PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 163, 111–119 (1980)

Isolated Hearts from Obese Rats Show Impaired Function during Hypoxia (40731)

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Cardiac failure in morbidly obese individuals with neither hypertensive, coronary, nor valvular heart disease has been reported by several investigators (1–5). Whether or not myocardial impairment actually accompanies obesity itself and the mechanism of such cardiac dysfunction remain obscure. To date, these problems have not been studied using animal models. This report is the first such experimental investigation of cardiac function in obesity. We chose congenitally obese Zucker rats for study because they develop morbid obesity early in their life (6). An isolated ejecting whole rat heart preparation (7, 8) was utilized to directly assess cardiac hemodynamics in the absence of extracardiac influences. Preliminary experiments with 32-week-old rats indicated that hearts from obese rats could not maintain function as well as did hearts from lean rats when isolated and perfused with an hypoxic medium. Thus, this study was designed to quantify possible developmental changes in obese rat heart function by examining ventricular function curves in hypoxia and response to the sympathomimetic agent, dobutamine.

Materials and Methods. Hearts from 28 male Zucker rats from our established inbred colony were evaluated. The Zucker obese rat was developed from a spontaneous mutation in a cross between Sherman and Merck Stock M rats (6). The obese homozygous recessive animals (*fa/fa*) are distinguishable from their lean (*Fa/?*) littermates at 4 to 5 weeks of age by their body conformation and increased body weight, although body fat of the obese is increased by 2 weeks of age (9). Animals were studied at 9 and 19 weeks of age [mean ages were 62 (range 58 to 75) and 136 (range 131 to 144) days, respectively]. All animals were allowed free access to Purina Lab Chow and water. On the evening before perfusion, they were weighed and fasted overnight.

The heart was excised from the heparinized, anesthetized (sodium pentobarbital, 70 mg/kg, ip), ventilated rat and was arrested in iced perfusion medium (see below for composition) containing 1000 USP units of sodium heparin per liter. The heart was attached to the aortic cannula of the isolated working heart apparatus previously described in detail (7, 8) and perfusion with warm medium was begun within 90 sec of excision from the rat. For the present experiments, cannulae were PE 190 (left ventricular) and PE 240 (left atrial) and the aortic reservoir was set 72 cm above the heart. The perfusion medium contained 123 mM NaCl, 4.93 mM KCl, 2.85 mM $CaCl_2$, 1.36 mM KH_2PO_4, 1.36 mM $MgSO_4$, 11.1 mM glucose, 23.8 mM $NaHCO_3$, 0.5 mM disodium ethylenediaminetetraacetate. The pH was brought to 7.4 by bubbling with 100% CO_2, and was maintained throughout the experiment by bubbling with gases containing 5% CO_2. After an initial 10-min retrograde perfusion, the heart was perfused antegrade with fully oxygenated (equilibrated with 95% O_2/5% CO_2; pO_2 =

[1] This work was supported by Grants AA 00270 and AM 18899 from the USPHS and by a grant from the Central Mission Trails California Chapter of the American Heart Association. This work was presented at the April 1979 meeting of the Federation of American Societies for Experimental Biology and the abstract was published in *Fed. Proc.* 38, 1448 (1979). Address reprint requests to Leigh D. Segel, Section of Cardiovascular Medicine, Department of Medicine, University of California School of Medicine, Davis, Calif. 95616.

