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Catecholamine Stimulation of Myocardial Oxygen Consumption in Porcine Malignant Hyperthermia

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Malignant hyperthermia, a known disorder of skeletal muscle, probably also involves other organs and tissues. Because cardiac muscle is in some ways similar to skeletal muscle and because of clinical reports suggesting cardiomyopathies in susceptible families, it has been proposed that malignant hyperthermia may also involve cardiac muscle. To evaluate this, myocardial oxygen consumption was measured during malignant hyperthermia in 16 Poland China swine undergoing right-heart bypass. The progress of malignant hyperthermia was evaluated by determinations of whole-body oxygen consumption, lactate, potassium and catecholamine values, and acid–base balance. Ten genetically susceptible swine, five of which received propranolol, 40 μg/kg/min, continuously intravenously, were given halothane, 1 per cent, and succinylcholine, 3 mg/kg, to initiate malignant hyperthermia. Six normal swine, one of which received the same dose of propranolol, were also given halothane and succinylcholine to obtain control data.

During malignant hyperthermia without propranolol, mean myocardial oxygen consumption increased from 7 to 34 ml O_2/min/100 g heart. Swine given propranolol did not have increased myocardial oxygen consumption during malignant hyperthermia, but had myocardial oxygen consumption values similar to those of normal swine with or without propranolol. Also, during malignant hyperthermia, the myocardium did not release either lactate or potassium. The authors conclude that porcine malignant hyperthermia increases myocardial metabolism secondary to beta-adrenergic receptor stimulation due to increased release of catecholamines, and that it is unlikely that the myocardium is primarily involved in malignant hyperthermia. (Key words: Hyperthermia, malignant pyrexia. Heart: oxygen consumption. Oxygen: consumption. Sympathetic nervous system: beta-adrenergic receptors.

MALIGNANT HYPERTHERMIA (MH), a genetic disorder,[1,2] is similar in man and swine.[2] Abnormalities directly related to MH have been found in skeletal muscle,[1,2] but other reported abnormalities are not necessarily so related. For example, myocardial histologic changes[3] may have been due to the effects of acidosis, fever, hyperkalemia, ischemia, or postmortem autolysis. Also, dysfunctions of nerve,[4–6] pancreatic islet cells,[7] blood cells,[8,9] adrenal,[10] and thyroid[10] have been found in tissues of untriggered susceptible people or swine in various circumstances. Nonetheless, all of these findings are apparently related to abnormal outer cell membranes or intracellular organelles in which a common mediator of change in permeability is calcium ion.[1,2,11] Related gross dysfunction has been most obvious with skeletal muscle, because of the resulting changes in metabolism, acid–base balance, and circulation.[12] There has been, however, controversy as to the role the sympathetic nervous system may play in initiating these changes.[13,14] With dysfunction of skeletal muscle, the accompanying changes are thought to be due to uncontrolled increases in ionized intracellular calcium,[1,2] leading to compensatory increases in aerobic and anaerobic metabolism that result in increased levels of carbon dioxide, lactate, hydrogen ion, potassium, and catecholamine in blood.[12] These changes are all prevented or reversed by dantrolene,[15] and, based upon its proposed sites of action,[16–18] the abnormality in skeletal muscle is probably located in the sarcoplasmic reticulum (SR) or the coupling mechanism from the transverse tubule to the SR.

Because human families with individuals susceptible to MH are reported to have a relatively high incidence of sudden unexplained deaths, it has been suggested that the myocardium might be involved in MH.[19] This postulated involvement could be primary, due to abnormal structure or function of the myocardium or its SR, or secondary, due to effects of endogenous catecholamines released during the generalized stress reaction of MH. The present study has examined these questions by determining myocardial oxygen consumption ($M\dot{V}_{O_2}$) during porcine MH with and without blockade of beta-adrenergic receptors.

