Effects of Perfusion Pressure on Energy and Work of Isolated Rat Hearts

Thomas Watters, Joan Wikman-Coffelt, Shao Wu, Thomas L. James, Richard Sievers, and William W. Parmley

A chemomechanical study of hypertrophied hearts of 6-month-old spontaneously hypertensive rats (SHR) and that of age-matched Wistar-Kyoto (WKY) rats was carried out, analyzing the response of the heart to steady-state changes in coronary perfusion pressure. The ratio of heart (dry)-to-body (wet) weight of WKY rats was 0.37±0.02 (10⁻³) and for SHR was 0.58±0.03 (10⁻³) (p<0.01). In the apex-ejecting, isolated, pyruvate-perfused working hearts of WKY rats and SHR, coronary flow was constant when coronary perfusion pressure was set between 140 and 190 cm H₂O (range of autoregulation). Coronary flow was perfusion pressure dependent when the coronary perfusion pressure was set below 110 cm H₂O for both WKY rats and SHR. Cardiac output, developed pressure, rate of pressure development (dP/dt), and oxygen consumption were constant in the range of autoregulation but decreased directionally with coronary perfusion pressure below 110 cm H₂O for both SHR and WKY rats. There was a significantly lower phosphorylation potential in SHR as compared with WKY rats when coronary perfusion pressure was reduced to 80 cm H₂O. In the region of autoregulation, coronary flow and oxygen consumption were significantly less in SHR, although developed pressure was significantly greater at both high and low workloads. The importance of coronary perfusion pressure in SHR using the apex-ejecting working heart model was confirmed using other isolated perfused heart models (i.e., the Langendorff apex-vented heart model to simulate low workloads and the Langendorff isovolumic heart model to simulate high workloads). Furthermore, findings were not changed if FC-43 was added to the perfusate to facilitate delivery of oxygen to the myocardium and increase the viscosity of the perfusate. (Hypertension 1989;13:480–488)

Coronary flow depends on perfusion pressure and vascular resistance.1–7 Vascular resistance depends on neurohormonal factors, myocardial contraction, myocardial metabolites, partial gas pressure, and alterations in the vascular endothelium.1–10 Both in situ7 and in the isolated perfused heart4 there is a range of coronary perfusion pressures from about 100 to 180 cm H₂O where coronary perfusion pressure does not influence coronary flow; however, with values lower than 100 cm H₂O, alterations in perfusion pressure result in a direct correlation between coronary flow and coronary perfusion pressure. With coronary perfusion pressures below 100 cm H₂O, coronary vessels become maximally dilated and flow becomes pressure dependent; that is, autoregulation of coronary blood flow is lost and control resides mainly in the endothelium of the vascular bed. An increase in coronary perfusion pressure results in an increase in water and cation content of endothelial cells, which leads to stretch of endothelial cells and an elevation in coronary flow.2 Vasodilators have little effect at the low perfusion pressure, but augment flow in the region of autoregulation in the isolated perfused heart, including that of spontaneously hypertensive rats (SHR).11

Hypertension, such as that found in SHR or rats with aortic coarctation, is associated with abnormalities in the endothelium of the vasculature, especially capillaries.9,10 Because coronary flow is susceptible to coronary perfusion pressure,1–9 the present studies were carried out first to determine how coronary perfusion pressure influences coronary flow in SHR,
and second to determine how dependence of coronary flow on alterations in perfusion pressure may be related to energy metabolites, especially at high workloads, in SHR versus WKY rats.

Materials and Methods

Animal Models

Six-month-old SHR and Wistar-Kyoto (WKY) control rats were obtained from Taconic Farms, Germantown, New York. Rats were individually caged and fed standard rat chow.