0037-9727/80/010111-09$01.00/0

623 ± 3 mm Hg) solution. After 10 min, electrical stimulation at a rate of 330 pulses/min (5.5 msec duration) was initiated and maintained throughout the experiment. A bipolar stimulating electrode attached to the right atrium delivered the electrical pulse at a voltage just sufficient for capture. Measurements of cardiac function in normoxia were obtained after 5 min at a filling pressure of 2.5 to 3.0 mm Hg (end-diastolic pressure). Perfusion was then switched to a parallel antegrade system having reduced oxygenation (50% O_2/45% N_2/5% CO_2; pO_2 = 330 ± 2 mm Hg). A ventricular function curve in this hypoxic condition was obtained by progressively raising the atrial reservoir and measuring variables of cardiac function at filling pressures of 4, 6, and 10 mm Hg. A 13-mm Hg filling pressure was also used in some of the 19-week-old obese rat hearts. The atrial reservoir was then returned to its original hypoxia height and the parameters of cardiac performance were determined before and during perfusion with medium containing 0.1 μM dobutamine HCl (Eli Lilly and Co.). Finally, normoxic perfusion was resumed without dobutamine at the initial atrial reservoir height. Measurements of function began 5 to 7 min (when function was stable) after each preload or inotropic intervention and required 7 min to complete.

The parameters determined at each measurement period during ejection were: left ventricular maximum systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), left ventricular maximum rate of pressure rise (dP/dt), aortic flow, peak aortic flow, coronary artery flow, myocardial oxygen consumption, and total cardiac output. Left ventricular and aortic pressures were monitored using Hewlett–Packard pressure transducers (Model 1280B). Aortic flow was monitored with a 3.0-mm Statham cannulating flow probe (Model SP 7517) and a Statham blood flowmeter (Model SP 2202). Total coronary artery flow was electronically recorded at each measurement period using a calibrated pressure–volume apparatus which collected the coronary venous effluent that flowed from the pulmonary artery. The pO_2 values of arterial (atrial) and venous (coronary venous effluent) perfusates were measured by withdrawing samples directly into a microsample thermoregulated chamber (Radiometer Model D616) containing a Radiometer oxygen electrode (Model E5046) connected to a Radiometer acid–base analyzer (Model PHM 72). Pressure and flow data were analyzed using a PDP 11/10 minicomputer (Digital Equipment Corp.). Ten heart beats at each measurement period were computer-analyzed and averaged for all parameters except oxygen consumption, coronary artery flow, and cardiac output. Aortic flow was computed from the area under the positive portion of the flow tracing obtained from the flowmeter. Total cardiac output was obtained as the sum of the aortic output (overflow from the aortic reservoir positioned 72 cm above the heart collected for a timed interval at each measurement period) plus coronary artery flow. Myocardial oxygen consumption (Q_{O_2}) was calculated using the arterial (A) and venous (V) pO_2 measurements, coronary flow (CF), and dry heart weight (DHW):

$$Q_{O_2}\ (\text{mmole } O_2/\text{hr}\cdot\text{g dry heart weight}) = \frac{(A_{pO_2} - V_{pO_2})\ (\text{mm Hg}) \times 0.0244\ (\text{ml gas/ml soln}) \times 60\ (\text{min/hr}) \times \text{CF (ml soln/min})}{760\ (\text{mm Hg}) \times 22.4\ (\text{ml gas/mmole}) \times \text{DHW (g)}}.$$

Power, stroke work, and cardiac efficiency were computed from the LVSP and aortic flow (AF) recordings as described by Bersohn and Scheuer (10):

$$\text{Power}(t)\ (\text{ergs/g}\cdot\text{sec}) = \frac{1333\ (\text{dyn/cm}^2\cdot\text{mm Hg}) \times \text{LVSP}(t)\ (\text{mm Hg}) \times \text{AF}(t)\ (\text{ml/sec})}{\text{DHW (g)}}.$$

$$\text{Stroke work (ergs/g)} = \int \text{power}(t)\, dt \quad \text{(during ejection)}.$$

$$\text{Efficiency} = \frac{4.72 \times 10^{-9} \times \text{stroke work (ergs/g)} \times \text{heart rate (beats/min)}}{\text{oxygen consumption (ml/g}\cdot\text{min)}}.$$

The equation for efficiency assumes that oxygen was utilized entirely for oxidation of glucose.

