EXERCISE INTOLERANCE is a salient feature of congestive heart failure during exercise in conscious dogs with heart failure. Neumann, Till, and Gerd Heusch. Myocardial, skeletal muscle, and renal blood flow during exercise in conscious dogs with heart failure. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2452–H2457, 1997.—The present study characterizes the hemodynamic and neurohumoral responses to moderate treadmill exercise in conscious dogs with pacing-induced heart failure. Seven dogs were instrumented with a left ventricular micromanometer, ultrasonic crystals for the measurement of systolic wall thickening, left atrial and aortic catheters for the injection of colored microspheres and reference withdrawal, respectively, and ventricular pacing leads with a subcutaneous pacemaker. Dogs were run on a treadmill at a speed of 5 km/h. After control studies, heart failure was induced by rapid left ventricular pacing at 350 beats/min for (mean ± SD) 23 ± 6 days. In the control state, cardiac output was increased to 4.5 ± 1.5 to 7.9 ± 1.4 l/min (P < 0.05 vs. rest). With heart failure, cardiac output was decreased to 2.5 ± 0.5 l/min at rest (P < 0.05 vs. control state) and was only 3.0 ± 0.3 l/min during exercise (P < 0.05 vs. control state; not significant vs. rest). Myocardial and, more so, skeletal muscle blood flows at rest were reduced in heart failure; their increases with exercise were attenuated. An increase in renal blood flow during exercise in the control state was no longer seen in heart failure. Increases in plasma catecholamines and lactate during exercise were more pronounced in heart failure. Heart failure increases cardiovacular output during exercise was largely attenuated. Increased catecholamine levels may have contributed to splanchnic vasoconstriction and preferential distribution of cardiac output into the working skeletal muscle. Myocardial, skeletal muscle, and renal blood flow during exercise in conscious dogs with heart failure.
Induction of heart failure. After completion of the control studies, a pacemaker (Legend II 8424 and 8426, type VVI; Medtronic) was implanted under local anesthesia (2% lidocaine) in a subcutaneous pocket. Heart failure was induced by rapid LV pacing, as originally reported by Coleman et al. (5). The pacing rate was set to 250 beats/min, and minimal voltage and pulse duration for capture were determined, using a programming unit (model 9710; Medtronic). The presence of heart failure was determined from both clinical signs, such as ascites, pulmonary edema, and cachexia, and hemodynamic parameters, such as the increase in LV end-diastolic pressure (LVEDP) and the decrease in LV maximal pressure (LVPmax), maximum rate of LV pressure rise (LV dp/dtmax), and systolic wall thickening. The mean time (± SD) to induce heart failure was 23 ± 6 days, ranging from 15 to 30 days.

Protocols. Seven to ten days after surgery, when the dogs had fully recovered from surgery, control measurements were performed. Measurements were taken with the dog standing on the treadmill and during exercise. Measurements included the assessment of systemic hemodynamics and regional dimensions, microsphere injection for the assessment of cardiac output and regional blood flow, and arterial blood withdrawal for the analysis of plasma catecholamines and lactate. The dogs were run at a speed of 5 km/h for 10 min. Measurements were performed in a hemodynamic steady state, i.e., between 5 and 10 min into the run.

The studies were repeated at an identical exercise level in heart failure. After completion of the study, the dogs were euthanized with a lethal dose of KCl (10 ml, 1 M).

Measurement of cardiac output and regional blood flow. Cardiac output and regional blood flow were determined with a technique developed in our laboratory (15) using colored microspheres (DyeTrak; Triton Technologies). For each experiment, 8 x 10^9 to 12 x 10^9 microspheres suspended in saline solution (containing 0.02% Tween 80) were injected into the left atrium. The number of microspheres was adjusted with respect to the specific absorbance of the respective dye. Simultaneous arterial reference samples were withdrawn from the descending aorta at a constant rate of 5.3 ml/min with a Harvard withdrawal pump (model 901A; Harvard Apparatus, South Natick, MA), starting 30 s before the microsphere injection and continuing for 150 s.

