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Research Article

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

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Abstract

Malignant Hyperthermia, a lethal genetic disease in humans, is the same metabolic disease as the Porcine Stress Syndrome in pigs. The human disease and the porcine disease are characterized by a metabolic engine that is running at a maximum rate with heat as the primary product.

A secondary physiologic response is an intense peripheral vasoconstriction that contributes to core temperature rise and impedes blood flow in peripheral and core vascular beds to the point where arterial blood pressure exceeds 400 mmHg. The pulmonary, skin, and CVP vascular beds are also affected. Heart rate is driven to over 200 bpm which places an excessive workload on the heart and results in heart failure.

Methods and Materials: 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.

We can assume that by concentrating the MH genetic defect in the F_1 generatioon that the population of defective sodium chanels in the acetylcholine receptor was present at a high concentration. Since the acetylcholine receptors are spatially located under the foot piece of the myoneural junction which makes them a bank of receptors that are readily accessible when acetylcholine is released by the nerve, and the action of acetylcholine is very rapid. Therefore, the electromyographic data reflects the genetically defective sodium channels as the major functional component when we recorded the data.

We would suggest that the sodium channel at the acetyl choline receptor has been adapted to produce heat as well as muscle contraction and that the ability to produce copious amounts of heat is the biological mechanism that differentiates warm blooded animals from cold blooded animals.

The metabolic engine, we know as life, is operating at full throttle and in afterburner mode 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.

Keywords: Intense; Vasoconstriction; O_2

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. 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.

They were 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 kept 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. Three animals, a male and two females were recovered before being slaughtered

Mating MH positive pigs to MH positive pigs produces an F_1 generation that is highly stress susceptible. Recording the MUP shows MH + pigs have a higher u voltage than control pigs. Older MH+ pigs have an even higher u voltage than control pigs. The duration of the voltage spike is also increased in MH+ pigs versus control pigs and older MH+ pigs have even a longer duration of the voltage spike.

We can assume that by concentrating the MH genetic defect in the F_1 generation that the population of defective sodium channels in the acetylcholine receptor was present at a high concentration. Since the acetylcholine receptors are spatially located under the foot piece of the myoneural junction which makes them a bank of receptors that are readily accessible when acetylcholine is released by the nerve, and the action of acetylcholine is very rapid. Therefore, the electromyographic data reflects the genetically defective sodium channels as the major functional component when we recorded the data.

The sodium channels can be likened to a low voltage switch in a telephone circuit that is used to route telephone calls.

We would suggest that the sodium channel at the acetyl choline receptor has been adapted to produce heat as well as muscle contraction and that the ability to produce copious amounts of heat is the biological mechanism that differentiates warm blooded animals from cold blooded animals.

The metabolic engine, we know as life, is operating at full throttle and in afterburner mode 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.

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 3. The metabolic data showed that the metabolic rate increased over 10 times during the MH syndrome. 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^{0}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 began to fail and the animal died. PAP also increased at this time and probably accounts 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.