At the conclusion of the experiment, the heart was trimmed of large vessels and atria, and the ventricles were dried at 105°C for 16 hr to obtain a dry weight. Two hearts were perfused daily to obtain seven lean and seven obese 9-week-old rats and seven lean and seven obese 19-week-old rats.

Following heart excision, contents of the thoracic and abdominal body cavities, including retroperitoneal fat deposits, were removed and the carcass weighed. Carcasses were frozen at −80°C until analysis of body composition was performed (9). After rehydration, the dried hearts were homogenized and then analyzed gravimetrically for lipid, after extraction with chloroform/methanol (2/1) (11), and for ash. Protein content of the heart was calculated by difference [dry heart weight − (fat + ash)].

Comparisons between obese rats (OB) and lean controls (C) were made using Student's t test for unpaired data (two-tailed) (12) and the level of significance was taken as $P < 0.05$. Data are reported as mean ± standard error of the mean.

Results. Body and heart composition. The body weights, dry heart weights, and carcass compositions of the 28 rats studied are shown in Table I. Mean body weights of OB prior to the overnight fast were significantly greater than C at both ages studied. Dry heart weights were not significantly different at either age, although at 19 weeks of age heart weights of OB tended to be slightly greater than those of C. Indeed, comparison of the dry heart weights of a larger group of 19-week-old OB ($n = 15$) and C ($n = 17$) male Zucker rats indicated that at this age OB did exhibit slight hypertrophy: C = 0.187 ± 0.006 g, OB = 0.220 ± 0.005 g; $P < 0.001$. Body weights of these larger groups were 393 ± 10 (C) and 568 ± 15 g (OB), $P < 0.001$. These groups included the animals used in the present study plus animals used in other experiments. Analysis of the carcass compositions of the rats in the present study indicated significantly greater fat content and significantly less protein and less ash in OB compared with C at both ages. However, when the weight of ash or protein was expressed as a percentage of the fat-free weight [e.g., g ash/(g carcass − g fat) × 100], no differences were observed between C and OB. This is consistent with our previous findings in Zucker rats (9).

Compositional analysis of the heart tissue indicated that, on a dry weight basis, both the absolute and relative amounts of lipid, ash, and protein were comparable (no significant differences) in OB and C hearts at each age. For example, in the 19-week-old animals, C hearts were 15.5 ± 0.8% lipid, 4.4 ± 0.2% ash, and 80.1 ± 0.8% protein, and OB hearts were 16.4 ± 0.8% lipid, 5.2 ± 0.5% ash, and 78.4 ± 0.9% protein.

Isolated working heart function. Nine-week-old rats. The perfusion experiments

TABLE I. BODY WEIGHT, HEART WEIGHT, AND CARCASS COMPOSITION OF MALE ZUCKER RATS

Group[a]	Body weight (g)	Dry heart weight (g)	Carcass composition (g)			
			Wet weight	Fat	Ash	Protein
9-week-old						
Lean	220 ± 8	0.117 ± 0.003	157 ± 5	9.1 ± 1.2	6.6 ± 0.4	36.1 ± 1.0
Obese	246 ± 6	0.114 ± 0.004	170 ± 6	56.2 ± 3.3	5.1 ± 0.3	28.3 ± 1.7
	$P < 0.05$	ns[b]	ns	$P < 0.001$	$P < 0.02$	$P < 0.01$
19-week-old						
Lean	392 ± 16	0.192 ± 0.011	311 ± 7	34.5 ± 3.8	14.9 ± 1.0	72.2 ± 1.4
Obese	537 ± 22	0.211 ± 0.008	389 ± 15	166.2 ± 7.7	10.8 ± 0.5	59.4 ± 2.0
	$P < 0.001$	ns	$P < 0.001$	$P < 0.001$	$P < 0.005$	$P < 0.001$

[a] $n = 7$ for each group.
[b] Not significantly different.

