Role of Sympathetic Activity in Porcine Malignant Hyperthermia

Gerald A. Gronert, M.D.,* James H. Milde,† Richard A. Theye, M.D.‡

Malignant hyperthermia (MH) is characterized in part by sympathetic hyperactivity associated with increased levels of circulating catecholamines. Controversy exists as to whether the sympathetic nervous system is in some way abnormal and primarily contributing to MH, or whether the sympathetic response is secondary to the stress of MH originating from skeletal muscle. Total spinal anesthesia with resulting sympathetic denervation was used in genetically susceptible Poland China swine to investigate this question. Isoxicarte tetracaine, 1.2—2.2 mg/kg, was injected via the sacral hiatus into the cerebrospinal fluid to produce total spinal anesthesia (paralysis of all four limbs). Total spinal anesthesia failed to prevent the occurrence or attenuate the course of MH in swine given halothane, 1 per cent (five pigs) or halothane and succinylcholine, 3 mg/kg (one pig). Total spinal anesthesia did prevent the expected increases in norepinephrine and epinephrine during MH in all six swine. Since dantrolene is specifically therapeutic in MH, its effect on the sympathetic response to stress was measured in two other susceptible swine. Treatment with dantrolene, 10 mg/kg, intravenously, did not prevent increases in catecholamines due to stress caused by either respiratory and metabolic acidosis (Paco₂, 110 torr, base excess —20) combined or hemorrhagic hypotension (mean pressure 40 torr). The authors conclude that the sympathetic nervous system is involved in porcine MH only as a secondary response to stress; that conduction anesthesia will not protect pigs from MH; and that the efficacy of dantrolene in porcine MH is due to its effects on the skeletal muscle rather than to depression of the sympathetic nervous system. (Key words: Hyperthermia, malignant pyrexia; Sympathetic nervous system, alpha-adrenergic receptors; Neuromuscular relaxants, dantrolene; Anesthetic techniques, spinal.)

While malignant hyperthermia (MH) is undoubtedly a disease involving skeletal muscle, several investigators1—3 have proposed that the sympathetic nervous system plays a major role in its genesis. Support for this position also arises indirectly from the reported protective effect of epidural anesthesia against initiation of porcine MH by halothane. Kerr, Wingard and Gatz4 evaluated MH by observations of muscle tone and temperature and found that hind limbs caudal from the level of block did not become rigid, while fore limbs did. They concluded that intact neural pathways were necessary for MH to occur. Also, while the direct-acting muscle relaxant dantrolene both prevents and reverses porcine MH in doses greater than 5 mg/kg.5 Hall, Lucke and Lister have suggested that these effects might be due to depression of the sympathetic nervous system.6

The present study was designed to evaluate the extent of involvement of the sympathetic nervous system in producing porcine MH and the possible protective effects of conduction anesthesia. Total spinal anesthesia acutely denervates both somatic and sympathetic nervous systems.7 If denervation is established prior to the introduction of a known MH trigger, and MH occurs, then somatic blockade is not protective. If, in addition, "typical" MH occurs without the usual increases in circulating epinephrine and norepinephrine, then the sympathetic nervous system is unlikely to be a causative factor in MH. We also evaluated possible depression by dantrolene of sympathetic activity by pretreating swine with dantrolene and then stressing them with combined respiratory and metabolic acidosis or with hemorrhagic hypotension.

Materials and Methods

Eight Poland China swine weighing 45—65 kg and previously identified as susceptible to MH by a screening test with halothane were prepared as previously described.8 In brief, anesthesia consisted of nitrous oxide—oxygen, 50 per cent each, via an endotracheal tube and intermittent intravenous injection of thiopental. During the control period ventilation was mechanically controlled, with PaCO₂ maintained at 40 torr ± 2. Ventilation was not changed after MH began. Appropriate catheters were inserted to permit measurement of cardiac output, arterial and mixed venous blood oxygen contents, and whole-body oxygen consumption; blood lactate, catecholamines, ionized calcium (Ca⁺⁺), pH, PaO₂, and Pa₂; serum sodium (Na⁺) and potassium (K⁺); and esophageal temperature and blood pressure. Ca⁺⁺ was measured using the calcium electrode, Orion SS20.

