Whole-Body Venous Capacity and Effective Total Tissue Compliance in SHR

NICK C. TRIPPODO, PH.D., JIN YAMAMOTO, M.D., AND EDWARD D. FROLICH, M.D.

SUMMARY Whole-body venous capacity was examined in conscious 4-month-old male spontaneously hypertensive rats (SHR) and Wistar-Kyoto normotensive (WKY) rats by determining mean circulatory filling pressure (MCFP) and blood volume. The MCFP was determined in conscious animals after briefly arresting the circulation by inflating an indwelling balloon in the right atrium. Blood volume was determined by dilution of "I-albumin and "Cr-red cells. Although blood volume was not significantly different between SHR (60.9 ± 0.7 ml/kg, SE) and WKY (59.6 ± 0.8 ml/kg), MCFP was slightly, but significantly elevated in the SHR (9.5 ± 0.3 vs 8.5 ± 0.2 mm Hg, mean ± SE, p < 0.05). Increased MCFP with normal blood volume suggests decreased venous capacity in the SHR. In addition, effective total tissue compliance (ETTC) was measured in conscious 5-month-old female SHR and WKY. A decrease in tissue fluid volume was induced by i.v. infusion of hyperoncotic albumin solution. Changes in interstitial fluid pressure were monitored continuously with implanted tissue capsules. Changes in tissue fluid volume were estimated from changes in plasma volume and urine volume. In SHR 3 hours postinfusion, tissue fluid volume decreased by 38.7 ± 2.7 ml/kg and interstitial fluid pressure decreased from −1.4 ± 0.3 to −6.6 ± 1.5 mm Hg. In WKY, tissue fluid volume decreased by 32.5 ± 2.7 ml/kg and interstitial fluid pressure decreased from −1.4 ± 0.4 to −3.9 ± 0.5 mm Hg. The linear regression line for Δ interstitial fluid pressure and Δ fluid volume was estimated for each rat and the inverse of this slope represented ETTC, which averaged 7.4 ± 1.0 and 9.6 ± 2.1 ml/kg/mm Hg (p > 0.3) in SHR and WKY respectively. Thus, there were no significant differences in interstitial fluid pressure or ETTC between female SHR and WKY. The results of this study confirm a decreased venous capacity in male SHR with established hypertension and provide new information indicating no measurable abnormalities in interstitial fluid pressure or effective total tissue compliance in adult female SHR as compared with WKY. (Hypertension 3: 104-112, 1981)

KEY WORDS • spontaneously hypertensive rats • mean circulatory filling pressure • blood volume • interstitial fluid pressure

V EINS and venules serve as a readily adjustable volume reservoir which can shift blood to or from the heart by both passive and active processes.1 The interstitium serves a similar function, since it also provides the circulation with an accessible reservoir from which to draw, or in which to empty, fluid.2 Thus the normal function of these two reservoir systems is to buffer the effects of body fluid volume perturbations and help maintain circulatory homeostasis.

In end-stage renal disease and anephric patients, it has been shown that volume expansion elevates arterial pressure only in those with a history of hypertension.3, 4 It is possible that in these apparently "volume-sensitive" individuals decreased venous or interstitial capacitance reflects some "intrinsic" inability of these systems to buffer volume changes, thereby making these individuals more susceptible to the effects of the volume load. Indeed, patients with essential hypertension as well as spontaneously hypertensive rats have demonstrated reduced venous capacitance.8 9 In contrast to the many studies on venous capacitance in hypertension, few studies of interstitial capacitance have been made. Floyer and Richardson10 found that, in rats joined in parabiosis, when one member was made hypertensive by renal artery constriction, there was a relative decrease in blood volume of the clipped animal and a relative increase in its partner. They suggested that increased tone of the capacitance vessels of the clipped rats was responsible for the fluid shift. Later, Lucas and Floyer11, 12 reported evidence of decreased interstitial compliance in experimental hypertension; and Floyer13 suggested that a primary fall in the interstitial compliance could be the mechanism responsible for these and many

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The MCFP was measured using the technique of
Samar and Coleman as modified in this laboratory. In this study whole body venous capacity and effective total tissue compliance in the conscious intact spontaneously hypertensive rat.

