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Cardiovascular and Metabolic Responses to Anesthetic-induced Malignant Hyperthermia in Swine

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Background: **Several cardiovascular disturbances, such as tachycardia and hypotension, are observed during human and porcine malignant hyperthermic (MH) crises. However, the pathophysiologic mechanisms responsible for the deterioration of cardiovascular function during MH are not completely known. The purpose of this study was to elucidate the changes in left ventricular (LV) function and metabolism and the systemic and regional hemodynamics during anesthetic-induced MH in swine.**

Methods: **The study was carried out in 12 open-chest MH-susceptible pigs and in 8 healthy control (non–MH-susceptible) pigs under the same conditions. The cardiovascular and metabolic responses to halothane (1% inspired) and succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane administration) were studied. Global hemodynamic and LV variables (expressed as means ± SEM) were determined over a period of 90 min after the beginning of halothane exposure. Simultaneous investigations were performed on hind-leg and cardiac muscle to compare the regional functional and metabolic changes in these tissues.**

Results: **MH was triggered in all MH-susceptible pigs. Early (10–30 min) cardiovascular changes during the development of MH consisted of a rapid increase in heart rate (from 86 ± 4 to 204 ± 8 beats · min^{-1}), cardiac index (+84%), and peak rate of change in LV pressure (+150%); stroke volume index (−24%) and mean aortic pressure (−13%) decreased progressively even in the early stage of MH. These alterations were accompanied by an early and persistent reduction in systemic vascular resistance (maximally −57%) with an increase in aortic pressure amplitude. Early changes in coronary and peripheral hemodynamics during the development of MH consisted of a threefold increase in coronary blood flow in conjunction with a marked decrease (−77%) in coronary vascular resistance. The early circulatory changes were associated with a fourfold increase in myocardial and a 2.5-fold increase in peripheral O_2 consumption. The ratio of the LV stroke work index (LVWI) to myocardial O_2 consumption ($M\dot{V}_{O_2}$) was significantly decreased, by a factor of 5. Increased catecholamine concentrations and myocardial lactate and H^+ production could be demonstrated throughout the MH crisis. In the late stage of MH (>30 min), pronounced hypotension and a subsequent decrease in cardiac index were noted. These changes were associated with a significant reduction in LV end-diastolic pressure, from 9 ± 1 to 6 ± 1 mmHg ($P < 0.05$), and in the rate of change in LV pressure, by a maximum of −25%. Coronary vascular resistance remained reduced while coronary blood flow decreased. Peripheral (hind-leg) blood flow initially increased by 48% while peripheral vascular resistance decreased by 42%, followed by a fivefold increase in peripheral vascular resistance with a marked decrease in peripheral blood flow (−88%) in the late phase of MH.**

Conclusions: **The current findings indicate that metabolic status during MH is characterized by a demand ischemia of the heart and of the skeletal muscle. Insufficient coronary blood flow and increased metabolism as a result of tachycardia and increased concentrations of catecholamines are the dominant factors contributing to the dramatic alteration in cardiac performance during porcine MH. Acidosis, hypovolemia, and hyperkalemia, especially in the late phase of MH, are additional essential factors responsible for the progressive cardiovascular deterioration and cardiac death. (Key words: Anesthetics, volatile: halothane. Heart, left ventricle: function; metabolism. Hemodynamics: coronary; peripheral; systemic. Hyperthermia: malignant.)**

MALIGNANT hyperthermia (MH), a latent disorder affecting humans and swine, is caused by a genetic defect involving myoplasmic Ca^{2+} homeostasis and is manifested as a hypermetabolic derangement.[1–6] Among predisposed individuals, the life-threatening MH syndrome may be triggered by a variety of factors, particularly general anesthesia with depolarizing muscle relaxants and volatile anesthetics.

Cardiovascular function is severely altered during human and porcine MH, as indicated by the early ap-

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pearance of tachycardia and arrhythmias and later by hypotension, decreased cardiac output, and eventually cardiac arrest.[7] Although cardiovascular disturbances predominate in the MH crisis and death results from cardiac arrest, only a few experimental studies to date have systematically analyzed the hemodynamic changes during MH.[8–10] Right-side heart bypass studies by Gronert *et al.*[9] have demonstrated that porcine MH is associated with a fivefold increase in $M\dot{V}_{O_2}$ in conjunction with an eightfold decrease in myocardial efficiency. However, little is known about left ventricular (LV) function and metabolism or about systemic and coronary vascular alterations during MH. Furthermore, there are no data regarding cardiovascular function during the final stage of MH. It has been suggested that hypotension, decreased cardiac output and, finally cardiac death during MH are the result of acute heart failure or rigor of the heart muscle.[11]

The current study was designed to assess cardiovascular performance during the various stages of porcine MH. In addition, we investigated the changes in coronary hemodynamics and LV metabolism during porcine MH. Simultaneous investigations were performed on the hind leg and skeletal muscle, respectively, to compare the functional and metabolic changes in these tissues. The cardiovascular responses to halothane and succinylcholine were also studied in healthy control pigs under the same conditions.

Materials and Methods

Twelve MH-susceptible (MHS) swine from a colony of Pietrain pigs (weight 37 ± 4 kg, age 3–7 months) whose lines have been maintained for the past 10 yr and 8 control, non-MHS (nMHS) German Landrace swine (weight 38 ± 3 kg, age 3–7 months) were studied. Susceptibility to MH was tested by challenge with halothane 4–6 weeks before the investigation, as previously described.[12] The procedures used in the study were approved by the institutional animal care and use committee and performed in accordance with the legal regulations for use of laboratory animals.

Instrumentation

Each animal was fasted overnight with free access to water. Anesthesia was induced with intraperitoneal injections of azaperone (Stresnil) 30–50 mg and metomidate hydrochloride (Hypnodil) 10 $mg \cdot kg^{-1}$. All pigs were placed in the supine position, and body temperature was monitored by a rectal probe and later by an additional probe placed in the ascending aorta. Temperature was maintained at 37–38°C by means of a warming pad beneath the pig and an infrared heating lamp. After intravenous administration of methohexital 100–150 mg, laryngeal administration of lidocaine 4%, and manual hyperventilation with 100% O_2 (3–5 min), the trachea was intubated. Mechanical ventilation (air–O_2 mixture 4 $l \cdot min^{-1}$ and fraction of inspired O_2 0.3–0.35; Romulus 800, Dräger, Lübeck, Germany) was set to maintain an end-expiratory CO_2 tension (Normocap, Datex, Finland) between 33 and 35 mmHg. Positive end-expiratory pressure (2 cmH_2O) was applied to prevent major collapse in the open-chest animals. Throughout the study anesthesia was maintained with intravenous fentanyl 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and intravenous metomidate hydrochloride (Hypnodil) 0.3–0.5 $mg \cdot kg^{-1} \cdot h^{-1}$. Both fentanyl and metomidate were continued during administration of halothane in both groups of experiments. During surgical preparation, vecuronium (0.1 $mg \cdot kg^{-1}$ intravenously) and additional fentanyl were given as indicated by increases in heart rate and blood pressure. Ringer's solution was given at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$. Glucose 5% was substituted when plasma glucose concentrations were less than 4.2 mM and titrated to achieve a plasma concentration between 4.5 and 5.5 mM.

After median sternotomy, the pericardium was carefully incised about the proximal part of the left anterior descending coronary artery (LAD), and the LAD was freed without cutting for a distance of 1 cm. Simultaneously, a preparation of the right hind-limb artery (distal part of the femoral artery) was performed. For regional blood flow analysis, precalibrated electromagnetic flow probes (Stölzer Meβtechnik, Germany) of appropriate sizes to ensure a snug fit were placed around the right hind-limb artery and the LAD distal to its first large diagonal branch. The calibrated flow probes were connected to flow meters with incorporated nonocclusive zero (Hellige, Freiberg, Germany).

Cardiovascular catheterization was performed by using fluoroscopic monitoring or pressure signals. For pressure recordings, catheter-tip manometers with an incorporated fluid-filled lumen (6-French, Honeywell, Germany) were inserted through the left carotid and the left femoral artery and advanced into the left ventricle (LV) and the ascending aorta just above the aortic valve, respectively. The catheter-tip manometers were prewarmed in a water bath at 37°C for several hours and were simultaneously calibrated immediately before

insertion and after extraction. Baseline stability of the high-fidelity signals was checked repeatedly during the experiment by superimposing the manometer-derived pressures on those derived from the fluid-filled lumina incorporated in the catheter-tip manometers using transducers (Statham P23, Gould, Oxnard, CA).

The ascending aorta, the pulmonary artery, and the coronary sinus were catheterized *via* the left brachial artery, the right jugular vein, and a branch of the right jugular vein, respectively, using catheters with a fluid (0.9% NaCl)–filled lumen (5- to 7-French, United States Catheter Instruments, Billerica, MA) for blood sampling. The tip of the coronary sinus catheter was advanced into the vena cordis magna in a range of 25–40 mm from the ostium of the coronary sinus. The localization of the catheter tip was controlled by palpation, inspection, fluoroscopy, and blood gas analysis. Further fluid-filled catheters (6- to 7-French, USCI) were inserted through another right jugular branch vein into the right atrium to inject ice-cold Ringer's solution for cardiac index (CI) determinations by the thermodilution technique (Cardiac Output Computer, Hoyer, Germany) and through the left femoral vein into the left hind limb vein to obtain peripheral venous blood samples. A thermistor probe (Hoyer) was placed into the ascending aorta *via* a branch of the left femoral artery to measure the blood temperature and CI. All fluid-filled catheters were automatically flushed with 0.9% NaCl plus heparin (CFS2–3, Abbott, Germany).

Measurements

All signals were displayed on a monitor (Hellige) and continuously recorded on a multichannel paper recorder (Graphtec, Japan). The peak positive and peak negative rates of change in LV pressure (LV +dp/dt and LV −dp/dt, respectively) were derived from LV high-fidelity signals with amplifiers connected to a differentiator (Hellige). For direct calibration of the LV dp/dt signals, a triangular wave signal of known slope was substituted for the pressure signal. For an accurate assessment of LV end-diastolic pressure, the gain of the of the LV pressure signal was magnified during part of the recording. End diastole was defined as the beginning of the sharp upslope in the expanded LV pressure tracings, and end systole by the dicrotic notch in the aortic pressure signal as derived from the catheter-tip manometers. The flows were registered as mean flow. The flow curves were displayed on the monitor to guarantee adequate signal quality. Heart rate, LV systolic pressure and mean aortic pulse pressure were obtained on-line by electronic calculation and the average pressure during diastole was determined later from the recordings as an average of the preceding 10 s. Cardiac output and blood temperature were recorded by an analyzer (Buxco cardiovascular Analyser, Hugo Sachs Elektronik, Germany) combined with a computer (International Business Machines, Germany) and printer in triplicate at each interval (injectate: 8.5 ml ice-cold 0.9% NaCl).

The systemic vascular resistance index was calculated as the ratio of mean aortic pressure and CI. LV minute index and LVWI were computed (in joules) as the product of the mean aortic pressure and CI and stroke volume index (SVI), respectively, multiplied by 133. Using high speed recordings, a further pressure derived contractility index was obtained: as an approximate value for the contractile element velocity, LV +dp/dt was divided by the product of the instantaneous pressure and the constant K (= 32) to approximate the peak contractile element velocity at zero load.[13] Instantaneous pressure was computed as the pressure difference between LV end-diastolic pressure and the LV pressure at the time of its greatest rate of change (LV +dp/dt). The LV tension time (TT), ejection time, and filling time plus relaxation time were determined by intermittent high speed (200 mm s^{-1}) recordings from the multichannel recorder, using standard criteria.[14]

Blood samples were collected simultaneously from the aorta and pulmonary artery at defined intervals for analysis of hemoglobin concentration, hemoglobin O_2 saturation (2500 CO-oximeter, Corning, Germany), and blood gases (178/pH/Blood Gas Analyser, Corning). The O_2 content was calculated as the sum of the O_2 bound to hemoglobin (the product of hemoglobin concentration, O_2 saturation, and binding capacity [1.39 ml $O_2 \cdot g$ hemoglobin^{-1}]) and the dissolved O_2 (the product of O_2 tension and 0.003). Arterial − venous O_2 content difference (avD_{O_2}) was calculated by taking the difference between arterial and mixed venous blood O_2 content. Total O_2 consumption was calculated by multiplying avD_{O_2} with CI. Additional arterial blood samples were drawn simultaneously to measure the plasma K^+, lactate, and epinephrine and norepinephrine concentrations (high-pressure liquid chromatography; ESA Coulochem 5100A, Bedford, MA).

