Myocardial transcapillary exchange in the hypertrophied heart of the dog

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Laughlin, M. Harold, and John N. Diana Myocardial transcapillary exchange in the hypertrophied heart of the dog. Am. J. Physiol. 229(3): 838-846. 1975.—Myocardial transcapillary exchange was investigated in control hearts and in two types of hypertrophied hearts: exercise hypertrophy and pathological hypertrophy due to tricuspid insufficiency. Using the single-injection indicator-diffusion method (6, 28), myocardial extractions (E), capillary clearances (C), and permeability-surface area products (PS) of urea, sucrose, and inulin were measured in intact, pump-perfused, working hearts of anesthetized dogs. Both types of cardiac hypertrophy were associated with a decreased coronary vascular resistance. Myocardial E, C, and PS values from the exercised group were not significantly different from control. Dogs with pathological hypertrophy exhibited increased central venous pressures, RVEDP's, and heart rates which were greater than control values. The E, C, and PS values from the pathologically hypertrophied hearts were significantly greater than control. These increases in myocardial transcapillary exchange can be explained either by increasing the equivalent pore radius of myocardial capillary membranes from a control value of 70 to 100 Å or by assuming that pathologically hypertrophied hearts have a myocardial capillary surface area available for exchange which is twice that of control hearts.

PATHOLOGICAL CARDIAC HYPERTROPHY has been associated with several observations which suggest that myocardial perfusion may be altered. First, local hypoxic scar patterns have been found in hypertrophied, failing hearts (4). Second, histological studies have shown that the number of capillaries per square millimeter of myocardium is decreased in pathological cardiac hypertrophy (40, 49). Third, it has been shown that the diameter of the coronary arteries may not increase at a rate that is consistent with delivery of an increased blood flow to the increased myocardial muscle mass (11, 24, 26, 35, 50). On the other hand, in myocardial hypertrophy of physiologic origin (exercise hypertrophy), none of the above factors appears to be true (25, 26, 34, 46, 49). These observations indicate that there may be some fundamental difference in the ability of the coronary circulation to adapt to myocardial muscle needs in the two different types of hypertrophy.

A link between substrate delivery and use in myocardial tissue is the process of transcapillary exchange. There are no studies in the literature which address themselves to the important problem of transcapillary exchange of substances in any form of cardiac hypertrophy. This study will present data which show that transcapillary exchange of lipid-insoluble substances is increased above control values in the hypertrophied hearts of dogs subjected to pathophysiologic stress, whereas myocardial transcapillary exchange is not changed from control in exercise-induced cardiac hypertrophy.

METHODS

Experimental Animals

Experiments were conducted on 49 anesthetized, mongrel dogs of both sexes, weighing 15–25 kg. These animals were from three groups: control, exercised, and tricuspid insufficient.

Control. The control animals consisted of two groups: 16 control dogs and 3 sham-operated dogs. There was no difference in results between the 16 control dogs and the 3 sham-operated dogs.

Exercised. Nine dogs were run on a belt-type, motor-driven treadmill 5 times/wk for a period of 10 wk using an exercise program designed by Tipton (45). The speed, treadmill grade, and duration of running were increased progressively from speeds of 5–8 km/h and grades of 0–20% for 15 min during the 1st wk to speeds of 10–20 km/h and grades of 10–20% for periods of 50 min during the last week.

Tricuspid-insufficient dogs. Tricuspid insufficiency was produced in 14 dogs using the surgical technique of Rubin (42) under sterile conditions. These animals were allowed a period of 6–10 mo for the development of cardiac hypertrophy.