Methods

Sixteen littermate Poland China swine weighing 32 ± 3 kg (SE) and previously identified as normal (six) or susceptible to MH (ten) by testing with a brief period of inhalation of halothane[20] were studied. Anesthesia for the surgical preparation included thiopental, 15–30 mg/kg, and atropine, 0.4 mg, intravenously, supplemented by nitrous oxide–oxygen 50 per cent each, administered by a Harvard pump via a cuffed endotracheal tube.[20] After heparin, 3 mg/kg, intravenously, right-heart bypass[21] was achieved by diversion of inferior and superior vena caval flow to a reservoir–roller pump–heat ex-

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changer (37 C) and reinfusion into the main pulmonary artery. The azygos vein was ligated. Timed collection of flow from the right ventricle enabled direct measurement of myocardial blood flow, and $M\dot{V}_{O_2}$ was calculated as the product of flow and arterial–myocardial venous blood oxygen content difference. Whole-body oxygen consumption was calculated as the product of pump flow ($\dot{Q}$) and arterial–pulmonary arterial blood oxygen content difference. Myocardial efficiency was calculated as the quotient of left ventricular external work ($\dot{Q}$ times mean arterial blood pressure) and $M\dot{V}_{O_2}$.[22]

Blood gas, oxyhemoglobin, and pH values (37 C) were measured in arterial, myocardial venous, and pulmonary arterial samples. Blood lactate, pyruvate, and ionized calcium, and plasma potassium and sodium values, were measured in arterial and myocardial venous samples; epinephrine and norepinephrine values were determined in arterial blood samples. Analyses were as before[20] except for ionized calcium (Orion SS20 calcium electrode).[23] Additional measurements included mean arterial ($\bar{P}$) and left atrial pressure, heart rate, and esophageal temperature.

Pump flow was held constant at approximately 80 ml/kg/min, and was considered equivalent to left ventricular output. When flows and pressures were stable and arterial carbon dioxide partial pressure (Pa_{CO_2}) was 40 ± 3 torr, control values were determined in triplicate at 5-min intervals. MH was initiated by adding halothane, 1 per cent, to the inspired gases, followed by succinylcholine (SCh), 3 mg/kg, intravenously, 15 min later.[12] Ventilation was not changed during MH.

Five susceptible pigs ("MH swine") and five normal pigs ("normal swine") received no additional drug prior to the introduction of halothane. The remaining five susceptible swine received propranolol, 40 μg/kg/min,[24] intravenously, continuously after initial control measurements ("propranolol–MH swine"). After 20 min of beta-adrenergic receptor blockade, control values were repeated in triplicate and halothane–SCh introduced as described above. Propranolol was continued throughout. The one remaining normal pig was also given propranolol, halothane and SCh exactly as the propranolol–MH swine were. In all 16 pigs, serial measurements were made over the next 40 min.

Pilot studies in one extra 40-kg Poland China pig examined the competitive effect of propranolol on serial isoproterenol dose–response curves.[25] With anesthesia and ventilation as described above, the dose of isoproterenol necessary to increase pulse rate 25/min was determined before propranolol and again after 30 min of each of the following continuously administered propranolol infusions—2.5, 5, 10, 20, and 40 μg/kg/min. Through 10 μg/kg/min, successive curves were shifted in parallel to the right. The 20 μg/kg/min dose did not shift the isoproterenol response curve further to the right. The 40 μg/kg/min dose began to depress the response to isoproterenol, in that the slope of the semilog dose–response curve was decreased slightly. Dose ratios (effective isoproterenol dose with propranolol/effective isoproterenol dose without propranolol) were, respectively, 7, 20, 75, 65, and 150 for doses of propranolol of 2.5 μg/kg/min, 5, etc). We selected 40 μg/kg/min for the experimental protocol because it produced the greatest competitive beta-adrenergic receptor inhibition with apparently only slight myocardial depression and because it was reported to have been well tolerated in Lister's studies.[24] Propranolol may depress myocardial membrane function at concentrations exceeding 10^{-6} M,[26] a tissue concentration that could theoretically have been reached in our protocol after 30–40 min. For this reason we included the one normal pig (not the pilot pig) that was treated exactly like the propranolol–MH swine.

Results are expressed as mean ± standard error of the mean (SE). Statistical evaluation was by Student's t test for paired data within groups and for unpaired data between groups, $P < 0.05$ considered significant.

Results

Myocardial oxygen consumption increased almost 500 per cent during MH, and propranolol blocked this increase, limiting $M\dot{V}_{O_2}$ to the range seen in normal swine (fig. 1, tables 1–3). Myocardial blood flow increased in every pig in the MH group (mean peak increase 218 ml/min/100 g heart). The increases in mean myocardial blood flow at specific intervals were not significant due to individual variation at these intervals (table 1). Myocardial venous oxygen tensions remained relatively high in the MH swine due to the rightward shift of the hemoglobin dissociation curve with low *p*H (table 1). Myocardial efficiency in the MH swine during the control period was 15 per cent; at 30 min it had decreased to 1.9 per cent.

