Microvascular Changes in the Heart During Chronic Arterial Hypertension

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Changes of myocardial microvascular permeability in chronic renovascular arterial hypertension were studied. Hypertension was induced in dogs utilizing a one-kidney, one-clip Goldblatt model. Systemic arterial pressure, coronary sinus pressure, systemic venous pressure, myocardial lymph flow rate, myocardial interstitial fluid pressure, and the lymph-to-plasma protein concentration ratio for total plasma proteins and for β-lipoprotein (Cp/Cp) were determined in control animals and 4–6 weeks following the Goldblatt procedure in hypertensive animals. Control values for the normotensive animals were 123 ± 17 mm Hg, 7.3 ± 1.3 mm Hg, 2.5 ± 2.1 mm Hg, 3.1 ± 2.1 ml/hr, 14.9 ± 3.1 mm Hg, 0.82, and 0.33, respectively, while control values for the chronically hypertensive dogs were 160 ± 20 mm Hg, 7.8 ± 1.9 mm Hg, 2.9 ± 2.5 mm Hg, 10.5 ± 2.5 ml/hr, 24.8 ± 3.7 mm Hg, 0.87, and 0.31, respectively. Under control conditions, myocardial lymph flow rate was significantly higher in the hypertensive group while no difference could be demonstrated in Cp/Cp, between the two groups. This is indicative of either a change in myocardial microvascular permeability or an increase in microvascular exchange surface area. Coronary sinus pressure was elevated in both groups in order to increase transmicrovascular fluid flux and determine the filtration-independent reflection coefficient (α) for each group. α is a surface area-independent indicator of microvascular permeability when determined for specific protein molecules at high transmicrovascular fluid fluxes. Although filtration independence for total plasma protein could not be reached in either group, α for β-lipoprotein decreased from 0.96 in the normotensive group to 0.80 in the hypertensive group, indicating an increase in microvascular permeability. Our results indicate a significant increase in myocardial microvascular permeability to macromolecules resulting from the one-kidney, one-clip Goldblatt model of chronic arterial hypertension. (Circulation Research 1988;62:953–960)

The accumulation of myocardial edema and increased pathogenicity of myocardial infarctions have been reported in patients with chronic arterial hypertension.1–3 Reports in the literature of increased microvascular leakage of macromolecules in various forms of chronic hypertension led us to believe that the microvascular exchange barrier may be directly affected by the development of arterial hypertension.4–7 We postulated that myocardial vascular permeability was increased in chronic arterial hypertension. Although control indexes of myocardial function may improve in hypertension because of ventricular hypertrophy, the increase in microvascular permeability would lead to myocardial edema formation and a decrease in the heart’s ability to function when stressed.8–10 To test our hypothesis, a mechanism was needed to evaluate myocardial microvascular permeability in both normotensive and hypertensive animals. Our previous experience with myocardial lymph collection allowed us to calculate the filtration independent reflection coefficient (α) of the microvascular exchange barrier for specific protein molecules.11–13 The reflection coefficient is a sensitive index of microvascular permeability and is independent of changes in microvascular surface area.13 Our findings indicate that chronic arterial hypertension increases myocardial microvascular permeability to plasma proteins and water. Prevention or reversal of the increased exchange vessel permeability may provide a mechanism to minimize both myocardial edema formation and severely compromised cardiac function, following myocardial infarction, in patients with chronic arterial hypertension.