One dog, which was expected to be a control animal, was found to have cardiac hypertrophy due to heart worms (Dirofilaria immitis). The results of myocardial transcapillary exchange measurements from this dog were found to be identical to those of the animals with cardiac hypertrophy due to tricuspid insufficiency. Therefore, the results from this animal were included as part of the total (means and SE's) tricuspid-insufficient data.
General Experimental Procedure

Transcapillary exchange experiments were conducted on 11 control, 6 tricuspid insufficient, and 9 exercise-trained dogs. Each dog was heparinized with sodium heparin (10 mg/kg body wt, iv). A midsternal incision was made and the heart suspended in a pericardial cradle. A cannula was advanced into the aorta via the internal thoracic artery for measurement of aortic pressures and sampling of aortic blood. The left anterior descending branch of the left coronary artery (LADCA) was dissected free and 00-silk thread passed beneath it. A polyethylene catheter (PE-260) with a flared end was inserted through the left common carotid artery to the level of the aortic valve. Perfusion of blood through the catheter was started and the catheter inserted and tied into the LADCA.

In a pilot study it was demonstrated that this cannulation procedure did not interfere with flow to the circumflex branch of the left coronary artery. Using the methods of Tschopp et al. (49), it was shown that the terminal vascular volume and nutritional blood flow of that portion of the heart perfused by the circumflex branch of the coronary artery in cannulated preparations were equal to the values of noncannulated or control hearts.

The LADCA was perfused at constant blood flow with a calibrated Sigmamotor pump as shown in Fig. 1. A Windkessel flask was interposed between the pump and the coronary artery. The coronary sinus was cannulated with a size 20 Foley catheter introduced into the sinus through a small incision in the right atrial appendage.

Areas of heart perfused. At the conclusion of each experiment in which transcapillary exchange was measured, T-1824 dye was injected through the LADCA cannula to outline those portions of the myocardium that had been perfused by the experimental setup. The stained areas were dissected from the nonstained areas and the weights of each determined. The results of this procedure in 26 hearts demonstrated that 38 ± 1 (SE) % of the total heart weight was perfused. The perfused portions of the control

![Fig. 1. Experimental preparation. 1, right ventricular pressure cannula. 2, coronary artery perfusion pressure (CAP). 3, coronary sinus pressure (CSP). 4, cannula in left anterior descending coronary artery. 5, Foley catheter in coronary sinus.](http://ajplegacy.physiology.org/)

as well as the hypertrophied hearts included 22 ± 4 (SE) % of the right ventricle, 47 ± 4 (SE) % of the left ventricle, and 56 ± 3 (SE) % of the interventricular septum.

Myocardial Transcapillary Exchange Measurements

The single-injection indicator diffusion method of Crone (6) and Martin de Julian and Yudilevich (28) was used to study myocardial transcapillary exchange. The parameters measured with this technique were the fractional extraction (E), capillary clearance (C), and permeability surface area product (PS) of the lipid-insoluble substances urea, sucrose, and inulin.

This method involves the rapid injection of a mixture of two or more radioactive tracers into the LADCA cannula followed by immediate, continuous sampling of the venous effluent from the coronary sinus. One of the tracers must be a solute that remains within the vasculature (reference tracer), and the others are solutes that can diffuse across the capillary membrane (diffusible tracer). The concentrations of the different tracers are measured in the venous samples and plotted against time. At any given time (t) for venous blood samples, extraction (E(t)) can be defined as (C_f - C_d)/C_f; where C_f represents the "normalized" venous concentration of the reference tracer and C_d represents the normalized venous concentration of the diffusible tracer. Venous concentrations were normalized by expressing them as a percent of the amount of that molecule injected on the arterial side, i.e., percent dose per milliliter (B).

In these experiments each 1-ml injection contained 12-16 μCi of ⁵¹Cr-labeled RBC's and 2 μCi of a ³H-labeled molecule and 2 μCi of a ¹⁴C-labeled molecule. The diffusible indicators used were [³H]sucrose, [³H]inulin, [¹⁴C]sucrose, and [¹⁴C]urea (Amersham/Searle Co.).

Extractions. The data produced by this method are similar to the sample concentration-time curve and extraction-time curve shown in Fig. 2. If a plateau (similar to the
one shown in Fig. 2) was obtained in the extraction-time curve, the average fractional extraction (E) was determined by averaging the E(t) values obtained on the plateau before the peak of the concentration time curve as done by Trap-Jensen and Lassen (48). If no plateau occurred, E was determined by averaging the E(t) value obtained at the peak of the concentration-time curve with the two E(t) values preceding it. One-hundred fifty-six E determinations were made in this investigation. Of the 156 determinations 21 were from extraction-time curves without a plateau.