Methods

Conscious male and female Okamato-Aoki spontaneously hypertensive rats (SHR) and Wistar-Kyoto normotensive (WKY) rats were used in this study. Both strains, originally obtained from the National Institutes of Health, have been maintained by strict brother-sister mating. At the time of this study, the SHR and WKY were in the F14 and F16 generations respectively.

Venous Capacity

Capacitance or capacity is defined here as the volume at a given filling pressure; it can be altered through a change in compliance (Δ volume/Δ pressure) or unstressed volume (the volume at "zero" filling pressure). In this study whole body venous capacity was assessed by measuring mean circulatory filling pressure (MCFP) and total blood volume (BV). The MCFP was measured using the technique of Samar and Coleman as modified in this laboratory. Male SHR and WKY (mean body weights and ages given in table 1) were briefly anesthetized with ether for the placement of catheters in the left femoral vein and the right carotid artery. The femoral vein catheter was advanced to the thoracic inferior vena cava for recording central venous pressure (CVP). Arterial pressure and CVP were recorded with Statham P23Db transducers, and a Grass oscillograph. A balloon-tipped catheter, as described previously, was placed in the right atrium through the right external jugular vein. Inflating the balloon by injecting 0.3 ml of water through the connecting catheter completely arrested the circulation, permitting the measurement of MCFP. The catheters were brought out at the back of the neck, the wounds closed, and the rat allowed to recover. Approximately 2½ hours after surgery, the rat was placed in an unconfining wooden box and allowed to rest comfortably for 30 minutes. Preliminary experiments indicated that mean arterial pressure and cardiac output became stable well within 3 hours after surgery. Plasma and red cell volumes were measured by dilution of 125I radioiodinated human serum albumin (RISA) and 51Cr-tagged red cells, as described in detail below. The MCFP was then determined by inflating the balloon and recording arterial pressure and CVP. During balloon inflation and circulatory arrest, CVP increased (reaching a plateau within 4–5 seconds) and arterial pressure decreased to an average of 39 mm Hg in SHR and 23 mm Hg in WKY. After venous pressure reached a plateau, the balloon was quickly deflated, restoring the circulation. Measurement of MCFP in this manner can be repeated several times in conscious rats without deleterious effects. Since the arterial and venous pressures do not completely equilibrate during this procedure, MCFP was calculated according to the equation: MCFP = VPP + K (final arterial pressure — VPP), where VPP is venous plateau pressure, final arterial pressure is the arterial pressure attained within 4 to 5 seconds, and K is the arterial-to-venous compliance ratio. As reported by Samar and Coleman, the values used for K in SHR and WKY were 1/100 and 1/75 respectively. The MCFP calculated in this manner correlated very closely with the MCFP actually measured by transferring blood from the arterial to the venous side of the circulation to effect complete equilibration of pressures.

Interstitial Fluid Pressure and Total Tissue Compliance

Female SHR and WKY (mean body weights and ages given in table 2) were used in these experiments. Tissue capsules were constructed from segments of plexiglass tubing (6.5 mm, i.d.; 9 mm, o.d.). Both ends of the cylindrical capsule were sealed with discs cut from plexiglass sheets. Each capsule was 16 mm long, 9 mm in diameter, contained approximately 60 1-mm pores, and were connected to PE-90 tubing. Four to 6 weeks prior to the experiments, each rat was anesthetized with ether and a tissue capsule with attached catheter was implanted subcutaneously in the dorsal shoulder area using sterile technique. The rat was given 100,000 units of penicillin G intramuscularly immediately and once daily for 5 days after the surgery.

