

# **Exercise Rhabdomyolysis & Malignant Hyperthermia Trait**

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## **Contents:**

- 1.** Final Draft paper for publication in AS&EM (1999/2000)
- 2.** Documentation for 1996 CAMFB
- 3.** Early draft for AS&EM paper containing more extensive reference list.

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**Title:** Exercise Rhabdomyolysis in Military Aircrew: Two cases and a review of aeromedical disposition.

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**Running Head:** Military Aircrew Rhabdomyolysis - Watson & Gray.

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## **Abstract.**

Rhabdomyolysis occurred in two military pilots as a result of their aircrew duties. One, an experienced pilot, suffered rhabdomyolysis as a result of centrifuge based G-training while the other, a cadet in training, suffered rhabdomyolysis precipitated by exertion during moderately warm weather. Further investigation revealed the second case to also have the Malignant Hyperthermia Trait.

Exercise rhabdomyolysis is a rare, sometimes catastrophic condition where muscle fibres breakdown in response to exertion and release their breakdown products into the circulation. While exercise rhabdomyolysis was brought to the medical community's attention largely through reports from military training establishments we are unaware of exercise rhabdomyolysis having resulted from the activities of military aircrew. This paper reports two cases of exercise rhabdomyolysis in military aircrew and discusses the condition and the approaches taken in determining their future aeromedical disposition.

After wide consultation and lengthy deliberations both of these aircrew were returned to their full previous flying status. No further complications or recurrences have occurred.

**Keywords:** Rhabdomyolysis, Exercise Rhabdomyolysis, Exertional Rhabdomyolysis, Myoglobinuria, Malignant Hyperthermia, Malignant Hyperpyrexia, Military Aircrew, Aeromedical Disposition.

## **Text.**

Rhabdomyolysis is the breakdown of skeletal muscle cells with the liberation of their contents into the circulation including creatine phosphokinase enzyme (skeletal muscle subtype) and myoglobin protein (6, 19). Myoglobinuria is one of the cardinal manifestations of rhabdomyolysis.

Rhabdomyolysis ranges in degree from an asymptomatic detection of muscle breakdown products in the blood through to a severe, sometimes fatal, condition involving collapse, hyperkalaemia, metabolic acidosis, hypocalcaemia, renal failure, compartment syndromes, and disseminated intravascular coagulation. There are many conditions that either cause or predispose to rhabdomyolysis although the most common precipitant of life threatening rhabdomyolysis appears to be physical exercise (19), or exercise rhabdomyolysis (ER).

Acute renal failure may complicate the more severe cases of exercise rhabdomyolysis. The renal failure is usually a result of acute tubular necrosis and is probably caused by direct myoglobin toxicity on the renal tubules of the dehydrated, acidotic individual (28).

## **Case Reports.**

### **Pilot 1: Canadian Forces pilot.**

This 26 year old previously healthy male took a one day G-training course at the Defence and Civil Institute of Environmental Medicine (DCIEM). The centrifuge profile included the following sequence; a gradual onset run to 8.7 G, followed immediately by two rapid onset runs, 6G for 30 seconds, and then 8G for 15 seconds wearing a G-suit. This last run was terminated after 10 seconds because of loss of abdominal bladder pressure and incipient G-LOC symptoms. He had been feeling in good health, with no intercurrent viral symptoms. After the G-training, he felt tired but well enough to fly commercially back to his home unit.

The next day, he awoke with some mild pain and stiffness in his lower back. This was not severe and he flew a transit-only formation cross-country flight in the CT114 Tutor for an airshow the following day. By that evening, his back was stiffer, and he noticed that his urine was a dark brown. The next morning, he felt even stiffer, with pain on sitting, walking, or bending. By afternoon, his urine was even darker and he presented at the local Emergency Room.

The urinalysis showed granular casts and myoglobinuria. Blood urea and creatinine levels were normal, but the serum transaminases were markedly elevated<sup>†</sup>: Aspartate Aminotransferase (AST, SGOT) 19.2  $\mu$ kat/L or 1152 U/L (Reference Range: 10 - 40 U/L or 16.7 - 66.7  $\mu$ kat/L), Alanine Aminotransferase (ALT, SGPT) 3.4  $\mu$ kat/L or 206 U/L (Reference Range: 6 - 37 U/L or 0.10 - 0.62  $\mu$ kat/L), Lactate Dehydrogenase (LD, LDH) 37.4  $\mu$ kat/L or 2241 U/L (Reference Range: 14 - 210 U/L or 0.23 - 3.50  $\mu$ kat/L), and Creatine Kinase (CK, CPK) >50  $\mu$ kat/L or >3000 U/L (Reference Range: 45 - 240 U/L or 0.75 - 4.00  $\mu$ kat/L). He was instructed to rest and to push oral fluids.

By the next day, he felt considerably better, and his urine had returned to normal colour. He flew back to his home base as a second pilot. On examination, there was still some lower back tenderness and decrease in flexion. Urinalysis showed no casts or myoglobin. His CK was 13.3  $\mu$ kat/L (800 U/L), AST 35.1  $\mu$ kat/L (2106 U/L), ALT 9.0  $\mu$ kat/L (538 U/L), and LD 31.8  $\mu$ kat/L (1910 U/L). The Gamma Glutamyl Transferase (GGT) levels were normal.

He was grounded and re-examined 7 days after G-training. He felt well, there were no positive physical findings, and his enzymes had returned to normal. Viral screen for Epstein-Barr, cytomegalovirus, HIV, and hepatitis B were negative. He was returned to flying.

He continued to have an intermittent mild elevation of AST, ALT, and CK enzymes. Enzyme levels before and after a three-week holiday break showed a mild elevation in AST and ALT, but normal CK, LD, and GGT levels. AST, ALT and CK levels monitored before and for three days after a one-hour aerobatic trip in the CT114 Tutor showed a persisting mild elevation in ALT a slight elevation in AST four hours post-flight, and a rise in CK within the normal range (Figure 1). Several serum specimens were noted to be lipemic with triglyceride levels 301 - 886 mg/dL (3.4 -10 mmol/L).

[Figure 1 Here]

**Fig. 1.** Post aerobatic flight enzyme levels for Pilot 1.

His past history was otherwise unremarkable. He maintained a regular mixed aerobic / isometric fitness program, and had never noted any similar symptoms in the past. There was no family history of a muscle disorder. He was a non-smoker and non-drinker.

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<sup>†</sup> 1  $\mu$ kat/L = 1  $\mu$ mol/sec/L = 60  $\mu$ mol/min/L = 60 U/L

Four months later, he returned to DCIEM and had a muscle biopsy and enzyme assays before and after +Gz exposure on the centrifuge. Both muscle biopsies were normal to light and electron microscopic examination. There was no evidence of fat droplet accumulation. The enzyme levels are shown in Table 1.

[Table 1 Here]

**Table 1.** Pilot 1 enzyme levels (U/L and  $\mu\text{kat/L}$ ) pre- and post- test centrifuge exposure.

An ischaemic tolerance test was carried out to screen for glycogen storage disorders. Serum lactate levels showed a normal increase from 0.09 to 0.38 mg/dL (0.8 mmol/L to 3.4 mmol/L) at 7 minutes with ischaemic exercise of the right forearm. Although there was ischaemic pain, there was no muscle cramping or tetany.

An open muscle biopsy was performed to permit various muscle enzyme assays. Carnitine palmitoyltransferase I and II assays were carried out in cultured skin fibroblasts and were normal. Muscle  $\beta$ -oxidation studies (Enoyl-Co A hydratase, L-3-hydroxyacyl-CoA dehydrogenase, & Acetoacetyl CoA thiolase) to investigate a possible lipids storage abnormality were also normal.

**Pilot 2: Royal Australian Air Force student pilot.**

This 25 year old male, in good health, flew as a passenger in a military transport aircraft to a tropical coastal region of Australia to undertake routine aircrew Combat Survival training in preparation for his flying training. On the morning of his flight he felt in good health although he hadn't slept well the preceding night and he had one liquid bowel movement. He drank a single cup of coffee (usual intake 1 - 2 cups per day). He was taking no medications.

Upon arrival at the Combat Survival Training facility he undertook a moderate amount of physical exercise consisting of not more than 30 minutes light jogging and some mixed upper and lower body exercises. Environmental conditions of approximately 25°C and low humidity were reported.

Pilot 2 felt tired prior to the run and felt very tired and unwell during the run. He was unable to complete the run, collapsed under a tree part way, and was reported as 'talking gibberish'. He was admitted to local Military Health Facility and was reported as being awake, agitated, confused, sweaty, & vomiting. No tenderness or soreness of muscles was noted. However discoloured urine was apparent upon initial examination.

Later that day he was transferred to a regional General Hospital where his haemoglobin (Hb) was found to be normal and his white cell count (WCC) moderately elevated. His plasma electrolytes and urea were within normal range but his plasma creatinine was mildly elevated. A urinary drug screen was negative. Intravenous infusion of 3 litres normal saline was undertaken and he was transferred to a regional Military Health Facility where a further 3 litres of intravenous fluid were infused.