Capillary clearance. The capillary clearance of a solute is the "imaginary volume of blood which, if completely equilibrated with tissue in a given time, would have transported the same quantity of solute" (40). Renkin (40) has also shown that E and blood flow (F) can be used to calculate the capillary clearance of a solute (C) as shown in equation 1.

\[ C = F \times E \]  

(1)

\[ PS = -F \ln (1 - E) \]  

(2)

Sampling and counting procedures. Venous blood samples were taken continuously at a rate of 1.33/s. One-quarter milliliter of each venous blood sample and hemolyzed with 2.4 \( \times \) \( 10^{-4} \) M phosphate buffer (0.204 g KH\(_2\)PO\(_4\) and 0.2068 g Na\(_2\)HPO\(_4\) per liter). Proteins were precipitated with 25% TCA and separated by centrifugation. One-half milliliter of the supernatant fluid was solubilized with NCS solubilizer (Amersham/Searle Co.) and added to 15 ml of cocktail (5 g PPO, 63 mg POPOP in toluene). The supernatant samples were counted for beta activity and the precipitate was counted for gamma activity. The processing separated the bound \( ^{61}\text{Cr} \) gamma label (precipitate) from the beta isotopes in the plasma (supernatant fluid).

A Nuclear-Chicago liquid scintillation counter (725) was used for beta-emitting isotopes, and a Nuclear-Chicago 8725 gamma counter was used for the \( ^{41}\text{Cr} \) and \( ^{111}\text{I} \) isotopes. All counting was done using standard techniques as outlined by Kisicleski (20). Each counting run was accompanied by internal standards for each isotope used. The amount of bound \( ^{61}\text{Cr} \) was determined for each experiment and found to range from 96 to 99%.

Fractional extractions were calculated from the raw data (counts/min) on a Linc 8 computer. Statistical significance was determined with the Student unpaired-\( t \) test unless otherwise specified. Differences were considered significant when \( P \leq 0.05 \).

Physiologic State of Animals

At the time of the myocardial transcapillary exchange determinations, the physiological condition of the dogs was assessed by measuring right ventricular end-diastolic pressure (RVEDP), central venous pressure in the superior vena cava (CVP), aortic pressure (AO\(_a\)), coronary perfusion pressure (CAP), coronary sinus pressure (CSP), right ventricular end-systolic pressure, and RV dP/dt. (Statham pressure transducers were used for all pressure measurements.) In the two experimental groups, myocardial hypertrophy was determined by comparing heart weight:body weight (HW/BW), right ventricular weight:body weight (RVW/BW), and wet weight/dry weight ratios with the values from the control dogs. The heart dissection procedures were designed after the method of Herman (12). Wet weight/dry weight ratios were determined by taking paired 5- to 10-g samples from the free walls of both ventricles and from the interventricular septum. The samples were blotted to remove excess fluid and wet weight was measured. The dry weight was determined after the samples had been in an oven at 200°F for 72 h. At the conclusion of the transcapillary exchange measurements, cardiac outputs (CO) were measured with standard indicator dilution techniques using \( ^{131}\text{I} \)-labeled albumin.

RESULTS

Physiologic State of Animals

Exercise trained. The effectiveness of this training program was evaluated by measuring the cytochrome oxidase activity of the gastrocnemius muscle (14, 38). The results of the cytochrome oxidase activity measurements show that the exercised animals had a mean value of 1,050 ± 100 \( \mu \text{mol} \text{O}_2/\text{g} \text{per min} \), which was 106% greater than the activities obtained from nonexercised control animals (510 ± 100 \( \mu \text{mol} \text{O}_2/\text{g} \text{per min} \)). These data indicate that the exercised dogs were exercise trained.