Mean control heart rate was 110–120 beats/min in the three groups. This decreased with propranolol to 94 ± 4 and remained 85–103 beats/min during MH. Mean heart rate in the MH group increased to about 150 beats/min during MH, significantly higher than the heart rate during MH in the propranolol–MH swine. Left atrial pressures ranged from 12 to 18 torr in the normal and MH groups. In the propranolol–MH swine a mean left atrial pressure of 25 torr developed during MH; due again to individual variation, these values were not significantly different from control values but nevertheless suggest a trend towards

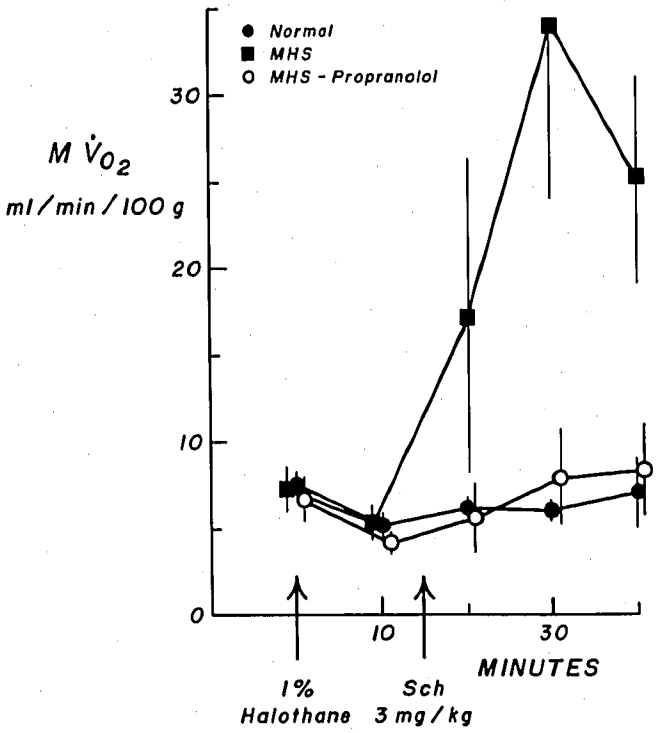

FIG. 1. Myocardial oxygen consumption in malignant hyperthermia. Myocardial oxygen consumption ($M\dot{V}_{O_2}$) in normal swine and in swine susceptible to malignant hyperthermia (MHS) with and without propranolol blockade (40 μg/kg/min) of beta-adrenergic receptors. Malignant hyperthermia initiated by halothane and succinylcholine (SCh), five pigs each curve, mean ± SE. Differences between MHS and MHS–propranolol swine achieved significance at 30 min.

left ventricular failure. Mean arterial blood pressure gradually decreased to about 50–60 torr in all three groups during the period of observation (tables 1–3). Weights of the hearts averaged 139 ± 11 g in the 16 swine.

Comparing MH, propranolol–MH, and normal swine, there were minor differences with respect to lactate, ionized calcium, potassium, and sodium across the heart (table 4). Plasma potassium progressively increased and the heart accumulated potassium in all three groups. The greatest uptake, considering changes in myocardial blood flow, was in the MH group. Changes in sodium across the heart suggest exchange for potassium or an uptake of water in all three groups, but again these were greatest in the MH group. Pyruvate tended to decrease during MH, while lactate increased.

Malignant hyperthermia occurred with and without propranolol, as indicated by increases in whole-body oxygen consumption, Pa_{CO_2}, hydrogen ion, catecholamine (tables 1 and 2), lactate, potassium, and sodium values (table 4). During MH in the MH and propranolol–MH groups, the heart did not release lactate or potassium. In this right-heart-bypass preparation, temperature during MH increased moderately without propranolol, and not at all with propranolol (tables 1 and 2). The above mentioned values did not change in normal swine (tables 3 and 4), except for expected minor increases in potassium after succinylcholine. The condition of the single normal

TABLE 1. Myocardial $\dot{V}_{O_2}$ in Malignant Hyperthermia, Five Swine, Mean ± SE