Materials and Methods

Chronic Surgical Preparation

A chronic one-kidney, one-clip renal hypertensive model was produced in 12 heartworm-free, conditioned dogs.6 All animals had body weights in excess of 17 kg. Anesthesia was induced with sodium pentothal (20 mg/kg) and maintained with 1–2% halothane. Animals were ventilated with a Harvard respirator (Harvard Apparatus, Boston, Massachusetts) set to deliver room air at a volume of 25 ml/kg and at a rate that maintained PaCO2 between 35–40 mm Hg. All chronic work was carried out under sterile conditions. The renal artery, vein, and ureter from one kidney were double tied and cut; this kidney was then removed. An electromagnetic flow probe was placed around the renal artery of the remaining kidney. Flow from the renal artery was reduced by 50% with one of several ligatures or clips. A small abdominal artery was cannulated with a heparin-filled catheter that was then advanced into the abdominal aorta. This catheter was exteriorized on the rear of the animal’s neck in such a manner that tampering would not present a problem. Following
The left ventricular myocardium was removed from each animal to quantitate extravascular fluid volume (EVF). At the conclusion of each experiment, animals were euthanized with 20 ml of a saturated solution of potassium chloride injected intravenously. Evans blue dye solution (T-1824) was injected in the left ventricular myocardium utilizing the method of Gee. Blood urea nitrogen and serum potassium levels were closely monitored. Arterial pressure was monitored throughout the development of hypertension. Four to six weeks were allowed for the development and maintenance of arterial hypertension before using animals in the acute preparation. A group of normotensive, sham-operated control animals were maintained under the same housing and feeding conditions as the single-kidney animals.

Acute Surgical Preparation
Anesthesia and ventilation for the acute experiments were the same as those used in the chronic preparation. The left femoral vein and right carotid artery were exposed and cannulated. A midline incision was made into the chest cavity along the full length of the sternum. To facilitate access to the base of the heart, both mammary arteries were tied and cut. The right jugular vein was then cannulated with a Swan Ganz balloon catheter (American Edwards Labs, Anasco, Puerto Rico). The Swan Ganz catheter was advanced through the superior vena cava and into the right atrium, finally coming to rest in the coronary sinus. The Swan Ganz catheter was sutured to the wall of the coronary sinus in such a manner as not to occlude venous drainage from the sinus. Evans blue dye solution (T-1824) was injected into the left ventricular myocardium using a 27-gauge needle. The tissue near the aorta, lying between the superior vena cava and the brachiocephalic artery, was carefully dissected until the area containing several cardiac lymph nodes was located. A tie was placed around the lymphatic entering the cardiac lymph node that contained blue lymph from the left ventricle. This results in lymphatic congestion and bulging upstream from the tie. The prenodal lymphatic trunk flowing from the left ventricle was then cannulated using a 22-, 21-, or 18-gauge Medicut (Sherwood Medical Industries, St. Louis, Missouri). The lymphatic cannula was sutured in place followed by the application of cyanoacrylate (Super Glue*) at the point of cannulation to stabilize the cannula and prevent lymph seepage around the cannula. Any lymphatics entering the area of cannulation that did not contain blue dye and appeared to arise from the lung, mediastinum, or other areas of the heart were ligated to prevent contamination. Microtip pressure transducers (Millar, Houston, Texas) encased in thin-walled 18-gauge needles previously filled with porous polyethylene were acutely implanted in the left ventricular myocardium. All dogs were given sodium heparin, 300 units/kg body wt (Elkins-Sinn, Cherry Hill, New Jersey), intravenously before the experimental protocol was continued. At the conclusion of each experiment, animals were euthanized with 20 ml of a saturated solution of potassium chloride injected intravenously. The left ventricular myocardium was removed from each animal to quantitate extravascular fluid volume (EVF).