The following day mild generalised muscle soreness and lethargy was noted. His WCC was still moderately elevated, as were his plasma creatinine and urea. His first CK assay was reported as 1080  $\mu\text{kat/L}$  (64,800 U/L). An intercurrent herpes labialis infection was noted and treated with topical acyclovir. Oral fluids were well tolerated, and he was polyuric.

Over the next few days his CK climbed (peaking, on day 5 at 7708  $\mu\text{kat/L}$  or 462,400 U/L) as did his plasma creatinine and urea levels. IV and oral fluid loading was continued and intravenous dopamine and furosemide infusion was commenced along with alkalinization of the urine. Deterioration in urine output was noted and the patient complained of generalised skin itching. The first of five renal dialysis treatments was undertaken the following day with noted improvement in patient comfort and wellbeing. His haematology, renal function and CK levels gradually returned to normal and he was discharged from inpatient care at three weeks post-incident.

Six months later he was reviewed to determine his aeromedical disposition. He had no family history of anaesthetic complications, one parent and both his sisters having undergone uncomplicated general anaesthesia. He himself had undergone two uncomplicated general anaesthetics. His only other past history was of occasional minor sporting injuries. There was no family history of any muscle or neurological disorder.

A muscle biopsy was examined by light microscopy, electron microscopy, and in-vitro halothane / caffeine contracture testing. The histology proved normal but the contracture test supported a diagnosis of Malignant Hyperthermia Trait.

## **Discussion.**

Rhabdomyolysis ranges in degree from the detection of muscle breakdown products in the blood of asymptomatic individuals through to a severe, sometimes fatal, condition associated with collapse, hyperkalaemia, metabolic acidosis, hypocalcaemia (27), renal failure, compartment syndromes (17), and

disseminated intravascular coagulation (3, 20). There are many conditions that either cause or predispose to rhabdomyolysis although physical exercise and alcohol abuse appear to be the commonest precipitants of severe rhabdomyolysis (19).

Exercise rhabdomyolysis is the breakdown of skeletal muscle cells and the release of their contents into the circulation as a result of physical exertion. Many forms of exertion have been reported as leading to exerciser rhabdomyolysis (2, 10, 21, 26, 28).

The skeletal muscle breakdown of rhabdomyolysis results in the release of many different products into the circulation. The most commonly measured of these breakdown products are myoglobin protein, which when excreted into the urine results in myoglobinuria, one of the cardinal manifestations of rhabdomyolysis, and the creatine phosphokinase enzyme (skeletal muscle subtype).

Acute renal failure is often a complication of the more severe cases of exercise rhabdomyolysis (2) and is usually a result of acute tubular necrosis which appears to be caused by direct myoglobin toxicity on the renal tubules of the dehydrated, acidotic individual (28).

Exercise rhabdomyolysis has usually been of concern to military physicians dealing with ground troops (1, 5, 11, 12, 16) and sports physicians dealing with a variety of endurance athletes. While the literature has gradually filled with exercise rhabdomyolysis cases precipitated by a wide variety of activities we are aware of no cases precipitated by the duties of either military or civil aircrew. We are similarly unaware of any report of exercise rhabdomyolysis resulting from +Gz exposure.

Pilot 1's final diagnosis is exercise rhabdomyolysis which was precipitated by G exposure. No underlying abnormality or predisposing condition has been identified. There were no unusual circumstances surrounding the centrifuge training, nor any symptoms of viral infection. The profile was a standard G training profile without excessive straining. DCIEM centrifuge subjects have frequently exceeded this level of +Gz exposure without symptoms or signs of rhabdomyolysis, although a degree of muscle stiffness is common in both subjects and students following high levels of +Gz. Although no specific enzyme deficiency has been identified, a mild indolent metabolic disorder remains a possibility. Our investigations have ruled out the most common metabolic disorders including inborn errors of glycogen and lipid storage, but there are other possible enzyme defects for which substrates are not available. He has not been specifically tested for malignant hyperthermia trait. Whatever his underlying defect it appeared to manifest as mild, subclinical rhabdomyolysis following G-exposures; on one occasion this resulted in a clinical

presentation. He subsequently completed a full tour on the Canadian Forces aerobatic team without any untoward muscle signs or symptoms, and he has had no further evidence of muscle pathology in over eight years of follow-up.

In the case of Pilot 2 the cause of rhabdomyolysis has been identified as his underlying malignant hyperthermia trait coupled with exertion in a warm environment. His condition presented via a bout of Exercise Rhabdomyolysis which was, in turn, complicated by acute tubular necrosis and acute renal failure requiring renal dialysis.

### **Malignant Hyperthermia.**

The Malignant Hyperthermia Syndrome (MHS) is a poorly understood condition that occasionally complicates general anaesthesia in some susceptible individuals (4, 9, 14, 23, 29). MHS is characterised by temperature elevation, muscle rigidity, systemic acidosis, muscle breakdown (rhabdomyolysis), and cardiac arrhythmia's, and often results in death (23). MHS is precipitated by exposure to inhalation anaesthetic agents (eg. halothane, enflurane, or isoflurane) and / or depolarising muscle relaxants (eg. suxamethonium, suxethonium, or decamethonium).

In the absence of an underlying genetic disorder being identified, individuals susceptible to Malignant Hyperthermia are considered as having the Malignant Hyperthermia Trait (MHT) and are usually identified through their suffering MHS as an anaesthetic complication or the occurrence of associated phenomena such as exercise rhabdomyolysis. The diagnosis of MHT is made through an in vitro contraction test of a biopsy sample of muscle exposed to halothane and caffeine (14, 22).

There are also a number of identified genetic causes of Malignant Hyperthermia including Myotonia Congenita, Myotonic Muscular Dystrophy, Duchenne Muscular Dystrophy, Chondrodystrophic Myotonia, the King Syndrome, and Central Core Disease (25).

### **Aeromedical Disposition.**

The aeromedical disposition of each of these military aircrew members was decided by their service's relevant personnel authorities. The authors played a role in providing medical information and recommendations to those authorities. In this section we will attempt to outline our rationale and the data that was available to us as we independently reached the conclusion that both Pilot 1 and Pilot 2 were medically fit to continue their military flying careers, although there were obvious concerns in both cases. The prime

considerations were of flight safety, operational effectiveness, and of the risk to the individuals health in performance of aircrew duties, ordinary or potentially extraordinary such as with escape and evasion.

### **Risk to Flight Safety / Flight Operations**

There does not appear to be a risk to flight safety in either case. If Exercise Rhabdomyolysis were to be experienced during a flying mission it is extremely unlikely to have an initial presentation of collapse or acute incapacitation. Pilot 1 was re-exposed to the acceleration environment in controlled conditions both in aerobatic jet aircraft and in the centrifuge without recurrence of symptomatic rhabdomyolysis. For Pilot 2, it is possible that air operations in a hot environment, specifically in a hot aircraft might increase the risk of a bout of Exercise Rhabdomyolysis. MHT is a predisposing factor to exercise rhabdomyolysis, but the degree of risk must be very low, given that the incidence of ER in individuals with MHT is remote in circumstances other than anaesthetic exposures (7-9, 15). The very unlikely occurrence of an accidental leak of anaesthetic gas cargo on a transport mission seems so remote as to be dismissed, and Pilot 2 had been previously exposed to inhalation agents on two occasions without incident.

The physical workload during flight, even the most demanding of air combat manoeuvring, rarely exceeds what would generally be considered as being moderate exertion. Exercise Rhabdomyolysis appears to occur mainly after prolonged or high workload exertion, often during hot weather, in people who are not well trained and acclimatised to the workload or environmental conditions. Maintenance of a high level of fitness, compared to the exertion to be undertaken, and acclimatisation to the conditions is thought to reduce the risk of Exercise Rhabdomyolysis (18, 19, 24, 28).

The routine and emergency duties of military aircrew require the maintenance of a reasonable degree of physical fitness and may demand the occasional exposure to moderate - heavy work in a hot environment, including the possible situation of escape and evasion. These situations do not present a risk for a bout of Malignant Hyperthermia Syndrome but there is probably a small increased risk of Exercise Rhabdomyolysis. Operationally, to reduce fatigue and heat stress in normal operations, efforts are constantly being made (air-conditioned accommodation, briefing areas, crew vans etc) to minimise exposure to high physical workload and high thermal workload environments. Escape, evasion, and capture scenarios have the potential to expose military aircrew to unpredictable and extreme environments under adverse circumstances. The risk of ER in hot, stressful environments can be further reduced by the susceptible individual maintaining a high level of physical fitness, good hydration, and good heat acclimatisation (21). Military Combat Survival training provides aircrew with skills to cope with such situations.