Coronary (LAD) and peripheral (hind-leg) vascular resistances were calculated as the ratios of mean diastolic aortic pressure to mean coronary flow and mean aortic pressure to mean peripheral flow, respectively. Simultaneously with the collection of blood samples from the aorta and pulmonary artery, additional blood

samples were withdrawn from the coronary and peripheral vein at defined intervals for analysis of hemoglobin concentration, hemoglobin O_2 saturation (2500 CO-oximeter, Corning), blood gases (178/pH/Blood Gas Analyser, Corning), lactate, and K^+. Blood was slowly withdrawn from the coronary sinus catheter to prevent contamination of the vena cordis magna sample with blood from the right atrium. Samples were quickly chilled, precipitated with 8% perchloric acid, and centrifuged at 3°C. After centrifugation, the supernatant was removed, frozen, and later analyzed with an enzymatic–spectrophotometric technique.

Regional avD_{O_2} values were calculated as the differences between arterial and coronary or peripheral venous blood O_2 content. Regional myocardial and peripheral O_2 supplies were calculated as the products of arterial O_2 content and coronary and peripheral blood flow, respectively. Regional myocardial and peripheral O_2 extraction rates (percentages) were calculated as the regional avD_{O_2} values (coronary and peripheral, respectively) divided by the arterial O_2 content. Regional myocardial and peripheral O_2 consumption were calculated from the product of the corresponding avD_{O_2} and the coronary blood flow (CBF) and peripheral blood flow, respectively. Regional myocardial and peripheral uptakes of lactate and H^+ were calculated as the products of the corresponding arterial − venous concentration differences and the regional myocardial and peripheral flows, respectively.

Experimental Protocol

After instrumentation, stable hemodynamic conditions were established over 60–90 min. Any adjustments in ventilation, acid–base status, and fluid administration were made no later than 30 min before the start of the experiment. After control data (0 min) were obtained, halothane (1% inspired, end-tidal concentration 0.7%) was administered, followed 15 min later by intravenous succinylcholine 3 $mg \cdot kg^{-1}$. The apparatus used to maintain temperature was switched off for the MHS animals. Ventilation was not changed during MH. Blood sampling and triplicate CI measurements were repeated every 10 min. The infusion of Ringer's solution was increased to 10 $ml \cdot kg^{-1} \cdot h^{-1}$. Blood loss resulting from sampling was replaced by hydroxyethyl starch 6%. MHS animals were studied until death.

Statistical Analysis

The values presented are means ± SEM. The data were analyzed with repeated measurement analysis of variance, followed by paired and unpaired Student's *t* test with Bonferroni's corrections. A *P* value of <0.05 was considered statistically significant.

Results

MH occurred in all animals of the MHS group, as indicated by marked increases in blood temperature, arterial CO_2 tension, total O_2 consumption, and plasma catecholamine concentrations and by marked decreases in arterial *p*H, O_2 tension, and hemoglobin O_2 saturation (table 1). Total O_2 consumption increased to approximately 350% of its baseline value during an MH crisis. Table 2 gives the corresponding data for the nMHS animals.

Systemic Hemodynamics and Left Ventricular Function

Heart rate in the MHS group (table 3) increased from 86 ± 4 to a maximum of 204 ± 8 beats · min^{-1} (30 min) and then decreased continuously to 135 ± 9 beats · min^{-1} (90 min). Spontaneous supraventricular, or a rapid ventricular arrhythmia such as ventricular extrasystoles, or ventricular tachycardia occurred intermittently in all MHS animals during each phase of MH. During the final phase of MH, the electrocardiogram of all animals was characterized by wide QRS complexes and elevated T waves (fig. 1) at a time when serum K^+ values were typically increased by more than twofold. Cardiac death occurred by weak or asystolic heart action. All MHS animals died within 92–106 min of the start of halothane exposure. At this time, the body temperature was 40.9 ± 0.2°C. In the nMHS group, halothane and succinylcholine administration led to a small but significant ($P < 0.05$) increase in heart rate (table 4) but did not induce any dysrhythmias throughout the 90-min measurement.

Systolic aortic pressure in the MHS group was characterized by a triphasic course (table 3): a moderate decrease by approximately 14% (10 min after halothane administration), a second increase nearly to the initial level (30 min), and a marked decrease by approximately 40% (90 min). Diastolic aortic pressure decreased continuously to an extremely low value of 27 ± 1 mmHg (−61%) at the final stage (90 min), which was significantly less than diastolic aortic pressure in the nMHS group (−30%) (table 3). Based on the different courses of systolic and diastolic aortic pressures during the early MH crisis, the aortic pressure

Table 1. Temperature, Arterial Blood Gases, Metabolic Parameters, Plasma K^+, and Plasma Catecholamines in MHS Swine (n = 12) before and during Halothane Exposure in Addition to Succinylcholine (3 mg · kg^{-1} iv) 15 min after Starting Halothane Exposure (1% inspired)

	0 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
T_B (°C)	37.6 ± 0.1	37.6 ± 0.1	38.1 ± 0.2*	38.9 ± 0.2*	39.6 ± 0.2*	40.2 ± 0.2*	40.6 ± 0.2*	40.8 ± 0.2*	41.0 ± 0.2*	40.9 ± 0.2*
pH	7.45 ± 0.01	7.39 ± 0.01*	7.09 ± 0.04*	6.81 ± 0.03*	6.71 ± 0.02*	6.70 ± 0.02*	6.72 ± 0.03*	6.74 ± 0.03*	6.77 ± 0.03*	6.77 ± 0.04*
P_{O_2} (mmHg)	144 ± 2.5	130 ± 4.9*	79.0 ± 4.0*	69.9 ± 2.1*	78.6 ± 2.9*	83.2 ± 3.9*	92.6 ± 3.3*	97.0 ± 4.2*	103 ± 3.7*	106 ± 3.4*
S_{O_2} (%)	97.7 ± 0.2	97.6 ± 0.3	84.6 ± 3.3*	72.0 ± 1.9*	73.5 ± 1.9*	79.3 ± 1.6*	83.3 ± 1.4*	84.8 ± 1.4*	88.0 ± 1.4*	88.7 ± 1.3*
P_{CO_2} (mmHg)	37.1 ± 0.5	41.7 ± 1.5*	58.8 ± 3.3*	53.7 ± 4.7*	49.3 ± 4.2*	83.5 ± 5.2*	72.0 ± 3.9*	58.8 ± 3.3*	53.7 ± 4.7*	49.3 ± 4.2*
Hgb (g/dl)	12.2 ± 0.4	12.3 ± 0.4	13.5 ± 0.4*	13.7 ± 0.4*	10.7 ± 0.4*	12.8 ± 0.4	11.9 ± 0.4	11.9 ± 0.4	10.7 ± 0.4*	10.2 ± 0.3*
avD_{O_2} (ml · 100 ml^{-1})	5.3 ± 0.4	5.3 ± 0.4	8.5 ± 0.6*	9.6 ± 0.5*	9.5 ± 0.6*	9.3 ± 0.6*	8.8 ± 0.5*	8.5 ± 0.6*	8.2 ± 0.5*	7.4 ± 0.5*

Table 1. Temperature, Arterial Blood Gases, Metabolic Parameters, Plasma K^+, and Plasma Catecholamines in MHS Swine (n = 12) before and during Halothane Exposure in Addition to Succinylcholine (3 mg · kg^{-1} iv) 15 min after Starting Halothane Exposure (1% Inspired)

	0 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
T_B (°C)	37.6 ± 0.1	37.6 ± 0.1	38.1 ± 0.2*	38.9 ± 0.2*	39.6 ± 0.2*	40.2 ± 0.2*	40.6 ± 0.2*	40.8 ± 0.2*	41.0 ± 0.2*	40.9 ± 0.2*
*p*H	7.45 ± 0.01	7.39 ± 0.01*	7.09 ± 0.04*	6.81 ± 0.03*	6.71 ± 0.02*	6.70 ± 0.02*	6.72 ± 0.03*	6.74 ± 0.03*	6.77 ± 0.03*	6.77 ± 0.04*
P_{O_2} (mmHg)	144 ± 2.5	130 ± 4.9*	79.0 ± 4.0*	69.9 ± 2.1*	78.6 ± 2.9*	83.2 ± 3.9*	92.6 ± 3.3*	97.0 ± 4.2*	103 ± 3.7*	106 ± 3.4*
S_{O_2} (%)	97.7 ± 0.2	97.6 ± 0.3	84.6 ± 3.3*	72.0 ± 1.9*	73.5 ± 1.9*	79.3 ± 1.6*	83.3 ± 1.4*	84.8 ± 1.4*	88.0 ± 1.4*	88.7 ± 1.3*
P_{CO_2} (mmHg)	37.1 ± 0.5	41.7 ± 1.5*	73.8 ± 5.6*	98.0 ± 4.8*	95.8 ± 2.8*	83.5 ± 5.3*	72.0 ± 3.9*	58.8 ± 3.3*	53.7 ± 4.7*	49.3 ± 4.2*
Hgb (g/dl)	12.2 ± 0.4	12.3 ± 0.4	13.5 ± 0.4*	13.7 ± 0.4*	13.3 ± 0.4*	12.8 ± 0.4	11.9 ± 0.4	11.3 ± 0.4	10.7 ± 0.4*	10.2 ± 0.3*
avD_{O_2} (ml · 100 ml^{-1})	5.3 ± 0.4	5.3 ± 0.4	8.5 ± 0.6*	9.6 ± 0.5*	9.5 ± 0.6*	9.3 ± 0.6*	8.8 ± 0.5*	8.5 ± 0.6*	8.2 ± 0.5*	7.4 ± 0.5*
$\dot{V}_{O_2}$ (ml · min^{-1} · kg^{-1})	4.3 ± 0.4	5.0 ± 0.4*	12.8 ± 1.5*	14.2 ± 1.6*	11.7 ± 1.4*	8.8 ± 0.9*	7.6 ± 0.7*	6.6 ± 0.6*	5.7 ± 0.5*	3.7 ± 0.3*
Lactate (mM)	1.9 ± 0.2	2.3 ± 0.3	6.7 ± 1.0*	10.6 ± 0.8*	12.8 ± 0.8*	13.4 ± 0.8*	13.2 ± 0.7*	12.7 ± 1.0*	13.3 ± 1.0*	12.3 ± 0.9*
K^+ (mM)	4.27 ± 0.18	4.43 ± 0.13	5.16 ± 0.22*	5.89 ± 0.25*	6.54 ± 0.19*	6.83 ± 0.28*	7.47 ± 0.33*	8.13 ± 0.37*	8.66 ± 0.52*	9.27 ± 0.40*
NE (ng · ml^{-1})	0.43 ± 0.08	0.58 ± 0.09	6.56 ± 3.55	22.1 ± 4.2*	33.9 ± 5.5*	26.0 ± 4.6*	22.4 ± 5.2*	25.0 ± 6.3*	20.2 ± 7.6*	16.2 ± 3.1*
E (ng · ml^{-1})	0.12 ± 0.05	1.02 ± 0.22*	4.61 ± 1.17*	13.0 ± 2.85*	15.5 ± 2.07*	10.1 ± 1.49*	8.81 ± 1.70*	9.59 ± 1.91*	8.16 ± 1.62*	8.75 ± 1.93*

T_B = blood temperature; P_{O_2} = partial oxygen pressure; S_{O_2} = oxygen saturation; P_{CO_2} = partial carbon dioxide pressure; Hgb = hemoglobin concentration; avD_{O_2} = arteriovenous O_2 content difference; $\dot{V}_{O_2}$ = total oxygen consumption; NE = norepinephrine; E = epinephrine.

* $P < 0.05$ *versus* baseline data before halothane exposure (time 0).