For spinal anesthesia, a polyethylene catheter was passed through a 16-gauge Touhy needle placed into the subarachnoid space via the sacral hiatus, and verified by free aspiration of cerebrospinal fluid. The doses of isoxicarte tetracaine, 1 per cent, necessary for total spinal anesthesia as evidenced by paralysis of all four limbs, ranged from 1.2 to 2.2 mg/kg. The level of motor block was estimated by determining the segment at which shivering occurred in the lightly

* Associate Professor of Anesthesiology, Mayo Medical School.
† Research Technician.
‡ Professor of Anesthesiology, Mayo Medical School.

Received from the Department of Anesthesiology, Mayo Clinic and Mayo Medical School, Rochester, Minnesota 55901. Accepted for publication May 23, 1977. Supported in part by Research Grant GM-21729, from NIH, PHS. An abstract of this work was presented at the Second International Symposium on Malignant Hyperthermia in April 1977, in Denver, Colorado.

Address reprint requests to Dr. Gronert.

411
### Table 1. Malignant Hyperthermia Preceded by Total Spinal Anesthesia, Five MHS Swine, Mean ± SE

<table>
<thead>
<tr>
<th>Control (Total Spinal Anesthesia Prior to Control)</th>
<th>Minutes after 1 Per Cent Halothane</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood lactate (μmol/ml)</td>
<td></td>
<td>1.2 ± 0.2</td>
<td>4.9* ± 1.9</td>
<td>11.1*† ± 3.2</td>
<td>15.0* ± 3.2</td>
<td>18.6* ± 3.6</td>
<td>18.8* ± 2.6</td>
</tr>
<tr>
<td>Oxygen consumption (ml/min/kg body wt)</td>
<td></td>
<td>8.4 ± 1.1</td>
<td>7.9 ± 2.3</td>
<td>12.2 ± 2.9</td>
<td>11.8* ± 1.3</td>
<td>12.4 ± 1.4</td>
<td>13.2* ± 1.7</td>
</tr>
<tr>
<td>P&lt;sub&gt;H&lt;/sub&gt; (torr) /P&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td>40 ± 2</td>
<td>41 ± 3</td>
<td>70* ± 12</td>
<td>77* ± 7</td>
<td>84* ± 3</td>
<td>91* ± 13</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td></td>
<td>124* ± 7</td>
<td>153 ± 21</td>
<td>149 ± 27</td>
<td>161 ± 25</td>
<td>168* ± 19</td>
<td>178*† ± 23</td>
</tr>
<tr>
<td>Temperature, esophageal (°C)</td>
<td></td>
<td>38.6 ± 0.3</td>
<td>38.7 ± 0.3</td>
<td>39.1 ± 0.5</td>
<td>39.8 ± 0.6</td>
<td>40.8* ± 0.8</td>
<td>41.4* ± 0.8</td>
</tr>
<tr>
<td>Whole blood ionized Ca&lt;sup&gt;2+&lt;/sup&gt; (mEq/l)</td>
<td></td>
<td>2.53 ± 0.07</td>
<td>2.70 ± 0.09</td>
<td>2.92 ± 0.16</td>
<td>3.09* ± 0.14</td>
<td>3.08* ± 0.11</td>
<td>3.01* ± 0.07</td>
</tr>
<tr>
<td>Na&lt;sup&gt;+&lt;/sup&gt; (mEq/l)</td>
<td></td>
<td>143 ± 2</td>
<td>146 ± 3</td>
<td>153 ± 4</td>
<td>156* ± 3</td>
<td>156* ± 3</td>
<td>160* ± 2</td>
</tr>
<tr>
<td>K&lt;sup&gt;+&lt;/sup&gt; (mEq/l)</td>
<td></td>
<td>4.85 ± 0.2</td>
<td>4.7 ± 2</td>
<td>5.3 ± 4</td>
<td>6.1* ± 0.5</td>
<td>6.6* ± 0.5</td>
<td>7.5* ± 0.4</td>
</tr>
<tr>
<td>Cardiac output (ml/min/kg body wt)</td>
<td></td>
<td>115* ± 4</td>
<td>82 ± 20</td>
<td>96 ± 10</td>
<td>90* ± 6</td>
<td>87* ± 12</td>
<td>91 ± 12</td>
</tr>
<tr>
<td>Arterial pressure, mean (torr)</td>
<td></td>
<td>122 ± 7</td>
<td>88* ± 11</td>
<td>75* ± 7</td>
<td>60*† ± 4</td>
<td>59* ± 5</td>
<td>59* ± 6</td>
</tr>
</tbody>
</table>