The exercise-trained dogs were found to have increased HW/BW ratios (Fig. 3), and a wet weight/dry weight ratio of 5.5 ± 0.5 (SE), which was not significantly different from the control value of 5.4 ± 0.3 (SE). These data indicate the presence of cardiac hypertrophy and eliminate fluid accumulation as a factor responsible for the increased heart weights. Exercise cardiac hypertrophy was associated with a decreased coronary vascular resistance. The mean cardiac output of the exercise-trained dogs was 79 ± 24 (SE) ml/(min X kg), which was not significantly different from the control value of 64 ± 9 (SE) ml/(min X kg).

Tricuspid insufficient. The tricuspid-insufficient dogs were found to have definite cardiac hypertrophy as demon-
TABLE 1. Hemodynamic measurements

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Ao</th>
<th>RVEDP</th>
<th>RVESP</th>
<th>RV(dP/dl)</th>
<th>CVP</th>
<th>Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Central</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>16</td>
<td>135</td>
<td>0.9</td>
<td>36</td>
<td>627</td>
<td>2.0</td>
<td>205</td>
</tr>
<tr>
<td>Exercise</td>
<td>9</td>
<td>131</td>
<td>-1.0</td>
<td>33</td>
<td>580</td>
<td>-0.3</td>
<td>244</td>
</tr>
<tr>
<td>Tricuspid insufficient</td>
<td>14</td>
<td>131</td>
<td>6.0</td>
<td>37</td>
<td>632</td>
<td>7.4</td>
<td>237</td>
</tr>
<tr>
<td>B) Coronary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11</td>
<td>127.6</td>
<td>5.8</td>
<td>61.7</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>6</td>
<td>90.7</td>
<td>-0.6</td>
<td>3.4</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid insufficient</td>
<td>9</td>
<td>92.3</td>
<td>6.5</td>
<td>81.5</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. All pressures are in units of millimeters Hg. n = Number of animals. Ao = aortic pressure. RVEDP = right ventricular end-diastolic pressure. RVESP = right ventricular end-systolic pressure. CVP = central venous pressure. CAP = coronary arterial pressure. CSP = coronary sinus pressure. * P < .0005. † P < .05. ‡ P < .0025.

Myocardial Transcapillary Exchange

Extractions. Figure 4 presents the mean extraction data obtained by standardizing all E(t) versus time curves by setting time 0 equal to the peak of the respective concentration-time curves and averaging the E(t) values at each time. It can be seen that the majority of the mean E(t) values in the myocardium of tricuspid-insufficient dogs are significantly greater than those of control animals, whereas the mean E(t) values obtained from the hearts of the exercise-trained animals were identical to those of control dogs. These data demonstrate that the qualitative result of these experiments does not depend on the method used to determine E, since all E(t) values are increased.

The mean E data are presented in Table 2A. The mean E for hearts hypertrophied due to tricuspid insufficiency was significantly increased above control values for all three molecules while the mean E for the exercise-trained hearts was identical to those of control hearts.

Extraction has been shown to be inversely related to

TABLE 2. Transcapillary exchange

<table>
<thead>
<tr>
<th></th>
<th>Urea</th>
<th>Sucrose</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Extractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>16</td>
<td>0.61</td>
<td>0.56</td>
</tr>
<tr>
<td>Exercise</td>
<td>23</td>
<td>0.60 NS</td>
<td>0.56 NS</td>
</tr>
<tr>
<td>Tricuspid insufficient</td>
<td>13</td>
<td>0.75 P &lt;</td>
<td>0.56 P &lt;</td>
</tr>
</tbody>
</table>

Values are means ± SE. n = Number of experimental observations. The determinations were made on 11 control, 10 exercise-trained, and 6 tricuspid-insufficient dogs. NS = not significantly different from control.
blood flow as shown in Fig. 5. The data in Fig. 5 demonstrate that the changes in extractions observed in these experiments are not due to differences in flow rates since, at any given blood flow, the myocardial extraction values for tricuspid-insufficient dogs are greater than those of control and exercise-trained dogs.