Table 2. Temperature, Arterial Blood Gases, Metabolic Parameters, Plasma K^+, and Plasma Catecholamines in nMHS Swine (n = 8) before and during Halothane Exposure in Addition to Succinylcholine (3 mg · kg^{-1} iv) 15 min after Starting Halothane Exposure (1% Inspired)

	0 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
T_B (°C)	37.5 ± 0.2	37.6 ± 0.2	37.5 ± 0.1	37.6 ± 0.2	37.6 ± 0.2	37.6 ± 0.1	37.6 ± 0.2	37.6 ± 0.2	37.5 ± 0.2	37.5 ± 0.1
*p*H	7.45 ± 0.01	7.45 ± 0.02	7.44 ± 0.02	7.44 ± 0.01	7.43 ± 0.02	7.43 ± 0.02	7.43 ± 0.02	7.42 ± 0.02*	7.41 ± 0.01*	7.42 ± 0.02*
P_{O_2} (mmHg)	150 ± 4.4	157 ± 4.6	150 ± 5.1	150 ± 5.0	145 ± 5.7	145 ± 4.9	138 ± 3.7*	138 ± 4.2*	138 ± 3.9*	139 ± 3.7*
S_{O_2} (%)	97.9 ± 0.2	97.5 ± 0.2	97.7 ± 0.3	97.5 ± 0.2	97.5 ± 0.3	97.6 ± 0.3	97.3 ± 0.2	97.4 ± 0.3	97.3 ± 0.3	97.5 ± 0.2
P_{CO_2} (mmHg)	36.0 ± 0.3	35.5 ± 0.6	36.4 ± 0.8	36.4 ± 0.6	36.6 ± 0.9	36.6 ± 0.6	37.2 ± 0.7	37.1 ± 0.9	37.3 ± 0.8	37.3 ± 0.7
Hgb (g/dl)	12.3 ± 0.5	12.2 ± 0.4	11.8 ± 0.3	11.7 ± 0.3	11.3 ± 0.3*	11.0 ± 0.3*	10.8 ± 0.3*	10.6 ± 0.3*	10.3 ± 0.3*	10.3 ± 0.4*
avD_{O_2} (ml · 100 ml^{-1})	4.7 ± 0.4	4.3 ± 0.5	4.1 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.4 ± 0.3	4.2 ± 0.4	4.0 ± 0.4	4.0 ± 0.4	3.9 ± 0.3*
$\dot{V}_{O_2}$ (ml · min^{-1} · kg^{-1})	4.0 ± 0.4	3.5 ± 0.4	3.1 ± 0.3*	3.4 ± 0.3	3.3 ± 0.3	3.4 ± 0.3*	3.3 ± 0.3	3.1 ± 0.3*	3.1 ± 0.3	3.0 ± 0.3*
Lactate (mM)	2.7 ± 0.3	2.5 ± 0.3	2.5 ± 0.3	2.3 ± 0.2	2.1 ± 0.2*	1.9 ± 0.2*	2.0 ± 0.1	2.1 ± 0.2	2.0 ± 0.2*	2.0 ± 0.2*
K^+ (mM)	4.13 ± 0.14	4.11 ± 0.13	4.23 ± 0.14	4.38 ± 0.10	4.44 ± 0.13	4.44 ± 0.13	4.39 ± 0.10	4.35 ± 0.13	4.24 ± 0.12	4.36 ± 0.13
NE (ng · ml^{-1})	0.39 ± 0.11	0.46 ± 0.14	0.43 ± 0.10	0.37 ± 0.09	0.41 ± 0.15	0.43 ± 0.14	0.30 ± 0.07	0.31 ± 0.06	0.30 ± 0.10	0.31 ± 0.10
E (ng · ml^{-1})	0.10 ± 0.04	0.08 ± 0.03	0.07 ± 0.02	0.08 ± 0.05	0.07 ± 0.03	0.07 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.04 ± 0.01*	0.05 ± 0.01

T_B = blood temperature; P_{O_2} = partial oxygen pressure; S_{O_2} = oxygen saturation; P_{CO_2} = partial carbon dioxide pressure; Hgb = hemoglobin concentration; avD_{O_2} = arteriovenous O_2 content difference; $\dot{V}_{O_2}$ = total oxygen consumption; NE = norepinephrine; E = epinephrine.

* $P < 0.05$ *versus* baseline data before halothane exposure (time 0).

Table 3. Global Hemodynamic and LV Variables in MHS Swine (n = 12) before and during Halothane Exposure in Addition to Succinylcholine (3 mg · kg^{-1} iv) 15 min after Starting Halothane Exposure (1% Inspired)

	0 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
HR (beats · min^{-1})	86 ± 4	123 ± 8*	174 ± 15*	204 ± 8*	200 ± 8*	183 ± 9*	163 ± 9*	151 ± 8*	144 ± 11*	135 ± 9*
AoP_s (mmHg)	114 ± 3	98 ± 4*	111 ± 5	116 ± 8	102 ± 8	90 ± 5*	86 ± 5*	81 ± 5*	71 ± 5*	71 ± 4*
AoP_d (mmHg)	70 ± 3	62 ± 3	55 ± 4*	52 ± 3*	41 ± 2*	37 ± 2*	36 ± 2*	32 ± 2*	29 ± 2*	27 ± 1*
AoP_m (mmHg)	84 ± 3	74 ± 3*	73 ± 4	73 ± 5	62 ± 4*	54 ± 3*	52 ± 3*	48 ± 3*	44 ± 2*	43 ± 3*
AoP_{md} (mmHg)	85 ± 3	72 ± 4*	67 ± 4*	63 ± 5*	51 ± 2*	45 ± 2*	43 ± 2*	39 ± 2*	37 ± 1*	33 ± 1*
SVI (ml · kg^{-1})	0.98 ± 0.08	0.82 ± 0.04*	0.90 ± 0.07	0.75 ± 0.08*	0.60 ± 0.06*	0.52 ± 0.04*	0.54 ± 0.04*	0.53 ± 0.05*	0.51 ± 0.05*	0.38 ± 0.03*
CI (ml · min^{-1} · kg^{-1})	81 ± 4	98 ± 5*	148 ± 11*	149 ± 15*	119 ± 10*	93 ± 6	86 ± 5	78 ± 6	69 ± 5	50 ± 4*
SVRI (mmHg/ L · min^{-1} · kg^{-1})	893 ± 56	657 ± 48*	391 ± 37*	386 ± 40*	383 ± 44*	435 ± 52*	440 ± 48*	452 ± 62*	454 ± 49*	566 ± 50*
LVMI (mJ · min^{-1} · kg−1)	745 ± 34	810 ± 66	1,080 ± 111*	1,078 ± 151*	656 ± 69	453 ± 32*	406 ± 38*	332 ± 29*	266 ± 20*	178 ± 12*
LVWI (mJ · kg^{-1})	9.0 ± 0.6	6.8 ± 0.5*	6.5 ± 0.5*	5.3 ± 0.7*	3.3 ± 0.3*	2.5 ± 0.1*	2.5 ± 0.2*	2.3 ± 0.2*	2.0 ± 0.2*	1.3 ± 0.1*
V_{CE} (s^{-1})	2,562 ± 161	2,508 ± 602	6,195 ± 936*	9,236 ± 1,124*	6,247 ± 854*	3,638 ± 517*	2,716 ± 351	2,189 ± 247	1,676 ± 163*	1,315 ± 178*
TT (ms)	113 ± 9	109 ± 7	74 ± 5*	74 ± 7*	75 ± 10*	75 ± 9*	81 ± 8*	84 ± 8*	86 ± 9*	86 ± 9*
TT_c	165 ± 19	225 ± 24*	214 ± 24*	251 ± 26*	245 ± 30*	223 ± 26*	216 ± 21*	208 ± 20	203 ± 24	189 ± 20
FT + RT/ET	1.75 ± 0.08	1.13 ± 0.07*	0.89 ± 0.13*	0.71 ± 0.06*	0.79 ± 0.08*	0.88 ± 0.09*	1.02 ± 0.10*	1.26 ± 0.14	1.35 ± 0.17	1.62 ± 0.20

HR = heart rate; AoP_s = systolic aortic pressure; AoP_d = diastolic aortic pressure; AoP_m = mean aortic pressure; AoP_{md} = mean diastolic aortic pressure; SVI = stroke volume index; CI = cardiac index; SVRI = systemic vascular resistance index; LVMI = left ventricular minute index; LVWI = left ventricular stroke work index; V_{CE} = peak contractile element velocity; TT = left ventricular tension time; TT_c = TT divided by cycle length; FT + RT/ET = ratio of left ventricular filling time plus relaxation time to ejection time.

* $P < 0.05$ *versus* baseline data before halothane exposure (time 0).

amplitude at 30 min was nearly twice the amplitude in nMHS. Within this time, mean aortic pressure (table 3) decreased slightly, from 84 ± 3 to 73 ± 5 mmHg (not significant), and then decreased progressively to 43 ± 3 mmHg (90 min). The systemic vascular resistance index decreased in the initial 20 min of halothane administration by approximately 56% and then increased slightly after 40 min halothane exposure (table 3). In nMHS animals, halothane caused a reduction in the systemic vascular resistance index of approximately 20% (table 4).

Simultaneously with the increase in heart rate, a significant increase in CI occurred within 10 min of halothane administration in the MHS animals (table 3). CI reached its maximum at 30 min (184% from baseline value). The CI increase resulted from an increase in heart rate, because SVI decreased (−23% at 30 min) (table 3). A progressive decrease in SVI (maximum −61%) and heart rate were the cause of the CI decrease in the later MH phase (maximum −38%). In nMHS swine, halothane administration led to a reduction in CI by maximally 12% and in SVI by maximally 25% (table 4). In analogy to the alterations in SVI and afterload, LVWI was reduced in both groups (tables 3 and 4). The reduction was significantly higher in the MHS group (−86% at 90 min) than in the nMHS group (−44% at 90 min). The alterations in LV minute index (tables 3 and 4) corresponded to the changes of CI.

LV end-systolic pressure showed a course equivalent to the aortic pressures in both groups (fig. 2A). LV end-diastolic pressure decreased significantly, from 9 ± 1 to a minimum of 6 ± 1 mmHg, (50 min) in the MHS animals, whereas the LV end-diastolic pressure in normal pigs did not change significantly (fig. 2B). LV end-systolic volume decreased in the initial phase of MH (−30% at 30 min) and then showed a tendency to increase in the later phase (fig. 2A). LV TT decreased sharply during the MH crisis (table 3). This effect was frequency dependent: TT as related to cycle length (TT divided by cycle length in milliseconds) even increased slightly in the early MH crisis. After frequency correction, no significant TT differences between the groups could be observed. The ratio of filling time plus relaxation time (diastole) to ejection time initially decreased from 1.7 ± 0.1 to 0.7 ± 0.1 (30 min), primarily because of a significant reduction in filling time plus relaxation time (389 ± 26 to 96 ± 11 ms; data not shown). The ratio then increased to 1.6 ± 0.2 at 90 min, while the heart rate was still increased approximately 50% above the control level (table 3).

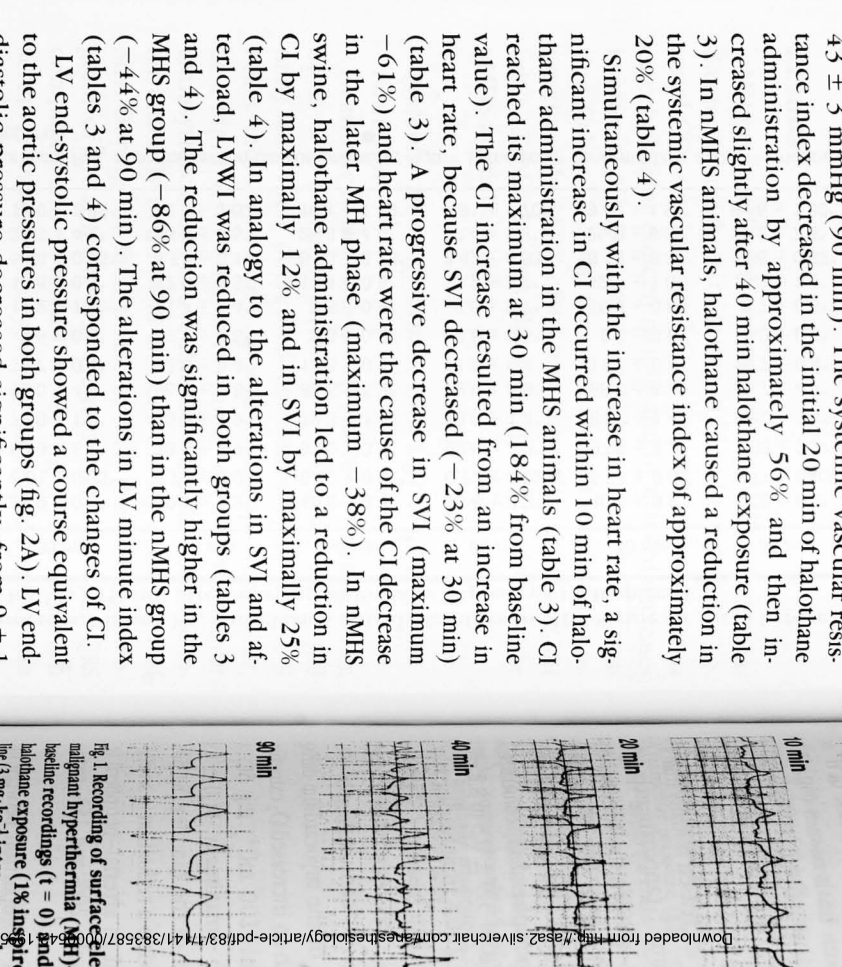

Fig. 1. Recording of surface electr
malignant hyperthermia (MH)–su
baseline recordings (t = 0) and af
halothane exposure (1% inspired)
line (3 mg · kg^{-1} intravenously 15
thane exposure). This recording is
of the MHS group because arrythr
during each phase of MH. However
elevated T waves occurred in the

LV +dp/dt and the peak co
at zero load increased signific
MH (30 min: 250% and 360
respectively) and decreased
phase (90 min: 75% and 51
respectively) (fig. 2C and tab
halothane depressed LV +dp/
ile element velocity at zero
and 31% of their baseline valu
and table 4). In the early phas
+dp/dt to LV −dp/dt increase
± 0.03 to a maximal value of
whereas in nMHS swine, the r
duced from 0.83 ± 0.06 to 0.
2D).

