterial system is an in-

**Figure 4.** Relationship between the $\Delta TBV/\Delta CVP$ ratio and peripheral venous compliance in the overall population (normotensives plus hypertensives). For simplicity, peripheral venous compliance was multiplied by $10^2$. 
significant fraction of the total compliance, the reduced \( \Delta TBV/\Delta CVP \) ratio indicates a disturbance in the pressure-volume relationship of the venous bed. In favor of this interpretation is the finding of a positive correlation between the ratio and peripheral venous compliance (fig. 4). Thus, the reduced \( \Delta TBV/\Delta CVP \) ratio points to the existence of a reduced systemic venous distensibility in hypertensives, as previously observed in experimental hypertension and in spontaneous hypertension in rats.\(^2\), \(^25\)–\(^27\)

In a previous report,\(^9\) we have emphasized the importance of volume factors in the control of CO of hypertensive patients. This role was suggested by the observation of a higher correlation coefficient of the relationship between CO and blood volume in hypertensives than in normotensives. In the present study, the elevated correlation coefficient was related to a steeper slope of the volume-flow curve. Moreover, the steeper slope was explained by the finding of a reduced effective compliance of the vascular bed in hypertension. As shown in figure 5, the more reduced the compliance, the higher the increase in CO and stroke volume and, consequently, the higher the slope of the relationship between CO and blood volume. The decreased compliance is difficult to explain in hypertension. It could represent a primary or a secondary defect.\(^18\), \(^25\) Whatever the mechanisms involved, such a result points to the role of venous compliance in the control of CO in hypertensive patients.\(^10\), \(^18\), \(^28\)

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