On the day of the experiment, each rat was briefly anesthetized with ether for placement of catheters in the carotid artery and external jugular vein, and for exposing the catheter connected to the tissue capsule. The arterial and venous catheters were brought out at the back of the neck, the wounds were closed, and the rat was allowed to recover for at least 3 hours. During recovery, the rat was placed in an unconfining box designed for urine collection, where it also remained throughout the experiment. Plasma and red cell volumes were measured as described below. Arterial and interstitial fluid (IFP) pressures were measured with Statham P 23Db transducers (calibrated as described below) and recorded continuously on a Grass oscillograph. Urine output was collected and the volume determined gravimetrically, as described below. Measurements of variables were taken during a 30-minute control period and for 3 hours after infusing hypertonic bovine albumin solution (29 g/dl, 1.1 g/kg) intravenously over a 10-minute period. At the end of the experiment, the rat was killed with an intra-
TABLE 1. Vascular Pressure-Volume Data in Male SHR and WKY

<table>
<thead>
<tr>
<th>Measurement</th>
<th>SHR (n = 8)</th>
<th>WKY (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>128±2</td>
<td>128±2</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>307±4</td>
<td>318±6</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>173±4</td>
<td>119±2</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>-1.1±0.2</td>
<td>-1.3±0.3</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>399±10</td>
<td>395±14</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>47.3±0.6</td>
<td>44.9±1.1</td>
</tr>
<tr>
<td>Plasma volume (ml/kg)</td>
<td>36.2±0.8</td>
<td>36.6±1.0</td>
</tr>
<tr>
<td>Red cell volume (ml/kg)</td>
<td>24.7±0.4</td>
<td>23.0±0.7</td>
</tr>
<tr>
<td>Blood volume (ml/kg)</td>
<td>60.9±0.7</td>
<td>59.6±0.8</td>
</tr>
<tr>
<td>Fc<em>0</em></td>
<td>0.865±0.009</td>
<td>0.860±0.010</td>
</tr>
<tr>
<td>Mean circulatory filling pressure (mm Hg)</td>
<td>9.5±0.3</td>
<td>8.5±0.2</td>
</tr>
</tbody>
</table>

*<p < 0.05.

venous injection of lidocaine (10 mg), and the capsule was removed for examination. Overt signs of abscess or a large degree of intracapsular tissue infiltration were almost invariably associated with bizarre pressure recordings, and these rats were excluded from the study.

Changes in total tissue fluid volume (TFV) were estimated from changes in plasma volume and urine volume. Since interstitial fluid volume was not measured directly, the terms "TFV" and "total tissue compliance" will be used. The linear regression line using the method of least squares for ΔIFP and ΔTFV was determined from eight data points for each rat; the inverse of this slope represented total tissue compliance (ml/kg/mm Hg). Although most rats rested quietly throughout the experiment, some rats (especially SHR) exhibited continuous movement, making accurate measurements of IFP impossible. To establish an objective criterion for excluding experiments from the study, experiments having a correlation coefficient less than 0.7 for the ΔIFP vs ΔTFV relationship were arbitrarily excluded. Upon completion of the study, it was found that most successful experiments had correlation coefficients greater than 0.8 (average, 0.86) and the ones that were excluded had values less than 0.6 (average, 0.29).

Calibrations

The transducer-recorder channel used for measuring arterial pressure was calibrated in the usual manner, using a mercury manometer and setting the

TABLE 2. Tissue Pressure-Volume Data in Female SHR and WKY

<table>
<thead>
<tr>
<th>Measurement</th>
<th>SHR (n = 8)</th>
<th>WKY (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>146±5</td>
<td>153±3</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>216±3</td>
<td>220±5</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>196±6</td>
<td>135±3</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>394±15</td>
<td>396±11</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>45.5±0.4</td>
<td>44.6±0.5</td>
</tr>
<tr>
<td>Plasma volume (ml/kg)</td>
<td>39.8±1.2</td>
<td>40.3±1.4</td>
</tr>
<tr>
<td>Red cell volume (ml/kg)</td>
<td>24.2±0.3</td>
<td>22.6±0.3</td>
</tr>
<tr>
<td>Blood volume (ml/kg)</td>
<td>65.0±1.3</td>
<td>62.9±1.6</td>
</tr>
<tr>
<td>Fc<em>0</em></td>
<td>0.833±0.013</td>
<td>0.869±0.022</td>
</tr>
<tr>
<td>Interstitial fluid pressure (mm Hg)</td>
<td>-1.4±0.3</td>
<td>-1.4±0.4</td>
</tr>
<tr>
<td>Effective total tissue compliance (ml/kg/mm Hg)</td>
<td>7.4±1.0</td>
<td>9.6±2.1</td>
</tr>
</tbody>
</table>