	Control	10 Min	20 Min	30 Min	40 Min
Myocardial oxygen consumption (ml O_2/min/100 g)	7 ± 1	5 ± 1	17 ± 9	34 ± 10*†	25 ± 6*†
Myocardial blood flow (ml/min/100 g)	91 ± 12	68 ± 11*	143 ± 62	306 ± 89	261 ± 95
Myocardial venous oxygen tension (torr)	37 ± 2	36 ± 2	31 ± 1*	32 ± 2	32 ± 3
*p*H, arterial blood	7.40 ± 0.01	7.41 ± 0.02	7.17 ± 0.03*	6.96 ± 0.03*	6.84 ± 0.04*
Epinephrine, arterial blood (ng/ml)	0.6 ± 0.1	0.6 ± 0.2	0.7 ± 0.4	3.8 ± 1.6*	5.7 ± 2.0*
Norepinephrine, arterial blood (ng/ml)	0.3 ± 0.1	0.8 ± 0.5	2.1 ± 0.7*	10.1 ± 2.4*	11.0 ± 3.0*
Whole-body oxygen consumption (ml O_2/min/kg)	6 ± 0.3	6 ± 0.4	10 ± 1*	11 ± 1*	10 ± 1*
Cardiac output (ml/min/kg)	76 ± 5	80 ± 1	80 ± 1	84 ± 3	85 ± 4
Mixed venous oxygen tension (torr)	37 ± 1	39 ± 2	25 ± 3*	23 ± 3*	20 ± 3*
Carbon dioxide tension, arterial blood (torr)	39 ± 1	40 ± 1	66 ± 5*	83 ± 8*	89 ± 12*
Arterial blood pressure (torr)	101 ± 11	71 ± 9*	56 ± 8*	53 ± 5*	55 ± 8*
Temperature, esophageal (C)	37.6 ± 0.4	37.7 ± 0.3	38.1 ± 0.5	38.9 ± 0.6	39.2 ± 0.5*

Malignant hyperthermia produced by halothane, 1 per cent, continuous after control measurements, and succinylcholine, 3 mg/kg, at 15 min.

* Different from control, $P < 0.05$.
† Different from propranolol–MH group, Table 2, $P < 0.05$.

TABLE 2. Propranolol Blockade of Increased Myocardial $\dot{V}_{O_2}$ in Malignant Hyperthermia, Five Swine, Mean ± SE

	Control	Propranolol Control	10 Min	20 Min	30 Min	40 Min
Myocardial oxygen consumption (ml O_2/min/100 g)	7 ± 1	7 ± 1	4 ± 1*	6 ± 2	8 ± 3†	8 ± 3†
Myocardial blood flow (ml/min/100 g)	97 ± 16	99 ± 20	72 ± 10	71 ± 20	85 ± 25	94 ± 28
Myocardial venous oxygen tension (torr)	39 ± 3	40 ± 2	43 ± 4	38 ± 5	34 ± 3	32 ± 3
*p*H, arterial blood	7.35 ± 0.04	7.41 ± 0.03	7.41 ± 0.04	7.25 ± 0.02	7.12 ± 0.06*	7.05 ± 0.05*
Epinephrine, arterial blood (ng/ml)	1.1 ± 0.4	2.0 ± 1.2	1.3 ± 0.8	3.3 ± 1.6	7.1 ± 2.9	8.0 ± 2.6*
Norepinephrine, arterial blood (ng/ml)	0.3 ± 0.1	0.3 ± 0.2	0.6 ± 0.4	2.6 ± 1.6	8.5 ± 3.8	8.0 ± 2.9*
Whole body oxygen consumption (ml O_2/min/kg)	7 ± 0.4	7 ± 0.3	6 ± 1	9 ± 1*	9 ± 1*	9 ± 0.2*
Cardiac output (ml/min/kg)	81 ± 1	81 ± 0.4	81 ± 0.4	81 ± 0.4	82 ± 0.4	82 ± 0.4
Mixed venous oxygen tension (torr)	37 ± 1	36 ± 1	38 ± 2	27 ± 2*	18 ± 3*	16 ± 3*
Carbon dioxide tension, arterial blood (torr)	41 ± 1	38 ± 3	39 ± 2	56 ± 3*	68 ± 4*	72 ± 5*
Arterial blood pressure (torr)	100 ± 5	89 ± 12	69 ± 7*	57 ± 6*	57 ± 3*	49 ± 4*
Temperature, esophageal (C)	37.1 ± 0.1	37.3 ± 0.2	37.2 ± 0.2	37.1 ± 0.2	37.3 ± 0.2	37.6 ± 0.3

Propranolol, 40 μg/kg/min, continuous after control measurement; propranolol control 20 min after control.
Malignant hyperthermia produced by halothane, 1 per cent, continuous after propranolol control, and succinylcholine, 3 mg/kg, at 15 min.
* Different from control, $P < 0.05$.
† Different from MH Group, table 1, $P < 0.05$.

