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The Development of Lethal MH-PSS with the Secondary Development of an Intense Peripheral Vasoconstriction: A Review

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Introduction

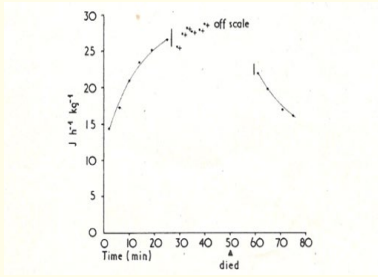
The pigs used in these experiments were raised from the initial five pigs reserved as breeding stock in January 1969 from stock at the Arlington Farm, UW. They were challenged with 3% Halothane in O_2 and identified as MH susceptible whenever the rear legs became extended and appeared to be in rigor. The Halothane challenge was stopped and the animals spontaneously recovered and were raised for breeding stock. The two males and three females were raised in UW Swine Barn A under Leo's supervision. Unfortunately, when they reached 225-240 lbs. in weight, they were hauled off to the UW slaughter house. Leo found them missing and called the slaughter house and recovered one male and two females that had not been slaughtered. We relocated the MH breeding stock to the UW Sheep Farm so there could not be any other possible confusion with other pigs in Swine Barn A. I moved the key MHS breeding animals to Sinclair Research Farm at MZZOU in 1973 when I relocated to MIZZOU for a new research position. Later in 1982, the entire stock of MHS susceptible breeding animals were moved to TTUHSC at El Paso, TX. They were housed on a pig farm near El Paso, TX.

Our first experiments in the Whole animal calorimeter in T-13 at MIZZOU produced some very surprising data which was published in BMJ. A summary of that data is in Figure 1. The metabolic data showed that the metabolic rate increased over 10 times during the MH s yyndrome. Water vapor and convection heat went off scale. Radiation heat increased dramatically, and then dropped below zero indicating that an intense vasoconstriction shut down heat loss via the skin. The hot dead body began radiating heat at levels which approached that of the living animal.

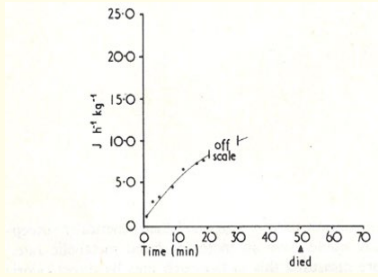
A second animal waiting for its turn to go into the calorimeter developed full blown MH in the transport crate, apparently from transport stress, and had labored breathing and was agitated. I gently released the animal from the transport crate, it circled around two or three times, then laid down and died. It was a white pig so the mottled purple on the skin on each side was readily visible.

We then designed experiments to measure hemodynamics in the MHS pigs during the MH syndrome. That data is shown in Figure 2. The 8-channel recorder shows that core temperature increased rapidly after the intense peripheral vasoconstriction started and reached 45.2°C. Arterial pressure was running over 300 mmHg and increased to over 400 mmHg. This placed a heavy workload on the heart and after several minutes the heart begin to fail and the animal died. PAP also increased at this time and probably account for the labored breathing noted in conscious animals that die after transport stress.

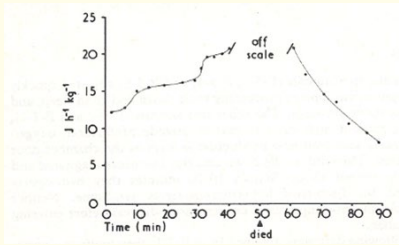
Note that venous O_2 saturation dropped rapidly whereas expired CO_2 increased.



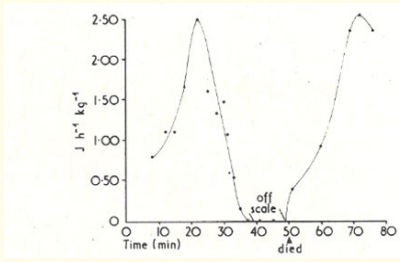
Total heat production recorded for P-7-1. "Off scale" (●+) indicates value exceeding range of recorders.



Heat losses recorded as evaporation of water (P-7-1).



Heat losses by convection (P-7-1).



Heat losses by radiation (P-7-1).