*p < 0.05.
by guest on July 9, 2017

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Plasma, Red Cell, Blood, Urine, and Tissue Fluid Volumes

Approximately 10 μCi/kg of RISA (Mallinkrodt/Nuclear) was injected through the venous catheter. Ten minutes postinjection, approximately 0.1 ml of blood was collected directly from the arterial catheter into two heparinized capillary tubes. After centrifugation, three aliquots (0.004 ml) of plasma were transferred to smaller, calibrated capillary tubes and counted in a Packard gamma scintillation spectrometer. Plasma volume was calculated as: plasma volume (ml) = radioactivity injected (cpm) ÷ average cpm/ml plasma sample. Previous experiments indicated that our method for determining plasma volume was quantitatively insignificant. Furthermore, possible errors due to differences in loss rate of RISA from the circulation between hypertensive (Goldblatt) and normotensive rats were quantitatively insignificant.

Red blood cells were labeled with 51Cr by incubating fresh, donor, strain-matched blood with 51Cr (approximately 50 μCi/ml blood) at room temperature for 30 minutes. The red cells were washed and resuspended in isotonic saline to a hematocrit of about 40. Approximately 36 μCi/kg of 51Cr-labeled red cells in 0.2 ml was injected through the venous catheter. Fifteen minutes post-injection, 0.069 ml of blood was collected directly from the arterial catheter into three capillary tubes, each precalibrated to 0.023 ml. After centrifugation, hematocrits were recorded and the blood samples were counted as above. Red cell volume was calculated as: red cell volume (ml) = radioactivity injected (cpm) × hematocrit/100 ÷ average cpm/ml blood sample. Total blood volume was obtained by the summation of plasma and red cell volumes. The Fcell ratio was obtained by: red cell volume ÷ blood volume ÷ hematocrit/100.19,20

In experiments requiring multiple measurements of plasma and red cell volumes, subsequent blood samples (0.023 ml) were collected in duplicate. Red cell volume was calculated as: red cell volume (ml) = (amount of radioactivity injected — amount of radioactivity lost through cumulative sampling) × hematocrit/100 ÷ average cpm/ml of blood sample. Blood and plasma volumes were calculated as: blood volume (ml) = red cell volume ÷ (Fcell ÷ hematocrit/100); plasma volume (ml) = blood volume — red cell volume. Preliminary experiments indicated that plasma volume expansion had very little effect on the Fcell ratio.

Urine was collected from the rats after spontaneous micturition in preweighed vessels and volume was determined gravimetrically with an analytical balance. To compensate for the sporadic urine output, the collection periods were extended over one hour. Due to the large urine output after albumin infusion, these hourly collection periods proved to be adequate. To obtain the estimated urine output for each time interval of data recording (15-minute intervals for the first hour after albumin infusion and 30-minute intervals for the second and third hours), urine volumes were averaged according to the number of data intervals within each hourly period (4 for the first and 2 for the second and third hourly periods). At the termination of the experiment, the urinary bladder was aspirated by direct puncture, and this volume was added to that collected during the last hourly period. We assumed the bladder to be empty at initiation of the albumin infusion. The error involved in this assumption was estimated to be minimal (see Discussion).

Tissue fluid volume was not measured directly, but cumulative changes in this variable after infusion of albumin solution were estimated by: ΔTBFW = volume infused — Δplasma volume — cumulative urine volume output. This relationship was based on the following considerations. Intravenous infusion of hyperoncotic albumin solution results in an immediate increase in plasma oncotic pressure causing a net transfer of fluid from the tissues into the intravascular compartment. As fluid is drawn into the plasma compartment from the tissues, urine volume output increases as a result of the increased plasma volume. The cumulative decrease in tissue fluid volume is equal to the increase in plasma volume (minus the volume infused) plus the cumulative urine volume output.