Physiological Measurements and Experimental Protocol
A Grass recorder (Grass Instruments, Quincy, Massachusetts) and Statham transducers (P23Db, Hato Rey, Puerto Rico) were utilized to record all pressures. The left femoral vein catheter was used to record systemic venous pressure (SVP). Arterial blood pressure was recorded from the previously cannulated right carotid artery (Pm). Heart rate was obtained by triggering a Grass tachograph from the carotid artery pressure signal. Mean pressure within the coronary sinus was recorded from the Swan Ganz catheter (Pw). An index of myocardial interstitial hydrostatic pressure (Pw) was obtained from the acutely implanted Millar microtip pressure transducers imbedded in porous polyethylene.15,19 Since bleeding is associated with the trauma of acutely inserting the Millar transducer, and there is some controversy regarding the interpretation of myocardial interstitial pressure recordings using the various measurement techniques,15,20 we consider our values for Pw to be an index that may or may not be quantitatively correct. It should be noted that, following equilibration, the values for Pw obtained from the acutely implanted Millar are very similar to values obtained with chronic Millar and porous polyethylene capsule implants. The chronic implantation of Millar and porous polyethylene capsules do not suffer from the same trauma and tissue deformation problems associated with acute measurements. The acute Millar implants also respond to changes in plasma colloid osmotic pressure and tissue volume in the expected manner. We, therefore, believe that our index reliably portrays changes in Pw. Since myocardial interstitial pressure varies as a function of the contractile state of the heart, reaching a minimum during diastole, maximum left ventricular transmircovascular fluid flux should take place during this period. Therefore, results are expressed in terms of myocardial interstitial fluid pressure recorded during the diastolic phase of the cardiac cycle. Lymph flow rate and lymph samples were obtained from the left ventricular lymphatic trunk cannula. Lymph was allowed to flow through a calibrated 1-ml pipette and returned to the central veins through a pressure tight system. Any variation in systemic venous pressure, which may alter lymph flow from uncannulated myocardial lymphatics, would also alter the flow in our cannulated lymphatic in a similar manner.21 Protein concentrations in the lymph and plasma were measured with a refractometer (model 10400A TS Meter, American Optical, Buffalo, New York). The osmotic pressures of the lymph and plasma were determined utilizing Prather's membrane-type colloid osmometer with a molecular weight cut-off of 10,000 daltons. Lymph samples were obtained by opening our lymph flow meter to atmospheric pressure and plasma samples were obtained by centrifugation of blood withdrawn from the coronary sinus. Lymph and plasma samples were fractionated with polyacrylamide gradient gel electrophoresis and quantified utilizing a scanning densitometer. EVF was determined on the left ventricular myocardium utilizing the method of Gee.22
Values for EVF are expressed in a dimensionless format as the ratio of extravascular fluid weight to blood-free dry weight.

The results presented in the present study represent the data from a total of 38 dogs. All animals fell into one of the following groups: normotensive controls from the present study (7 dogs), normotensive controls from the previous study (14 dogs), sham-operated controls (5 dogs), and chronic one-kidney, one-clip hypertensive animals (12 dogs). No significant difference could be shown between the data from our current and previous control animals. Therefore, the data from these two groups was pooled. Sham-operated animals showed no increase in systemic arterial blood pressure and no change in myocardial microvascular permeability.

All animals were subjected to the same experimental protocol. At the beginning of each experiment, steady-state measurements of systemic arterial and venous blood pressure, coronary sinus pressure, myocardial interstitial fluid pressure, lymph flow rate, total protein concentration in the plasma and lymph, and an electrophoretic fractionation and quantitative analysis of each of the plasma protein fractions found in the plasma and lymph were performed. Pressure within the coronary sinus was then elevated to near maximum by inflation of the Swan Ganz balloon tip catheter within the coronary sinus. Although filtration independence for β-lipoprotein can be obtained at coronary sinus pressures below 25 mm Hg, we normally elevated coronary sinus pressure to between 45 and 50 mm Hg in each experiment for consistency. This is an established procedure that produces a small amount of myocardial edema and no other documented adverse side effects.12,15 Elevation of coronary sinus pressure to these levels also serves to maximize myocardial microvascular exchange surface area. To ensure that good data would be obtained both at control and at filtration independence, no intermediate coronary sinus pressure elevations were performed, thus minimizing the time course of the procedure and optimizing the potential for success in estimating myocardial microvascular permeability. Following approximately 1 hour of re-equilibration, all of the parameters measured under control conditions were again determined during venous hypertension. Coronary sinus pressure was further elevated at the conclusion of each experiment to ensure that filtration independence for β-lipoprotein had been attained. Following the completion of each experimental protocol, data from the normotensive animals was compared with the values obtained from the chronic hypertensive animals.