* Different from control.
† Different from non-spinal group, table 2.

**anesthetized animal. Duration of spinal anesthesia was determined in one pig not triggered into MH which was allowed to awaken from general anesthesia during the block. The front limbs recovered apparently normal strength in about 80 min, and the hind legs in 110 min. In pilot studies we found that, during total spinal anesthesia, pigs were quite sensitive to halothane, 1**

### Table 2. Malignant Hyperthermia Without Prior Spinal Anesthesia, Five MHS Swine, Mean ± SE

<table>
<thead>
<tr>
<th>Control</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood lactate (μmol/ml)</td>
<td>1.1 ± 0.1</td>
<td>1.6* ± 0.2</td>
<td>2.8*† ± 0.4</td>
<td>9.0* ± 2.7</td>
<td>15.4* ± 3.2</td>
<td>19.5* ± 3.0</td>
</tr>
<tr>
<td>Oxygen consumption (ml/min/kg body wt)</td>
<td>8.0 ± 0.3</td>
<td>6.7 ± 0.9</td>
<td>10.2 ± 2.4</td>
<td>14.1 ± 3.1</td>
<td>13.4* ± 1.7</td>
<td>10.8 ± 1.5</td>
</tr>
<tr>
<td>P&lt;sub&gt;H&lt;/sub&gt; (torr) /P&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-41 ± 1.4</td>
<td>38 ± 1.8</td>
<td>43 ± 2.7</td>
<td>62* ± 4.9</td>
<td>68* ± 6.6</td>
<td>60 ± 6.5</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>166* ± 12</td>
<td>161 ± 22</td>
<td>164 ± 27</td>
<td>196* ± 15</td>
<td>244*± 21</td>
<td>246*± 13</td>
</tr>
<tr>
<td>Temperature, right atrial (°C)</td>
<td>38.7 ± 0.1</td>
<td>38.5 ± 0.2</td>
<td>38.4 ± 0.2</td>
<td>38.0 ± 0.3</td>
<td>39.7* ± 0.4</td>
<td>40.4* ± 0.4</td>
</tr>
<tr>
<td>K&lt;sup&gt;+&lt;/sup&gt; (mEq/l)</td>
<td>4.0* ± 0.1</td>
<td>4.3 ± 0.1</td>
<td>4.5* ± 0.2</td>
<td>5.7* ± 0.7</td>
<td>7.1* ± 0.7</td>
<td>7.7* ± 0.5</td>
</tr>
<tr>
<td>Cardiac output (ml/min/kg body wt)</td>
<td>90* ± 5</td>
<td>80* ± 6</td>
<td>102 ± 22</td>
<td>113 ± 15</td>
<td>94 ± 12</td>
<td>72 ± 12</td>
</tr>
<tr>
<td>Arterial pressure, mean (torr)</td>
<td>107 ± 9</td>
<td>80* ± 9</td>
<td>85 ± 8</td>
<td>80*† ± 4</td>
<td>70* ± 4</td>
<td>57* ± 2</td>
</tr>
</tbody>
</table>

* Different from control.
† Different from spinal anesthesia group, table 1.
Data from Gronert and Theye,* table 2.
per cent, which caused marked hypotension, low cardiac output, bradycardia, and death. It was further determined that administration of cross-matched whole blood from other MH-susceptible Poland China swine would lessen the circulatory instability and obviate the need for inotropic or pressor drugs. Transfusions were given as halothane was introduced and generally totaled 8 to 10 per cent of the estimated blood volume. Transfusions alone did not induce MH in pilot-study animals.