on hearts from 9-week-old rats revealed minimal functional differences between OB and C. The OB hearts developed greater LVSP than did C hearts at the first (normoxic) measurement period (93.0 ± 1.3 vs 88.1 ± 1.3 mm Hg; $P < 0.05$) and during the recovery period following hypoxia (84.0 ± 1.5 vs 78.9 ± 1.5 mm Hg; $P < 0.05$). The *dP/dt* of OB hearts was significantly greater than that of C hearts in hypoxia at 10 mm Hg LVEDP (2.60 ± 0.09 vs 2.32 ± 0.06 mm Hg/msec; $P < 0.05$) and during the normoxic recovery period following hypoxia (2.93 ± 0.10 vs 2.66 ± 0.06 mm Hg/msec; $P < 0.05$). These observations suggest the possibility of slightly improved systolic performance in OB hearts at an early age when there is only a 12% increase in body weight over C. Coronary artery flow was slightly lower in OB hearts throughout perfusion and was significantly lower at the first normoxic period (77.3 ± 2.8 vs 91.1 ± 2.8 ml/min·g dry heart weight; $P < 0.01$), and in hypoxia at 4 mm Hg LVEDP (85.5 ± 3.8 vs 100.5 ± 1.5 ml/min·g dry heart weight; $P < 0.01$). No other significant differences were observed at 9 weeks between OB and C in either absolute values of cardiac performance parameters, or in percentage change of parameters when hearts were stimulated with dobutamine. Stroke work, maximum developed power, and efficiency were also comparable (no significant differences) in OB and C. The overall similarity of cardiac performance of the 9-week-old OB and C hearts is demonstrated in Fig. 1a by the ventricular function curves obtained in hypoxia which show nearly identical cardiac output values at each ventricular filling pressure.

Nineteen-week-old rats. In contrast to the relatively similar performance of the 9-week-old C and OB hearts, 19-week-old OB hearts (when body weight was 37% greater than that of C) exhibited a number of significant functional differences compared with C. Although LVSP of the two groups was comparable at the one filling pressure studied in normoxia, LVSP of OB hearts decreased significantly more than in C when perfusion was switched from normoxia to hypoxia, resulting in a significantly lower LVSP at 4 mm Hg LVEDP in hypoxia (Table II). The LVSP of C and OB were comparable throughout the remainder of the experiment except during the dobutamine challenge (Table II). The response of LVSP to dobutamine challenge was less in OB on both a percentage basis (9.1 ± 0.7 vs 13.4 ± 0.7%; $P < 0.001$) and on an absolute basis (Fig. 2). Upon dobutamine challenge, the *dP/dt* also increased less in OB than in C on both a percentage basis (15.2 ± 1.8 vs 25.1 ± 1.5%; $P < 0.005$) and on an absolute basis (Fig. 2). Absolute *dP/dt* values throughout the experiment were comparable in C and OB except in hypoxia at LVEDP of 10 mm Hg, at which point OB exhibited a significantly greater *dP/dt* than that of C (Table II). Peak aortic flow was lower in OB throughout the experiment (Table II), although the differ-

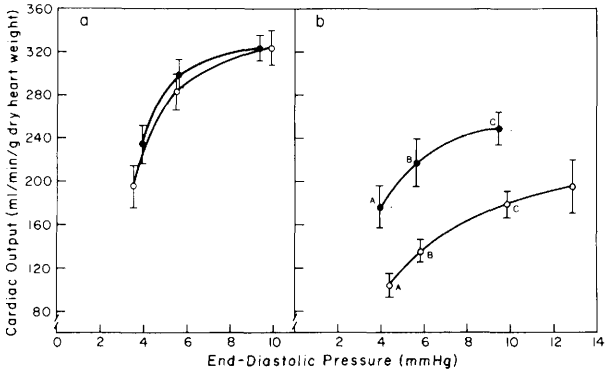

FIG. 1. Ventricular function curves of hearts from (a) 9-week-old and (b) 19-week-old lean (●) and obese (○) male Zucker rats during hypoxic perfusion. Cardiac output values at a given filling pressure designated by the same capital letter are significantly different from each other. $n = 7$ for each group.