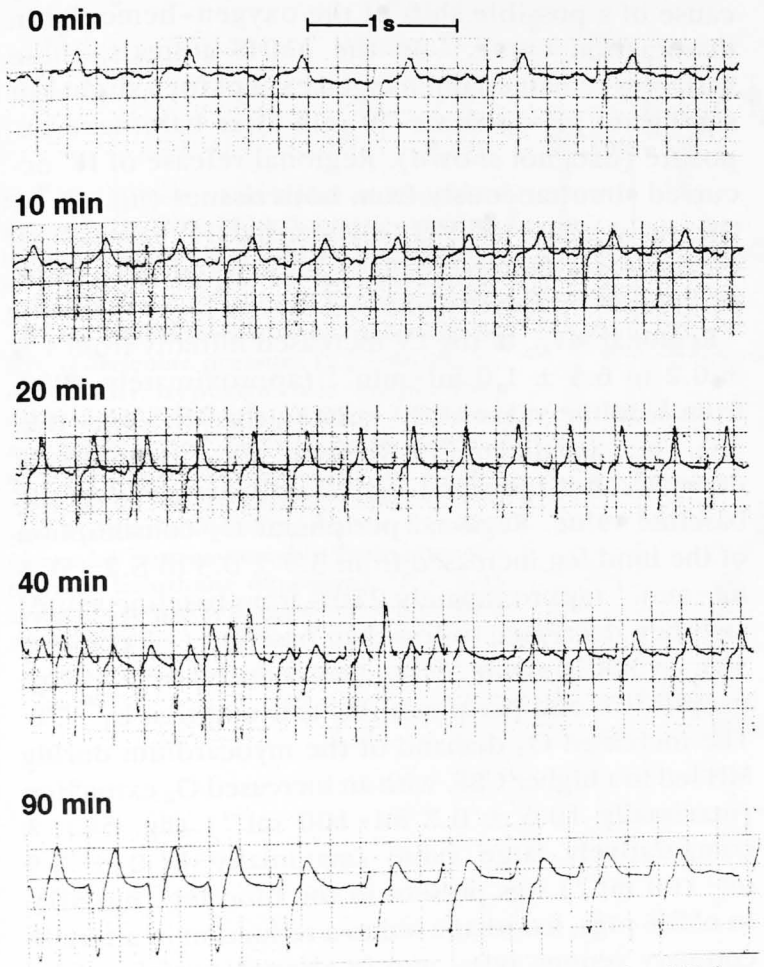

Fig. 1. Recording of surface electrocardiographic lead V_6 in a malignant hyperthermia (MH)–susceptible (MHS) pig during baseline recordings (t = 0) and after 10, 20, 40, and 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane exposure). This recording is not entirely representative of the MHS group because arrhythmias occurred intermittently during each phase of MH. However, wide QRS complexes and elevated T waves occurred in the final phase of MH.

LV +dp/dt and the peak contractile element velocity at zero load increased significantly in the early stage of MH (30 min: 250% and 360% from baseline values, respectively) and decreased progressively in the later phase (90 min: 75% and 51% from baseline values, respectively) (fig. 2C and table 3). In normal swine, halothane depressed LV +dp/dt and the peak contractile element velocity at zero load maximally to 55% and 31% of their baseline values, respectively (fig. 2C and table 4). In the early phase of MH, the ratio of LV +dp/dt to LV −dp/dt increased significantly from 0.79 ± 0.03 to a maximal value of 1.21 ± 0.05 (30 min), whereas in nMHS swine, the ratio was significantly reduced from 0.83 ± 0.06 to 0.62 ± 0.06 (30 min) (fig. 2D).

Coronary and Peripheral Hemodynamics

In the MHS animals, halothane administration quickly led to a small but significant increase (from 24 ± 2 to 28 ± 3 ml · min^{-1}) of CBF within the first 10 min. In the early course of the clinically apparent MH crisis (10–30 min) the CBF further increased to 69 ± 8 ml · min^{-1} (approximately 300% from baseline value at 30 min). In the late phase of MH (>30 min), CBF decreased but remained significantly increased above the baseline (approximately 40%). The peripheral (hind-leg) blood flow increased from 66 ± 8 to 93 ± 12 ml · min^{-1} (148% from baseline value) in the early stage of MH, but, in contrast to CBF, the peripheral flow decreased rapidly and clearly below the baseline value in the late MH phase (−88% at 90 min). In the nMHS group, halothane caused a slight but significant decrease in CBF from 29 ± 3 to 26 ± 12 ml · min^{-1} (−11%) and of the peripheral blood flow from 102 ± 9 to 74 ± 7 ml · min^{-1} (−27%) after 90 min. Figures 3A and 3B show the CBF and peripheral blood flow changes as percentages after the administration of halothane in both groups.

With the CBF increase, a marked reduction (−77%) in coronary vascular resistance was noted in the early phase of MH (from 3.9 ± 0.4 to 0.9 ± 0.05 mmHg · ml^{-1} · min). As the MH progressed, the coronary vascular resistance remained at nearly this level, while the CBF decreased as the result of the progressive decrease in the coronary perfusion pressure and mean diastolic aortic pressure, respectively. The peripheral vascular resistance showed a biphasic course that was nearly reciprocal to the peripheral blood flow. After a short initial decrease from 1.2 ± 0.2 to 0.7 ± 0.1 mmHg · ml^{-1} · min (−42%), the peripheral vascular resistance again increased to 5.8 ± 1.1 mmHg · ml^{-1} · min (+483%). Among the nMHS pigs, halothane did not cause a significant change in peripheral vascular resistance whereas the coronary vascular resistance decreased by approximately 20%. Figures 3C and 3D show the percent changes of coronary vascular resistance and peripheral vascular resistance, respectively.

Left Ventricular and Hind-leg Metabolism

Table 5 gives the data on *p*H and O_2 saturation in coronary venous and peripheral blood for MH group. In contrast to the regional venous *p*H values, the regional venous O_2 saturations did not decrease significantly within the first 10 min in the MH pigs, but were markedly decreased only after 20 min, and—as the acidosis progressed—appeared to increase be-

Table 4. Global Hemodynamic and LV Variables in nMHS Swine (n = 8) before and during Halothane Exposure in Addition to Succinylcholine (3 mg · kg^{-1} iv) 15 min after Starting Halothane Exposure (1% Inspired)

	0 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
HR (beats · min^{-1})	82 ± 3	85 ± 4	94 ± 5	96 ± 5*	98 ± 5*	98 ± 5*	95 ± 5*	93 ± 4	95 ± 5*	95 ± 4*
AoP_s (mmHg)	113 ± 4	101 ± 3*	90 ± 3*	87 ± 3*	87 ± 2*	84 ± 2*	85 ± 2*	84 ± 2*	83 ± 2*	83 ± 2*
AoP_d (mmHg)	70 ± 5	62 ± 3*	57 ± 3*	55 ± 3*	53 ± 3*	52 ± 2*	51 ± 2*	51 ± 2*	49 ± 2*	49 ± 3*
AoP_m (mmHg)	83 ± 5	74 ± 3*	67 ± 3*	65 ± 3*	63 ± 3*	61 ± 2*	61 ± 2*	59 ± 2*	58 ± 2*	58 ± 2*
AoP_{md} (mmHg)	83 ± 5	73 ± 3*	67 ± 3*	64 ± 3*	62 ± 3*	61 ± 2*	60 ± 2*	60 ± 2*	58 ± 2*	58 ± 3*
SVI (ml · kg^{-1})	1.06 ± 0.05	0.98 ± 0.07	0.85 ± 0.08*	0.83 ± 0.07*	0.80 ± 0.05*	0.80 ± 0.06*	0.84 ± 0.06*	0.86 ± 0.05*	0.85 ± 0.06*	0.85 ± 0.05*
CI (ml · min^{-1} · kg^{-1})	86 ± 4	82 ± 4*	77 ± 5*	77 ± 4*	76 ± 3*	77 ± 4*	78 ± 4	79 ± 3	79 ± 4	79 ± 4
SVRI (mmHg/ L · min^{-1} · kg^{-1})	826 ± 77	768 ± 60	749 ± 58	714 ± 43	699 ± 31	680 ± 35	655 ± 34*	643 ± 36*	628 ± 43*	624 ± 45*
LVMI (mJ · min^{-1} · kg^{-1})	796 ± 61	671 ± 52*	589 ± 49*	566 ± 48*	546 ± 44*	527 ± 36*	529 ± 38*	536 ± 34*	514 ± 38*	513 ± 36*
LVWI (mJ · kg^{-1})	9.8 ± 0.7	8.1 ± 0.8*	6.5 ± 0.8*	6.1 ± 0.7*	5.7 ± 0.6*	5.5 ± 0.5*	5.7 ± 0.5*	5.8 ± 0.5*	5.5 ± 0.5*	5.5 ± 0.5*
V_{CE} (s^{-1})	3,729 ± 533	2,221 ± 256*	1,503 ± 250*	1,555 ± 255*	1,349 ± 195*	1,306 ± 195*	1,221 ± 122*	1,195 ± 169*	1,145 ± 1,485*	1,185 ± 162*
TT (ms)	111 ± 14	117 ± 14	118 ± 12	118 ± 12	117 ± 9	119 ± 9	115 ± 12	117 ± 11	114 ± 11	111 ± 11
TT_c	152 ± 21	164 ± 20	182 ± 14*	190 ± 23*	191 ± 20*	192 ± 16*	180 ± 19*	181 ± 17	179 ± 19	175 ± 18
FT + RT/ET	1.77 ± 0.09	1.50 ± 0.15*	1.44 ± 0.09*	1.44 ± 0.09*	1.35 ± 0.06*	1.26 ± 0.09*	1.30 ± 0.10*	1.33 ± 0.06*	1.20 ± 0.07*	1.18 ± 0.10*

HR = heart rate; AoP_s = systolic aortic pressure; AoP_d = diastolic aortic pressure; AoP_m = mean aortic pressure; AoP_{md} = mean diastolic aortic pressure; SVI = stroke volume index; CI = cardiac index; SVRI = systemic vascular resistance index; LVMI = left ventricular minute index; LVWI = left ventricular stroke work index; V_{CE} = peak contractile element velocity; TT = left ventricular tension time; TT_c = TT devided by cycle length; FT + RT/ET = ratio of left ventricular filling time plus relaxation time to ejection time.

* $P < 0.05$ *versus* baseline data before halothane exposure (time 0).

cause of a possible shift of the oxygen–hemoglobin dissociation curve.[15] In the nMHS animals, these variables remained unchanged except for a slight but significant *p*H decrease 70 min after halothane exposure (data not shown). Regional release of H^+ occurred simultaneously from both tissues (fig. 4). In the early phase of MH, myocardial H^+ release increased by a factor of 29 (30 min) and peripheral H^+ release by factor of 13.