Statistical Analysis

Differences between SHR and WKY were assessed with Student’s t test, and p < 0.05 was considered significant.
Results

Venous Capacity

The male SHR and WKY used for these experiments were closely matched for age and body weight; mean arterial pressure was significantly increased in SHR, but there was no significant differences in heart rate between groups (table 1). There were no significant differences in plasma volume, red cell volume, or blood volume (BV) between male SHR and WKY, although red cell volume and hematocrit tended to be greater in SHR. The MCFP was significantly increased in SHR (9.5 ± 0.3 vs 8.5 ± 0.2 mm Hg, p < 0.05). There was no difference between groups in central venous pressure.

Interstitial Fluid Pressure and Total Tissue Compliance

To determine the stability of our measurements of interstitial fluid pressure (IFP) and blood volume, five conscious female WKY were monitored as usual for the 3½-hour experimental period, but without infusing albumin. An analysis of variance on repeated measures revealed no significant changes in IFP or red cell volume with respect to time. During the first 30 minutes, IFP averaged −1.9 ± 0.3 mm Hg and after 3 hours of continuous recording it averaged −1.7 ± 0.4 mm Hg. However, the Neuman Keuls range test showed that plasma volume increased during the last 2 hours of measurement. During the first 30 minutes, plasma volume averaged 11.8 ± 0.9 ml and during the third hour it averaged 13.0 ± 0.8 ml.

In conscious female SHR and WKY receiving albumin infusion, control values were taken as the average of three measurements during the 30-minute control period (table 2). Mean arterial pressure was significantly increased in SHR, but there were no differences in age, body weight, or heart rate between groups. Red cell volume was significantly increased in female SHR, but the differences in BV and plasma volume between groups were not statistically significant. The IFP averaged −1.4 mm Hg in both groups.

Fifteen minutes after infusion of hyperoncotic albumin solution (average volume, 0.9 ml), plasma volume was increased by 2.5 and 3.3 ml in SHR and WKY respectively (figs. 1 and 2). Since red cell volume did not change appreciably in either group, the changes in BV reflected changes in plasma volume.

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

**Figure 1.** Mean values and SE of fluid volumes and hematocrit in conscious, female spontaneously hypertensive rats (SHR, n = 8) and WKY (n = 9) before and after infusion of 0.9 ml (average) hyperoncotic albumin solution (arrows). Early changes in volume partly reflected rapid fluid migration from the tissues into the intravascular space.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Mean changes in plasma volume (■—■), cumulative urine output (○—○), and calculated tissue fluid volume (△—△) after albumin infusion in conscious female SHR and WKY.
solely. In general, urine output increased to a greater extent in SHR than in WKY (fig. 3). Changes in tissue fluid volume were calculated from changes in plasma volume and cumulative urine output (fig. 2). In general, there was a slightly greater decrease in tissue fluid volume and IFP in SHR than in WKY (fig. 3).

The changes in tissue fluid volume and IFP were analyzed for each rat by linear regression analysis using eight paired data points. The inverse of the slope of this relationship represented compliance. Thus, effective total tissue compliance was determined for each rat in each group, and averaged 7.4 ± 1.0 and 9.6 ± 2.1 ml/kg/mm Hg in SHR and WKY respectively. The difference in effective total tissue compliance between groups was not found to be statistically significant (table 2). The relationships between the mean changes in tissue fluid volume and IFP illustrated that both groups had similar slopes (fig. 4).

**Discussion**

The technical aspects and validation of our technique for measuring mean circulatory filling pressure (MCFP) in conscious rats have been recently discussed. In this earlier study the value obtained for MCFP (7.9 mm Hg) in normotensive, conscious Wistar rats was similar to that (7.6 mm Hg) reported by Samar and Coleman who used a slightly different technique. The value obtained for MCFP (8.5 mm Hg) in the present study in normotensive WKY was somewhat different from that previously obtained in the American Wistar rats; the implications of this difference is unknown.

The MCFP is a function of total BV and total vascular capacity. However, since arterial capacity is quantitatively insignificant as compared with venous capacity, it is generally accepted that, at any given

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**Figure 3.** Mean values and SE of variables in conscious, female SHR and WKY before and after infusion of 0.9 ml hyperoncotic albumin solution (arrows). SHRs showed a greater diuresis, which resulted in a more rapid return of plasma volume toward the control level and in a greater depletion of tissue fluid volume as compared with WKY.