TABLE II. ISOLATED HEART FUNCTION OF 19-WEEK-OLD LEAN AND OBESE ZUCKER RATS

Group	Normoxia	Hypoxia[a]					Normoxia recovery
		ED = 4	ED = 6	ED = 10	Control for DB	+ DB	
				Left ventricular maximum systolic pressure (mm Hg)			
Lean	91.7 ± 1.3[b]	78.2 ± 1.1	77.3 ± 1.1	76.1 ± 0.8	77.2 ± 1.0	87.5 ± 1.2	82.5 ± 0.8
Obese	91.1 ± 0.9	72.1 ± 1.0***	74.7 ± 0.9	77.1 ± 0.8	74.2 ± 1.1	81.0 ± 1.4***	82.1 ± 1.2
				Peak aortic flow (ml/min)			
Lean	149.1 ± 4.7	114.0 ± 5.9	120.3 ± 6.3	124.5 ± 4.5	111.7 ± 5.5	139.3 ± 5.2	127.5 ± 3.7
Obese	139.6 ± 4.0	85.2 ± 5.5**	98.9 ± 4.5*	115.3 ± 4.3	91.0 ± 4.3*	112.7 ± 5.7***	120.5 ± 4.1
				End-diastolic pressure (mm Hg)			
Lean	2.4 ± 0.1	3.9 ± 0.2	5.6 ± 0.1	9.4 ± 0.2	3.5 ± 0.2	3.9 ± 0.3	3.0 ± 0.2
Obese	2.6 ± 0.1	4.4 ± 0.2	5.8 ± 0.1	9.8 ± 0.1	5.3 ± 0.5***	6.4 ± 0.8**	4.2 ± 0.3***
				Left ventricular maximum *dP/dt* (mm Hg/msec)			
Lean	3.01 ± 0.04	2.43 ± 0.05	2.33 ± 0.05	2.19 ± 0.05	2.43 ± 0.07	3.03 ± 0.09	2.63 ± 0.05
Obese	3.13 ± 0.10	2.34 ± 0.05	2.41 ± 0.06	2.43 ± 0.07*	2.58 ± 0.08	2.97 ± 0.10	2.84 ± 0.10
				Cardiac output (ml/min/g dry heart weight)			
Lean	193.1 ± 9.7	177.8 ± 19.9	218.5 ± 22.3	250.7 ± 16.7	182.9 ± 15.5	181.5 ± 16.8	189.5 ± 7.6
Obese	150.0 ± 8.9**	105.2 ± 11.6*	137.0 ± 11.1**	182.0 ± 13.5**	117.4 ± 11.6**	123.9 ± 12.7*	148.3 ± 8.8***
				Coronary artery flow (ml/min·g dry heart weight)			
Lean	73.2 ± 1.0	83.5 ± 3.8	86.6 ± 3.8	86.1 ± 3.9	88.4 ± 4.2	89.5 ± 4.1	72.7 ± 2.9
Obese	65.5 ± 5.5	67.7 ± 2.8*	73.2 ± 5.9	75.7 ± 6.7	73.7 ± 5.8	74.1 ± 6.0	61.7 ± 4.6
				Myocardial oxygen consumption (mmole/hr·g dry heart weight)			
Lean	2.72 ± 0.11	2.05 ± 0.09	2.14 ± 0.08	2.10 ± 0.08	2.08 ± 0.08	2.32 ± 0.10	2.33 ± 0.07
Obese	2.62 ± 0.24	1.70 ± 0.07*	1.81 ± 0.12	1.89 ± 0.14	1.80 ± 0.11	1.97 ± 0.16	2.29 ± 0.14

[a] ED, End-diastolic pressure in mm Hg; DB, dobutamine HCl at 0.1 μM.
[b] Mean values ± SEM for seven lean and seven obese rat hearts.
* $P < 0.02$.
** $P < 0.01$.
*** $P < 0.005$.