## **Risk to the Individuals**

Pilot 1's clinical rhabdomyolysis presentation after centrifuge training and subclinical rhabdomyolysis after aerobatic flight suggested that he may suffer some degree of rhabdomyolysis during future high-G flight, centrifuge training, and possibly other strenuous activities. However, further monitored +Gz exposures in the air and centrifuge did not result in significant biochemical rhabdomyolysis or untoward symptoms, and he completed a full aerobatic flying tour without further incident. Little is known about the degree of rhabdomyolysis in normal individuals during centrifuge training or high +Gz exposure. This is a potential area for further research

Pilot 2's underlying Malignant Hyperthermia Trait exposes him to an elevated but unquantified risk of rhabdomyolysis recurrence as well as the risk of malignant hyperthermia under various circumstances, most notably general anaesthesia employing inhalation induction agents and/or depolarising muscle blocking agents. While an anaesthetic using either volatile agents or depolarising muscle relaxants is potentially fatal for a MHT individual, a wide variety of anaesthetic agents can be employed without the risk of MHS. These agents include all of the narcotics, all non-depolarising muscle relaxants, all local anaesthetic agents, nitrous oxide, and adrenaline. No deaths from Malignant Hyperthermia Syndrome have occurred in previously diagnosed individuals when the anaesthetics team have been aware of their malignant Hyperthermia Trait (23). Given the range of drugs that can be used, with relative safety, for anaesthetising an MHT individual there is no reason that elective, or emergency, anaesthesia cannot be provided to military aircrew with MHT should the need arise. Pilot 2's medical documents have been clearly marked and he has been provided with a Medical Alert Bracelet to clearly identify his condition in the case of emergency surgery. Should an inappropriate anaesthetic be given and an episode of MHS be triggered it is possible to treat the latter condition with Sodium Dantrolene. However Dantrolene does not have good storage characteristics and is not likely to be held by every military medical facility at all times.

While it is not well reported it is also possible that MHT individuals may have an increased risk of de novo bouts of Malignant Hyperthermia, without preceding general anaesthesia. These bouts may be precipitated by stress and anxiety (4, 13) and could explain the increased incidence of unexplained deaths that has been noted amongst MHT families (30).

Pilot 2's renal failure indicated a more severe episode of rhabdomyolysis at the time of initial presentation but having fully resolved was of little further clinical concern.

Pilot 2's condition presents an unusual situation where we believe he has less of a risk of problems during military flight than during some of the non-flight aspects of his military duties. Pilot 2 commenced his flying ground school and then flight training while formal deliberations on his aeromedical disposition continued. After a prolonged period of deliberation he was returned to unrestricted military aircrew duties and was allowed to complete his flying training. There were no further incidents over the first six years of follow-up and he has spent most of this time posted to a hot tropical region.

### **Conclusion.**

After researching the available literature, it was our opinion that the medical conditions of both Pilot 1 and Pilot 2 were compatible with all of the duties of a military pilot. We agreed that there was a slightly increased risk of a recurrence of rhabdomyolysis or other complication of Malignant Hyperthermia Trait but we estimated the chances of such a complication occurring to be suitably low and if it did occur the chances of it actually resulting in an acute incapacitation to be remote.

### **Acknowledgments & Disclaimers.**

The opinions expressed in this article are those of the authors and should in no way be construed as reflecting the opinion or policy of either the Australian Defence Force, the Canadian Forces, or any other institution or agency. The authors acknowledge and appreciate the support provided by Ms Kaaren Sephton in the library at the RAAF Institute of Aviation Medicine in performing the extensive literature searches required and obtaining the many papers reviewed.

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**Tables, Figures, and Illustrations.**

P15 Figure 1: Figure

P16 Figure 1: Legend

P17 Table 1: Complete

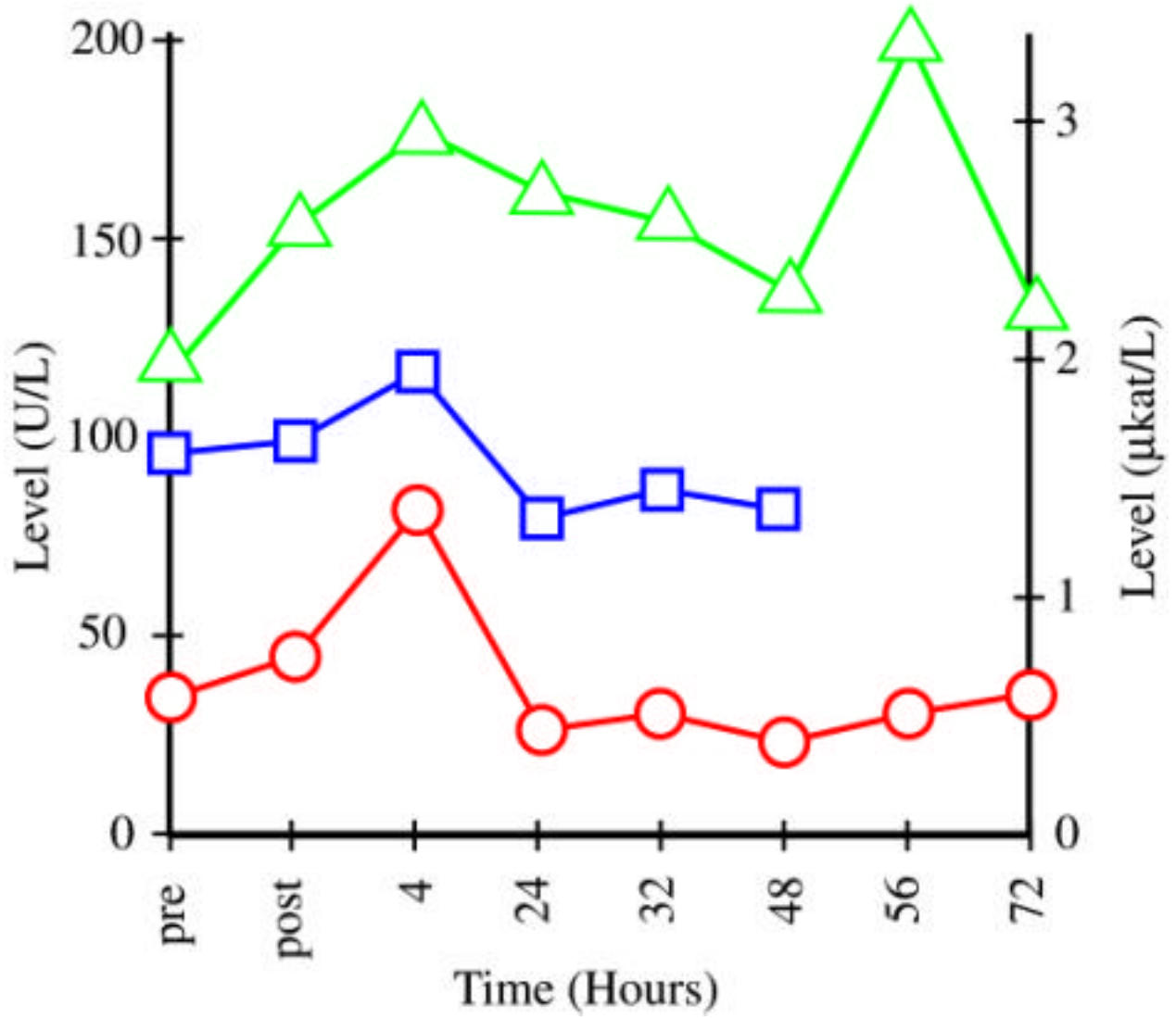


Fig. 1. Post aerobic flight enzyme levels for Pilot 1.

 AST Aspartate Aminotransferase	 ALT Alanine Aminotransferase	 CK Creatine Kinase
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Table 1: Table

	<b>CONTROL</b>	<b>POST-FLIGHT</b>	<b>24 HOURS</b>
<p><b>Aspartate Aminotransferase</b> (N = 10 - 40 U/L or 16.7 - 66.7 <math>\mu</math>kat/L)</p>	<p>53 U/L 0.88 <math>\mu</math>kat/L</p>	<p>59 U/L 0.98 <math>\mu</math>kat/L</p>	<p>64 U/L 1.07 <math>\mu</math>kat/L</p>
<p><b>Alanine Aminotransferase</b> (N = 6 - 37 U/L or 0.10 - 0.62 <math>\mu</math>kat/L)</p>	<p>158 U/L 2.63 <math>\mu</math>kat/L</p>	<p>149 U/L 2.48 <math>\mu</math>kat/L</p>	
<p><b>Creatine Kinase</b> (N = 45 - 240 U/L or 0.75 - 4.00 <math>\mu</math>kat/L)</p>	<p>253 U/L 4.22 <math>\mu</math>kat/L</p>	<p>294 U/L 4.90 <math>\mu</math>kat/L</p>	<p>2903 U/L 48.39 <math>\mu</math>kat/L</p>
<p><b>Gamma-Glutamyl Transferase</b> (N = 11 - 63 U/L or 0.18 - 1.05 <math>\mu</math>kat/L)</p>	<p>22 U/L 0.37 <math>\mu</math>kat/L</p>	<p>22 U/L 0.37 <math>\mu</math>kat/L</p>	<p>21 U/L 0.35 <math>\mu</math>kat/L</p>
<p><b>Lactate Dehydrogenase</b> (N = 14 - 210 U/L or 0.23 - 3.50 <math>\mu</math>kat/L)</p>	<p>136 U/L 2.27 <math>\mu</math>kat/L</p>	<p>157 U/L 2.62 <math>\mu</math>kat/L</p>	<p>174 U/L 2.90 <math>\mu</math>kat/L</p>

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## **Abstract.**

Rhabdomyolysis occurred in two military pilots as a result of their aircrew duties. One, an experienced pilot, suffered rhabdomyolysis as a result of centrifuge based G-training while the other, a cadet in training, suffered rhabdomyolysis precipitated by moderate exertion during moderately warm weather. Further investigation revealed the second case to also have the Malignant Hyperthermia Trait.