Perfused Heart Models

Apex-ejecting working heart model. The apex-ejecting working rat heart preparation has been described in detail. With this model the heart ejected through the ventricular apex and a check valve to a windkessel, which was raised or lowered to set afterload pressure independent of coronary perfusion pressure. Coronary perfusion pressure was varied by raising and lowering the aortic windkessel. The left atrial filling pressure was held constant at 10 cm H₂O. When coronary perfusion pressure was varied, the height of the ventricular afterload windkessel was held constant at 70 cm H₂O. A cannula, exiting from the apex of the left ventricular chamber to the check valve, was fitted with a t-tube, one end lead connected to a Statham pressure transducer, (Gould, Cleveland, Ohio) for measurement of left ventricular pressure. The other end lead connected to the windkessel for apex ejection. For all heart models, lungs were tied off tightly so that coronary flow exited from the heart through the pulmonary artery. This flow represents total coronary return since all other arteries and veins exiting or entering the heart were tied off. Cardiac output was monitored by collecting the perfusate from the aortic chamber. For these collections the pump effluent was diverted from the aortic chamber directly to the condenser as described earlier. Coronary flow was not included in cardiac output.

Langendorff apex-vented heart model. For the apex-vented hearts, a 2.2-mm diameter plastic tube was sutured into the apex for lowering developed pressure. A polyethylene cannula was inserted through the left atrium and mitral valve into the left ventricle, then sutured in place. The cannula was connected to a Statham P23Db pressure transducer, (Gould, Cleveland, Ohio) for measurement of left ventricular pressure. The other end lead connected to the windkessel for apex ejection. For all heart models, lungs were tied off tightly so that coronary flow exited from the heart through the pulmonary artery. This flow represents total coronary return since all other arteries and veins exiting or entering the heart were tied off. Cardiac output was monitored by collecting the perfusate from the aortic chamber. For these collections the pump effluent was diverted from the aortic chamber directly to the condenser as described earlier.

Langendorff isovolumic heart model. In the isovolumic rat hearts, a 100-μl latex balloon was inserted into the left ventricle via the left atrium as described earlier. A plastic tube for measuring left ventricular pressure was placed inside the latex balloon, sutured to the balloon’s proximal end, and directed out through the nuclear magnetic resonance (NMR) bore to allow volume changes while the heart was in the NMR bore. Volume in the latex balloon was monitored with a calibrated microsyringe (accuracy 0.001 ml). Two three-way stopcocks between the transducer, syringe, and tube leading to the heart allowed for continuous monitoring of the left ventricular developed pressure throughout the study. The beating heart was placed in a 20-mm NMR tube and then lowered into the magnetic resonance spectrometer bore. Coronary flow was continuously siphoned from the NMR tube (above the heart) through a peristaltic pump, and flow rate was measured during all stages of the experiment by collecting the effluent from the right ventricular outflow tract in a calibrated cylinder. Pacing leads designed to prevent noise artifact were inserted at the base of the right ventricle and connected to a Medtronic Model 5320 (Quincy, Massachusetts) pulse generator for pacing the heart at a constant rate. All hearts were paced at the same rate.

Perfusion Conditions

Hearts were perfused with a modified Krebs-Henseleit solution containing: 117 mM NaCl, 4.3 mM KCl, 2.0 mM CaCl₂, 1.2 mM MgCl₂, 0.1 mM KH₂PO₄ (the lower inorganic phosphate [P₄] was used to prevent interference with MRS analysis of intracellular P₄), 25 mM NaHCO₃, 0.5 mM NaEDTA, 10 mM pyruvate, 2 mg/l insulin, and 10⁻⁶ M isoprenal. In some studies the hearts were perfused with 50:50 FC-43 (Green Cross Corp., Osaka, Japan), a perfluorocarbon perfusate, to increase the viscosity of the perfusate and the oxygen carrying capacity of the medium, thereby lowering coronary flow. The media was bubbled with 95% O₂ and 5% CO₂ at 25° C, and the temperature was raised subsequent to flushing with gases to dissolve maximum oxygen in the perfusate. The oxygen tension in the perfusate was maintained between 650 and 700 mm Hg. “Arterial” samples were aspirated from the aortic chamber and “venous” samples were drawn from a catheter introduced into the right ventricular outflow tract for oxygen measurements before introducing the heart into the magnet bore. Similarly, oxygen was measured at the end of each experiment or removed and oxygen measured similarly intermittently. PaO₂ was measured and oxygen content calculated as described earlier.