After total spinal anesthesia was established, control values were determined in triplicate, halothane, 1 per cent, was administered to induce MH (five swine), and all measurements were repeated each ten minutes for 70 minutes. Succinylcholine bypasses the muscle end-plate effects of spinal anesthesia and does not have recognized sympathetic preganglionic effects, but the combination of it and halothane is the most potent known stimulus for MH. Therefore, one other pig with prior total spinal anesthesia was given halothane, 1 per cent, continuously, and succinylcholine, 3 mg/kg, intravenously after 15 minutes. Serial measurements were again made every 10 minutes. Studies in individual animals were completed 60–107 minutes after establishment of total spinal anesthesia.

The remaining two genetically susceptible swine were subjected to stress to examine the possibility that dantrolene, 10 mg/kg, might block catecholamine release by the sympathetic nervous system. Anesthetic care and surgical preparation were identical except that spinal anesthesia was not used. To duplicate some of the stresses of MH, the first pig was given sufficient inspired carbon dioxide to increase P_{A\text{CO}_2} to 110 torr and a lactic acid infusion to produce a blood lactate of 17 μmol/ml and a base excess of ~20. The second pig was stressed by decreasing mean blood pressure to 40 torr by acute hemorrhage.9 These changes were maintained in each pig for one hour. In each animal, dantrolene, 5 mg/kg, was given intravenously prior to the onset of the stress and 5 mg/kg by constant infusion during the first 30 minutes of stress. Measurements were made each 20 minutes.

Results are expressed as mean ± standard error of the mean (SE). Statistical evaluation was by Student’s test for paired data within groups and for unpaired data between groups, P < 0.05 considered significant.

Results

Total spinal anesthesia did not prevent MH initiated by halothane, 1 per cent (table 1). The observed changes were similar to those seen in a prior study8 in related genetically susceptible swine (table 2), in which the only differences in treatment were the absence of prior spinal anesthesia and extracorporeal re-circulation of blood from the hind limb for measurement of hind-limb oxygen consumption. Muscular rigidity occurred in all animals, and, as is typical, earlier in the hind limbs than in the fore limbs. Mean increases in temperature in the present study (table 1) were not different from those in the prior study (table 2). The trend toward lower temperatures in the latter was probably due to heat loss secondary to extracorporeal re-circulation of blood. Ca^{2+} increased progressively during MH, as did Na^{+} and K^{+}. One animal died between 40 and 50 minutes, another between 50 and 60 minutes.

Total spinal anesthesia prevented the increases in both norepinephrine and epinephrine that are usually associated with MH8 (fig. 1). These animals had slower heart rates during MH, and cardiac output and arterial blood pressure were more stable. This was associated with a trend towards higher whole-body oxygen consumption and P_{A\text{CO}_2} late in MH (tables 1 and 2). In the single animal given both halothane and succinylcholine, total spinal anesthesia also did not block MH, but did block the increase in catecholamines (data not reported).

Dantrolene did not block the increase in circulating catecholamines associated with the stress of

---

**Fig. 1.** Arterial norepinephrine and epinephrine values during MH with and without total spinal anesthesia, five animals each curve, mean ± SE. Differences between spinal and non-spinal animals achieved significance at 40 minutes. (Data without spinal anesthesia from Gronert and Theye,8 table 2.)
either combined respiratory and metabolic acidosis or hemorrhagic hypotension. At 40 and 60 minutes, respectively, epinephrine had increased progressively to 8 and 12 ng/ml in the former animal, and to 6 and 8 ng/ml in the latter. At the same times norepinephrine had increased to 15 and 19 ng/ml in the former and to 2 and 6 ng/ml in the latter. The duration of action of dantrolene is sufficient for this study, and the dose used is effective in preventing or treating MH. There was no sign of MH in either stressed animal.