TABLE 3. Myocardial $\dot{V}_{O_2}$ in Five Normal Swine Given Halothane and Succinylcholine, Mean ± SE

	Control	10 Min	20 Min	30 Min	40 Min
Myocardial oxygen consumption (ml O_2/min/100 g)	7 ± 0.5	5 ± 1*	6 ± 1	6 ± 1	7 ± 2
Myocardial blood flow (ml/min/100 g)	108 ± 12	88 ± 28	108 ± 28	103 ± 29	122 ± 32
Myocardial venous oxygen tension (torr)	36 ± 4	38 ± 4	37 ± 4	40 ± 4	43 ± 5
*p*H, arterial blood	7.40 ± 0.02	7.42 ± 0.03	7.36 ± 0.02	7.33 ± 0.03	7.34 ± 0.03
Epinephrine, arterial blood (ng/ml)	0.7 ± 0.0	0.3 ± 0.1	0.5 ± 0.1	0.6 ± 0.2	0.6 ± 0.1
Norepinephrine, arterial blood (ng/ml)	0.1 ± 0.1	0.1 ± 0.0	0.2 ± 0.0	0.3 ± 0.1	0.3 ± 0.1
Whole-body oxygen consumption (ml O_2/min/kg)	6 ± 0.3	6 ± 0.1	6 ± 0.4	6 ± 0.3	6 ± 0.3
Cardiac output (ml/min/kg)	76 ± 3	77 ± 2	77 ± 2	77 ± 2	79 ± 1
Mixed venous oxygen tension (torr)	35 ± 1	37 ± 0	32 ± 1	34 ± 1	38 ± 1
Carbon dioxide tension, arterial blood (torr)	37 ± 1	38 ± 2	46 ± 6	48 ± 5	45 ± 4
Arterial blood pressure (torr)	89 ± 6	60 ± 3*	57 ± 2*	59 ± 2*	61 ± 2*
Temperature, esophageal (C)	37.1 ± 0.1	37.1 ± 0.1	37.0 ± 0.2	37.1 ± 0.2	37.3 ± 0.3

Halothane, 1 per cent, given continuously after control measurements, succinylcholine, 3 mg/kg, at 15 min.
* Different from control, $P < 0.05$.

TABLE 4. Myocardial Venous and Arterial Blood Values, Five Swine in Each Group, Mean ± SE