Data Interpretation and Statistical Analysis

The foundation of our data interpretation rests on two basic relations. These two relations are obtained by the algebraic grouping of the forces and microvascular membrane characteristics that govern the movement of solvent (water) and solute (osmotically active proteins) across the microvascular exchange barrier. A brief description of these relations along with limitations of their use will help in the evaluation of our findings. The factors that govern fluid movement into the myocardial interstitium may be expressed in the form:

\[ J_v = K_t \left[ (P_c - P_m) - \sigma (\pi_c - \pi_m) \right] \] (1)

where \( J_v \) is the total volume of fluid crossing the microvascular exchange barrier and entering the myocardial tissue spaces.35 Normally a volume of fluid equal to \( J_v \) is removed from the heart via the myocardial lymphatics (\( Q \)). \( K_t \) is the filtration coefficient that is a function of the hydraulic conductivity of the microvascular exchange barrier as well as the surface area over which water exchange may take place. \( P_c \) is the hydrostatic pressure within the microvascular exchange vessels and acts to force fluid into the interstitium. \( P_m \) is the hydrostatic pressure within the interstitial matrix and functions to oppose fluid movement into the interstitium. \( \pi_c \) and \( \pi_m \) are the colloid osmotic pressures within the microvessels and interstitium, respectively. The plasma colloid osmotic pressure normally tends to retard the movement of fluid out of the circulation. The interstitial colloid osmotic pressure also results from protein molecules within the interstitial spaces and tends to promote the movement of water out of the microcirculation. The reflection coefficient (\( \sigma \)) determines what portion of the potential osmotic pressure associated with the protein molecules will actually be manifest across the microvascular exchange barrier. Values for \( \sigma \) vary from 0 to 1 and are both molecule and pore specific. When permeability to a given molecule is low, \( \sigma \) will be high (close to 1) and the osmotic pressure gradient generated by that molecule will be near its maximum. When the permeability to a given molecule is high, \( \sigma \) will approach 0 and little osmotic pressure will be manifest. Since \( \sigma \) is a direct indication of microvascular permeability, it is central in our second important fundamental relation.

\[ C_l/C_p = \frac{1 - \sigma}{1 - \sigma e^{-x}} \] (2)

Equation 2 may be utilized in the estimation of \( \sigma \).32,34 \( C_l \) and \( C_p \) are the concentrations of osmotically active protein molecules within the lymph and plasma, respectively. The protein concentration in the lymph is assumed to be a reliable indicator of interstitial protein concentration. In Equation 2, \( x \) is equal to \( J/(1 - \sigma)/PS \) where \( J \), and \( \sigma \) are the same as those values found in Equation 1. PS is the permeability surface area product for the diffusive flux of plasma proteins. It is critical to note from Equation 1 that when microvascular pressure (\( P_c \)) is elevated, \( J_v \) will increase. As \( J_v \) increases, the limiting value of Equation 2 becomes

\[ C_l/C_p = 1 - \sigma \] (3)

At this point, the system is said to be at filtration independence since increases in the microvascular filtration rate no longer affect \( C_l/C_p \). Equation 3 is surface area-independence since the PS term no longer
appears in the expression. This holds true when the relation between the molecular protein dimensions and pore size provide a Peclet number sufficiently large to support our contention that \( C_i/C_p \) is approaching \( 1 - \sigma \). In our preparation, it was necessary to fractionate the plasma and lymph proteins and to utilize \( \beta \)-lipoprotein as the permeability indicator due to its large size and acceptable Peclet number. The application of Equations 1, 2, and 3 will then allow evaluation of myocardial microvascular permeability when myocardial microvascular pressure is elevated, \( J_L \) increases, and \( C_i/C_p \) is measured.

All data analysis was carried out on a VAX-8600 computer using the SAS software package. All means were compared using the two-sample \( t \) test.