Discussion

Support for the role of the sympathetic nervous system in MH is based upon the following evidence: MH is probably a disorder involving calcium transients; calcium mediates the release of adrenergic transmitters; catecholamines stimulate skeletal muscle and its metabolism; circulating catecholamines increase markedly during MH; α-adrenergic blocking agents may be partially protective against MH; susceptible swine appear to have excessive sympathetic activity. Lister et al. characterize MH as an initial exaggerated muscular response that leads to metabolic and respiratory acidosis, which is then exacerbated by increases in catecholamines. Moulds expands this by including the possibility of enhanced tissue sensitivity to catecholamines. The hypothesis of Williams relates MH to deficient catabolic enzymes—monoamine oxidase or catechol-ortho-methyl transferase—that cannot efficiently metabolize norepinephrine released from peripheral adrenergic terminals. The rapid release of norepinephrine is then claimed to result in an "acute norepinephrine toxicity reaction."

The present data fail to provide any support for the preceding theories, and indeed indicate that porcine MH can be triggered and maintained during complete sympathetic blockade. Because of the many similarities between porcine and human MH, this may also be true for human MH. It is recognized that patients who have disorders of the sympathetic nervous system, e.g., pheochromocytoma, can and do show metabolic and circulatory derangements, but they have not been associated with symptoms typical of MH. While Harrison found no protection from α-adrenergic blocking agents in MH, Williams’ group and Lister et al. have felt that partial protection did occur. It may be that vasodilation increases muscle perfusion and cutaneous heat loss and improves the clinical picture without being specifically therapeutic. In the present study the vasodilation of sympathetic blockade apparently resulted in better maintenance of cardiac output and arterial pressure and, secondarily, because of better tissue perfusion, more sustained increases in oxygen consumption than have been seen in MH without vasodilation.

Although dantrolene is believed to act primarily within the muscle fiber to reverse dramatically the signs of MH, recent evidence suggests that it also affects the nerve terminal, as manifested by less frequent miniature end-plate potentials. If dantrolene depresses other nerve terminals, e.g., sympathetic pre- or postganglionic fibers, then its effects in lowering catecholamine concentrations in MH might be primary rather than secondary to its intramuscular effects. To the contrary, the present data from two stressed pigs suggest that the sympathetic nervous system is able to respond to stress during therapy with dantrolene. Therefore, the increases in catecholamines during MH are very likely secondary to the generalized stress of MH.

Although sympathetic blockade is more extensive and persists longer than motor block, the sympathetic block may have been fading in several animals near the end of the study. This may account for the trend toward an increase in mean norepinephrine values after 40 minutes (fig. 1); epinephrine values, however, did not tend to increase. Assuming that the porcine adrenal medulla predominantly releases epinephrine, release would not begin again until the level of sympathetic blockade decreased to T10–L2.7 Since blockade at these segments would be late in recovery, increases in epinephrine should lag behind those in norepinephrine.

Our data, as well as McLoughlin’s, contradict those of Kerr et al. that demonstrate protection from halothane-induced MH after epidural block, and we are unable to explain the differences.

Changes in whole-blood ionized Ca++ during MH have not been reported before. Ca(++), Na+, and K+ increased progressively during the first 40 minutes. The increases in Na+ are consistent with a rapid shift of water out of the vascular bed into other spaces. The proportionate changes in Ca++ were greater than those in Na+ and imply that there was an additional movement of Ca++ into the circulating blood volume. However, even if intracellular membranes collapsed, the muscle concentration of Ca++ would increase to only 10^-6 m, still insufficient to provide a concentration gradient into blood. Although acidosis should theoretically result in an increase in ionized Ca++, it decreased or remained the same in the two stressed animals, who both had arterial blood pH < 7.20. Thus, the increases in ionized Ca++ during MH remained unexplained. Serum K+ increased propor-
tionately more than both Na⁺ and Ca²⁺, as would be expected with an increase in cellular permeability.

We conclude that because porcine MH can be triggered in the presence of total spinal anesthesia, the role of the sympathetic nervous system in MH is not primary, but rather a usual and expected adrenergic response to major stress. We find no experimental support for the contention that conduction anesthesia might be protective against malignant hyperthermia.

References