	Control	Propranolol Control	10 Min	20 Min	30 Min	40 Min
Lactate (μm/ml)						
MH						
Arterial	3.1 ± 0.5	—	3.1 ± 1	10 ± 1*	15 ± 1*	17 ± 2*
Venous	2.9 ± 0.4	—	2.6 ± 0.5	9 ± 0.5*	15 ± 1*	16 ± 1*
Propranolol–MH						
Arterial	4.4 ± 1	2.8 ± 1	2.4 ± 1	6.4 ± 1	9 ± 1*	11 ± 2*
Venous	3.8 ± 1	2.3 ± 1	2.0 ± 1	4.5 ± 1	9 ± 1*	10 ± 1*
Normal						
Arterial	3.2 ± 0.4	—	2.6 ± 0.4	3.2 ± 0.5	3.3 ± 0.4	3.0 ± 0.4
Venous	3.0 ± 0.4	—	2.2 ± 0.4	2.8 ± 0.5	2.8 ± 0.5	2.7 ± 0.5
Pyruvate (μm/ml)						
MH						
Arterial	0.22 ± 0.03	—	0.22 ± 0.02	0.21 ± 0.03	0.18 ± 0.03	0.15 ± 0.02
Venous	0.19 ± 0.03	—	0.15 ± 0.02	0.20 ± 0.03	0.17 ± 0.02	0.14 ± 0.01
Propranolol–MH						
Arterial	0.22 ± 0.04	0.19 ± 0.02	0.16 ± 0.02	0.17 ± 0.01	0.15 ± 0.01	0.15 ± 0.01
Venous	0.19 ± 0.03	0.15 ± 0.02	0.14 ± 0.02	0.17 ± 0.02	0.19 ± 0.03	0.15 ± 0.04
Normal						
Arterial	0.22 ± 0.02	—	0.20 ± 0.02	0.19 ± 0.02	0.22 ± 0.02	0.21 ± 0.02
Venous	0.22 ± 0.02	—	0.19 ± 0.02	0.20 ± 0.02	0.21 ± 0.02	0.19 ± 0.02
Calcium (whole blood, ionized, mEq/l)						
MH						
Arterial	2.4 ± 0.1	—	2.4 ± 0.1	2.6 ± 0.1*	2.5 ± 0.2	2.5 ± 0.2
Venous	2.4 ± 0.1	—	2.4 ± 0.1	2.6 ± 0.0*	2.4 ± 0.2	2.4 ± 0.2
Propranolol–MH						
Arterial	2.4 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.1*	2.4 ± 0.1	2.4 ± 0.1
Venous	2.4 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.1
Normal						
Arterial	2.4 ± 0.0	—	2.5 ± 0.0	2.5 ± 0.1	2.4 ± 0.0	2.5 ± 0.0
Venous	2.4 ± 0.0	—	2.5 ± 0.0	2.5 ± 0.1	2.5 ± 0.0	2.6 ± 0.0
Potassium (plasma, mEq/l)						
MH						
Arterial	3.7 ± 0.1	—	3.7 ± 0.1	5.6 ± 0.2*	6.8 ± 0.6*	6.6 ± 0.6*
Venous	3.7 ± 0.1	—	3.7 ± 0.2	4.8 ± 0.1*	6.0 ± 0.5*	6.4 ± 0.6*
Propranolol–MH						
Arterial	3.8 ± 0.1	4.0 ± 0.1	4.2 ± 0.3	5.3 ± 0.2*	6.4 ± 0.5*	6.9 ± 0.6*
Venous	3.7 ± 0.2	4.0 ± 0.2	4.2 ± 0.3	4.8 ± 0.3*	6.1 ± 0.5*	6.9 ± 0.6*
Normal						
Arterial	3.6 ± 0.2	—	3.6 ± 0.2	4.2 ± 0.2*	4.6 ± 0.2*	4.5 ± 0.2*
Venous	3.5 ± 0.2	—	3.5 ± 0.2	4.0 ± 0.2*	4.4 ± 0.2*	4.4 ± 0.2
Sodium (plasma, mEq/l)						
MH						
Arterial	143 ± 2	—	144 ± 1	153 ± 2*	155 ± 2*	156 ± 2*
Venous	145 ± 4	—	147 ± 1	154 ± 1*	159 ± 2*	157 ± 2*
Propranolol–MH						
Arterial	145 ± 1	143 ± 1	143 ± 2	149 ± 1*	146 ± 3	147 ± 3
Venous	147 ± 2	149 ± 1	149 ± 2	150 ± 2*	153 ± 1*	155 ± 2*
Normal						
Arterial	144 ± 2	—	144 ± 2	144 ± 2	144 ± 2	144 ± 2
Venous	148 ± 2	—	147 ± 1	147 ± 1	148 ± 1	148 ± 2

Halothane, 1 per cent given continuously after control measurements (or propranolol control) and succinylcholine, 3 mg/kg, after 15 min.

MH = malignant hyperthermia-susceptible Poland China swine.

Propranolol–MH = propranolol, 40 μg/kg/min, after control; propranolol control 20 min after control.

Normal = Poland China swine not susceptible to MH.

* Different from control, $P < 0.05$.

pig given propranolol was stable during bypass, and the pig responded as did the normal swine.

Discussion

The present data demonstrate that porcine malignant hyperthermia is associated with a fivefold increase in myocardial oxygen consumption in conjunction with an eightfold decrease in myocardial efficiency. These changes are consistent with recognized beta-adrenergic effects, a conclusion supported by the blocking effect of propranolol.[22] Halothane and SCh thus do not directly initiate MH in the myocardium of

a susceptible swine, but increase metabolism via stimulation of beta-adrenergic receptors. Further interpretation of these findings must be related to generally accepted hypotheses of excitation–contraction coupling in skeletal muscle and myocardium.