Capillary clearances. Capillary clearances were calculated for each individual experiment using equation 2. The mean clearance data are presented in Table 2B. All myocardial capillary clearances were significantly increased above control values in the hearts of tricuspid-insufficient dogs, whereas only the urea capillary clearance was increased above control by 88, 101, and 383% for urea, sucrose, and inulin, respectively. The ratios of the coefficients of free diffusion are presented in Table 3C. The mean exercise and control myocardial PS ratios were not significantly different from the ratios of the D values. This supports similar observations by Alvarez and Yudilevich (1) and Duran et al. (8). The 55% decrease in $P_{a}/P_{b}$ and the 60% decrease in $P_{a}/P_{b}$ shown in Table 3A for tricuspid-insufficient hearts suggest an increase in myocardial capillary permeability; however, these decreases are not statistically significant.

Duran et al. (8) further reasoned that if $P_{a}$ and $P_{b}$ are both increased by some experimental intervention and $P_{a}/P_{b}$ = $P_{a}/P_{b}$ (where 1 represents the control condition and 2 to the experimental), then the PS values were increased due to an increased surface area with no change in permeability. It follows that if $P_{a}$ and $P_{b}$ are both increased and $P_{a}/P_{b} > P_{a}/P_{b}$, then the PS values were increased due to increased permeability or increased permeability and surface area.

Table 3A contains the ratios of the mean control and experimental myocardial PS values for urea, sucrose, and inulin. The ratios of the coefficients of free diffusion are obtained from a single injection made at flow rates high enough that PS is flow independent. The basis for this analysis is the assumption that PS values are a measure of diffusion through pores in the capillary membranes and that these membranes can be modeled by a membrane containing a group of pores with a given equivalent pore radius. The theory of restricted diffusion indicates that the restriction to transmembrane passage of a solute is dependent on the molecular size of the solute in relation to the size of the pores. Thus, large molecules are relatively more restricted in their diffusion through porous membranes than smaller molecules. Therefore, if molecule $a$ is smaller than molecule $b$ (and restricted diffusion occurs)

$$P_{a}/P_{b} = D_{a}/D_{b},$$

Duran et al. (8) postulated that a measure of restricted diffusion could be obtained by comparing the ratios of PS values for two solutes with the ratios of their coefficients of free diffusion ($D$). The basis for this analysis is the assumption that PS values are a measure of diffusion through pores in the capillary membranes and that these membranes can be modeled by a membrane containing a group of pores with a given equivalent pore radius. The theory of restricted diffusion indicates that the restriction to transmembrane passage of a solute is dependent on the molecular size of the solute in relation to the size of the pores. Thus, large molecules are relatively more restricted in their diffusion through porous membranes than smaller molecules. Therefore, if molecule $a$ is smaller than molecule $b$ (and restricted diffusion occurs)

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### Table 3. PS ratios

<table>
<thead>
<tr>
<th>Condition</th>
<th>$P_{a}/P_{b}$</th>
<th>$P_{a}/P_{b}$</th>
<th>$P_{a}/P_{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid in-</td>
<td>8.7 ± 1.31</td>
<td>3.5 ± 0.4</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Exercise</td>
<td>8.5 ± 1.5</td>
<td>6.2 ± 0.3</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>Tricuspid in-</td>
<td>4.9 ± 1.5</td>
<td>2.4</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>Exercise</td>
<td>5.0 ± 1.3</td>
<td>3.2 ± 0.3</td>
<td>2.9 ± 0.5</td>
</tr>
</tbody>
</table>

**A) Ratios of mean PS values**

<table>
<thead>
<tr>
<th>Condition</th>
<th>$P_{a}/P_{b}$</th>
<th>$P_{a}/P_{b}$</th>
<th>$P_{a}/P_{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11 ± 0.03</td>
<td>11 ± 0.03</td>
<td>11 ± 0.03</td>
</tr>
<tr>
<td>Exercise</td>
<td>9 ± 0.03</td>
<td>9 ± 0.03</td>
<td>9 ± 0.03</td>
</tr>
<tr>
<td>Tricuspid in-</td>
<td>6 ± 0.03</td>
<td>6 ± 0.03</td>
<td>6 ± 0.03</td>
</tr>
</tbody>
</table>