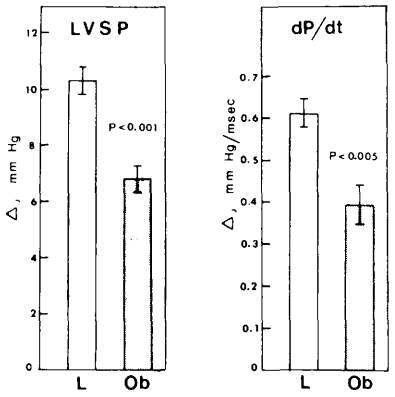

FIG. 2. Changes in left ventricular maximum systolic pressure (LVSP) and maximum rate of pressure rise (*dP/dt*) of isolated hearts from lean (L) and obese (Ob) 19-week-old rats upon exposure to 0.1 μM dobutamine HCl during perfusion in hypoxia. Changes are shown as absolute increments (Δ) of each parameter with the appropriate unit for each parameter indicated. $n = 7$ for each group.

ences between the two groups attained statistical significance at only four of the seven measurement points. Peak aortic flow was significantly lower in OB hearts compared with C during dobutamine challenge; however, absolute and relative increases in this index caused by dobutamine were similar (not significantly different) in C and OB. Cardiac output was significantly lower at every measurement period in normoxia and hypoxia in OB compared with C (Table II). Significantly diminished pump performance of OB hearts is demonstrated in Fig. 1b by the ventricular function curves of 19-week-old OB and C hearts obtained during hypoxia. Coronary artery flow and myocardial oxygen consumption were also consistently lower in OB but were significantly different in C and OB only at the first hypoxia measurement period (LVEDP = 4 mm Hg) (Table II). The LVEDP of OB and C was similar at each point on the ventricular function curve, but was slightly higher in OB at the last three measurement periods of the experiment when the atrial reservoir height was 10 cm (Table II). Despite this slightly increased filling pressure, OB hearts had significantly lower cardiac output at those three measurement periods and developed less LVSP with dobutamine stimulation (Table II).

Power, stroke work, and efficiency calculations for these hearts are shown in Table III. Maximum developed power was significantly lower in OB hearts except at the first (normoxic) period and in hypoxia at LVEDP of 10 mm Hg. Stroke work was significantly diminished in OB at every measurement point except the first (normoxic) period. Efficiency was significantly reduced in OB at three of the measurement periods in hypoxia (Table III). Since these indices are derived from a measured parameter that is depressed in OB (i.e., aortic flow), it is not surprising to find that they are likewise depressed.

Discussion. This investigation represents the first experimental documentation that hearts in chronic marked obesity have impaired cardiac performance as indicated by diminished response to hypoxic stress and dobutamine challenge. Comparable cardiac function during hypoxia in the younger, 9-week-old obese and lean rat hearts coupled with the data showing diminished cardiac function in the 19-week-old obese compared with lean indicate that the depression of pump function is the result of a prolonged process. The depressed ventricular function curve (Fig. 1b) and associated decrease in stroke work and power (Table III), and the diminished response to dobutamine in hypoxia (Fig. 2), characteristic of the hearts from the 19-week-old obese rats, suggest that ventricular function of the obese rats is compromised under hypoxic conditions. It cannot be determined from the present study whether diminished coronary flow in the obese animals contributed to the reduced functional response to hypoxia and dobutamine. Since coronary flow did not increase in either group upon dobutamine stimulation in hypoxia (Table II), it is likely that the coronary vasculature was maximally dilated at that point in the experiment.