Prior to further interpretation, it is necessary to examine the experimental conditions. Because MH is in itself an unsteady state of metabolism and circulation, calculations based upon the Fick principle are subject to inaccuracies.[27] A reproducible and consistent pattern of MH results in swine when using the potent MH trigger halothane combined with SCh,[12] providing both the directions and relative magnitudes of metabolic and circulatory changes. During MH in both groups of susceptible animals, both right-heart bypass and propranolol apparently altered the course of the disease. With right-heart bypass, constant $\dot{Q}$ limited perfusion to hypermetabolic tissues and the extracorporeal 37 C heat exchanger limited temperature increases. We speculate that propranolol might have produced relative muscle ischemia, since blood flow to muscle probably could not increase[28] and because muscle is the tissue primarily responsible for the metabolic changes of MH.[29] Also, the large dose of propranolol may have resulted in some direct depression of metabolism.[26] Lister, Hall, and Lucke[24] support this viewpoint with their report of smaller increases in P_{CO_2}, hydrogen ion concentration, and temperature during MH in pigs treated with the same dose of propranolol. However, they found no increase in survival. In the present study the MH group with right-heart bypass alone showed a smaller increase in mean temperature than is generally observed in the intact pig during acute MH. The swine with propranolol in addition to right-heart bypass remained afebrile and tended to have smaller increases in lactate, P_{CO_2}, and hydrogen ion concentration.

Some might contend that malignant hyperthermia without hyperthermia is not MH at all. Fever is due to heat production greater than heat loss. Heat production in MH is due to increased aerobic and anaerobic metabolism, hydrolysis of high-energy phosphates, and neutralization of hydrogen ion.[30] Effective cooling during MH can limit fever without stopping the associated metabolic and acid–base reactions.[15] Further, propranolol may decrease heat production by limiting perfusion of muscle[28] or by direct depression (after large doses[26]).

Interpretation of the effect of propranolol on $M\dot{V}_{O_2}$ during MH hinges upon the differences between activation of contraction of skeletal muscle and cardiac muscle. The crucial area, namely, the mechanism whereby the muscle action potential in the transverse tubule initiates the release of ionic calcium within the fiber, is poorly understood. Two favored hypotheses[31] are depolarization-induced release of calcium and calcium-induced release of calcium. The former proposes that the action potential in the transverse tubule is transmitted to and depolarizes the terminal cisterna of the SR, thereby increasing its permeability to calcium. The latter theory proposes that an amount of trigger calcium too small to cause contraction directly[31,32] enters the fiber with depolarization and regenerates at least a hundredfold increase in calcium release by increasing the permeability of the SR. The first hypothesis is favored as the probable mechanism for excitation–contraction coupling in skeletal muscle,[31] and the second for amphibian cardiac muscle,[31,32] but not for mammalian cardiac muscle. In the latter, depolarization apparently releases calcium from rapidly exchangeable stores in the surface and tubular membranes, and SR functions mainly in calcium uptake.[33]

Beta-adrenergic receptor agonists have complex direct and indirect effects. They increase the rate of calcium entry across the myocardial cell membrane during depolarization, and indirectly increase the concentration of cyclic 3′-5′-adenosine monophosphate (cyclic AMP or cAMP),[32,34] which in turn increases the rate of accumulation of calcium by SR,[34] inhibits accumulation by the mitochondrion,[34] increases phosphorylation of certain target proteins,[35] and variously affects metabolism.[32,34,35] It is suggested that the increased entry of calcium results in increased release of ionic calcium and hence a stronger contraction.[34] Increased contractility may also result from increased phosphorylation of various target proteins.[35] Catecholamines are less effective in increasing contractility in skeletal muscle,[36] but their action is also mediated by beta-adrenergic receptors, *i.e.*, blocked by propranolol. The mechanism of action is also thought to be via an increase in intracellular ionized calcium levels due to effects on SR release or uptake.