Exercise rhabdomyolysis is a rare, often catastrophic, condition where muscle fibres breakdown in response to exertion and release their breakdown products into the circulation. While exercise rhabdomyolysis was brought to the medical community's attention largely through reports from military training establishments we are unaware of exercise rhabdomyolysis having resulted from the activities of military aircrew. This paper reports two cases of exercise rhabdomyolysis in military aircrew and discusses the condition and the approaches taken in determining their future aeromedical disposition.

After wide consultation and lengthy deliberations both of these aircrew were returned to their full previous flying status. No further complications or recurrences have occurred.

## **Text.**

Rhabdomyolysis is the breakdown of skeletal muscle cells with the liberation of their contents into the circulation (1, 2). While there is debate about the utility of using the term rhabdomyolysis rather than myoglobinuria (3) its literal translation from Greek does appear appropriate: A loosening of striped muscle (rhabdo from meaning 'rod', myo from  $\mu$  meaning 'muscle', and lysis or meaning 'a loosening').

Exercise rhabdomyolysis is, as the name implies, the breakdown of skeletal muscle cells and the release of their contents into the circulation as a result of physical exercise. Many forms of exertion, some seeming quite bizarre (4-6), have been described as leading to Exercise Rhabdomyolysis (Table 3).

The skeletal muscle breakdown of rhabdomyolysis results in the release of many different products into the circulation. The most commonly measured of these breakdown products are the Creatine Phosphokinase enzyme (skeletal muscle subtype) and the Myoglobin protein, which when excreted through the urine results in myoglobinuria, one of the cardinal manifestations of rhabdomyolysis.

Acute renal failure is often a complication of the more severe cases of exercise rhabdomyolysis. The renal failure is usually a result of acute tubular necrosis and is probably caused by direct myoglobin toxicity on the renal tubules of the dehydrated, acidotic individual.

## **Case Reports.**

### **Case 1: Captain I. M. A. Cannuck, Canadian Forces pilot.**

This 26 year old previously healthy male took a one day G-training course at the Defence and Civil Institute of Environmental Medicine. The centrifuge profile included the following sequence; a gradual onset run to 8.7 G, followed immediately by two rapid onset runs, 6G for 30 seconds, and then 8G for 15 seconds wearing a G-suit. This last run was terminated after 10 seconds because of loss of abdominal bladder pressure and incipient G-LOC symptoms. He had been feeling in good health that day, with no intercurrent viral symptoms. After the G-training, he felt tired but well enough to fly commercially back to his home unit.

The next day, he awoke with some mild pain and stiffness in his lower back. This was not severe and he flew a transit-only formation cross-country flight in the CT114 Tutor for an airshow the following day. By that evening, his back was stiffer, and he noticed that his urine was a dark brown. The next morning, he felt even stiffer, with pain on sitting, walking, or bending. By afternoon, his urine was red and he presented at the local Emergency Room.

The urinalysis showed granular casts and myoglobinuria. Blood urea and creatinine levels were normal, but the serum transaminases were markedly elevated; SGOT 1152 U/L, SGPT 206, LDH 2241 and CPK>3000. He was instructed to rest and to push oral fluids.

By the next day, he felt considerably better, and his urine had returned to normal colour. He flew back to his home base as a second pilot. On examination, there was still some lower back tenderness and decrease in flexion. Urinalysis showed no casts or myoglobin. His CPK was 800 U/L, SGOT 2106, SGPT 538, LDH 1910. The GGT was normal.

He was grounded and re-examined 7 days after his day of G-training. He felt well, there were no positive physical findings, and his enzymes had returned to normal. Viral screen for Epstein-Barr, cytomegalovirus, HIV, and hepatitis B were negative. He was returned to flying.

He continued to have an intermittent mild elevation of AST, ALT and CK enzymes. Enzyme levels before and after a three-week holiday break showed a mild elevation in AST and ALT, but normal CPK, LDH, and GGT levels. AST, ALT and CK levels monitored before and for three days after a one-hour aerobatic trip in the CT114 Tutor are shown in Figure 1. There was a persisting mild elevation in ALT, a slight elevation in AST four hours post-flight, and a rise in CK within the normal range. Several serum specimens were noted to be lipemic with triglyceride levels 3.4 -10 mmol/L.

His past history was otherwise unremarkable. He maintains a regular mixed aerobic/isometric fitness program, and had never noted any similar symptoms in the past. There is no family history of a muscle disorder. He is a non-smoker and non-drinker.

Four months later, he returned to DCIEM and had a muscle biopsy and enzymes done before and after +Gz exposure on the centrifuge. Both muscle biopsies were normal on examination with both light and electron microscopy. There was no evidence of fat droplet accumulation. The enzyme levels are shown in Table 1.

An ischemic tolerance test was carried out to screen for glycogen storage disorders. Serum lactate showed a normal increase from 0.8 mmol/L to 3.4 mmol/L at 7 minutes with ischemic exercise of the right forearm. Although there was ischemic pain, there was no muscle cramping or tetany.

An open muscle biopsy was performed to permit various muscle enzyme assays. Carnitine palmitoyltransferase I and II assays were carried out in cultured skin fibroblasts and were normal. Muscle  $\beta$ -oxidation studies (Enoyl-Co A hydratase, L-3-hydroxyacyl-CoA dehydrogenase, & Acetoacetyl CoA thiolase) to investigate a possible lipids storage abnormality were also normal.

CAPT Cannuck was returned, unrestricted, to Canadian Forces aircrew duties and subsequently completed a two year tour with the Snowbirds air demonstration team flying a very demanding airshow schedule. Over five years have elapsed since the centrifuge incident with no recurrence of clinical rhabdomyolysis or myoglobinuria.

## **Case 2: Officer Cadet I. M. N. Aussie, Royal Australian Air Force student pilot.**

This 25 year old male, in good health, flew as a passenger in a military transport aircraft to a tropical coastal region of Australia, during Winter months, to undertake routine aircrew Combat Survival training in preparation for his flying training. On the morning of his flight he was in good health although he hadn't slept well the preceding night (which he attributed to 'nerves'), drank a single cup of coffee (usually drinks 1 - 2 cups per day), was taking no medications, and had one liquid bowel movement (which he again attributed to 'nerves' concerning the rigors of his Combat Survival training).

Upon arrival at the Combat Survival Training facility he, and some colleagues, undertook a moderate amount of physical exercise - Although the medical notes and the history later obtained by the author (Watson) do not entirely agree it is unlikely than in excess of 30 minutes light jogging and some mixed upper and lower body exercises was undertaken. Environmental conditions of approximately 25°C and low humidity were reported.

OFFCDT Aussie felt tired prior to the run and felt very tired and unwell during the run. He was unable to complete intended run, collapsed under a tree part way, and was reported as 'talking gibberish'. He was admitted to local Military Health Facility and was reported as being awake, agitated, confused, sweaty, & vomiting.

No tenderness or soreness of muscles was noted and discoloured urine was apparent upon initial examination.

Later that day he was transferred to a regional General Hospital where his Haemoglobin (Hb) was found to be normal and his White Cell Count (WCC) moderately elevated. His plasma electrolytes and urea were within normal range but his plasma creatinine was mildly elevated. A urinary drug screen was undertaken and indicated no illicit drugs nor medications had been ingested. Intravenous infusion of 3 litres Normal Saline was undertaken and he was transferred to a regional Military Health Facility. Upon arrival there a further 3 litres of intravenous fluid was infused.

The following day mild generalized muscle soreness and lethargy was noted, his WCC was still moderately elevated, as were his plasma creatinine and urea. His first CPK assay was reported as 64,800 IU (CK-MB=0.9%). An intercurrent Herpes Labialis infection was noted and treated with topical acyclovir, oral fluids were well tolerated, and he was polyuric.

Over the next few days his CPK climbed (peaking, on day 5 at 462,400 IU) as did his plasma creatinine and urea levels. An intravenous fluid push was instituted along with oral alkalinization. The next day the IV fluid loading was continued and intravenous dopamine and frusemide infusion commenced. A deterioration in urine output was noted and the patient complained of generalised skin itching.

The first of five renal dialysis treatments was undertaken the following day with noted improvement in patient comfort and wellbeing.

Subsequently he was transferred to progressively more peripheral health facilities and was discharged from inpatient care at three weeks post-incident. His haematology and renal function gradually returned to normal over this period as had his CPK levels.

Six months later he was reviewed as part of the deliberations to determine his ongoing aeromedical disposition. He had no family history of anaesthetic complications, one parent and both his sisters having undergone uncomplicated General Anaesthesia. He had undergone two successful General Anaesthetics himself (Surgery on his toes in childhood and extraction of impacted wisdom teeth in his late teens). His only other past history was of occasional sporting injuries treated with first aid, rest, and occasional physiotherapy. There was no family history of any muscle disorder, neurological disorder, or the Sudden Infant Death Syndrome.