Regional $M\dot{V}_{O_2}$ of the LV increased initially from 1.8 ± 0.2 to 6.5 ± 1.0 ml · min^{-1} (approximately 400% from baseline value at 30 min) in the MHS pigs (fig. 5A). Then, parallel to CBF decrease, $M\dot{V}_{O_2}$ progressively decreased but remained significantly greater than the baseline value. Regional peripheral O_2 consumption of the hind leg increased from 3.9 ± 0.3 to 8.2 ± 1.3 ml · min^{-1} (approximately 250% from baseline value) and then decreased to less than baseline (−74%) (fig. 5B). In nMHS swine, $M\dot{V}_{O_2}$ was reduced by approximately 30% and peripheral O_2 consumption by 37%. The increased O_2 demand of the myocardium during MH led to a higher CBF, with an increased O_2 extraction (maximally 10.6 ± 0.7 ml · 100 ml^{-1}) (fig. 5C). A comparatively large value (maximally 11.0 ± 0.9 ml · 100 ml^{-1}) was present in the hind leg (fig. 5D). In nMHS pigs, halothane led to a reduction in arterial–coronary venous avD_{O_2} and in arterial–peripheral venous avD_{O_2} by approximately 20% and 15%, respectively.

Figure 6 allows a direct comparison between the myocardial and peripheral O_2 extraction rates. Among these variables, there were no significant differences between the two tissues during MH. Before halothane exposure, the myocardial O_2 extraction rate was significantly higher than the peripheral. This finding was expected, because the O_2 extraction from coronary blood is normally higher than from peripheral blood in the resting state. In analogy with the O_2 extraction rates, the mean ratio of O_2 supply to O_2 consumption decreased significantly from 2.0 to 1.4 in the LV and from 2.4 to 1.4 in the hind leg during the early phase of MH. In the advanced stage of MH, the ratio remained decreased in favor of the O_2 consumption. In the hind leg of normal pigs, the ratio remained unchanged in the presence of halothane. However, a tendency toward an increased ratio (from 1.9 to 2.1, not significant) was noted in the LV of nMHS pigs.

In the nMHS group, a reduction in LV minute index was associated with a corresponding decrease in $M\dot{V}_{O_2}$, whereas in MH a proportional change between

Fig. 2. (*A*) Left ventricular end-systolic pressure (LVESP), (*B*) left ventricular end-diastolic pressure (LVEDP), (*C*) peak positive rate of change in left ventricular pressure (LV +dp/dt), and (*D*) ratio of +dp/dt to peak negative rate of change in left ventricular pressure (LV −dp/dt) in malignant hyperthermia susceptible (MHS) swine (filled circles; n = 12) and non-MHS (nMHS) swine (open circles; n = 8) during baseline recordings (t = 0 min), after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after start of halothane exposure), * $P < 0.05$ versus baseline; triangles = $P < 0.05$ versus nMHS.

Fig. 3. (*A*) Coronary blood flow (CBF) in the anterior descending coronary artery, (*B*) peripheral blood flow (PBF; femoral artery), (*C*) coronary vascular resistance (CVR), and (*D*) peripheral vascular resistance (PVR) in malignant hyperthermia susceptible (MHS) (filled circles; n = 12) and non-MHS (nMHS) swine (open circles; n = 8) during baseline recordings (t = 0 min) and after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane exposure). * $P < 0.05$ versus baseline; triangles = $P < 0.05$ versus nMHS. Scales of the ordinates differ.

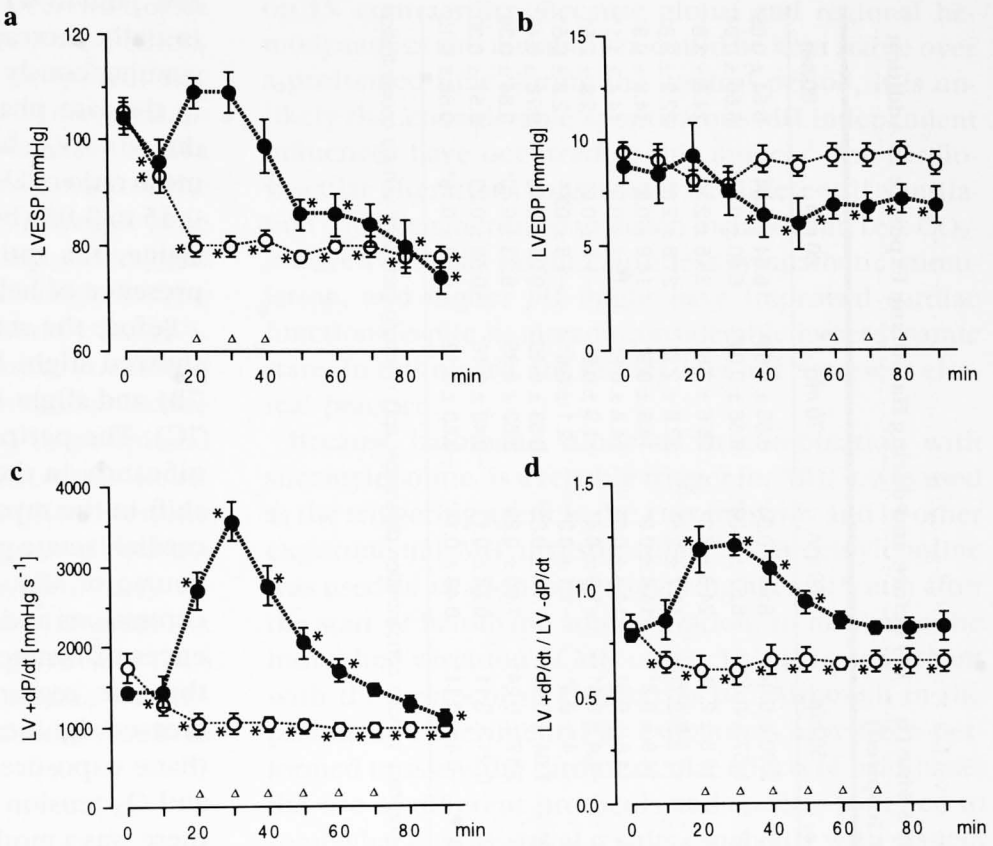

Fig. 2. (*A*) Left ventricular end-systolic pressure (LVESP), (*B*) left ventricular end-diastolic pressure (LVEDP), (*C*) peak positive rate of change in left ventricular pressure (LV +dp/dt), and (*D*) ratio of LV +dp/dt to peak negative rate of change in left ventricular pressure (LV −dp/dt) in malignant hyperthermia–suspectible (MHS) swine (filled circles; n = 12) and non-MHS (nMHS) swine (open circles; n = 8) during baseline recordings (t = 0) and after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane exposure). *$P < 0.05$ *versus* baseline; triangles = $P < 0.05$ MHS *versus* nMHS.

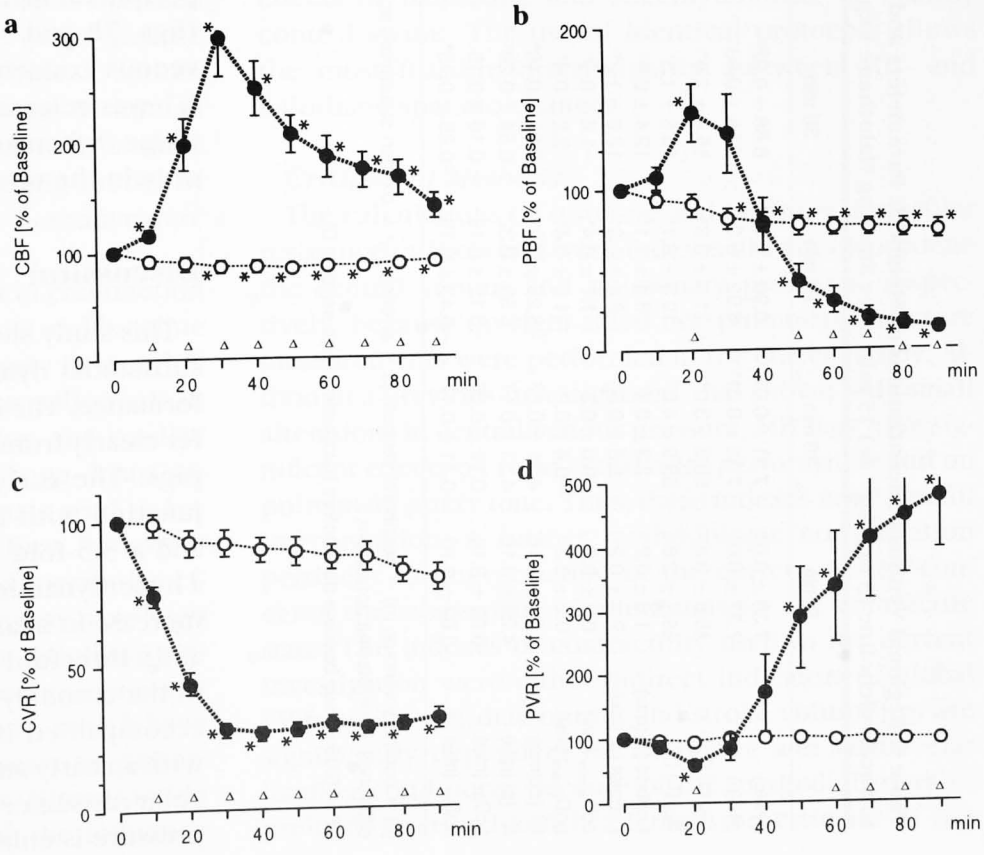

Fig. 3. (*A*) Coronary blood flow (CBF) [left anterior descending coronary artery], (*B*) peripheral blood flow (PBF) [femoral artery], (*C*) coronary vascular resistance (CVR), and (*D*) peripheral vascular resistance (PVR) in malignant hyperthermia–susceptible (MHS) (filled circles; n = 12) and non-MHS (nMHS) swine (open circles; n = 8) during baseline recordings (t = 0) and after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane exposure). Data are expressed as percentages of baseline values. Scales of the ordinates differ. *$P < 0.05$ *versus* baseline; triangles = $P < 0.05$ MHS *versus* nMHS.

Table 5. Regional Venous Concentrations of Metabolic Parameters and K^+ in MHS Swine (n = 12) before and during Halothane Exposure in Addition to Succinylcholine (3 mg · kg^{-1} iv) 15 min after Starting Halothane Exposure (1% Inspired)

	0 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
*p*H (c)	7.38 ± 0.01	7.31 ± 0.01*	6.90 ± 0.04*	6.68 ± 0.02*	6.62 ± 0.03*	6.60 ± 0.04*	6.64 ± 0.04*	6.65 ± 0.04*	6.64 ± 0.04*	6.64 ± 0.05*
*p*H (p)	7.37 ± 0.01	7.32 ± 0.01*	6.92 ± 0.04*	6.65 ± 0.03*	6.58 ± 0.02*	6.57 ± 0.02*	6.57 ± 0.03*	6.58 ± 0.04*	6.60 ± 0.04*	6.60 ± 0.04*
S_{O_2} (c) (%)	45.8 ± 3.4	50.5 ± 3.0*	21.9 ± 3.3*	15.4 ± 2.6*	19.4 ± 3.4*	19.8 ± 2.7*	24.8 ± 3.2*	25.6 ± 2.5*	23.5 ± 2.1*	24.8 ± 3.8*
S_{O_2} (p) (%)	56.1 ± 2.6	55.9 ± 4.0	19.3 ± 3.1*	10.6 ± 1.6*	16.4 ± 3.6*	17.2 ± 2.7*	19.7 ± 2.5*	22.8 ± 2.7*	21.8 ± 2.5*	22.9 ± 2.8*
Lactate (c) (mM)	1.6 ± 0.2	2.3 ± 0.3*	8.4 ± 1.1*	12.4 ± 0.9*	14.1 ± 0.8*	14.8 ± 0.8*	14.4 ± 0.9*	14.6 ± 0.9*	14.8 ± 0.9*	14.8 ± 0.9*
Lactate (p) (mM)	2.1 ± 0.2	2.8 ± 0.3*	8.4 ± 1.2*	12.8 ± 1.2*	14.6 ± 0.8*	14.8 ± 0.8*	14.4 ± 0.8*	14.8 ± 0.9*	15.1 ± 0.8*	14.4 ± 1.1*
$acD_{lactate}$ (mM)	0.3 ± 0.2	0.0 ± 0.2	−1.7 ± 0.4*	−1.8 ± 0.5*	−1.3 ± 0.5*	−1.4 ± 0.4*	−1.2 ± 0.4*	−1.9 ± 0.9*	−1.5 ± 0.5*	−2.6 ± 0.5*
$apD_{lactate}$ (mM)	−0.2 ± 0.2	−0.4 ± 0.2	−1.6 ± 0.4*	−2.2 ± 0.6*	−1.9 ± 0.5*	−1.4 ± 0.4*	−1.1 ± 0.3*	−2.1 ± 0.6*	−1.8 ± 0.4*	−2.2 ± 0.5*
K^+ (c) (mM)	4.24 ± 0.16	4.31 ± 0.07	5.28 ± 0.23*	6.05 ± 0.18*	6.72 ± 0.22*	7.04 ± 0.29*	7.70 ± 0.33*	8.53 ± 0.40*	9.24 ± 0.43*	9.78 ± 0.48*
K^+ (p) (mM)	4.29 ± 0.16	4.53 ± 0.17	5.59 ± 0.32*	6.54 ± 0.29*	6.90 ± 0.16*	7.17 ± 0.24*	7.90 ± 0.29*	8.63 ± 0.35*	9.33 ± 0.40*	9.84 ± 0.39*
acD_{K^+} (mM)	0.03 ± 0.10	0.12 ± 0.08	−0.12 ± 0.19	−0.16 ± 0.16	−0.18 ± 0.10	−0.21 ± 0.11	−0.23 ± 0.11	−0.40 ± 0.16*	−0.56 ± 0.23	−0.51 ± 0.30
apD_{K^+} (mM)	−0.02 ± 0.10	−0.11 ± 0.17	−0.43 ± 0.19*	−0.65 ± 0.15*	−0.36 ± 0.08*	−0.4 ± 0.11*	−0.43 ± 0.14*	−0.50 ± 0.12*	−0.66 ± 0.19*	−0.58 ± 0.13*

(c) = coronary venous; (p) = peripheral venous; (a = arterial; S_{O^2} = oxygen saturation; acD = arterio-coronary venous concentration difference; apD = arterio-peripheral venous concentration difference; K^+ = plasma potassium.