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Figure 1

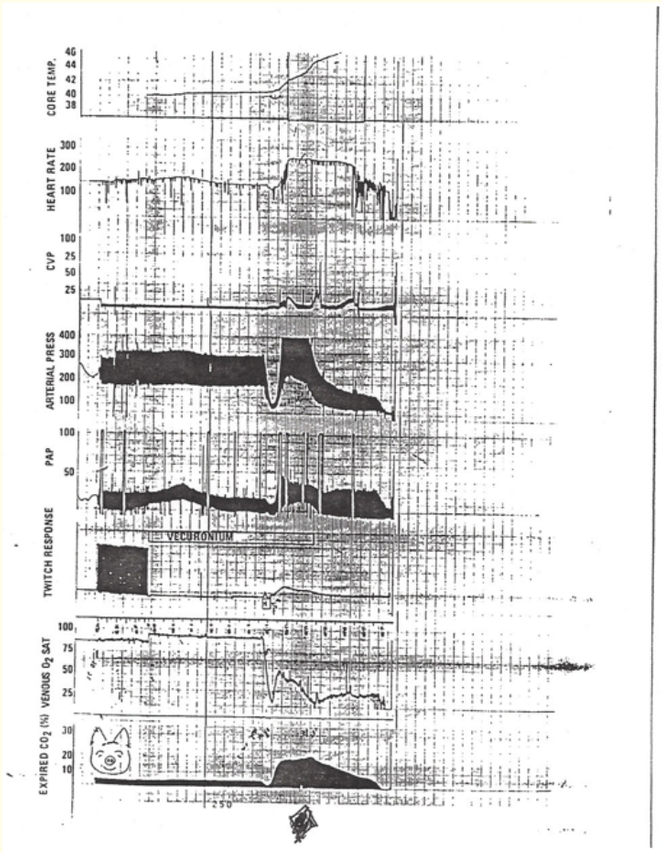
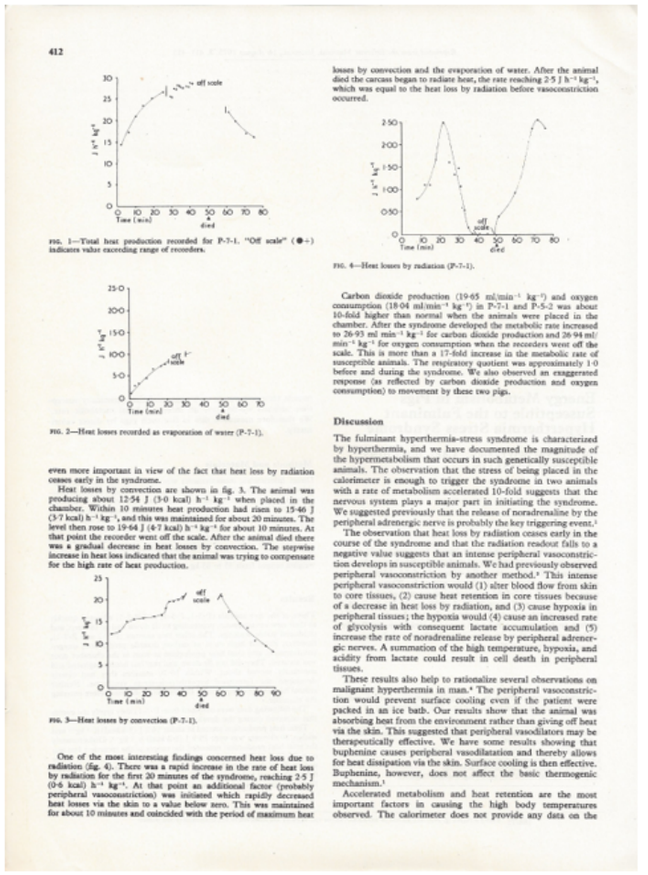


Figure 2: Typical in vivo recordings in an MHS pig with the very rapid development of MH. Total halothane exposure was for four minutes.



412

losses by convection and the evaporation of water. After the animal died the carcass began to radiate heat, the rate reaching 2·5 J h^{-1} kg^{-1}, which was equal to the heat loss by radiation before vasoconstriction occurred.

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

FIG. 4—Heat losses by radiation (P-7-1).

FIG. 2—Heat losses recorded as evaporation of water (P-7-1).

Carbon dioxide production (19·65 ml/min^{-1} kg^{-1}) and oxygen consumption (18·04 ml/min^{-1} kg^{-1}) in P-7-1 and P-5-2 was about 10-fold higher than normal when the animals were placed in the chamber. After the syndrome developed the metabolic rate increased to 26·93 ml min^{-1} kg^{-1} for carbon dioxide production and 26·94 ml/min^{-1} kg^{-1} for oxygen consumption when the recorders went off the scale. This is more than a 17-fold increase in the metabolic rate of susceptible animals. The respiratory quotient was approximately 1·0 before and during the syndrome. We also observed an exaggerated response (as reflected by carbon dioxide production and oxygen consumption) to movement by these two pigs.

even more important in view of the fact that heat loss by radiation ceases early in the syndrome.