**Figure 4.** Relationship between mean changes in interstitial fluid pressure and tissue fluid volume in conscious female SHR and WKY after infusion of hyperoncotic albumin solution.
BV, MCFP is a reliable index of venous capacity.\textsuperscript{1, 31} We found a small, but significantly, higher MCFP in SHR than in WKY, yet there was no significant difference in BV between groups (table 1). These results suggest that SHRs at this age have reduced venous capacity and confirm the findings of Samar and Coleman.\textsuperscript{8}

Regarding BV, it is important to point out that BV in SHR relative to that in WKY seems to depend on age and body weight. Rippe et al.\textsuperscript{27} determined BV in SHR and WKY over the weight range of about 25–225 g. From their plot of body weight vs BV, it appeared that the SHR had a slightly decreased BV over the weight range of 125–225 g, whereas over the range of 25–100 g there appeared to be very little difference in BV or plasma volume between SHR and WKY. Trippodo et al.\textsuperscript{2} likewise found no significant difference in plasma volume between SHR and WKY over the weight range of 20–100 g. However, in older SHR, BV may be increased.\textsuperscript{32, 34} Similar weight- and age-dependent findings were reported in genetic hypertensive rats of the New Zealand strain.\textsuperscript{26, 36}

### Interstitial Fluid Pressure

Chemical\textsuperscript{8} and morphological\textsuperscript{28} analyses suggest that the interstitial reticulum is a gel composed mostly of mucopolysaccharides slightly cross-linked with collagen fibers.\textsuperscript{29} Interstitial fluid is held tightly within this gel, probably through a combination of both physical and chemical forces. Snashall et al.\textsuperscript{30} '81 view the interstitium as a homogeneous gel having no free fluid, whereas Guyton et al.\textsuperscript{29} and Widerhielm\textsuperscript{32} assume that the interstitium is composed of a small free-fluid phase as well as the gel phase. Two currently used methods to measure the hydrostatic pressure in the interstitial space (the chronically implanted perforated capsule technique developed by Guyton\textsuperscript{30} and the cotton wick method developed by Scholander et al.)\textsuperscript{31} measure subatmospheric pressures in subcutaneous and muscle tissues, with the Wick method usually giving slightly higher (less subatmospheric) values.\textsuperscript{30, 35, 36} The physical and chemical bases of the measured interstitial pressure is currently controversial.\textsuperscript{29-31} Nevertheless, irrespective of the origin of the subatmospheric interstitial pressure measured by the capsule and wick techniques, the pressure is believed to exert its influence on the fluid filtered from the capillaries and therefore is an important factor in Starling's consideration of transcapillary fluid migration.\textsuperscript{39, 40} The capsule method was used in the present study because of its more consistent responses to acute changes in tissue hydration as compared with other methods.\textsuperscript{39, 40, 35, 46} An earlier suggestion that the intracapsular pressure was an artifact due to the influence of tissue protein osmotic forces acting across the capsule lining\textsuperscript{46} has been discounted on both experimental and theoretical grounds.\textsuperscript{39, 47}

Our values for IFP, which ranged from +0.3 to −2.8 mm Hg and averaged −1.5 mm Hg in all rats included in this study, were slightly higher (less negative) than that (−2.5 mm Hg) reported by others using the capsule technique in rats.\textsuperscript{38, 43} However, measurements in the present study were made in conscious rats from capsules implanted subcutaneously in the dorsal shoulder area, whereas in the previous studies, measurements were made in anesthetized rats from capsules implanted subcutaneously in the groin\textsuperscript{44} or thigh\textsuperscript{45} areas. These differences in technique might be responsible for the small difference in the results between the present and the previous studies.

We found no difference in IFP between female SHR with established hypertension and age-matched normotensive WKY. This is the first report on IFP in rats with genetically determined hypertension. Lucas and Floyer\textsuperscript{12} reported increased IFP in rats with chronic one-kidney, one clip Goldblatt hypertension, and Doublas et al.\textsuperscript{14} reported a transient increase in IFP in hypertensive, sodium-loaded, partially nephrectomized dogs during the period when BV was increased. Perhaps the altered IFP in the hypertensive animals of the previous studies was related to a disturbance in body fluid volume homeostasis associated with altered renal function. The results of the present study in female SHR suggest that alterations in IFP or body fluid volumes do not play a significant role in the maintenance of this form of genetic hypertension.