A Muscle Biopsy was taken and examined by light microscopy, electron microscopy, and in-vitro halothane/caffeine contracture testing. The histology proved normal, some non-specific changes were noted on EM, and the contracture test supported a diagnosis of Malignant Hyperthermia Trait.

It was recommended that he commence his flying ground school and then flight training while formal deliberations on his aeromedical disposition continued. After a prolonged period of deliberation OFFCDT Aussie was returned, unrestricted, to RAAF aircrew duties and was allowed to continue his flying training.

OFFCDT Aussie is now 12 months post rhabdomyolysis and diagnosis of Malignant Hyperthermia Trait without further sequelae or complications.

## **Discussion.**

CAPT Cannuck's final diagnosis is Exercise Rhabdomyolysis which was precipitated by G exposure. No underlying abnormality or predisposing condition has been identified.

OFFCDT Aussie's final diagnosis is Malignant Hyperthermia Trait. His condition presented via a bout of Exercise Rhabdomyolysis which was, in turn, complicated by acute tubular necrosis and acute renal failure requiring renal dialysis.

## **Rhabdomyolysis.**

As mentioned in our introduction rhabdomyolysis is the breakdown of skeletal muscle cells with the liberation of their contents into the circulation.

Rhabdomyolysis ranges in degree from the detection of muscle breakdown products in the blood of asymptomatic individuals through to a severe, sometimes fatal, condition associated with collapse,

hyperkalaemia, metabolic acidosis, hypocalcaemia (7, 8), renal failure (8-46), compartment syndromes (47), and disseminated intravascular coagulation (27, 48). There are many conditions that either cause or predispose to rhabdomyolysis (Tables 2 and 3) although physical exercise and alcohol abuse appear to be the commonest precipitants of severe rhabdomyolysis (2, 49).

Exercise rhabdomyolysis is, as the name implies, the breakdown of skeletal muscle cells and the release of their contents into the circulation as a result of physical exertion. Many forms of exertion have been reported as leading to Exercise Rhabdomyolysis (Table 3).

The skeletal muscle breakdown of rhabdomyolysis results in the release of many different products into the circulation. The most commonly measured of these breakdown products are the Myoglobin protein, which when excreted into the urine results in myoglobinuria one of the cardinal manifestations of rhabdomyolysis, and the Creatine Phosphokinase enzyme (skeletal muscle subtype).

Acute renal failure is often a complication of the more severe cases of exercise rhabdomyolysis (8-46, 50, 51) and is usually a result of acute tubular necrosis which appears to be caused by direct myoglobin toxicity on the renal tubules of the dehydrated, acidotic individual (6).

Exercise rhabdomyolysis has usually been of concern to military physicians dealing with ground troops (42, 52-60) and sports physicians dealing with a variety of endurance athletes (Table 3). While the literature has gradually filled with exercise rhabdomyolysis cases precipitated by a wide variety of activities (Table 3) we are aware of no cases precipitated by the duties of either military or civil aircrew. We are similarly unaware of any report of exercise rhabdomyolysis resulting from +Gz exposure.

The cause of rhabdomyolysis in CAPT Cannuck's case remains a mystery. There were no unusual circumstances surrounding the centrifuge training, nor any symptoms of viral infection. The profile was a standard G training profile without excessive straining. DCIEM centrifuge subjects have frequently exceeded this level of +Gz exposure without symptoms or signs of rhabdomyolysis, although a degree of muscle stiffness is common in both subjects and students following high levels of +Gz.

In the case of OFFCDT Aussie the cause of rhabdomyolysis has been identified as his underlying malignant hyperthermia trait coupled with exertion in a warm environment.

Although no specific enzyme deficiency has been identified, one possible explanation of CAPT Cannuck's rhabdomyolysis is an unidentified indolent mild metabolic disorder. Inborn errors of glycogen storage or lipid storage may present with rhabdomyolysis (Table 2). Our investigations have ruled out the most common metabolic disorders, but there are other possible enzyme defects for which substrates are not available. He has not been specifically tested for Malignant Hyperthermia Trait. Whatever his underlying defect it appears to manifest as subclinical rhabdomyolysis following the majority of his G-exposures and only on the one occasion has resulted in a clinical presentation.

## **Malignant Hyperthermia.**

Malignant Hyperthermia (also called Malignant Hyperpyrexia) is a poorly understood condition that occasionally complicates general anaesthesia in some susceptible individuals (60-69). The Malignant Hyperthermia Syndrome is characterised by temperature elevation, muscle rigidity, systemic acidosis, muscle breakdown (rhabdomyolysis), and cardiac arrhythmia's, and often results in death (64). The precipitation of the Malignant Hyperthermia Syndrome is caused by exposure to inhalation anaesthetic agents (eg. halothane, enflurane, & isoflurane) and / or depolarising muscle relaxants (eg. suxamethonium, suxethonium, & decamethonium).

There are also a number of identified genetic causes of Malignant Hyperthermia including Myotonia Congenita, Myotonic Muscular Dystrophy, Duchenne Muscular Dystrophy, Chondrodystrophic Myotonia, the King Syndrome, and Central Core Disease(3).

In the absence of an underlying genetic disorder being identified individuals susceptible to Malignant Hyperthermia are considered as having the Malignant Hyperthermia Trait (MHT) and are usually identified through their suffering Malignant Hyperthermia as an anaesthetic complication, their having a family history of such anaesthetic complications, or the occurrence of associated phenomena such as exercise rhabdomyolysis. The diagnosis of MHT is made through an in vitro contraction test of a biopsy sample of muscle exposed to halothane and caffeine (67, 69, 70).

## **Aeromedical Disposition.**

The aeromedical disposition of each of these military aircrew members was decided by their service's relevant personnel authorities. The authors played a role in providing medical information and recommendations to those authorities. In this section we will attempt to outline our rationale and the data that was available to us as we independantly reached the conclusion that both CAPT Cannuck and OFFCDT Aussie were medically fit to continue their military flying careers.

There is a paucity of literature available to offer guidance in deciding the aeromedical disposition of military aircrew who have suffered exercise rhabdomyolysis and/or who have the Malignant Hyperthermia Trait. We have attempted to piece together what little information is available and where necessary have filled the gaps with (hopefully) educated assumptions.

## **Incidence and Recurrence Risks.**

Rhabdomyolysis is rare in the general population. Exercise Rhabdomyolysis is also rare and is usually seen in males undertaking unaccustomed levels of exercise. Only one case of Exercise Rhabdomyolysis in a woman appears to have been reported (35) which may reflect the differing muscles masses between males and females or some underlying protective factor afforded to females. Exercise Rhabdomyolysis is less rare amongst people identified as having the Malignant Hyperthermia Trait but the degree of this predisposition is not quantified (17, 65, 66, 75, 76).

Acute Renal Failure is not common in the general population but is a regular complication of severe Exercise Rhabdomyolysis (8-46).

Malignant Hyperthermia Trait is rare. MHT occurs in both sexes but with a 3:1 male preponderance. It's population incidence probably lies somewhere between 1 in 10,000 and 1 in 250,000 (63, 72).

The Malignant Hyperthermia Syndrome complicates approximately 1 in 15,000 general anaesthetics (60, 61, 63) and is usually fatal unless treated with Sodium Dantrolene (73). Malignant Hyperthermia Syndrome does not occur on every occasion that a MHT individual undergoes a general anaesthetic using one of the provocative agents (74). One patient has been reported to have had twelve uneventful general anaesthetics before Malignant Hyperthermia Syndrome complicated the thirteenth (74).

CAPT Cannuck's clinical rhabdomyolysis presentation after centrifuge training and subclinical rhabdomyolysis after aerobatic flight suggests that he will suffer some degree of rhabdomyolysis during future high-G flight and possibly other strenuous activities.

OFFCDT Aussie's underlying Malignant Hyperthermia Trait exposes him to an elevated but unquantified risk of rhabdomyolysis recurrence as well as the risk of malignant hyperthermia under various circumstances, most notably general anaesthesia employing inhalational induction agents (halothane et al) and/or depolarizing muscle blocking agents (suxamethonium et al). OFFCDT Aussie's renal failure indicates a more severe form of rhabdomyolysis but having fully resolved is of little further clinical concern.

While it is not well reported it is also possible that MHT individuals have an increased risk of de novo bouts of Malignant Hyperthermia, without preceding general anaesthesia. These bouts may be precipitated by stress and anxiety (62, 68) and could explain the increased incidence of unexplained deaths that has been noted amongst MHT families (71).

### **In-flight considerations.**

Our concerns here are whether the patients' exercise rhabdomyolysis, or underlying cause/precipitant exposes them to an unacceptable risk of in-flight performance impairment sufficient to compromise their safety or effectiveness during routine and emergency air operations.

There are two conceivable circumstances where Malignant Hyperthermia Syndrome (MHS) might occur during military flying: An accident or leakage in the cargo compartment of a transport aircraft carrying medical / anaesthetic supplies or de novo precipitation of MHS through stress or anxiety. The first scenario is exceedingly unlikely. It is not known for sure whether the second scenario is a valid or real concern but if a stress-MHS link does exist (71) the lack of case reports suggests it to be an exceedingly rare cause of MHS induced incapacitation.