After euthanasia of the dogs, tissue samples were taken from the left side (18 samples/animal, i.e., 9 each/transmural layer; weight 0.40 ± 0.10 g) and right ventricles (6 samples/animal; weight 0.57 ± 0.27 g), musculus triceps (8–10 samples/animal; weight 0.74 ± 0.16 g), musculus biceps femoris (8–10 samples/animal; weight 0.70 ± 0.12 g), diaphragm (7 samples/animal; weight 0.48 ± 0.18 g), and the renal medulla (4–6 samples/animal; weight 0.34 ± 0.17 g) and cortex (4–5 samples/animal; weight 0.68 ± 0.31 g). The regional myocardial blood flow in the subendocardium, midmyocardium, and subepicardium of the left ventricle was separately determined. After extraction of the dye from the microspheres, the color spectra of each tissue sample and arterial reference withdrawal sample were measured with a spectrophotometer (model 8452A; Hewlett-Packard, PaloAlto, CA). The absorbance was determined as specific absorbance for each color. Separation of overlapping spectra was performed with a matrix inversion technique. Cardiac output was determined from the measurement of an aliquot of the injected microspheres and the arterial reference withdrawal rate, using the equation cardiac output = reference withdrawal rate × total absorbance of injected microspheres ÷ absorbance in the arterial reference withdrawal sample. The regional blood flow per sample, corrected for wet weight, was calculated according to the equation regional tissue blood flow = reference withdrawal rate × absorbance of sample ÷ absorbance in the arterial reference withdrawal sample. The blood flow values of the respective tissue samples were averaged for each animal.

Measurement of catecholamines. For catecholamine analysis, the blood samples were centrifuged immediately after withdrawal, and the plasma was frozen in liquid nitrogen and stored at −70°C. After thawing, 1 ng/ml 3,4-dihydroxobenzyl-amine was added as an internal standard. The samples were deproteinized (trichloroacetic acid, 0.3 M final concentration), and the catecholamines were adsorbed to purified alumina (1) at pH 8.6 [2.5 M tris(hydroxymethyl)aminomethane-HCl buffer containing 10 mM mercaptoethanol]. The aluminabound catecholamines were washed three times with 0.8 M acetate buffer, pH 7.5, and once with water. Then the catecholamines were dissolved in 200 ml 1.0 N acetic acid. An aliquot of this solution was used for high-performance liquid chromatography. Separation was achieved on a 3.9 × 150 mm column (Nova-Pak-C18; Millipore, Eschborn, Germany), the mobile phase consisting of 1.0 N acetic acid, 22 mM 1-octanesulfonic acid sodium salt monohydrate, 0.2 mM EDTA-Na2, with a flow of 1.3 ml/min (pump: Waters M510, Millipore; pulse dampener: LP-21, Scientific Systems, State College, PA). A glassy carbon electrode set to 650 mV against Ag-AgCl was used for electrochemical detection (model 400 EC Detector; EG & G Princeton Applied Research, Princeton, N J).

Measurement of lactate. Lactate was determined from KF-EDTA-stabilized blood samples, using the lactate dehydrogenase reaction combined with transamination of the formed pyruvate for quantitative NADH formation (18). NADH was measured photometrically.

Data analysis and statistics. LVP, LV rate of pressure rise (LV dp/dt), and regional wall thickness were simultaneously recorded on an eight-channel recorder (model RS800; Gould, Cleveland, OH) and a personal computer. Hemodynamic data were digitized at a rate of 200 Hz and directly stored on hard disk with the use of Cordat II software (28). Systemic hemodynamic and regional wall function data of 15 sequential beats were averaged. End diastole was defined as the time point at which LV dp/dt started its rapid upstroke after crossing the zero line. Regional end systole was defined as the point of maximal wall excursion within 20 ms before peak negative dp/dt. The measured parameters were heart rate, LVPmax, and LVEDP, LV dp/dtmax, end-diastolic wall thickness, and systolic wall thickening, presented as the percent change from the end-diastolic thickness. End-diastolic wall thickness was normalized to 10 mm under control conditions (19).

Statistical analysis was performed with Sigma Stat software (Jandel Scientific, San Rafael, CA). Data were analyzed by two-way analysis of variance for repeated measures. When a significant overall effect was detected, single mean values were compared by paired t-tests and subsequent Bonferroni’s adjustment. Data are reported as mean values ± SD and are considered statistically significant at P < 0.05.