P-31 Nuclear Magnetic Resonance

P-31 NMR spectra of the beating heart were obtained on a 5.6 Tesla vertical 76-mm bore spectrometer. The home-built spectrometer is connected to a 1180 Nicolet computer, a Nicolet 2938 pulse programmer, and a high-resolution 20-mm broad band probe. P-31 NMR spectra were obtained without proton decoupling at a 97.3 MHz.
Pulse angle was 75°, recycle time 2.25 seconds, and spectral width 4,000 Hz. Chemical shifts refer to the resonance position of phosphocreatine (PCr) at 0 parts per million (ppm). Transients were accumulated for 5 minutes. For each spectrum, the characteristic peaks of P, PCr, and phosphate groups of adenosine triphosphate (ATP) were identified. The area of each peak was hand planimetered with an electronically computerized integrator and normalized with the peak area of methylenediphosphonic acid sealed in a capillary tube as a signal standard and glued to the sides of the NMR tube. The concentrations of each phosphate peak was then standardized by equilibrating the mean value integral of individual NMR spectra with the measured mean value for the specific metabolites obtained from freeze-clamped hearts measured under identical control conditions. Changes in the NMR spectra were expressed relative to measured values for control spectra. Ratios of the NMR integrated peaks were similar to mean values of the extract-analyzed metabolites, provided freeze-clamped P, samples were corrected for 8% bound P, in the cytosolic fraction as described earlier.16 No correction was made for bound ATP, PCr, or creatine (Cr). Dry-to-wet weight was measured as described earlier.16 Percent intracellular and extracellular water was measured using K(CoEDTA) as an extracellular marker.18 The μmol/g dry wt was then converted to millimolar using parameters described above. Intracellular pH was estimated from the chemical shift of the pH-dependent peak of P, relative to the independent peak of PCr. After comparison with fully relaxed spectra obtained at a 15-second recycle time, PCr and P, peaks were corrected 3% and 5%, respectively, for saturation. The relaxation rates expressed as T, under these conditions are 0.2–1.0 seconds for free β-ATP, 1.5–2.0 seconds for PCr, and 2.5–3.0 seconds for P,.

Biochemical Analysis of Freeze-Clamped Tissue

Termination of metabolic processes at a predetermined phase of the cardiac cycle using the rapid freeze-clamp technique has been described in detail earlier.19 The pneumatic cylinders were driven at 75 psi allowing the temperature in the center of the heart to drop to −80° C within 5 msec, while simultaneously recording the left intraventricular pressure to discern the termination point in relation to the pressure tracing.19

Preparation of acid extracts were similar to those described by Morgan et al20 and detailed earlier.16 The frozen flakes fell from the anvils into liquid nitrogen. An approximate 100-mg sample of the pulverized material was removed, weighed, dried, and weighed again for assessing wet-to-dry weight. The 3 ml frozen pulverized HCLO (-195° C) (10% perchloric acidic acid) were added to the remaining pulverized frozen tissues. Pulverization under liquid nitrogen continued. The frozen mixture was transferred to a mortar. The weight of the cold tube and acid were eliminated when calculating the wet tissue weight. The tissue and acid were pulverized under increasing temperature until the mixture thawed. After centrifugation (20,000g for 5 minutes), the extract was weighed, neutralized with 5N KOH, and weighed again to determine volume. The mixture was centrifuged to remove KClO4, and the supernatant was stored at −80° C.