* $P < 0.05$ *versus* baseline data before halothane exposure (time 0).

$M\dot{V}_{O_2}$ and LVWI was no longer observed. Although LVWI initially increased by only approximately 45%, $M\dot{V}_{O_2}$ simultaneously increased by approximately 300%. Also, in the late phase of MH, when LVWI was clearly reduced, $M\dot{V}_{O_2}$ was still increased above baseline. The mean ratio of LVWI to $M\dot{V}_{O_2}$ decreased significantly from 0.45 to 0.09 (by factor 5) during MH (fig. 7A). In nMHS swine, the ratio did not change significantly in the presence of halothane.

Before the start of halothane exposure, both groups showed slight lactate uptake in the myocardium (fig. 7B) and slight lactate production in the hind leg (fig. 7C). The peripheral lactate production increased significantly in the early phase of MH. Simultaneously, a shift in the myocardial lactate balance occurred. Myocardial lactate production also was noted in the further course of MH. The arterial and regional venous concentrations and arterial – venous concentration differences of lactate are listed in table 5. The table shows that the regional venous lactate concentrations increased significantly within the first 10 min after halothane exposure, while hemoglobin oxygen saturation and O_2 tension even increased. In the nMHS animals, there was a moderate but significant ($P < .05$) decrease in the lactate concentrations in the presence of halothane (data not shown). However, the myocardial and peripheral lactate balance did not change significantly (figs. 7B and 7C). The time courses of the arterial – venous concentration differences of K^+ indicate that K^+ was released from the hind leg in the early MH phase, whereas a myocardial release of K^+ occurred only in the terminal stage of MH (table 5).

Discussion

This study shows that porcine MH is associated with substantial dynamic alterations in cardiovascular performance. The changes show a biphasic course and differ clearly from changes caused by halothane in normal pigs. The early MH crisis is characterized—in conjunction with high concentrations of catecholamines and a 3.5-fold increase in total O_2 consumption—by a hyperdynamic cardiovascular function with a marked increase in heart rate, cardiac output, LV contractility, and a threefold increase in CBF with a marked decrease in the coronary vascular resistance. These changes are accompanied by a decrease in mean aortic pressure with an early and substantial reduction in systemic vascular resistance, whereas the amplitude of aortic pulse pressure is enlarged. The coronary vascular resistance

remained reduced in late MH and
decreasing systemic blood press
leg) blood flow initially increa
cular resistance decreased, follo
crease in the peripheral vasc
marked decrease in the periph
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1,2,5-fold increase in peripher
mean ratio of the LVWI to $M\dot{V}_{O_2}$
Myocardial lactate and H^+
throughout the MH crisis. Incr
and H^+ concentration in coron
venous blood occurred earlier
ginal venous O_2 saturation and
late phase of MH (>30 min) is
polydynamic cardiovascular situ
duced cardiac output and syst
Cardiac failure with increased
not occur during MH. Rather,
poperfusion of the hypodyna
hypostole and subsequent as

Critique of the Model

Extrapolation of these results
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remained reduced in late MH and CBF decreased with decreasing systemic blood pressure. Peripheral (hindleg) blood flow initially increased as peripheral vascular resistance decreased, followed by an essential increase in the peripheral vascular resistance with a marked decrease in the peripheral blood flow in the late phase of MH. The early circulatory changes were associated with a fourfold increase in myocardial and a 2.5-fold increase in peripheral O_2 consumption. The mean ratio of the LVWI to $\dot{M}V_{O_2}$ decreased by factor 5. Myocardial lactate and H^+ production occurred throughout the MH crisis. Increases in venous lactate and H^+ concentration in coronary and in peripheral venous blood occurred earlier than decreases in regional venous O_2 saturation and tension. However, the late phase of MH (>30 min) is distinguished by a hypodynamic cardiovascular situation with clearly reduced cardiac output and systemic arterial pressure. Cardiac failure with increased LV filling pressure does not occur during MH. Rather, hyperkalemia and hypoperfusion of the hyperdynamic ventricle result in hyposystole and subsequent asystole.

Critique of the Model

Extrapolation of these results to humans must be done with care, because the pig is more closely inbred and because genetic studies indicate differences between MHS humans and MHS pigs with respect to the genetic MH locus.[16–19] On the basis of several clinical reports, there are also some phenotypic differences in human MH.[1–5] However, both do have the common features of hypermetabolism, and therefore the pig model of MH can provide some insights into the hemodynamic derangements.

Limitations of the experimental model in conjunction with the use of an acute open-chest animal and baseline anesthesia have been discussed previously in detail.[20] The acute loss of intrathoracic pressure will result in reduction of the venous filling gradient, the cardiac filling pressures and of lung volume. Lung–heart interaction will be reduced and the animals tend to become hypothermic more readily. Therefore, it must be considered that the cardiovascular and metabolic effects observed on MHS and normal swine may have been modified by the open-chest preparation. Baseline anesthesia was maintained with an α_2-adrenergic agonist (metomidate)[21] and an opioid (fentanyl), which have a relatively small influence on cardiovascular performance in comparison with barbiturates. Nitrous oxide was not used in this study to minimize the influence on LV contractility. Because global and regional hemodynamics and metabolism could be kept stable over a prolonged time during the control period, it is unlikely that considerable spontaneous MH independent influences have occurred in this model.[2] The cardiovascular alterations might well be different if ventilation had been increased to match metabolism. Less CO_2-induced acidosis might cause less sympathetic stimulation, and higher *p*H might have improved cardiac function despite its already considerable hyperdynamic state. In this regard, the model does not represent clinical practice.

Because halothane, alone or in combination with succinylcholine, is a reliable trigger for MH, it was used as the triggering agent in the current study and in other experimental MH investigations.[8–10] Succinylcholine was used as an additional triggering agent 15 min after the start of halothane administration, to minimize the individual variation of MH onset. This is in agreement with the protocol of Gronert *et al.*[9] Although in the past many experimental investigations have been performed to assess the cardiovascular effects of halothane, the use of different protocols and species have led to somewhat controversial results especially with respect to the extend of negative inotropic effects.[22–30] Therefore, we performed comparative investigations on the effects of halothane and succinylcholine in healthy control swine. The use of identical protocols allows the most feasible discrimination between MH- and halothane-specific changes.

Critique of Methods

The calculations of systemic and peripheral vascular resistance indexes and work indexes did not incorporate the central venous and pulmonary pressures, respectively, because no right-sided nor pulmonary pressure measurements were performed in the current study. Although a previous investigation[10] has shown only small alterations in central venous pressure, MH may have significant effects on right ventricular performance and on pulmonary artery tone. Thus, these indexes need careful interpretation. A further methodologic consideration pertinent to interpretation of the current results concerns the assessment of alterations in the contractile state. The indexes of contractility used in the current investigation were either indirect indicators of global LV function (cardiac output and stroke volume) or are significantly dependent on heart rate and ventricular loading conditions. Because of the marked changes in preload, afterload and heart rate, the estimate of the

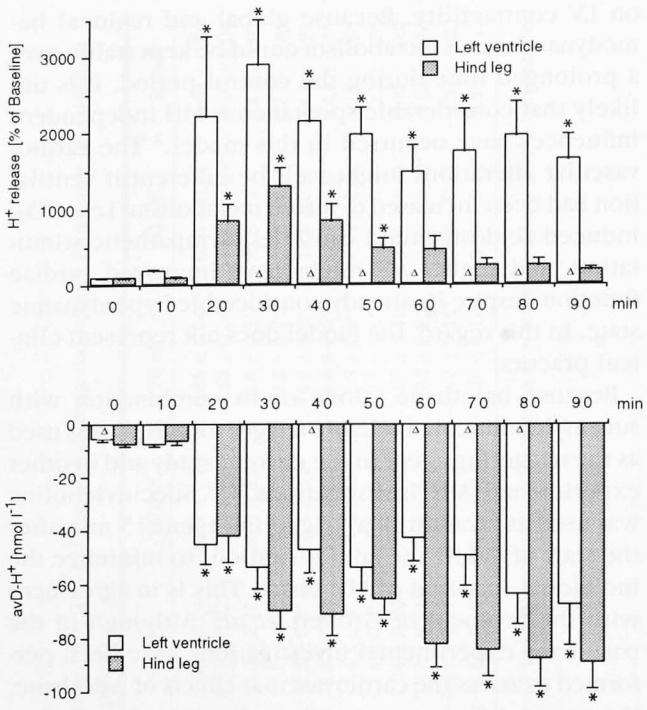

Fig. 4. Myocardial and peripheral release of H^+ (percentages of baseline values) and regional arterial − venous H^+ concentration differences ($avDH^+$) in malignant hyperthermia–susceptible (MHS) swine (n = 12) during baseline recordings (t = 0) and after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane exposure). *$P < 0.05$ *versus* baseline; triangles = $P < 0.05$ MHS *versus* nMHS.

inotropic state from +dp/dt and derived variables also requires careful interpretation.

The best position of the flow probes and the suitable gage for the LAD and for the hind-limb artery had been determined in pretests. Both measuring locations only serve for the determination of regional blood flow in heart and skeletal muscle. Therefore, no statement can be made about the total blood flow of the LV using this method. However, regional blood flow of the LAD can be considered as being representative for the total perfusion of the LV. The absolute data were less interesting in this respect than the trend of the regional changes measured during MH in general. The regional parameters including blood flow were therefore presented as relative changes deviating from baseline values.

For peripheral blood flow measurements, a stable and comparable position of the flow probe with different pigs could be attained at the hind-limb artery. A more proximal flow probe position had to be chosen at the hind-limb artery in the nMHS pigs because of the anatomical differences between the two breeds. This explains why the baseline flow in the hind-limb artery was higher in nMHS than in MHS pigs. The O_2 consumption and lactate uptake are representative only for those parts of the LV and hind leg the blood of which drains into the vena cordis magna and hind-limb vein, respectively. This is how the expression "regional" uptake and release are meant to be understood. Furthermore, it has to be taken into consideration that the start of MH may initiate a variety of changes such as redistribution of blood flow depending on the extent of ischemia and shunting, so that the hind-limb artery blood flow may not be synonymous with that of the entire hind leg. Therefore, the metabolic information concerning the hind leg is somewhat restricted.

Systemic Hemodynamics and Left Ventricular Function

The current results confirm previous studies in swine in which tachycardia was among the first symptoms of an MH crisis.[8,10,31–33] In the early phase of MH, the increase in heart rate was most pronounced. Cardiac output increased as a result of the strong increase in heart rate, because stroke volume did not increase and later even decreased. Also, as the systemic vascular resistance decreased, one would anticipate that ventricular ejection would be augmented, so it seems unlikely that these factors played a major role in stroke volume reduction. This assumption is supported by a decrease in the mean aortic pressure and an increase in the peak rate of LV pressure development (LV +dp/dt). When the influences of heart rate, preload and afterload on this contractility parameter are taken into consideration, the real increase in contractility may have to be estimated to be higher in view of the afterload reduction yet lower in view of the strong heart rate increase. The current data suggest that myocardial contractility is not impaired during the MH crisis, but is clearly augmented at least in the early phase. This is also shown by the peak contractile element velocity at zero load, derived from LV +dp/dt, which may allow a better approximation of the inotropic situation. Hence, an impaired ventricular ejection does not seem to be responsible for the stroke volume reduction during MH.