Heat losses by convection are shown in fig. 3. The animal was producing about 12·54 J (3·0 kcal) h^{-1} kg^{-1} when placed in the chamber. Within 10 minutes heat production had risen to 15·46 J (3·7 kcal) h^{-1} kg^{-1}, and this was maintained for about 20 minutes. The level then rose to 19·64 J (4·7 kcal) h^{-1} kg^{-1} for about 10 minutes. At that point the recorder went off the scale. After the animal died there was a gradual decrease in heat losses by convection. The stepwise increase in heat loss indicated that the animal was trying to compensate for the high rate of heat production.

FIG. 3—Heat losses by convection (P-7-1).

One of the most interesting findings concerned heat loss due to radiation (fig. 4). There was a rapid increase in the rate of heat loss by radiation for the first 20 minutes of the syndrome, reaching 2·5 J (0·6 kcal) h^{-1} kg^{-1}. At that point an additional factor (probably peripheral vasoconstriction) was initiated which rapidly decreased heat losses via the skin to a value below zero. This was maintained for about 10 minutes and coincided with the period of maximum heat

Discussion

The fulminant hyperthermia-stress syndrome is characterized by hyperthermia, and we have documented the magnitude of the hypermetabolism that occurs in such genetically susceptible animals. The observation that the stress of being placed in the calorimeter is enough to trigger the syndrome in two animals with a rate of metabolism accelerated 10-fold suggests that the nervous system plays a major part in initiating the syndrome. We suggested previously that the release of noradrenaline by the peripheral adrenergic nerve is probably the key triggering event.[1]

The observation that heat loss by radiation ceases early in the course of the syndrome and that the radiation readout falls to a negative value suggests that an intense peripheral vasoconstriction develops in susceptible animals. We had previously observed peripheral vasoconstriction by another method.[2] This intense peripheral vasoconstriction would (1) alter blood flow from skin to core tissues, (2) cause heat retention in core tissues because of a decrease in heat loss by radiation, and (3) cause hypoxia in peripheral tissues; the hypoxia would (4) cause an increased rate of glycolysis with consequent lactate accumulation and (5) increase the rate of noradrenaline release by peripheral adrenergic nerves. A summation of the high temperature, hypoxia, and acidity from lactate could result in cell death in peripheral tissues.

These results also help to rationalize several observations on malignant hyperthermia in man.[4] The peripheral vasoconstriction would prevent surface cooling even if the patient were packed in an ice bath. Our results show that the animal was absorbing heat from the environment rather than giving off heat via the skin. This suggested that peripheral vasodilators may be therapeutically effective. We have some results showing that buphenine causes peripheral vasodilatation and thereby allows for heat dissipation via the skin. Surface cooling is then effective. Buphenine, however, does not affect the basic thermogenic mechanism.[3]

Accelerated metabolism and heat retention are the most important factors in causing the high body temperatures observed. The calorimeter does not provide any data on the

Figure 3

Discussion

Figure 3 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 presure after being exposed to halothane for four minutes which trigers 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. This is the afterburner stage that ultimately kills the animal.

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_2 is blown off by the lungs, core temperature goes as high as 118°F, and the heart goes into failure leading to death.

The cascades of 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.

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 [1,2].

Conclusion

The development of an intense peripheral vasoconstriction during the MH episode is a lethal development which makes MH a difficult disease to treat and have a successful outcome. The preferred approach is to preclude the development of MH by using sevoflurane as the anesthetic and non-depolarizing muscle relaxants such as Organon 9426 to prevent MH.

Bibliography

1. Williams CH., *et al.* BMJ 16: 411-413.

2. Stiess JE., *et al*, "Electromyographic evaluation of Malignant Hyperthermia susceptible pigs". *American Journal of Veterinary Research* 42 (1981): 1173-1176

3. Williams CH., *et al.* "Hemodynamics in Malignant Hyperthermia susceptible (MHS) pigs during Malignant Hyperthermia". *Experimental Malignant Hyperthermia* (1988): 30-45.

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