Another concern is the risk of a recurrence of Exercise Rhabdomyolysis. The possibility further rhabdomyolysis during flight appears unlikely in the case of OFFCDT Aussie but seems quite likely to occur in CAPT Cannuck whenever high-G manoeuvres are flown.

The physical workload during flight, even the most demanding of air combat manoeuvring, rarely exceeds what would generally be considered as being moderate exertion. Exercise Rhabdomyolysis appears to occur mainly after prolonged or high workload exertion, often during hot weather, in people who are not well trained and acclimatised to the workload or environmental conditions. Maintenance of a high level of fitness, compared to the exertion to be undertaken, and acclimatisation to the conditions is thought to reduce the risk of Exercise Rhabdomyolysis.

Our first case proves to be an exception to these generalities in that the rhabdomyolysis, while mild in severity, occurred after quite moderate physical exertion during G-training and aerobatic flight. While we consider this as being a case of exercise rhabdomyolysis it is also possible that the aetiology of his muscle destruction was direct pressure trauma rather than the exertion.

If Exercise Rhabdomyolysis were to be experienced during a flying mission it is likely to present as a general, possibly progressive feeling of being unwell and is extremely unlikely to have an initial presentation of collapse or other acute incapacitation.

It is possible, but not certain, that air operations in a hot environment, specifically in a hot aircraft might increase the risk of a bout of Exercise Rhabdomyolysis in a susceptible individual.

It is postulated that maintaining a high level of physical fitness, good hydration, and good heat acclimatisation would reduce the risk of Exercise Rhabdomyolysis in a susceptible individual (2, 6, 77, 78).

While we accept that these patients probably have a slightly elevated risk of suffering a future incapacitating event related to rhabdomyolysis or Malignant Hyperthermia Trait we believe this risk is very, very low.

### **On-ground considerations.**

The routine and emergency duties of military aircrew require the maintenance of a reasonable degree of physical fitness and the occasional exposure to moderate - heavy work in a hot environment. Neither of these situations presents a risk for a bout of Malignant Hyperthermia Syndrome but there is probably a small increased risk of Exercise Rhabdomyolysis.

While this is accepted, it should also be noted that aircrew performance is also degraded by fatigue and heat stress and that efforts are constantly being made (airconditioned accommodation, briefing areas, crew vans etc) to reduce aircrew exposure to high physical workload and high thermal workload environments.

The possible on-ground operations of a military pilot have the potential to lead to a bout of Exercise Rhabdomyolysis in susceptible individuals. The probability of this happening is very low. This probability can be reduced by the susceptible individual maintaining a high level of physical fitness, good hydration, and good heat acclimatisation (50) .

As with the in-flight considerations above any further rhabdomyolysis attacks, however unlikely, would probably present as an easily detected gradual deterioration in well being. An acute incapacitation is extremely unlikely.

### **Escape, evasion, and capture.**

Escape, evasion, and capture scenarios have the potential to expose military aircrew to unpredictable and extreme environments under adverse circumstances. Military Combat Survival training attempts to train aircrew to cope with such situations.

Exercise rhabdomyolysis occurs in non Malignant Hyperthermia Trait individuals in sufficiently hot, physically demanding environments. It is possible that susceptible, Malignant Hyperthermia Trait, individuals have an increased chance of Exercise Rhabdomyolysis in such adverse circumstances.

There is the possibility of exposure to a variety of psychoactive drugs during interrogation procedures. Many drugs have been reported as producing rhabdomyolysis (15, 26, 32, 34, 37, 49, 79-84). Exposure to certain anaesthetic agents could precipitate Malignant Hyperthermia Syndrome in a MHT individual (see below).

Physical trauma and torture can also lead to rhabdomyolysis (16, 29, 85). No data could be found discussing the risk of Malignant Hyperpyrexia Trait individuals suffering rhabdomyolysis upon receipt of physical trauma.

### **Emergency and elective anaesthesia.**

Individuals with MHT are much more likely to suffer Malignant Hyperthermia Syndrome during an anaesthetic where volatile anaesthetic agents (including halothane, enflurane, and isoflurane) and/or depolarising muscle relaxants (suxamethonium, suxethonium, and decamethonium) are used. It is, however, possible for a MHT individual to undergo many general anaesthetics, employing these agents, without suffering MHS (74, 86).

Prior to the use of Sodium Dantrolene the mortality rate for anaesthetic induced MHS was approximately 80% (64, 73). Now that Dantrolene is available and anaesthetists are more aware of Malignant Hyperthermia the mortality has dropped to approximately 20% (64, 73). There may also be a role for Dantrolene usage in a prophylactic manner to prevent MHS in at-risk anaesthetics (87).

While an anaesthetic using either the volatile agents or the depolarising muscle relaxants is potentially fatal for a MHT individual a wide variety of anaesthetic agents can be employed without the risk of

MHS. These agents include all of the narcotics, all non-depolarising muscle relaxants, all local anaesthetic agents, nitrous oxide, and adrenaline (88). No deaths from Malignant Hyperthermia Syndrome have occurred in previously diagnosed individuals when the anaesthetics team have been aware of their malignant Hyperthermia Trait (64).

Given the range of drugs that can be used, with relative safety, for anaesthetising an MHT individual there is no reason that elective, or emergency, anaesthesia cannot be provided to military aircrew with MHT should the need arise. It is imperative that any MHT individual's medical documents be clearly marked and that some form of permanent record (eg. a MedicAlert bracelet, neckchain, or similar) be worn by the patient. It has been suggested, in jest but not without some validity, that MHT individuals might consider having a tattoo on their chest or arm to advise possible future emergency anaesthetists of their condition.

While an elective or emergency anaesthetic is possible in an MHT individual it is not without risk. In the emergency situation anaesthetic induction and intubation, using non-depolarising muscle relaxants, presents the anaesthetists with a higher risk of regurgitation and inhalation of vomitus. This is primarily due to the slower onset of action of the non-depolarising muscle relaxants.

Should an inappropriate anaesthetic be given to a MHT individual and an episode of MHS be triggered it is possible to treat the latter condition with Sodium Dantrolene. However Dantrolene does not have good storage characteristics and is not likely to be held by every military medical facility at all times.

### **Conclusion.**

These medical conditions presents military personnel managers with a number of difficult considerations. The medical conditions are rare and not thoroughly understood. The medical conditions have the potential to cause any of several dramatic complications although this is very unlikely.

It was our belief that both OFFCDT Aussie's and CAPT Cannuck's medical conditions were compatible with all of the flying duties of a military pilot. We agreed that there was a risk of a recurrence of Rhabdomyolysis or another complication of Malignant Hyperthermia Trait and that such an event has the potential to lead to acute incapacitation. The chances of such a complication occurring are extremely low and if it did occur the chances of it actually resulting in an acute incapacitation are also very low. The overall probability of an acutely incapacitating complication of his condition during military flight is, in our opinion, infinitesimally low.

We acknowledge that there are probably higher risks attached to OFFCDT Aussie's non-flying duties of a military pilot (On-ground operations; escape, evasion, and capture; emergency and elective anaesthesia.) than to his flying duties. He is probably at risk of a recurrence of Rhabdomyolysis during heavy work in a hot environment, during escape and evasion, or during rigorous physical

interrogation. There is probably a low - very low chance of such a Rhabdomyolysis relapse. This risk can probably be further reduced through the maintenance of a high level of physical fitness and heat acclimatisation. He is at risk of Malignant Hyperthermia Syndrome if administered an inappropriate anaesthetic agent. The chances of such an inappropriate agent being given are very low while the chances of him being afflicted are probably moderate.

We have no data to suggest that CAPT Cannuck has any higher risk during non-flying duties than during flying duties.

It is also possible that OFFCDT Aussie could suffer a mild bout of Malignant Hyperthermia syndrome precipitated by stress or anxiety. This relationship is postulated in the literature but far from confirmed. The chances of this occurring are felt to be extremely low.

OFFCDT Aussie's condition presents an unusual situation where we believe he has less of a risk of problems during military flight than during some of the non-flight aspects of his military duties. The risks of problems are all quite low but some of the sequelae are potentially quite dramatic, including death.

CAPT Cannuck's history suggests that he is probably at risk primarily as a result of flying duties but that risk is also extremely low.