### Results

Portions of chart recordings from a normotensive and hypertensive animal are shown in Figure 1. The two panels on the left show \( P_{ev} \), \( P_{es} \), myocardial lymph flow rate, and \( P_a \) when transmicrovascular fluid flux is at control. The two panels on the right depict the same parameters at maximum transmicrovascular fluid flux following elevation of coronary sinus pressure. Note that although interstitial fluid pressure attains values of near systolic blood pressure during the contractile phase of the cardiac cycle, we show no pressures higher than 50 mm Hg. This is done so that changes in end-diastolic interstitial fluid pressure may be more clearly noted.

Table 1 provides a summary of all the pertinent data at both control and elevated transmicrovascular fluid flux. Under control conditions, \( P_{ev} \) was significantly higher in the hypertensive group. No significant difference could be demonstrated for \( P_a \) and SVP between the two groups. Myocardial lymph flow rate and myocardial interstitial fluid pressure were both significantly elevated in the hypertensive group. No significant difference could be shown between the two groups for the lymph–to–plasma protein concentration ratios for total protein or \( \beta \)-lipoprotein. When transmicrovascular fluid flux was elevated by increasing coronary sinus pressure, \( P_{ev} \) in the hypertensives remained significantly greater than in the normotensives. No significant difference could be demonstrated between normotensive and hypertensive values for coronary sinus pressure or SVP. The fact that systemic venous pressure did not vary between the two groups is significant since an elevation of SVP may perpetuate edema formation. Both myocardial lymph flow rate and interstitial fluid pressure were elevated following coronary sinus pressure elevation. Although no significant difference could be shown between the normotensive and hypertensive values for \( P_{ev} \), \( Q_L \) was significantly different (\( p<0.1 \)). At the maximal elevation of transmicrovascular fluid flux, the lymph–to–plasma protein concentration ratios for total protein and \( \beta \)-lipoprotein were significantly higher in the hypertensive group. The values for \( P_{ev} \) and \( C_i/C_p \) for total protein at maximum transmicrovascular fluid flux in the normotensive group were obtained from regression lines and therefore have no standard deviations. When testing for significant differences between means, the variance of the sample was assumed to equal the variance of the population.

Significant excess myocardial edema formation was found in the hypertensives both under control conditions and following coronary sinus pressure elevation. At baseline, EVF was 2.9 ± 0.2 in the normotensive group and 3.5 ± 0.3 in the hypertensive group. Following elevation of coronary sinus pressure for 3 hours, EVF increased to 3.4 ± 0.3 in the normotensive group while the hypertensive group increased to 4.1 ± 0.1.

Figure 2 depicts the relation between myocardial lymph flow and coronary sinus pressure. Lymph flow from the heart was significantly greater in the hyper-
TABLE 1.  Comparison of Normotensive and Hypertensive Animals at Control and During Maximally Elevated Myocardial Transmicrovascular Fluid Flux Resulting From Coronary Sinus Occlusion