**B) PS ratios from individual experiments**

<table>
<thead>
<tr>
<th>Condition</th>
<th>$D_{a}/D_{b}$</th>
<th>$D_{a}/D_{b}$</th>
<th>$D_{a}/D_{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.5 ± 0.29</td>
<td>2.79</td>
<td>2.69 ± 0.33</td>
</tr>
<tr>
<td>Exercise</td>
<td>7.5 ± 0.29</td>
<td>2.79</td>
<td>2.69 ± 0.33</td>
</tr>
</tbody>
</table>

**C) Ratios of coefficients of free diffusion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>$D_{a}/D_{b}$</th>
<th>$D_{a}/D_{b}$</th>
<th>$D_{a}/D_{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.5 ± 0.29</td>
<td>2.79</td>
<td>2.69 ± 0.33</td>
</tr>
<tr>
<td>Exercise</td>
<td>7.5 ± 0.29</td>
<td>2.79</td>
<td>2.69 ± 0.33</td>
</tr>
</tbody>
</table>

$n =$ Number of experimental animals. The subscripts $U$, $S$, and $I$ represent urea, sucrose, and inulin, respectively. NS = not significantly different from control.

* Statistical significance was determined at the 95% confidence level with the ratio test from Goldstein (10). † Means do not differ from control. ‡ Statistical significance was determined using the unpaired t test. Values for the coefficients of free diffusion were taken from Landis and Pappenheimer (21).
pended. This can only be done if PS determinations are taken at several blood flows for each set of solutes and animal. The results of experiments where such determinations were made are summarized in Table 3B. The PS/PSI ratio is 44% lower than control values, whereas the PS/PSI ratio is 13% and the PS/PSI ratio 4% below control values. Although these data suggest an increase in myocardial capillary permeability, only the decrease in PS/PSI is statistically significant.

**DISCUSSION**

The results of these experiments indicate that extraction, capillary clearances, and PS products of lipid-insoluble molecules are significantly increased above control and sham-operated values in the myocardium of dogs with pathological cardiac hypertrophy due to tricuspid insufficiency. Extraction, capillary clearance, and PS products for the same solutes were not significantly different from control in the myocardium of dogs with exercise cardiac hypertrophy. Both types of cardiac hypertrophy were associated with significant decreases in coronary vascular resistance.

**Physiologic State of Experimental Animals**

Cardiac hypertrophy. Since the extensive investigation by Herrman (12), it has been well documented that the weight of the normal heart is highly correlated to the animal’s body weight (14, 15, 24, 46). Herrman (12) investigated the relationship between heart weights and body weights in 200 male and female dogs ranging from 1.3 to 27 kg body wt and found a mean HW/BW of 7.95 ± 0.05 (SE) g/kg. The mean HW/BW of 7.95 ± 0.2 (SE) g/kg obtained in the present study is nearly identical with the results of Herrman.

Both the tricuspid-insufficient and exercise-trained dogs appeared to have definite cardiac hypertrophy. In the tricuspid-insufficient group, the RVW/BW values support the conclusion that there was right ventricular cardiac hypertrophy as well.

To determine which stage of compensatory hyperfunction in which the experimental animals existed, Meerison’s (30) classification system was used. Using measurements of metabolic, structural, and functional parameters, Meerison has divided cardiac compensatory hyperfunction into three general phases: phase 1) damage phase, phase 2) phase of stable cardiac hypertrophy, and phase 3) failure phase or phase of gradual exhaustion.

The data from the exercise-trained animals, demonstrating cardiac hypertrophy in the absence of any sign of heart failure, indicate that these dogs were in a state of stable cardiac hypertrophy. The tricuspid-insufficient dogs (where there was also cardiac hypertrophy) exhibited the following clinical signs of heart failure: increased CVP, increased RVEDP, and increased heart rate, and thus would be classified in phase 3 of compensatory hyperfunction.