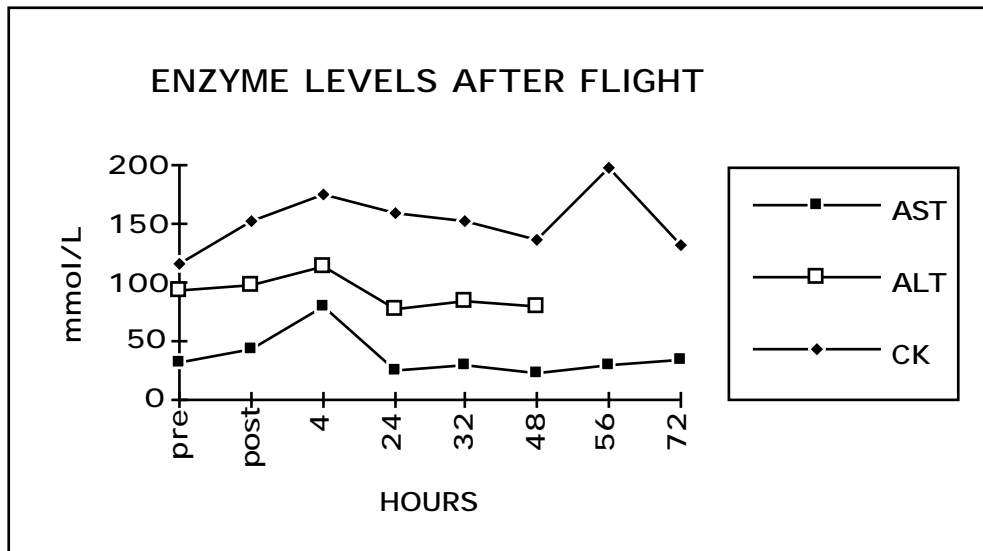
We recognise that our conclusions and recommendations concerning these two military pilots will not receive universal support amongst our military aeromedical colleagues. Our respective Armed Forces have chosen to accept the risks as we have outlined them. Time and experience will be the final arbiters.

### **Acknowledgements & Disclaimers.**

The opinions expressed in this article are those of the authors and should in no way be construed as reflecting the opinion or policy of either the Australian Defence Force, the Canadian Forces, or any other institution or agency. The authors acknowledge and appreciate the support provided by Ms Kaaren Sephton in the library at the RAAF Institute of Aviation Medicine in performing the extensive literature searches required and obtaining the many papers reviewed.

**Tables, Figures, and Illustrations.**

**Figure 1.**  
**CAPT Cannuck: Post aerobic flight enzyme levels.**



**Table 1.**

**CAPT Cannuck: Muscle enzyme levels before and after a test centrifuge exposure.**

	CONTROL	POST-FLIGHT	24 HOURS
AST (N = 10-40)	53	59	64
ALT (N = 6-37)	158	149	111
CK (N = 45-240)	253	294	2903
GGT (N = 11-63)	22	22	21
LDH (N = 14-210)	136	157	174

Table 1. Enzyme levels (U/L) pre- and post- test centrifuge exposure

**Table 2.**  
**Selected non-exercise causes of rhabdomyolysis.**  
 (After Rowland(3))

**Idiopathic causes.**

**Hereditary causes**

**Enzyme Abnormality known.**

Metabolic Myopathies.

- Carnitine Palmitoyl Transferase Deficiency(3, 89-95).
- Phosphoglycerate Kinase Deficiency(3, 96).
- Phosphoglycerate Mutase Deficiency(3, 97).
- Very Long-chain Acyl Coenzyme A Dehydrogenase Deficiency (98).
- Lactate Dehydrogenase-A Deficiency (3, 78, 99-101).
- Aldolase-A deficiency.
- Myoadenylate Deaminase Deficiency (102).
- Calcium adenosine triphosphate deficiency (103).

Glycogen storage diseases.

- Type II - Acid maltase Deficiency.
- Type III - Debranching Enzyme Deficiency.
- Type V - Myophosphorylase Deficiency (McArdle's) (3, 24, 30, 31, 104-107).
- Type VII - Phosphofructokinase Deficiency (Tarui-Layzer) (3, 104, 105).

**Enzyme defect incompletely characterized.**

- Excess lactate production (3).
- Impaired fatty acid oxidation(?) (3, 108).
- Malignant Hyperthermia/Hyperpyrexia (Impaired function of sarcoplasmic reticulum?) (17, 65, 66, 68, 70, 75, 109, 110).

**Enzyme abnormality uncharacterized.**

- Familial, biochemical abnormality unknown(3).
- Repeated attacks in an individual(3).
- Periodic paralysis.
- Paroxysmal myoglobinuria.
- Associated with stunted growth(111).

**Sporadic / Acquired causes.**

**Exertion**

See Table 3

**Crush and External Trauma.**

- Compression by fallen weights (16).
- Compression by body in prolonged coma.
- Blunt trauma.
- Physical torture (29).

**Ischaemic.**

- Occlusion of major artery.
- Ischaemia in compression or anterior tibial syndromes.
- Coagulopathy in Sickle Cell Disease(27, 46, 112-120).
- Disseminated Intravascular Coagulation.
- Ligation of Vena Cava.

**Metabolic Depression or Distortion.**

- Diabetic ketoacidosis.
- Nonketotic hyperglycaemia hyperosmolar states.

- Hypothyroidism (39, 121).
- Hypo-oestrogenaemia (122).
- Carbon Monoxide (See Drugs and Toxins).
- Barbiturates (See Drugs and Toxins).
- Narcotics (See Drugs and Toxins).
- Renal Tubular Acidosis.

**Electrolyte Imbalances.**

- Hyponatraemia (123, 124).
- Hypernatraemia.
- Hypokalaemia(50).
- Hypophosphataemia.

**Drugs and Toxins.**

Non-prescription drugs.

- Cocaine (32, 34, 79, 125-128).
- Heroin (26, 80).
- Amphetamines (37, 81).
- Alcohol (49, 83, 129-132).

Prescribed medications.

- Anaesthetic Agents(17, 65, 66, 68, 70, 75, 109, 110).
- Barbiturates.
- Phencyclidine(128, 133).
- Muscle Relaxants(17, 65, 66, 68, 70, 75, 109, 110, 134).
- Neuroleptic agents (82, 135) & possibly (136, 137).
- Vasopressin (15).
- Lovastatin & Gemfibrozil (138).
- Cytotoxic agents (139-141).
- Anti-HIV agents (142, 143).
- Carbimazole (144).
- And many more(3).

Envenomations .

- Insects.
- Spiders(145).
- Snakes(146, 147).

Other Agents.

- Carbon Monoxide (28).

**Abnormalities of Body Temperature.**

Hypothermia

- Cold exposure.
- Hypothyroidism.

Fever.

- Tetanus Toxin.
- Thyroid vaccine.
- Heat injury: Heat Cramps, Heat Exhaustion, Heat Stroke.
- Malignant Hyperthermia.
- Malignant Neuroleptic Syndrome.

**Infections.**

Bacterial.

- Staphylococcal Pyomyositis (148).
- Pneumococcal pneumonia(149).
- Typhoid Fever.
- E. Coli sepsis.

Viral.

Influenza virus(66, 150-152).  
Parainfluenza virus(50).  
Adenovirus.  
Enterovirus(153).  
Epstein-Barr Virus(154).  
Herpes Virus(155).  
Coxsackie Virus(3).  
Human Immunodeficiency Virus (156-158).

Parasitic.

Trichinosis(50).

Fungal.

Candida kruseii fungaemia (159).

Other Organisms.

Legionnaire's Disease(160).  
Mycoplasma(161).  
Toxic Shock Syndrome(162).

**Progressive Muscle Disease.**

Polymyositis.  
Dermatomyositis.

**Haematological.**

Sickle Cell Trait or Syndrome (See Ischaemic above).

**Table 3.**  
**Some exertional causes of rhabdomyolysis.**

Recreational exercise(163).	Swimming (183).
Endurance running (6, 13, 50, 164-166).	Football (184).
Triathlons (164).	Body building / Weight lifting (4, 6, 172, 185).
Conga drumming (167).	Rowing(186).
Karate kicking (168).	Skiing(187).
Mechanical bull riding (169).	Basketball(47).
Knee bends / Squats (5, 6).	Electrocution (85, 188).
Abdominal exercise (170-172).	Struggling against restraints(105, 189, 190).
Upper body exercise (6, 53, 172, 173).	<b><u>The bizarre or unusual.</u></b>
Judo (122, 174).	Sauna (4).
Military & paramilitary training (41, 52-56, 175-179).	Chess (5).
Cycling (180).	Dominoes (6).
Convulsions (110, 124, 181) (136, 137).	
Status asthmaticus(182).	

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**GDUNCAT, 2FTS.**

A1-G1-Z1

**17 / 18. Medical conditions, complications, and date of injury or onset.**

Malignant Hyperthermia Trait	Since birth
Exercise Rhabdomyolysis	04 June 1996
Acute Renal Failure	09 June 1996

**19. History.**

On 04 June 1996 XXXXXXXXX suffered a bout of Exercise Rhabdomyolysis during his first day at No 275 COMSURV CSE at CSTS. His rhabdomyolysis was complicated by acute tubular necrosis and acute renal failure which required renal dialysis (five treatments).

He has no relevant past medical history or family medical history. He has, on two occasions, undergone general anaesthesia without complication.

Possible causes of his rhabdomyolysis were sought and he was found to have a susceptibility to Malignant Hyperthermia (Malignant Hyperthermia Trait), but no susceptibility to Sickle Cell Anaemia (Sickle Cell Anaemia Trait). No other abnormalities of his muscle metabolism were identified during the further investigations.

Whilst at 2FTS XXXXXXXXX has been involved in physical activities in hot weather. He has had no problems with these activities and there was no suggestion of any recurrence of his Rhabdomyolysis.