The cause for the stroke volume reduction during MH must therefore be attributed to a diminished LV filling. One cause for the diminished LV filling in the hyperdynamic phase of MH might be found in the extreme increase in heart rate, which leads to a reduced

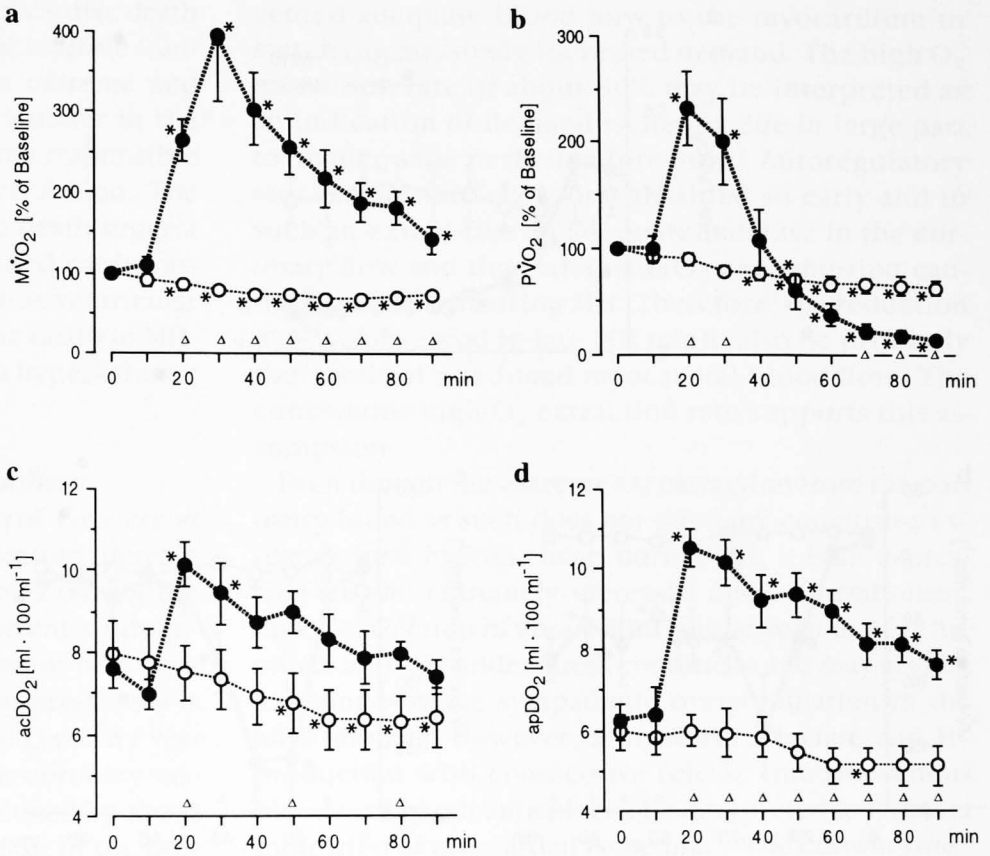

Fig. 5. (*A*) Myocardial O_2 consumption ($M\dot{V}_{O_2}$), (*B*) peripheral O_2 consumption ($P\dot{V}_{O_2}$), (*C*) arterial–coronary venous O_2 content difference (acD_{O_2}), and (*D*) arterial–peripheral venous O_2 content difference (apD_{O_2}) in malignant hyperthermia–susceptible (MHS) (filled circles; n = 12) and non-MHS (nMHS) swine (open circles; n = 8) during baseline recordings (t = 0) and after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane exposure). Data are expressed as percentages of baseline values. Scales of the ordinates differ in top panels. *$P < 0.05$ *versus* baseline; triangles = $P < 0.05$ MHS *versus* nMHS.

filling time under physiologic conditions. As our data show, the sum of the filling and relaxation time decreased stronger in relation to the ejection time, thus resulting in a decreased ratio of these parameters. This decreased ratio during early MH seems to be mainly frequency-dependent because the ratio increases again with the reduced heart rate in the later stage of MH. The increased ratio of LV +dp/dt to LV −dp/dt may also indicate an impairment of diastolic function during MH.

It is conceivable that a fluid loss may be an additional cause for the impaired LV filling during MH. Our data support this, because the LV filling pressure decreased. The transient increase in hemoglobin concentration that occurred despite the extensive blood sampling and the adequate substitution with hydroxyethyl starch suggests significant intravascular loss of fluid during MH, likely attributable to the extravasation of fluid into the interstitium and muscle, which becomes edematous and weeps.[1] Judging from the increase in hemoglobin concentration, hypovolemia seems extremely likely and may well have contributed to many of the hemodynamic derangements, decreased CBF resulting from decreased diastolic blood pressure, that were observed.

Our data show that the mean aortic pulse pressure already decreases in the early phase of MH. However, the blood pressure amplitude clearly increases during this stage of MH because of an increase in cardiac output (increasing systolic pressure) and a decrease in systemic vascular resistance (decreasing diastolic pres-

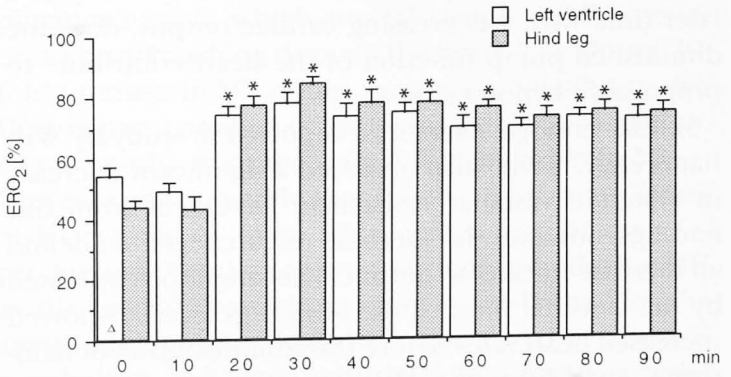

Fig. 6. Myocardial and peripheral O_2 extraction rates (ER_{O_2}) in malignant hyperthermia–susceptible (MHS) swine (n = 12) during baseline recordings (t = 0) and after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 mg · kg^{-1} intravenously 15 min after the start of halothane exposure). *$P < 0.05$ *versus* baseline; triangles = $P < 0.05$ MHS *versus* nMHS.

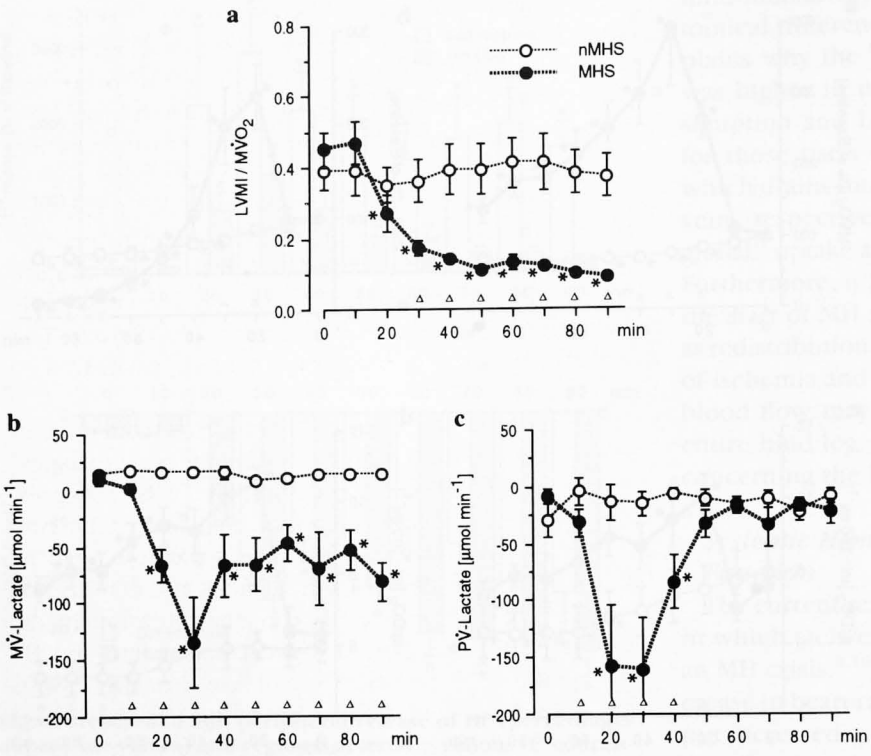

Fig. 7. (*A*) Ratio of left ventricular minute index (LVMI) and myocardial O_2 consumption ($M\dot{V}_{O_2}$), (*B*) myocardial uptake of lactate ($M\dot{V}$-lactate), and (*C*) peripheral uptake of lactate ($P\dot{V}$-lactate) in malignant hyperthermia–susceptible (MHS) (filled circles; n = 12) and non-MHS (nMHS) swine (open circles; n = 8) during baseline recordings (t = 0) and after 90 min of halothane exposure (1% inspired) in addition to succinylcholine (3 $mg \cdot kg^{-1}$ intravenously 15 min after the start of halothane exposure). *$P < 0.05$ *versus* baseline; triangles = $P < 0.05$ MHS *versus* nMHS.

sure). However, an excessive decrease in arterial systemic pressure especially in view of the reduced systemic vascular resistance is obviously counteracted by reflex mechanisms such as the increased cardiac output, which in turn is augmented by the adrenergic stimulation of the heart. It is conceivable that an early decrease in systemic vascular resistance provokes increased sympathetic tone, which probably offset a primary decrease in myocardial contractility. Only at a later time with a decreasing cardiac output, does the diminished pump function of the heart contribute to progressive hypotension.

Similar findings have been reported in study by Williams *et al.*[10] who also observed a significant decrease in systemic vascular resistance. Divergent from our findings, however, is that these researchers did not find an increase in cardiac output. This might be explained by the fact that most of the MHS pigs already showed increased heart rates before the administration of halothane. Apart from this, MH triggering times might also have varied strongly, as supported by the large variation in cardiac output. In agreement with our results, other researchers have noted a transient increase in cardiac output during porcine MH.[31,33,34] A decrease in mean arterial pressure was consistently observed. However, a transient subsequent increase in the mean arterial pressure can occur in the initial phase of MH if there has been a strong increase in systolic pressure.

In contrast to the early phase, the late phase of MH is—as our data demonstrate—defined by a hypodynamic cardiovascular situation with a pronounced reduction in cardiac output and blood pressure. Myocardial contractility appears to be reduced to a level with the halothane effects found in nMHS pigs. At this stage, impaired ventricular function may have been responsible for a portion of the deterioration of the MHS animals. Heart failure associated with high preload (LV filling pressure) or with clearly diminished contractility (LV +dp/dt) could not be detected in this phase either. The reduced LV preload still persisted when the initially increased contractility decreased again. The lack of heart failure from volume overload may result from extravasation of fluid and a decreasing LV filling. It is conceivable that heart failure from volume overload could well occur during clinical cases in which massive fluid administration was used to treat decreased arterial pressure. The reduced stroke volume during the advanced phase of MH initially remained constant, whereas the cardiac output was reduced as a result of the decreasing heart rate, which however remained

above the baseline level. Manifestations of cardiac death in MH were exclusively hyposystole and asystole. Acidosis, hypercapnia, and especially the extreme and progressive increase in serum K^+, particularly in the late phase of MH, may be essential factors responsible for the progressive cardiovascular deterioration. The wide QRS complexes preceding cardiac death suggest that conduction blockade may have caused cardiovascular collapse; serious dysrhythmias such as ventricular fibrillation are not responsible for cardiac death in MH. The final event appears consistent with a hyperkalemic arrest.