**Transcapillary Exchange**

Extractions and clearances. Alvarez and Yudilevich (1), studying isolated, nonworking dog hearts, found control average fractional extractions of 0.35 ± 0.12 and 0.57 ± 0.04 for sucrose and urea, respectively. The control extraction data presented in Table 2A are in agreement with the findings of these authors.

In this study myocardial extractions and capillary clearances of the tricuspid-insufficient dogs were found to be consistently higher than control values, whereas no consistent difference was observed in the myocardium of the exercised-trained dogs. The increased myocardial capillary clearance values observed in the tricuspid-insufficient dogs indicate that there is an increased ability for transport of solute from blood to tissue in this type of hypertrophied myocardium.

Control PS values. Although the data presented in Table 4 demonstrate that the control myocardial PS values determined in the present investigation are in the range of values reported by other investigators, the PS values determined in the present investigation tend to be higher than those published by Alvarez and Yudilevich (1). One possible reason for this difference is that the present experiments were conducted on the working heart while experiments by other authors have been conducted on nonworking hearts.

Using the nonworking heart perfused at constant flow, Duran et al. (8) have shown that maximal vasodilation of the coronary vascular bed can cause a twofold increase in myocardial PS values for Na and glucose. These increases are presumably due to an increased capillary surface area, i.e., redistribution of blood flow to exchange vessels. It is probable that the coronary vascular bed of the working heart is more vasodilated than that of a nonworking heart (due to the increased metabolic demand of the working heart) and as a result exhibits higher PS values resulting from an increased capillary surface area. Considering the dependence of myocardial oxygen consumption on developed tension and the effects of oxygen tension on coronary blood flow and resistance, it is surprising that there were not greater differences between the myocardial PS values obtained using the two different experimental preparations.

**Exercise PS’s.** Myocardial PS values did not appear to be affected by exercise cardiac hypertrophy, suggesting that cardiac hypertrophy due to exercise training has no significant effect on myocardial transcapillary exchange. This was not surprising, since the exercise-hypertrophied heart was a normal or increased capillary density (31, 35, 47, 50), and there was normal coronary blood flow (19, 22, 23) indicating adequate myocardial perfusion.

**Tricuspid-insufficient PS values.** Cardiac hypertrophy induced with tricuspid insufficiency was associated with a significant increase in myocardial PS values for urea.
sucrose, and inulin. The increase in myocardial PS values was surprising, since histological evidence showing a decreased capillary density (36, 41, 50) implies a possible decrease in PS values resulting from decreased capillary surface area.

The increase in PS values observed in these experiments could be explained by an increase in the effective capillary surface area available for diffusion, by an increase in capillary permeability (change in equivalent pore radius), or by an increase in capillary surface area and permeability. An increase in capillary surface area could result from an increased number of pores per square centimeter of capillary membrane or, more probably, from an increased area of capillary membrane due to an increased number of capillaries open per 100 g of tissue. The mechanism for an increased number of capillaries open for flow is presumably related to vasodilation of arterioles and/or opening of precapillary sphincters.

The possibility of finding increased PS values due to increased capillary surface area is supported by the data of Duran et al. (8), which demonstrated that coronary vasodilation can cause large increases in PS values. The decreased coronary vascular resistance observed in the tricuspid-insufficient animals implies vasodilation and supports the possibility of an increased capillary surface area.

It has been shown that the normal heart has from 30 to 50% of its capillaries open and functioning at any given time (16, 29, 32). This implies a coronary capillary reserve of 50–70%. If, in tricuspid insufficiency, myocardial PS values were increased due to a two- to fourfold increase in the number of capillaries open, the coronary capillary reserve would be greatly reduced. In fact, if increases in PS resulted only from increased surface area, it appears that nearly all the capillaries would be open in the pathologically hypertrophied heart under resting conditions, and coronary reserve capacity would be severely reduced. Such a situation has profound implications relative to the ability of the myocardium to adapt its nutrient supply to stresses which may be placed upon the heart.