RESULTS

Baseline hemodynamics. After 3–4 wk of rapid ventricular pacing, dogs developed heart failure, characterized by clinical signs, such as ascites, pulmonary edema, and cachexia (body weight decreased from 25.6 ± 3.4 to 22.4 ± 2.3 kg), and hemodynamic parameters, such as an increase in LVEDP and decreases in LVPmax, dp/dtmax, and systolic wall thickening.

Hemodynamic responses to exercise. In the control state, during moderate exercise, there were significant
In heart failure, starting from reduced levels at rest, there were still significant increases in heart rate, LVP\textsubscript{max}, dP/dt\textsubscript{max}, and cardiac output (Fig. 1; Table 1). In heart failure, starting from reduced levels at rest, there were still significant increases in LVP\textsubscript{max} and dP/dt\textsubscript{max}. Heart rate was not different at rest and increased to a similar extent as during control exercise. LVEDP at rest was significantly elevated and increased further during exercise. Cardiac output at rest was markedly reduced in heart failure, and there was no significant increase during exercise (Table 1). In contrast to the control state, all dogs in heart failure had obvious signs of discomfort during exercise.

Myocardial, skeletal muscle, and renal blood flow. In the control state, blood flow to the myocardium, the working skeletal muscle, including the diaphragm, and the kidney increased during exercise (Table 2). The increase in blood flow to the biceps femoris was most pronounced, whereas the increase in renal blood flow was only modest. In heart failure, blood flow at rest was reduced in all organs studied, particularly in the skeletal muscle. Also, the increases in myocardial and skeletal muscle blood flow during exercise were blunted. In heart failure, renal blood flow was no longer increased.

Plasma catecholamines and lactate. In the control state, plasma catecholamines and lactate were increased slightly during exercise (Table 3). In heart failure, plasma catecholamines were increased at rest and increased more markedly during exercise. Also, lactate increased markedly during exercise in heart failure.

**DISCUSSION**

The present study utilized an established experimental model of heart failure, i.e., chronic rapid ventricular pacing in conscious dogs (5, 10, 14, 17, 20, 22–24, 31, 35). This model mimics not only the clinical signs (ascites, pulmonary edema, cachexia) seen in patients with heart failure but also the associated hemodynamic changes.
and neurohumoral alterations (increases in LV end-diastolic pressure and plasma catecholamines, decreases in LV maximal pressure, dP/dt, and cardiac output).

The exact mechanisms underlying the development of heart failure with chronic rapid ventricular pacing are currently unclear (27) but may be related to abnormalities of intracellular calcium kinetics (20) and myocyte loss (11). To that extent, it is currently unclear whether pacing-induced heart failure shares the same pathophysiology as heart failure in humans. Important for the present study, however, is that exercise intolerance, which is a salient feature of heart failure in humans, is also evident in the pacing-induced heart failure model. The fairly mild severity of heart failure in the present study was similar to that previously reported by others, as judged by the impairment in baseline hemodynamics (2, 5, 11, 14, 20, 22–24, 31, 35) as well as by the increase in resting plasma catecholamines (2, 9, 21). The reduction in cardiac output at rest by an average of 44% in the present study was even more severe than in several prior studies (9, 14, 35), comparable only with that reported by Moe et al. (17).

From a comparison of the baseline data in the control state of the present study with those previously reported (9, 24), it appears from the catecholamine levels that dogs were under some adrenergic activation already at rest, possibly in anticipation of the run. This adrenergic activation was also associated with somewhat higher skeletal muscle blood flow levels compared with the study of Shen et al. (26). In contrast, the intensity of exercise in the present study was fairly mild, as reflected by the only modest increases in plasma catecholamines and lactate as well as the hemodynamic responses under control conditions. More significant increases in plasma catecholamines and lactate were seen only during such mild exercise after the development of heart failure. Such mild exercise intensity was chosen so that dogs could perform an identical exercise protocol in the control state and in heart failure.