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Arterial pressure (mm Hg)</th>
<th>Coronary sinus pressure (mm Hg)</th>
<th>Systemic venous pressure (mm Hg)</th>
<th>Myocardial lymph flow rate (QL) (ml/hr)</th>
<th>Myocardial interstitial fluid pressure (mm Hg)</th>
<th>C_l/C_P total protein</th>
<th>C_l/C_P 3-lipoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>123 ± 17*</td>
<td>7.3 ± 1.3</td>
<td>2.5 ± 2.1</td>
<td>3.1 ± 2.1</td>
<td>14.9 ± 3.1</td>
<td>0.82 ± 0.07</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>(n = 21)</td>
<td>(n = 10)</td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>160 ± 20</td>
<td>7.8 ± 1.9</td>
<td>2.9 ± 2.5</td>
<td>10.5 ± 2.5</td>
<td>24.8 ± 3.7</td>
<td>0.87 ± 0.10</td>
<td>0.31 ± 0.09</td>
</tr>
<tr>
<td>(n = 12)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td></td>
</tr>
<tr>
<td>Comparison</td>
<td>(p &lt; 0.05)†</td>
<td>NS</td>
<td>NS</td>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.05)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Maximally elevated transmicrovascular fluid flux</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>110 ± 9</td>
<td>52 ± 8</td>
<td>2.8 ± 1.9</td>
<td>29.5 ± 7.3</td>
<td>45‡</td>
<td>0.44‡</td>
<td>0.04 ± 0.03</td>
</tr>
<tr>
<td>(n = 20)</td>
<td>(n = 8)</td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>150 ± 18</td>
<td>48 ± 5.2</td>
<td>3.1 ± 2.6</td>
<td>42.2 ± 8.5</td>
<td>47±</td>
<td>0.60 ± 0.05</td>
<td>0.20 ± 0.07</td>
</tr>
<tr>
<td>(n = 12)</td>
<td>(n = 5)</td>
<td>(n = 8)</td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
<td>(n = 8)</td>
<td></td>
</tr>
<tr>
<td>Comparison</td>
<td>(p &lt; 0.05)†</td>
<td>NS</td>
<td>NS</td>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.05)</td>
<td>NS</td>
<td>(p &lt; 0.05)</td>
</tr>
</tbody>
</table>

NS, no significant difference; Q_L, lymph flow referenced to systemic venous pressure; and C_l/C_P, lymph-to-plasma concentration ratio.

*Values are mean ± SD.
†Means were compared using a one-tailed t test.
‡Regression values tested for differences from numeric means by assuming equal variances.

Discussion

Our interest in microvascular changes within the heart during chronic arterial hypertension stems from data on patients and animals that suggest that chronic elevation of arterial pressure portends a poor outcome following myocardial infarction.1-3 A literature base also exists that indicates that myocardial microvascular permeability (MMP) is altered in chronic arterial hypertension.4-7 We believed, and the literature supported our contention, that chronic arterial hypertension could produce myocardial edema formation, thus compromising the ability of the heart to contract when stressed.8-11 We postulated that chronic elevation of systemic arterial pressure resulted in an increased MMP. This increase in MMP at the exchange vessel level would increase the formation of myocardial edema. Although ventricular hypertrophy may increase contractility in control hypertensives, this may not be true when hypertensive hearts are stressed following infarction. Myocardial edema resulting from increased MMP could decrease contractility and promote growth of an infarction by increasing oxygen diffusion distances and increasing myocardial stiffness. A decrease in the ability of the heart to efficiently
contract in patients with chronic arterial hypertension could account for the relatively poor prognosis following myocardial infarction in those patients when compared with normotensive people. It was our intention to test the hypothesis that chronic elevation of systemic arterial pressure could increase myocardial microvascular permeability, thus promoting myocardial edema formation, and to determine the magnitude of any such change. We believe that increases in MMP and myocardial edema formation could contribute to the increased myocardial pathogenicity of chronic arterial hypertension in subjects already insulted by increased arteriosclerosis and increased work load on the heart.