If a permeability change was involved in the increase in myocardial PS values, the probable mechanism of this change is not clear at this time. Arturson et al. (2), using the plasma-lymph concentration ratio method in the isolated dog heart, have shown with computer modeling that acute elevations in venous pressure may result in an increase in myocardial capillary permeability. Although in the present investigation the measurements of PS values were conducted at equal coronary sinus pressures, it is possible that chronic exposure to increased CVP associated with tricuspid insufficiency could cause an increase in capillary permeability similar to that postulated by Arturson et al. (2).

The theory of restricted diffusion predicts that an increase in capillary permeability will have a relatively greater effect on a large molecular weight solute than on a smaller molecular weight solute (3, 38). This consideration alone, applied to the PS data showing a fourfold increase in inulin PS and a twofold increase in urea PS, indicates a possible increase in capillary permeability. A more quantitative approach for looking at these data is believed to be the use of PS ratios (1, 7–9). The PS ratio data presented in Table 3 indicate that a change in capillary permeability may be associated with tricuspid insufficiency. However, since the only significant difference was found for the $PS_n/PS_1$, and since it is possible that the inulin data may be inaccurate due to the variation in the molecular size of inulin (21, 33), it is difficult to make a definite conclusion from this type of analysis. It is also possible that the PS ratio relationship may not be sensitive enough to detect changes in capillary permeability because of the experimental variation inherent in the method used to measure PS. Because of these considerations, we have chosen to use PS values with the predictions of a restricted diffusion model for transcapillary exchange in an attempt to determine if a change in capillary permeability has occurred.

PS can be defined as shown in equation 3

$$PS = \frac{D_a A_{ad}}{\Delta X}$$

where $D_a$ is the coefficient of free diffusion for the solute, $A_{ad}$ is the total apparent area for solute diffusion, and $\Delta X$ is the thickness of the membrane. If we assume the capillary membrane equivalent to a thin membrane with rigid
cylindrical pores, the theory of restricted diffusion can be applied (44)

\[
\frac{A_{sd}}{A_p} = (1 - a/r)^2 \left\{ 1 - 2.104(a/r) + 2.09(a/r)^2 - 0.95(a/r)^3 \right\}
\]

where \(A_p\) is the total pore area per 100 g of tissue, \(a\) is the molecular radius of the solute, and \(r\) is the radius of the equivalent pore. If \(N\) represents the number of pores per 100 g of tissue, \(A_p\) can be defined as

\[
A_p = N\pi r^2
\]

The combination of equations 3, 4, and 5 yields equation 6.

\[
PS = \frac{N}{A_x} \pi r^2 (1 - a/r)^2 \left\{ 1 - 2.104(a/r) + 2.09(a/r)^2 - 0.95(a/r)^3 \right\}
\]

Using equation 6, theoretical curves of PS values versus molecular radius were calculated. The PS data were then fit to the curves and values for equivalent pore radius determined as shown in Figs. 6, 7, and 8.

Figure 6 demonstrates that there was no difference between the best-fit curves of the control and exercise-trained animals. The data from both groups fit curves describing a theoretical capillary membrane with an "equivalent" pore radius of 70 Å, 3 \times 10^2 pores/100 g, and a \(\Delta X\) of 4,800 Å. The value for \(\Delta X\) was chosen because it produced the best fit for the data and because Karnovsky (18) has shown that mouse myocardial endothelial cells have a thickness ranging between 1,000 and 5,000 Å. The 70 Å value for equivalent pore radius in myocardial capillaries is in good agreement with the values in the literature: greater than 50 Å (1), 60–160 Å (2), 20–100 Å (19), and 60 Å (Bassingthwaighte; personal communication).

Figures 7 and 8 present the results of curve-fitting procedures for myocardial PS data from tricuspid-insufficient animals. The data fit a theoretical curve for an equivalent pore size of 100 Å in the cases of urea and sucrose (Fig. 7) and support the contention that an increase in capillary permeability could explain the results of these experiments.

### REFERENCES


17. Kampp, M. The diffusion permeability of some artificial and...