Using the neutralized extract, energy metabolites were analyzed by high-performance liquid chromatography (HPLC), radioimmunoassays, or chemical analyses as described earlier.17 For separation of nucleotides, a Beckman HPLC with a C-18 reverse-phase column was used. For the mobile phase, 19% acetonitrile in 0.03 M KH2PO4 with 0.01 M tetrabutylammonium (TBA) phosphate (pH 2.65) was used. Elution was performed at a rate of 1 ml/min, and detection was performed with a Beckman ultraviolet spectrophotometer at 254 nm. Adenosine was analyzed by injecting 10-μl extract onto a Beckman C-18 reverse-phase column using a 10-ml gradient of 0–20% methanol in water, followed by a 10-minute elution time at 20% methanol. Detection and volume of elution were the same for ATP. PCr and Cr were analyzed on the same column except that elution was at a rate of 1.3 ml/min with 0.2% KH2PO4 and 0.1% TBA at pH 3.00. Detection was at 210 nm. cAMP was determined by radioimmunoassay as described earlier.16

Biochemical Calculations

P-31 NMR was standardized and concentration determined using baseline freeze-clamp values to allow comparison between P-31 NMR data and freeze-clamp data. All data were corrected for free cytosolic fraction as described previously using 40% wet weight as cytosolic. No correction was made for bound ATP, PCr, or cytosolic (Cr). Free adenosine diphosphate (ADP) was taken as (ATP)(Cr)/(K^d)(H +)(PCr). The creatine kinase equilibrium was taken as 2.36×1016. For derivation of P-31 NMR Cr values, Cr was determined using baseline freeze-clamp values to standardized by equivalating the mean value integrated peaks. Ratios of the NMR integrated peaks with the peak area of 0-20% methanol in water, followed by a 10-minute elution time at 20% methanol. Detection and volume of elution were the same for ATP. PCr and Cr were analyzed on the same column except that elution was at a rate of 1.3 ml/min with 0.2% KH2PO4 and 0.1% TBA at pH 3.00. Detection was at 210 nm. cAMP was determined by radioimmunoassay as described earlier.16

Statistics

Mean values, standard deviations, and statistical analyses of differences between groups were used to test the null hypothesis. The null hypothesis was rejected if the probability of error was <5%.

Results

The heart weights (dry) of the 6-month-old SHR were significantly greater (0.198±0.01 g) than that of the WKY rats (0.155±0.009 g, N=74), while body weights were significantly less in the SHR (340±22 g) compared with that of the WKY rats (420±18 g) (N=74).
Apex-Ejecting Working Rat Hearts

In the region from 80 to 140 cm H₂O, when there was a change in coronary flow (Figure 1), there was also a change in hemodynamic parameters (rate of change of pressure [dP/dt], developed pressure, oxygen consumption, end-diastolic pressure, and cardiac output) as well as biochemical parameters (phosphorylation potential, PCr, ATP, Pᵢ, and cAMP) for both sets of rats. In perfusion pressure ranges where there was no significant change in coronary flow (140–190 cm H₂O), all parameters were constant for each group of rat hearts. There were significant differences between SHR and WKY rats in coronary flow, phosphorylation potential, and developed pressure at both high and low perfusion pressures; however, differences were more pronounced at low perfusion pressures with reduced work. There were also significant differences in the phosphorylation potential, PCr, cAMP, and Pᵢ at the lower perfusion pressures between the two groups of rat hearts (Figure 1). Representative P-31 NMR spectra of the two sets of animal hearts at three perfusion pressures are shown in Figure 2.

By using the apex-ejecting heart and keeping coronary perfusion pressure constant at 150 cm H₂O, we varied the afterload chamber pressure to increase workload on the heart. When the afterload chamber was raised to 140 cm H₂O, developed pressure was significantly higher in SHR compared with WKY rats. There was no significant difference in dP/dt, end-diastolic pressure, heart rate, or cardiac output between the two groups of rats (Figure 3). On the other hand, coronary flow and oxygen consumption were significantly lower in SHR compared with WKY rats.

Figure 1. Mechanical and biochemical parameters obtained from apex-ejecting isolated working rat hearts of Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR). Afterload pressures were constant at 70 cm H₂O and left atrial filling pressure was constant at 10 cm H₂O. Values are given for (Panel A) coronary flow, rate of pressure development (dP/dt), developed pressure, and oxygen consumption; (Panel B) heart rate, end-diastolic pressure, and cardiac output; (Panel C) ln[(ATP)/(ADP)(Pᵢ)] and cyclic adenosine monophosphate (cAMP); and (Panel D) levels of adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphate (Pᵢ). p values and standard deviations are given in figure frames. p > 0.05 was not considered significant (n=7). ADP, adenosine diphosphate.
WKY rats at all settings of the afterload chamber. There is a greater coronary resistance in SHR, \( P_{c} \) was significantly higher in SHR compared with WKY rats at lower perfusion pressures (Figure 1D) and at higher perfusion pressures with low workload (Figure 3D).