Standard techniques for the evaluation of MMP were applied to both normotensive and chronically hypertensive dogs.1315 Our first indication that chronic arterial hypertension may have altered the microvasculature was obtained from Table 1. Under control conditions (i.e., for the same coronary sinus pressure), myocardial lymph flow was significantly greater in the chronically hypertensive group. This increase in lymph flow rate was driven by the significant increase seen in our index of myocardial interstitial fluid pressure within the hypertensive group. As pointed out in "Results," any change in transmicrovascular fluid flux per unit area of exchange vessel (increasing lymph flow) must produce a change in the lymph-to-plasma protein concentration ratio for each of the plasma proteins as well as for total plasma protein. Table 1 demonstrates that no significant change took place in C/ for either total protein or the individual plasma protein, β-lipoprotein. These results indicated that either MMP or microvascular exchange vessel surface area had increased. A second indicator of a possible increase in microvascular permeability was obtained from Figure 3. As coronary sinus pressure was elevated, the lymph-to-plasma protein concentration ratio for total protein decreased more in the hypertensive group when compared with the normotensive group. Again, this is indicative of either a change in microvascular permeability (α) or exchange vessel surface area. To differentiate between changes in MMP and exchange vessel surface area, the washdown technique for determination of the filtration independent reflection coefficient, as outlined in "Materials and Methods," was applied to our preparation. It is important to note that the determination of α is totally surface area-independent. Increases in exchange vessel surface area due to myocardial hypertrophy or decreases due to hypertensive rarefaction have no effect on this independent index of MMP.1223
By fractionating the plasma proteins, we were able to plot lymph flow as a function of the $C_l/C_p$ ratio for several of the endogenous plasma protein molecules. We found that $\beta$-lipoprotein has an acceptable Peclet number to be utilized as an indicator of MMP at filtration independence.\textsuperscript{11,15} Figure 4 demonstrates that a significant difference exists between the filtration-independent reflection coefficient ($\sigma$) for $\beta$-lipoprotein between the normotensive and hypertensive groups. $\sigma_{\text{hypertensive}}$ in fact decreased from 0.96 to 0.80. This is indicative of an increased MMP within the hypertensive group. We have recently confirmed this finding utilizing a new technique for the chronic evaluation of MMP.\textsuperscript{12}

Significant excess myocardial edema formation was noted at control coronary sinus pressures in hypertensive dogs when compared with the normotensive dogs. Following elevation of coronary sinus pressure, normotensive hearts accumulated edema fluid at the rate expected for control animals.\textsuperscript{29} When coronary sinus pressure was elevated for 3 hours in the hypertensive group, myocardial edema accumulation progressed to a level that has been associated with compromised myocardial function.\textsuperscript{12}

It is important to note that two of the myocardial defense mechanisms against edema formation are active in the hypertensive group. First, due to an increase in MMP and EVF, the control myocardial interstitial fluid pressure has increased significantly to 24.8 ± 3.7 mm Hg in an effort to oppose further movement of edema fluid into the myocardial interstitium. Second, myocardial lymph flow is elevated in the hypertensive group both under control conditions and for any given elevation in coronary sinus pressure (Figure 1). The third defense mechanism against edema formation is a decrease in interstitial colloid osmotic pressure. This mechanism is rendered largely ineffectual due to the increase in MMP.

Having determined that MMP is in fact increased in chronic arterial hypertension, two mechanisms present themselves as potential causes for a disruption in the myocardial microvascular endothelium. First is the possibility that the chronic elevation of arterial pressure directly damages the microvascular exchange barrier. We have reservations concerning this mechanism because Joyner et al found that small venules in hypertensive animals had a decrease in pressure of 50–60%.\textsuperscript{28} Others have found that exchange vessel pressure may be elevated, although we do not believe the increase found would disrupt the integrity of the microvascular endothelial lining.\textsuperscript{31} In fact, most vessels, when exposed to elevated pressures over time, will develop a thickening of the endothelial lining. A second possibility may be that chronic arterial hypertension produces circulating humoral factors, due to pressure effects or injury in larger vessels, which can disrupt microvascular integrity. Huxley\textsuperscript{32} recently reported that atrial natriuretic factor causes an increase in capillary hydraulic conductivity and Garcia et al\textsuperscript{33} demonstrated that atrial natriuretic factor is elevated in hypertensive subjects. These findings provide promising new directions for future studies. The factors we monitored during our study, such as renin, potassium, and blood urea nitrogen, either did not increase or returned to control within 1 week.

Further investigation into the mechanisms responsible for the increased microvascular permeability in chronic hypertension is certainly necessary. Clarification of the mechanism may signal a procedure by which the permeability change could be prevented or reversed. The maintenance of normal myocardial microvascular permeability would in turn reduce the potential for myocardial edema formation and its deleterious sequelae.

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