Flow measurements in the present study were based on the microspheres technique. We did not attempt to address a potential loss of microspheres over time in the present study. However, from previous studies using the model of pacing-induced heart failure in dogs and swine, no loss of microspheres was reported (25, 29, 30). Also, we did not perform morphological studies. However, prior studies using this model have not reported an increase either in LV muscle mass or in capillary density and cross-sectional area (25, 29).

In heart failure, blood flow to the myocardium at rest was somewhat less reduced (LV −30% on average; right ventricular −20% on average) than cardiac output (−44% on average). Also, blood flow to the renal cortex was better maintained than cardiac output (−28% on average). In contrast, blood flow to the skeletal muscle at rest, including the diaphragm, was much more markedly reduced (triceps −62%; biceps femoris −62%; diaphragm −68%). During exercise, the decrease in cardiac output by 62% on average was even more pronounced compared with rest (−44%), and the same was true for LV myocardial blood flow (−44% vs. −30% at rest). In contrast, the decreases in skeletal muscle blood flow during exercise were much less pronounced than those in cardiac output (triceps −25%; biceps femoris −45%; diaphragm −33%). Apparently, in heart failure there is a preferential distribution of cardiac output into the working skeletal muscle during exercise, as also evidenced by the concomitant albeit not significant decrease in renal blood flow seen in the present study. No increase in renal blood flow during exercise in the control state and a marked decrease in renal blood flow in exercising dogs with heart failure caused by tricuspid avulsion and pulmonary stenosis were previously reported (8). However, that particular study differed from the present one with respect to the heart failure model (tricuspid avulsion and pulmonary stenosis vs. pacing), exercise severity (heart rate of 281 ± 25 vs. 166 ± 19 beats/min), and method of flow measurement (Doppler flow probe vs. microspheres). Despite these differences, both studies indicate a reversal of the renal blood flow response to exercise with heart failure. Even with preferential perfusion (relative to cardiac output) of the working skeletal muscle, there was a significant increase in plasma lactate, supporting the notion that the skeletal muscle in heart failure is characterized not only by reduced perfusion (in absolute terms) but also by primary metabolic abnormalities (13, 16). However, we did not determine the exact source of increased plasma lactate (e.g., liver vs. skeletal muscle).

The coronary circulation in this heart failure model is under defective endothelial control (33). Reduced myocardial blood flow at rest and, in addition, in adenosine- or atroventricular pacing-recruitable coronary reserve has been reported previously in conscious dogs (25) and pigs (29) with pacing-induced heart failure. The impairment in coronary reserve in dogs was selective to the subendocardium (25). In the present study, however, a preferential impairment of subendocardial blood flow was not observed either at rest or during exercise, although extracellular compression, as reflected by LV end-diastolic pressure, was increased. Obviously, at this mild exercise intensity, an adequate coronary vasomotor response to increased cardiac work was still possible, indicating no enhanced vulnerability of the failing myocardium to ischemia.

Unfortunately, arterial pressure was not measured in the present study, since the arterial line was used for the reference withdrawal during the microsphere measurement of blood flow. Therefore, resistance values cannot be calculated and pressure-dependent changes in blood flow cannot be distinguished from active vasomotion. In particular, the attenuated increases in flow to myocardium and skeletal muscle during exercise and, even more so, the lack of flow increase to the kidney may, in part, be caused by an attenuated increase in arterial pressure, as has been reported in patients with heart failure during exercise (36).

A limitation of the present study is the lack of mechanistic information on the causal relation among
hemodynamics, blood flow distribution, plasma catecholamines, and lactate. However, this is the first study to provide integrative information on these parameters during exercise in the model of pacing-induced heart failure. Inadequate nutritive perfusion of skeletal muscle during exercise also has been reported in patients with heart failure (32, 36, 38) and has been related to impaired endothelial function (12). Also, increased lactate production during exercise has been related to impaired endothelial function (12). With increased lactate production during exercise has been related to impaired endothelial function (12). Also, increased lactate production during exercise has been reported in patients with heart failure (32, 36). With respect to the symptom of exercise intolerance and the reported in patients with heart failure (32, 36). With respect to the symptom of exercise intolerance and the reported in patients with heart failure (32, 36). With respect to the symptom of exercise intolerance and the reported in patients with heart failure (32, 36).

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Received 2 J une 1997; accepted in final form 1 August 1997.

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