**Isovolumic Langendorff Heart Preparation**

A decrease in perfusion pressure caused an immediate decrease in developed pressure with little change in the energy state of the isovolumic heart either in the SHR or WKY rats (Table 1). One hundred microliters of water was added to the balloon; maximum developed pressure was attained at this volume with no endocardial ischemia. The developed pressure of WKY rats varies little from this initial (10–30 second) drop after a 20-minute change in perfusion pressure. However, the heart reaches a new reduced phosphorylation potential at the reduced coronary perfusion pressure (15–20 minutes). This reduction in the phosphorylation potential was not severe enough to cause a further decrease in developed pressure in WKY rats, but may be the cause for a further decrease (from the initial decline in developed pressure) in SHR.

**Langendorff Apex-Vented and Isovolumic Langendorff Models**

Analyses were made by P-31 NMR after 20 minutes in the two sets of rats either at reduced (Langendorff-vented heart) or high (isovolumic heart) workload, or high workload with FC-43 present (Table 2). At the high perfusion pressure, SHR demonstrated a significantly higher developed pressure and \( P_{c} \), but a significantly lower coronary flow, perfusion pressure, and oxygen consumption, especially at the higher workload (isovolumic heart). Twenty minutes after dropping the perfusion pressure from 140 to 80 cm H2O, the developed pressure reached a steady state and was significantly lower in SHR compared with WKY rats. Similar findings were true for coronary flow, oxygen consumption, and the phosphorylation potential, whereas \( P_{c} \) was significantly higher. Both groups of animals responded to the perfusion pressure change with significant changes in all parameters except ATP.

**Discussion**

The findings reported in the present study describing the effects of altered perfusion pressure on hearts of SHR and WKY rats, in relation to metabolism and hemodynamic variables, confirm the existence of abnormalities in coronary flow in hypertensive hearts. Furthermore, these studies support earlier findings describing anomalies in the endothelium of the vasculature of hypertensive hearts. Hearts of SHR became ischemic at perfusion pressures below the range of autoregulation (i.e., in the range where vessels were maximally vasodilated and where regulation was dependent on the endothelium of the vasculature). Hearts of SHR performed well at high perfusion pressure, even when subjected to high afterloads. High energy phosphates and the phosphorylation potential were significantly lower in SHR compared with WKY rats, indicative of ischemia, at the low perfusion pres-
FIGURE 3. Mechanical and biochemical parameters obtained with the apex-ejecting working heart for spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. Perfusion pressure was constant at 150 cm H₂O and atrial filling pressure was set at 10 cm H₂O. The afterload chamber varies as indicated on the abscissa. Panel A, coronary flow, rate of pressure development (dP/dt), developed pressure, and oxygen consumption. Panel B, heart rate, end-diastolic pressure, and cardiac output. Panel C, ln[(ATP)/(ADP)(Pi)] and cyclic adenosine monophosphate (cAMP). Panel D, levels of adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphate (Pi). p>0.05 was not considered significant. *p<0.01 and **p<0.05 (n=7). ADP, adenosine diphosphate.
bolic parameters in this range of coronary perfusion pressures. The influence coronary perfusion pressure has on physiological and biochemical parameters is mediated through coronary flow. Coronary flow, influenced by perfusional pressure, causes stretch of myofibers,21,22 the Frank-Starling mechanism,23 and augments cAMP as described here. With an increase in flow, there is a concurrent increase in intracellular water and intracellular calcium24 of the myocardium. With the apex-ejecting heart at low workloads and the Langendorff apex-vented heart preparation, the heart is hyper-perfused in the range of autoregulation (i.e., at perfusion pressures greater than 140 cm H2O).8 Excess coronary flow, perhaps due to the dissolution of high concentrations of oxygen, destroys the dependence of coronary flow on oxygen consumption.24,26