We recently reported[13] that the complete sympathetic blockade caused by total spinal anesthesia abolished MH-related increases in circulating catecholamines without preventing or altering halothane-induced porcine MH. We discussed the controversy[13,14] concerning the role of catecholamines in initiating MH and concluded that the sympathetic hyperactivity observed in porcine MH was a secondary and typical adrenergic response to major stress. The depolarization-induced release of calcium theory of skeletal muscle activation and the effects of beta-adrenergic receptor agonists are consistent with those data and conclusions. However, the proposed mechanism of calcium release in mammalian myocardium, and the important myocardial effects of beta-adrenergic receptor agonists and cAMP, suggest that abnormal calcium transients in myocardial excitation–contrac-

tion coupling might be mediated by beta-adrenergic receptors. Thus, the increase in $M\dot{V}_{O_2}$ during MH could be a normal adrenergic response to marked stress, or could be an exaggerated adrenergic effect due to a myocardial abnormality.

Our data resolve this difficulty indirectly and suggest that the changes are a response of normal myocardium, for the following reasons. First, striated skeletal muscle produces lactate during MH, in addition to increasing its oxygen consumption.[12,20] While myocardium relies almost exclusively upon aerobic metabolism, it may under abnormal conditions produce lactate.[22] In the present study, however, the myocardium did not produce and release lactate during MH, despite high $M\dot{V}_{O_2}$ and low oxygen content of myocardial venous blood (about 4 vol per cent) in the MH swine. Second, plasma potassium increased during MH, as expected, due to release from skeletal muscle[12,20] in both MH and propranolol–MH groups. In both groups the myocardium did not release potassium but accumulated it during considerable increases in arterial values. Active MH generally involves increased permeability of cell membranes[1,2] with resulting movement of potassium along its concentration gradient.[12,13,20] Third, skeletal and heart muscle normally contract due to depolarization, and beta-adrenergic receptor agonists stimulate contraction and metabolism in both, but, as referred to above, acute sympathetic denervation caused by total spinal anesthesia did not prevent the occurrence of MH in skeletal muscle.[13] The present data demonstrate MH effects on myocardium that were prevented by beta-adrenergic receptor blockade, although we cannot say whether these responses were exaggerated or normal. Gross depression due to overdose of propranolol was unlikely because the condition of the one normal pig with propranolol and right-heart bypass was stable, and the pig did not react differently from the normal swine. Fourth, dantrolene, in contrast to its effects on skeletal muscle, has been reported neither to diminish canine cardiac contractility[37] nor to affect calcium binding and release in cardiac SR.[17] If cardiac muscle were also actively involved in MH, dantrolene would not be so effective in both preventing and treating MH *in vivo*.[15]

We have no data that specifically demonstrate abnormal intracellular calcium transients or abnormal function of the SR. The available reports indicate that fragmented skeletal muscle SR shows changes typical of a myopathy, but probably not severe enough to explain the mechanism of MH.[1,2,*] This information, plus that reporting the effectiveness of dantrolene and the ineffectiveness of acute somatic and sympathetic denervation in preventing MH, suggests that the disorder in skeletal muscle involves the excitation–contraction link from transverse tubule to SR, the enzymatic reactions supporting SR function, or a combination of minor abnormalities. This reasoning implies that findings in other tissues may be parallel (to skeletal muscle) abnormalities, since calcium alters permeability in inexcitable as well as excitable cells.[11]

The clinical relevance of these results depends in part upon the extent of similarity between porcine and human MH, and the present findings may be pertinent to one of the few recognized differences. MH can develop in susceptible swine while they are awake when they are stressed or excited, and they may die quickly, a disorder known as the porcine stress syndrome.[2] MH has not been observed in susceptible awake man, but only during general anesthesia with known triggers,[1] *e.g.*, the potent volatile anesthetic agents and the depolarizing relaxants. Wingard recently reported that families with individuals susceptible to MH have a higher incidence of sudden and unexplained deaths than the general population, a finding possibly related to lessened ability to tolerate stress.[19] Huckell *et al.* support this concept with a report of young MH-susceptible patients who had evidence of cardiomyopathy.[38] These two reports suggest myocardial dysfunction in susceptible man, but we speculate that this dysfunction could be secondary to repeated subclinical episodes of MH with repeated stress-induced release of catecholamines.

We conclude that beta-adrenergic receptor stimulation during porcine MH leads to increased myocardial oxygen consumption and decreased myocardial efficiency. We further conclude that porcine myocardium does not possess a genetic MH defect that responds to the usual triggers, *e.g.*, halothane and SCh. We cannot say whether the myocardial response to beta-adrenergic receptor stimulation is altered or normal.

* Heffron JJA, Theye RA, Gronert GA: Unpublished observations.

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