In long-standing obesity, the heart chronically operates at a high volume load to pump the increased cardiac output necessary to satisfy increased oxygen and nutrient demands of an enlarged body mass. Consequently, certain adaptive mechanisms such as ventricular dilation and hypertrophy may develop (13, 14) to

TABLE III. WORK, POWER, AND EFFICIENCY OF HEARTS FROM 19-WEEK-OLD LEAN AND OBESE ZUCKER RATS

Group	Normoxia	Hypoxia[a]					Normoxia recovery
		ED = 4	ED = 6	ED = 10	Control for DB	+ DB	
				Stroke work (10^5 ergs/g)			
Lean	0.579 ± 0.036[b]	0.437 ± 0.048	0.501 ± 0.052	0.549 ± 0.041	0.422 ± 0.042	0.497 ± 0.044	0.473 ± 0.028
Obese	0.500 ± 0.022	0.243 ± 0.023***	0.320 ± 0.023***	0.411 ± 0.030**	0.268 ± 0.026***	0.332 ± 0.032**	0.376 ± 0.022**
				Maximum power (J/g·sec)[c]			
Lean	0.144 ± 0.008	0.096 ± 0.009	0.102 ± 0.010	0.103 ± 0.008	0.092 ± 0.009	0.126 ± 0.010	0.110 ± 0.006
Obese	0.123 ± 0.005	0.056 ± 0.004****	0.070 ± 0.004**	0.085 ± 0.005	0.064 ± 0.006**	0.085 ± 0.007***	0.092 ± 0.004*
				Efficiency (%)			
Lean	8.9 ± 0.5	8.9 ± 0.8	9.7 ± 0.8	11.0 ± 0.8	8.5 ± 0.7	8.9 ± 0.6	8.5 ± 0.5
Obese	8.4 ± 0.8	5.9 ± 0.3***	7.5 ± 0.6*	9.2 ± 0.7	6.2 ± 0.6*	7.2 ± 0.7	7.0 ± 0.6

[a] ED, End-diastolic pressure in mm Hg; DB, dobutamine HCl at 0.1 μM.
[b] Mean values ± SEM for seven lean and seven obese rat hearts.
[c] 1 joule = 10^7 ergs.
* $P < 0.05$.
** $P < 0.02$.
*** $P < 0.01$.
**** $P < 0.005$.

help maintain the greatly augmented total systemic blood flow (14). The presence of ventricular dilation cannot be determined from our present data, but slight cardiac hypertrophy, which usually accompanies a high output state (15), was apparent in 19-week-old obese rats when sample size was increased.

When cardiac dilation accompanies chronic volume overload, the diastolic pressure–volume relationship may be flattened and shifted to the right (16). Consequently, differing ventricular function curves, such as observed in this study, might be a reflection of differences in initial fiber length at a given filling pressure, rather than differences in contractility. We could not test this possibility of differing compliance or left ventricular volume because we have not generated pressure–volume curves in our isolated rat hearts. A successful method of determining ventricular volume in the isolated ejecting rat heart (10) was not described until after our experiments were in progress.

The observation of a higher dP/dt in the obese rat hearts compared with controls at an elevated filling pressure (10 mm Hg) in association with significantly reduced cardiac output in hypoxia is an anomalous finding in this study. Further experiments are necessary to confirm this finding of elevated dP/dt in light of the larger body of evidence from this study indicating that during hypoxia cardiac performance of the obese rats is reduced compared with controls.

Another interesting finding is the decline in cardiac output in both lean and obese animals with age (Fig. 1). Although some studies have indicated a decline in cardiac performance or work capacity in older rats (17, 18), to our knowledge this phenomenon has not yet been systematically investigated in a single strain of rat beginning at an early age.