Regional Hemodynamics and Metabolism

In accordance with a previous study of Gronert *et al.*[9] a fourfold increase in $M\dot{V}_{O_2}$ and a threefold increase in CBF was also observed in our MHS pigs during the early phase of MH. In addition, the current study indicates that the increase in CBF—in view of a progressively decreasing coronary perfusion pressure—is based on a considerable dilatation of the coronary vessels. In the later phase of the disease, the coronary vascular resistance remained constantly reduced by about 70%, while the CBF decreased as the result of the progressive decrease in coronary perfusion pressure. This finding might provide evidence that maximum vasodilation was present, and thus CBF decreased in direct portion to coronary perfusion pressure. If coronary vascular resistance could not have decreased any further, then indeed the restriction occurs primarily because arterial blood pressure is too low and at the rapid heart rates, the diastolic interval was too short. On the other hand, if coronary vascular resistance could have decreased further, one must question whether the high catecholamine concentrations we documented are a contributing factor. A major problem with this interpretation seems to be the probable decrease in intravascular volume. If the animals had received more fluid repletion, then it seems likely that the systemic blood pressure and cardiac output would have been more adequately supported and the CBF could have been maintained at a higher level. In nMHS pigs, however, halothane reduced coronary vascular resistance to a much smaller extend. This effect and the other regional hemodynamic halothane findings on normal pigs are in agreement with the results found in other studies.[22,24,29,30]

Despite the obvious maximum dilatation of coronary vasculature and the high O_2 extraction, the decrease in systemic diastolic blood pressure prevented adequate blood flow to the myocardium to match the massively increased demand. The high O_2 extraction rate of about 80% may be interpreted as an indication of demand ischemia due in large part to inadequate perfusion pressure. Autoregulatory mechanisms are obviously disabled so early and to such an extent that an adequate increase in the coronary flow and thus adequate O_2 consumption cannot be obtained during MH. Therefore, the reduction in $M\dot{V}_{O_2}$ observed in late MH might also be primarily the result of a reduced myocardial blood flow. The continuous high O_2 extraction rate supports this assumption.

Even though the extreme O_2 extraction from the coronary blood as such does not offer any conclusive evidence for a hypoxic heart during MH, it is an expression for the extremely increased rate of metabolism. An O_2 extraction of about 80% may be seen in healthy, awake animals under stress conditions and may also be explained by the sympathetic overstimulation in the MHS animals. However, a myocardial lactate and H^+ production with consecutive release into the venous blood seen in our animals can be interpreted as a further indication of myocardial ischemia.[35] The current study clearly demonstrates a shift in the lactate balance in conjunction with a massive H^+ release into the coronary venous blood. The large imbalance between $M\dot{V}_{O_2}$ and supply appears to be responsible for the gradual increase in myocardial lactate and H^+ production. Because significant (negative) arterial–coronary venous concentration differences in lactate and H^+ were noted in the early phase and in the later phase of MH, it seems unlikely that the lactate and H^+ release into the vessels of the left heart are attributable to a "pass-through" phenomenon, in which arterial lactate and H^+ are increased and washing through the heart. The almost 29-fold increase in H^+ argues against the possibility that H^+ is in part a product of the increased CO_2 production, which results from the only 4-fold increase in $M\dot{V}_{O_2}$. However, it is possible that the bicarbonate buffering of lactate and H^+ is an additional source of the CO_2 production. Ventilation was not increased during MH as the animals would do spontaneously, and as the anesthesiologist would do in response to the increased metabolism associated with MH. As a result, arterial CO_2 tension increased to 98 mmHg and *p*H decreased to 6.7 during MH. Acidosis inhibits pyruvate dehydrogenase and limits entry of pyruvate into the Krebs citrate cycle. It is conceivable, that this effect enhances myocardial lactate production.

A quantitative assessment of hypoxia from the lactate balance is not possible,[35,36] because there is no constant or proportional relation between the extent of myocardial hypoxia and anaerobic glycolysis, respectively, and the amount of lactate release. This could explain—despite some essential methodologic differences such as right heart bypass with extracorporeal circulation—why Gronert *et al.*[9] could not demonstrate any lactate release from the heart. When interpreting their findings it must be taken into account that measurements of the lactate concentration in coronary blood are several steps away from the critical point at the mitochondrial level. Neither the cellular membrane is freely permeable for lactate, nor is there any balance between the mitochondrial and cytoplasmic nicotinamide adenine dinucleotide oxidation–reduction systems. As a result of the accumulation of the hydrogenated end products of glycolysis, especially lactate, an increase in the cytoplasmic lactate–pyruvate ratio is possible without necessarily leading to an immediate release of lactate into the coronary vein.[36,37] A failing lactate production can only be proven by measuring the cellular lactate concentration. Other findings by Gronert *et al.*[15] indirectly confirm this because they demonstrate a very high lactate gradient between the tissue and peripheral venous blood of skeletal muscle during MH. However, because the authors[9] did not make any statement to the *p*H reaction in coronary venous blood, these results must be interpreted carefully with regard to the exclusion of a primary involvement of the heart during MH.

In addition to a secondary hypoxia-induced lactate production, causes for a primary nonhypoxic related lactate production in the myocardium must also be considered. Gronert[38] makes this assumption with respect to skeletal muscle based on the observation that an increase in the venous lactate concentration in skeletal muscle occurs earlier than any signs of hypoxia.[8] The current study confirms these observations and demonstrates this phenomenon for the myocardium as well. The coronary venous lactate concentration increased significantly within the first 10 min after halothane exposure, while arterial lactate concentration did not increase and coronary venous O_2 saturation even increased. Hemodynamic alterations at this time probably would not result in ischemia. The causes for a primary nonhypoxic lactate production during early MH might be the result of a mitochondrial insufficiency or pathologic acceleration of glycogenolysis. The later mechanism would be explained by β-adrenergic overstimulation caused by excessive increase in circulating catecholamines or to an exaggerated response to them. By activation of adenylate cyclase, an increase in cyclic adenine dinucleotide phosphate, and activation of phosphorylase, both mechanisms could continue on the glycolytic pathway to an accumulation of pyruvate and lactate, which is associated with a shifting of the oxidation–reduction system of nicotinamide adenine dinucleotide. The consecutive increase in H^+ might explain the very early and prehypoxic decrease in the *p*H values in regional venous blood. However, to prove nonhypoxic lactate and H^+ production in tissue, independent and direct measures of tissue O_2 tension are required.

As the current results show, the LV contractility is initially maintained despite an early change in lactate balance. Thus, in the early phase of MH, the energy production not only from aerobic but also from anaerobic substrate utilization must obviously still have been sufficient. As a clear indicator of reduced left heart efficiency during MH, the ratio of LVWI to the $M\dot{V}_{O_2}$ decreased by a factor of 5 in the current study. Gronert *et al.*[9] presented similar results and showed an eightfold decrease in heart efficiency. This quantitative difference might be explained by the different test conditions already mentioned, because the right-side heart bypass with extracorporeal circulation might influence the course of MH. The right heart bypass might also explain the lack of tachycardia and lactate efflux. During right-side heart bypass, as the authors stated, the constant pump flow limited the perfusion to hypermetabolic tissues and the extracorporeal 37°C heat exchanger limited the temperature increases.

The early and extreme decrease in the LV efficiency during MH may lead to the assumption that the myocardium does not use its chemically available energy economically to preserve its cell function but rather contributes to an overflowing thermic energy release by means of its hypermetabolic reaction. However, it appears more likely that the heart may have become extremely inefficient because of catecholamine stimulation, increased heart rate, and acidosis. The high concentrations of catecholamines, which are markedly increased by 10 and 20 min, will increase intracellular Ca^{2+} stores and cycling in the myocardium. This effect can result in an increase in O_2 consumption. The increased heart rate can increase the Ca^{2+} cycling due the commonly positive treppe phenomenon. Acidosis may decrease the tropomyosin binding, also resulting in less tension for the same Ca^{2+} cycled. However, the important point is that the increased Ca^{2+} cycling car-

ries with it a substantial metabolic requirement, which can become more prominent and can constitute a greater component of O_2 consumption at small ventricular sizes. Consequently, it is not surprising that the efficiency of the heart decreases so dramatically within the first 0.5 h. On the other hand, the efficiency that is estimated here merely on the basis of O_2 consumption will not reflect the certainly very high anaerobic energy production or the entire chemically usable energy that is released. Furthermore, the observed increase in inotropy as an important determinant of $M\dot{V}_{O_2}$ plays only an indirect role in estimating left heart efficiency. To prove that the myocardial effects were primary, one would need to reproduce these features in a non MH animal and study the LV and coronary dynamics and metabolism.

The current findings indicate that the heart showed no changes comparable to the skeletal muscle contracture with a consecutively reduced flow. The K^+ release into the coronary venous blood—which appeared clearly later than in peripheral blood—might reflect a loss of integrity of the myocardial cell. The late occurrence of myocardial K^+ release appears to be the result of the relatively long maintenance of cell integrity in the heart. The finding of a myocardial release of K^+ only in the terminal stage also explains why Gronert *et al.*[9] could not detect any K^+ release from the heart, because their observation time was limited to 40 min.

Our study shows that the O_2 consumption of the skeletal muscle increases only by a factor of 2.5. On the other hand, even higher rates are often attained under extreme physical stress. According to Gronert[38] this paradoxical disparity between O_2 consumption and hyperthermic reaction cannot be explained by a mitochondrial defect alone. A possible explanation for this alleged discrepancy may be offered by the current hemodynamic findings: the aerobic energy production during MH is generally limited by the insufficient adaptation of the O_2 supply. A maximal extraction of the so-called aerobic capacity presupposes that the reflex mechanisms that control the cardiovascular system are intact and that sufficient O_2 is available. Even in the initial stage of MH, this is obviously no longer the case, such that the animals are forced to switch to an anaerobic energy production in a very early stage.

The metabolic situation during MH is characterized by a demand ischemia of the heart and of the skeletal muscle. The O_2 extraction rate (70–80%), which remains increased at a maximum throughout the MH crisis, is an expression of the insufficient adaptation of the peripheral blood flow to the increased O_2 demand of the skeletal muscle. The relatively low increase in peripheral O_2 consumption during the MH crisis (factor 2.5)–in view of the hyperthermia and acidosis—seems to result primarily from an inadequate increase in blood flow (factor 1.5). These data confirm previous studies by Gronert and Theye,[8] who observed a 2.7-fold increase in peripheral O_2 consumption with a 1.4-fold increase in blood flow under similar conditions. This initial increase in blood flow is—as our data show—based upon a considerable decrease in vascular resistance in skeletal muscle. These findings do not support the hypothesis[39,40] of a peripheral vasoconstriction as the result of high catecholamine concentrations during MH. However, the current data cannot fully exclude a vasoconstriction in other vessels (*i.e.,* the skin).

The increase in peripheral vascular resistance in advanced MH, which is in marked contrast to the uniphasic responses in coronary and systemic vascular resistance, does not appear to reflect the high sympathetic activity because the increase in plasma catecholamine concentrations occurred even in early MH. The increase in peripheral vascular resistance is probably the result of mechanical causes such as edema and increased muscle tension and contracture, which, with a progressive decrease in perfusion pressure, lead to considerable reduction in muscular blood flow. The progressive decrease in O_2 consumption therefore is not at all an expression of a diminished O_2 demand but again a result of reduced perfusion. This is also made obvious by the continuous highly increased O_2 extraction in the hind leg. Similarly, the observed decrease in lactate release does not allow speculation about the changes in lactate production occurring in the tissue because the (negative) arterial − venous concentration difference in lactate and in H^+ remained increased at the same time.

The comparative investigations on skeletal muscle have demonstrated that not only do the O_2 consumption and blood flow in the heart and skeletal muscle increase simultaneously during the initial phase of MH, but also lactate and H^+ release increase, changes that might be considered pathognomonic for MH. Although the appearance of such changes characteristic for MH in both tissues simultaneously and the "signs" of nonhypoxic lactate production might lead to the assumption that the cardiac symptoms during MH are in part primary in nature, there is no clear evidence to support this. Because several variables confound interpretation in the current experimental setting, it is not possible to

conclude clearly from the current results *in vivo* whether myocardial lactate production during MH is primarily the result of MH specific mechanisms. High heart rate and changes in $M\dot{V}_{O_2}$ as a result of sympathetic nervous stimulation also complicate the interpretation. Studies that include maintenance of hemodynamics and arterial blood gas tensions after triggering agents are administered, or studies on isolated heart and skeletal muscle in which substrate availability and *p*H could be carefully controlled probably provide a clearer answer.

On the basis of our results we conclude that the metabolic situation during MH is characterized by a demand ischemia of the heart. Whereas skeletal muscle demand ischemia involves hypermetabolism caused by deranged Ca^{2+} regulation, cardiac performance is dramatically altered by the decreased perfusion pressure and markedly increased metabolism caused by tachycardia and excessive catecholamine stimulation. Hypotension and decreased cardiac output in the advanced porcine MH crisis appear to occur because of cardiac failure not accompanied by an increase in LV filling pressure. Acidosis, hypovolemia, and the extreme and progressive increase in serum K^+, especially in the late phase of MH, may be additional essential factors responsible for the progressive cardiovascular deterioration and cardiac death.

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