### Effective Total Tissue Compliance

Several factors should be considered regarding our technique for estimating total tissue compliance. First, in a previous study designed to measure interstitial space compliance in rats using tissue capsules, intracapsular pressure progressively increased in the control animals during continuous measurement for 260 minutes.\textsuperscript{48} This might have reflected inadequate lymphatic drainage from the area surrounding the capsule due to prolonged inactivity\textsuperscript{49} or to an anesthesia-mediated decrease in lymphatic pumping ability. Mean intracapsular pressure in the present study remained essentially unchanged for 210 minutes in conscious WKY not receiving albumin infusion, indicating the stability of this measurement under the conditions of this experiment. Second, measurement of interstitial compliance not only requires measurement of changes in IFP after an experimentally-induced perturbation but also simultaneous changes in interstitial fluid volume. There are no established techniques currently available to accurately measure interstitial fluid volume under non-steady-state conditions. Therefore, in this study we estimated changes in tissue fluid volume by measuring changes in plasma volume and urine output after infusion of hyperoncotic albumin solution. The intravenously administered albumin had the net effect of transferring fluid from the tissues through the plasma volume compartment into the urine, thereby causing a progressive depletion of tissue fluid volume during the experimental period through diuresis. Estimation of changes in tissue fluid
volume rather than making actual measurements has been a generally-practiced and accepted method for estimating interstitial compliance.\textsuperscript{11, 40–42}

Finally, since the interstitial compartments of the various tissues throughout the body are not continuous, a true “whole-body” tissue compliance cannot be measured from the changes in IFP in only one region. For this reason, the term “effective” total tissue compliance is used to refer to the compliance values obtained in this study. As such, these values are not directly analogous to the compliance values obtained from studies on isolated limbs\textsuperscript{40–42} where volume and pressure changes were estimated within a single region. The compliance values in this study should therefore be considered valid only for comparing our two experimental groups, which were studied under identical conditions.

We found no significant difference in effective total tissue compliance between the female SHR and WKY (7.4 ± 1.0 and 9.6 ± 2.0 ml/kg/mm Hg respectively). All values in both groups fell within the range of 4.1 to 12.7 mm Hg, except for one extremely high (WKY) value of 24.4 ml/kg/mm Hg. If this high value is excluded, the WKY group’s mean ± SE then becomes 7.7 ± 1.0 ml/kg/mm Hg, and the close similarity between the groups is more apparent. Thus, the greater decrease in IFP in the SHR in response to a similar oncotic load, as compared with the WKY, can be explained by the greater decrease in tissue fluid volume in the SHR (fig. 3) and was not due to a difference in effective total tissue compliance.

Estimated Error Due to Unknown Initial Urinary Volume

Due to technical factors it was necessary to assume that the urinary bladder was empty in each rat immediately prior to albumin infusion. This assumption was probably correct in some rats, since we observed micturition in several animals during the control period. However, it is likely that the bladders of other rats actually contained various amounts of urine initially. This undoubtedly could contribute to variability in the results and might have influenced final estimates of compliance. To assess the possible extent of this error, effective total tissue compliance was also calculated for each rat, assuming an initial bladder volume of 2 ml (approximately the maximum expected for rats of this weight). It was further assumed that this entire 2 ml was eliminated from the bladder during the first hour after albumin infusion. Therefore, Δ tissue fluid volume was estimated in the usual manner, with the exception that 2.3 ml/kg (0.5 ml/0.22 kg) was subtracted from the absolute values of the first four 15-minute data points, to correct for the assumed “extra” volume. Effective total tissue compliances calculated in this manner were 8.3 ± 1.1 and 11.2 ± 2.2 ml/kg/mm Hg for the SHR and WKY respectively. Thus, the approximate maximum possible error in the mean effective total tissue compliance values due to an unknown initial urinary bladder volume was about 17%. However, it is unlikely that the initial bladder volume was as large as 2 ml in all rats or that it was completely eliminated during the first hour in all rats. Thus, the actual error was probably much less than the estimate above.

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