Figure 1

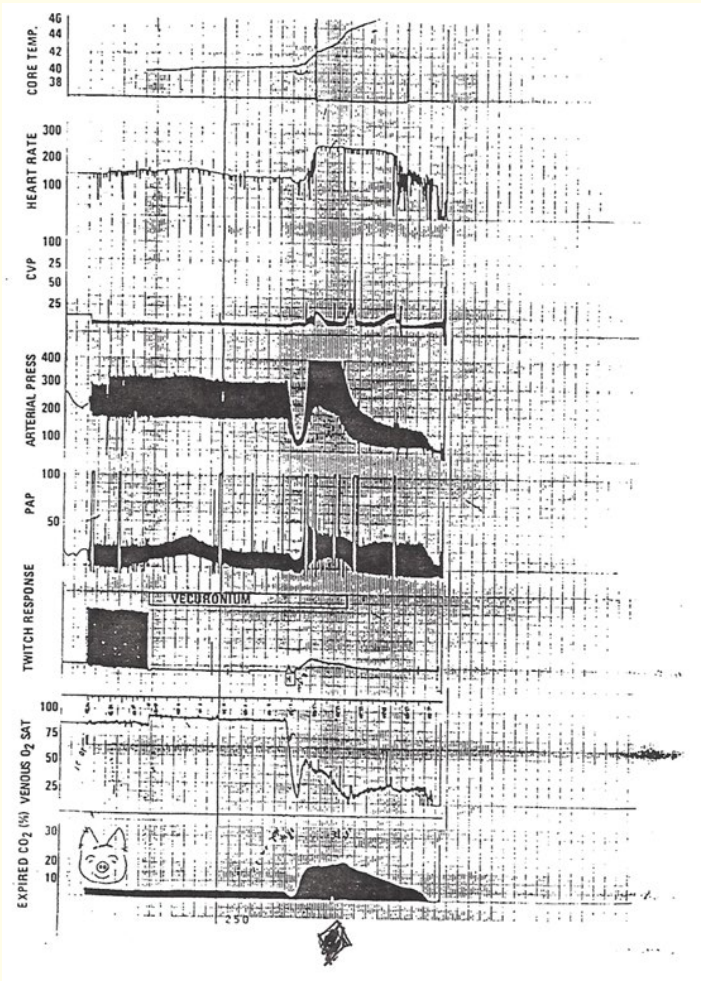


Figure 2: Typical *in vivo* recordings in an MHS pig with the very rapid development of MH. Total halothane exposure was for four minutes.

Discussion of the Data

Figure 1 shows the development of an intense peripheral vasoconstriction that is so intense that the radiation of heat via the skin is completely shut down. The skin becomes cold and the recording goes below the baseline. After death, the dead, hot body begins to radiate heat again and nearly reaches the level attained by the hot, living animal.

Figure 2 shows MH in a living animal that has a high blood pressure after being exposed to halothane for four minutes which triggers the MH syndrome that runs amok for several minutes. The heart begins to fail, blood pressure drops, and the there is a systemic response that increased heart rate to over 200 bpm and blood pressure rises to over 400 mmHg which sends the recorder off scale.

The vascular beds that we were able to measure all show vasoconstriction which increases systemic blood pressure. The heart is driven to very high rates which rapidly leads to heart failure and death of the animal. This animal had a core temperature that reached 45.2°C.

These changes in an uncontrolled metabolic rate, a rapidly increasing core temperature, a rapid consumption of oxygen and the production of large amounts of carbon dioxide. We then designed experiments to measure hemodynamics in the MHS pigs during the MH syndrome. The metabolic engine, we know as life, is operating at full throttle in an uncontrolled fashion which literally burns up/out the components of the system to produce high body temperatures, extremely high blood pressure, and intense peripheral vasoconstriction in all vascular beds (we were only able to measure some of the vascular beds) which causes a hammering effect at the skin arterioles to produce a mottled purple appearance on the skin surface of white pigs. Oxygen consumption reaches over 10x normal, CO is blown off by the lungs, core temperature goes as high as 118 °F, and the heart goes into failure leading to death.

All of these metabolic changes are caused by a genetic defect at the sodium channel which allows a rapid and uncontrolled influx of sodium ions which results in a cascade of metabolic changes to produce the Malignant Hyperthermia Syndrome. The same syndrome in pigs is known as Porcine Stress Syndrome.

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The results were very interesting and answered questions of why it is difficult to adequately treat and recover human patients that develop MH during an operation.

Fortunately, we have been able to help develop sevoflurane anesthesia which has reduced the incidence of MH to 1:550,000. Our work with Organon 9426 (*Rocuronium*) will prevent the development of the MH syndrome.

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