Hyperperfusion permits the heart to meet its requirements by greater oxygen extraction from the coronary perfusate instead of increasing flow.25,26 The isolated heart has no neurohumoral control and myocardial metabolites are diluted by the high volume of perfusate; thus, there is less regulation of coronary flow in the perfused heart compared with hearts in situ in this range of perfusion pressures. As workload is increased during hyperperfusion, maximum oxygen extraction occurs at high workloads.11 Workload on the heart, induced either by raising the apex chamber height or by alterations in balloon volumes, most likely causes a stretch of myofibers,8,13,27 the Frank-Starling mechanism.23,28 Stretch of myofibers activates the calcium channels, increases intracellular calcium concentration,29 and augments developed pressure.8,13,27 Stretch also appears to

### Table 1. Alterations in Perfusion Pressure: Immediate and Secondary Changes in Developed Pressure and Phosphorylation Potential

<table>
<thead>
<tr>
<th>Variable</th>
<th>80 cm</th>
<th>140 cm</th>
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<th>140 cm</th>
<th>80 cm</th>
<th>140 cm</th>
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<tr>
<td>Coronary flow (ml/min)</td>
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<tr>
<td>WKY</td>
<td>9.2±1.4</td>
<td>16.4±2.2</td>
<td>8.2±1.7</td>
<td>17.6±4.4</td>
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<td>10.7±0.9</td>
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<td>Oxygen consumption (μmol/g dry wt/beat)</td>
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<td>0.26±0.04</td>
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<td>0.14±0.03</td>
<td>0.28±0.05</td>
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<tr>
<td>WKY</td>
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<td>159±23</td>
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<td>Developed pressure (mm Hg)</td>
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<tr>
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<td>45±6</td>
<td>98±8†</td>
<td>51±9†</td>
<td>221±22†</td>
<td>48±8†</td>
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<td>16.2±0.5</td>
<td>12.2±0.8</td>
<td>16.5±1.1</td>
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<td>Phosphocreatine (mM free cytosolic)</td>
<td>9.8±0.9</td>
<td>16.8±0.9</td>
<td>8.5±0.9</td>
<td>15.8±0.8</td>
<td>9.6±0.8</td>
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<tr>
<td>WKY</td>
<td>8.7±0.9</td>
<td>8.8±0.8</td>
<td>8.4±0.6</td>
<td>9.1±0.9</td>
<td>8.0±0.9</td>
<td>8.8±1.0</td>
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<tr>
<td>SHR</td>
<td>7.6±0.8</td>
<td>9.1±0.7</td>
<td>7.2±1.1</td>
<td>8.7±0.6</td>
<td>7.8±0.5</td>
<td>8.9±1.2</td>
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<tr>
<td>Adenosine triphosphate (mM free cytosolic)</td>
<td>2.3±0.9</td>
<td>0.81±0.09</td>
<td>2.6±0.4</td>
<td>0.72±0.22</td>
<td>1.8±0.9</td>
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<tr>
<td>WKY</td>
<td>2.6±0.9</td>
<td>0.81±0.09</td>
<td>2.6±0.4</td>
<td>0.72±0.22</td>
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<td>7.8±0.5</td>
<td>8.9±1.2</td>
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<td>Creatine (mM free cytosolic)</td>
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<tr>
<td>WKY</td>
<td>14.0±1.4</td>
<td>10.9±1.4</td>
<td>14.9±0.9</td>
<td>10.6±0.8</td>
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<tr>
<td>SHR</td>
<td>17.1±0.9</td>
<td>10.5±0.8</td>
<td>18.9±0.8</td>
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<tr>
<td>Adenosine diphosphate (mM free cytosolic)</td>
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<td>0.025±0.001</td>
<td>0.041±0.003</td>
<td>0.026±0.002</td>
<td>0.041±0.003</td>
<td>0.024±0.003</td>
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<tr>
<td>WKY</td>
<td>0.051±0.002†</td>
<td>0.024±0.002</td>
<td>0.008±0.004†</td>
<td>0.027±0.003</td>
<td>0.058±0.002</td>
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<tr>
<td>SHR</td>
<td>7.90±0.01</td>
<td>7.04±0.02</td>
<td>6.95±0.02</td>
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<td>Intercellular pH (pH units)</td>
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<tr>
<td>WKY</td>
<td>7.02±0.02</td>
<td>7.05±0.02</td>
<td>7.03±0.03</td>
<td>7.06±0.02</td>
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<td>SHR</td>
<td>7.00±0.01</td>
<td>7.04±0.02</td>
<td>6.95±0.02</td>
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<tr>
<td>Phosphorylation potential ln[(ATP)/(ADP)(P</td>
<td>)]</td>
<td>3.03±0.03†</td>
<td>4.26±0.02†</td>
<td>2.63±0.05†</td>
<td>4.89±0.05†</td>
<td>3.04±0.13†</td>
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</table>