The utilization of an imposed stress (e.g., exercise) is a well-accepted technique for the detection of underlying cardiac functional disability. While global hypoxia and dobutamine challenge are nonphysiological stressors, we believe their use is justified as a technique for revealing cardiac functional abnormalities, particularly since myocardial ischemia and augmented sympathomimetic stimulation are conditions that can be encountered in the intact animal. The present investigation has focused on function in hypoxia because preliminary experiments had revealed marked differences between lean and obese rat heart function at 32 weeks of age under hypoxic conditions. Assessment of cardiac function of obese and lean rats in normoxia and with dobutamine stimulation in normoxia may yield additional information concerning the cardiac pathology of the obese rat.

In the intact animal, neural and humoral influences may adequately compensate cardiac functional disabilities. Nevertheless, the isolated working whole heart has provided important information regarding intrinsic myocardial performance.

The Zucker rat appears to be a useful model for the further investigation of the mechanism and pathology of cardiac dysfunction in obesity. In addition, this animal model readily lends itself to the systematic evaluation of the roles of exercise, food intake, and hormonal disturbances in the cause and prevention of this dysfunction.

Summary. Cardiac hemodynamic function of genetically obese male Zucker rats and lean male littermates was studied using an isolated ejecting whole heart preparation. Minimal differences in function were observed between hearts from 9-week-old lean and obese rats. In contrast, hearts from 19-week-old obese rats exhibited depressed ventricular function curves accompanied by decreased stroke work, maximum power, and efficiency in hypoxia, and reduced response to dobutamine in hypoxia compared with controls. These findings suggest that chronic severe obesity in the Zucker rat is associated with the development of diminished cardiac resistance to hypoxic stress.

We thank Linda Miwa for assistance with animal care, Perry Gee for computer assistance, Susan Brown and Mary-Lou Uyeyama for technical assistance, and Eli Lilly and Co. for the gift of dobutamine HCl.

1. Gordon, T., and Kannel, W. B., Clin. Endocrinol. Metab. **5**, 367 (1976).
2. Enachescu, M., Gartner, A., and Marinov, M., Gerontol. Clin. **8**, 134 (1966).
3. Spencer, I. O. B., Lancet **1**, 1288 (1968).
4. Alexander, J. K., Amer. J. Cardiol. **14**, 860 (1964).
5. Alexander, J. K., J. Chronic Dis. **18**, 895 (1965).
6. Zucker, L. M., and Zucker, T. F., J. Heredity **52**, 275 (1961).
7. Segel, L. D., Woliner, M. J., Miller, R. R., Amsterdam, E. A., Chacko, K., Drake, C., Stoll, P. J., and Mason, D. T., Res. Comm. Chem. Pathol. Pharmacol. **17**, 555 (1977).
8. Segel, L. D., Woliner, M., Stoll, P. J., Drake, C., and Mason, D. T., *in* "Advances in Heart Disease" (D. T. Mason, ed.), Vol. 2, p. 505. Grune & Stratton, New York (1978).
9. Bell, G. E., and Stern, J. S., Growth **41**, 63 (1977).
10. Bersohn, M. M., and Scheuer, J., Circ. Res. **40**, 510 (1977).
11. Folch, J., Lees, M., and Sloan-Stanley, G. H., J. Biol. Chem. **226**, 497 (1957).
12. Steel, R. G. D., and Torrie, J. H., "Principles and Procedures of Statistics," p. 73. McGraw–Hill, New York (1960).
13. Mason, D. T., Amer. J. Cardiol. **32**, 437 (1973).
14. Alexander, J. K., Mod. Conc. Cardiovasc. Dis. **32**, 799 (1963).
15. Ross, J., Jr., Circ. Res. **34/35** (Suppl. II), 64 (1974).
16. Glantz, S. A., and Parmley, W. W., Circ. Res. **42**, 171 (1978).
17. Lee, J. C., Karpeles, L. M., and Downing, S. E., Amer. J. Physiol. **222**, 432 (1972).
18. Shreiner, D. P., Solomon, N., and Shock, N. W., Gerontologist **7** (Part II), 21 (1967).

Received January 8, 1979. P.S.E.B.M. 1980, Vol. 163.