Values are mean±SEM. WKY, Wistar-Kyoto rats; SHR, spontaneously hypertensive rats; ATP, adenosine triphosphate; ADP, adenosine diphosphate; P|, inorganic phosphate.

*p<0.05 between sets indicated.
f<0.05 between WKY and SHR.
cause an increase in cAMP. It may be the hypertrophied myocardium requires maximum fiber stretch for optimum metabolism. There is no significant difference between SHR and WKY rats in high energy phosphates at maximum perfusion pressure and maximum workload.

The initial reduction in developed pressure with a decrease in perfusion pressure does not appear to be related to the energy state of the heart since there is no significant decrease in the phosphorylation potential with the first 10-30-second decrease in the coronary perfusion pressure, a time during which developed pressure has fallen approximately 50%. Stretch of myofibers may also regulate mitochondrial activity by augmenting intracellular calcium. Intracellular calcium augments mitochondrial activity. There is a linear relation between $J_{02}$ and developed pressure. Given a $J_{02}$ of 0.35 μmol/beat and g dry wt, ATP is being used at a rate of about 7.5 μmol/g dry wt/sec, which is approximately 3 nM/sec. Thus, the total PCR pool would be eliminated in less than 4 seconds if synthesis of ATP were stopped. However, studies on rapid changes in perfusion pressure indicate that developed pressure falls before there are observable changes in the phosphorylation potential. Turgor of the vasculature may be a compensatory mechanism that lowers developed pressure and oxygen consumption concurrently with a change in coronary flow. The lower oxygen consumption in SHR for higher or equal cardiac performance has been discussed in detail in earlier studies. This thermodynamic efficiency in SHR may be due to shifts in isomyosins toward the myosin, which uses less ATP per unit tension. Also, the reduced wall tension in the hypertrophied hearts may use less energy in developing comparable pressures.

In summary, first we observed that hearts of SHR were highly dependent on perfusion pressure for optimum coronary flow to meet work demands; hearts of SHR became significantly more ischemic than those of WKY rats when perfused at a low perfusion pressure. Second, the hearts of SHR worked at a lower phosphorylation potential than those of WKY rats; however, at maximum perfusion pressure and maximum workload the phosphorylation potential of hearts of SHR was not significantly different from that of WKY rats, indicative of the need for optimum stretch in the hypertrophied myocardium of SHR. Third, when working at perfusion pressures in the range of autoregulation, hearts of SHR developed comparable pressures but at the same time had less coronary flow and lower oxygen consumption than those of WKY rats. Experimental evidence suggests that the Gregg's phenomenon is only found in the isolated nonworking heart. The data described here extends the Gregg's phenomenon to the isolated working heart, but may not be physiologically applicable because coronary perfusion pressure cannot be separated from afterload of the left ventricle in physiological conditions.

**KEY WORDS** • hypertrophy • magnetic resonance spectroscopy • coronary perfusion • perfusion pressure • spontaneously hypertensive rats
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