Annex A is an in-depth discussion of his condition, its aeromedical implications, and the considerations of this CAMFB.

**20. Functional disabilities.**

XXXXXXXXXX has no functional disabilities.

**21. Prognosis.**

XXXXXXXXXX's Malignant Hyperthermia Trait is permanent and static. He is at risk of malignant hyperthermia if given an inappropriate general anaesthetic agent. He may be at risk of further bouts of exercise rhabdomyolysis.

His bout of rhabdomyolysis, and its complicating renal failure, has concluded and leaves him without impairment or impediment.

**22 / 23. Restrictions recommended and expected duration**

<b>AIR</b>		A1	Permanent
			To always wear MedicAlert bracelet or similar device.
<b>GROUND</b>	G1	Permanent	

ZONAL

Z1

Permanent

**24. Current duties and general comments.**

XXXXXXXXXX is currently undertaking flying training with 2FTS.

**25. Compensation.**

No.

## **CAMFB DELIBERATIONS: XXXXXXXXX.**

This Central Aircrew Medical Fitness Board (CAMFB) sat to consider the impact of XXXXXXXXX's medical conditions (Malignant Hyperpyrexia Trait, Exercise Rhabdomyolysis, and Acute Renal Failure) upon his fitness to continue his intended career as an RAAF pilot. Some of the medical conditions under consideration here are rare and poorly understood. The Officers of this CAMFB found these deliberations difficult and complex. This document is an attempt to present our reasoning and the information we used to reach our conclusions. The rarity of the conditions and the complexity of the issues necessitates a lengthy explanation.

Where the numerical risk, incidence, and probability information is known it is provided herein and referenced. Because we are considering rare diseases precise numerical data is not always available. Where precise numerical data cannot be obtained a word picture has been used to describe risk, incidence, and probability functions (eg. extremely rare, highly probably etc). While the word picture data should be interpreted as being both general and uncertain, it is based on the CAMFB members' medical training, understanding of RAAF aircrew requirements, and background reading on the topics under consideration.

### **The conditions.**

The medical conditions to be considered here are Exercise Rhabdomyolysis, Malignant Hyperthermia Trait, and Acute Renal Failure.

Rhabdomyolysis is the breakdown of skeletal muscle cells with the liberation of their contents into the circulation (1, 2). Rhabdomyolysis ranges in degree from an asymptomatic detection of muscle breakdown products in the blood through to a severe, life threatening, condition involving collapse, hyperkalaemia, metabolic acidosis, hypocalcaemia, renal failure, compartment syndromes, and disseminated intravascular coagulation. There are many conditions that either cause or predispose to rhabdomyolysis although the most common precipitant of life threatening rhabdomyolysis is probably physical exercise(2).

Exercise rhabdomyolysis is, as the name implies, the breakdown of skeletal muscle cells and the release of their contents into the circulation as a result of physical exercise. Many forms of exertion have been described as leading to Exercise Rhabdomyolysis.

The skeletal muscle breakdown of rhabdomyolysis results in the release of many different products into the circulation. The most commonly measured of these breakdown products are the Creatine Phosphokinase enzyme (skeletal muscle subtype) and the Myoglobin protein.

Acute renal failure is often a complication of the more severe cases of exercise rhabdomyolysis. The renal failure is usually a result of acute tubular necrosis and is probably caused by direct myoglobin toxicity on the renal tubules of the dehydrated, acidotic individual.

Malignant Hyperthermia (also called Malignant Hyperpyrexia) is a condition that occasionally complicates general anaesthesia in some susceptible individuals. The Malignant Hyperthermia syndrome is characterised by temperature elevation, muscle rigidity, systemic acidosis, muscle breakdown (rhabdomyolysis), and cardiac arrhythmia's, and often results in death (3). The precipitation of the Malignant Hyperthermia syndrome is caused by exposure to inhalation anaesthetic agents (eg. halothane, enflurane, & isoflurane) and / or depolarising muscle relaxants (eg. suxamethonium, suxethonium, & decamethonium).

Individuals susceptible to Malignant Hyperthermia are considered as having the Malignant Hyperpyrexia Trait (MHT) and are usually identified through their suffering Malignant Hyperpyrexia as an anaesthetic complication, their having a family history of such anaesthetic complications, or the occurrence of associated phenomena such as exercise rhabdomyolysis. The diagnosis of MHT is made through an in vitro contraction test of a biopsy sample of muscle exposed to halothane and caffeine.

While it is not well reported it is also possible that MHT individuals have an increased risk of de novo bouts of Malignant Hyperthermia, without preceding general anaesthesia. These bouts may be precipitated by stress and anxiety (4, 5) and could explain the increased incidence of unexplained deaths that has been noted amongst MHT families (6).

### **Incidences and statistics.**

Malignant Hyperthermia Trait is rare. MHT occurs in both sexes but with a 3:1 male preponderance. It's population incidence probably lies somewhere between 1 in 10,000 and 1 in 250,000 (7, 8).

The Malignant Hyperthermia Syndrome complicates approximately 1 in 15,000 general anaesthetics(7, 9, 10) and is usually fatal unless treated with Sodium Dantrolene (11). Malignant Hyperthermia Syndrome does not occur on every occasion that a MHT individual undergoes a general anaesthetic using one of the provocative agents (12). One patient has been reported to have had twelve uneventful general anaesthetics before Malignant Hyperthermia Syndrome complicated the thirteenth (12, 13).

Rhabdomyolysis is rare in the general population. Exercise Rhabdomyolysis is also rare and is usually seen in males undertaking unaccustomed levels of exercise. Only one case of Exercise Rhabdomyolysis in a woman appears to have been reported (14). Exercise Rhabdomyolysis is less rare amongst people identified as having the Malignant Hyperthermia Trait but the degree of this predisposition is unknown.

Acute Renal Failure is not common in the general population but is a regular complication of severe Exercise Rhabdomyolysis.

### **Terms of Reference.**

XXXXXXXXX experienced Acute Renal Failure as a complication of Exercise Rhabdomyolysis which was, in turn, largely a complication of his having the Malignant Hyperthermia Trait. While both his Acute Renal Failure and Exercise Rhabdomyolysis are important medical conditions they have been successfully managed and leave him with no adverse sequelae.

The prime concern of the subsequent discussion in this CAMFB will be his Malignant Hyperpyrexia Trait because it is both a permanent condition and it is the underlying cause of his Exercise Rhabdomyolysis and Acute Renal Failure.

### **Military Aeromedical Disposition.**

This CAMFB considered a number of issues in reaching our final recommendations. These considerations included:

- In-flight incapacitation during routine and emergency operations;
- On-ground incapacitation during routine and emergency operations;
- Escape, evasion, and capture;
- Emergency and elective anaesthesia.

## **In-flight considerations.**

Our concerns here are whether XXXXXXXX's Malignant Hyperthermia Trait exposes him, or the RAAF, to an unacceptable risk of in-flight performance impairment that would compromise operational safety or effectiveness.

There are two circumstances where Malignant Hyperthermia Syndrome (MHS) might occur during RAAF flying: An accident or leakage in the cargo compartment of a transport aircraft carrying medical / anaesthetic supplies or de novo precipitation of MHS through stress or anxiety. The first scenario is exceedingly unlikely. It is not known for sure whether the second scenario is a valid or real concern but if a stress - MHS link does exist it is a very rare cause of MHS induced incapacitation.

Another concern is the risk of a recurrence of Exercise Rhabdomyolysis. The possibility of another bout of rhabdomyolysis during flight is highly unlikely but the possibility requires consideration.

The physical workload during flight, even the most demanding of air combat manoeuvring, rarely exceeds what would generally be considered moderate exertion. Exercise Rhabdomyolysis appears to occur mainly after prolonged or high workload exertion, often during hot weather, in people who are not well trained and acclimatised. Maintenance of a high level of fitness, compared to the exertion to be undertaken, and acclimatisation to the conditions reduces the risk of Exercise Rhabdomyolysis.

If Exercise Rhabdomyolysis were to be experienced during a flying mission it is likely to present as a general, possibly progressive feeling of being unwell and is extremely unlikely to have an initial presentation of collapse or other acute incapacitation.

The Canadian Forces had a recent experience with a case of Exercise Rhabdomyolysis suffered by an aircrew member during high-G centrifuge training (15). This pilot suffered a moderate degree of rhabdomyolysis, without complicating renal failure, that caused him to present after completion of the centrifuge run. He was subsequently returned to full flying status (Flying Tutor jets, similar to the RAAF's Macchis) and has experienced no problems during the subsequent 2 years.

It is possible, but not certain, that air operations in a hot environment, specifically in a hot aircraft might increase the risk of a bout of Exercise Rhabdomyolysis in a susceptible individual.

It is likely that maintaining a high level of physical fitness, good hydration, and good heat acclimatisation would reduce the risk of Exercise Rhabdomyolysis in a susceptible individual.

There are no other known adverse interactions between Malignant Hyperpyrexia Trait and any other aspects of military flying.

## **On-ground considerations.**

The routine and emergency duties of RAAF aircrew require the maintenance of a reasonable degree of physical fitness and the occasional exposure to moderate - heavy work in a hot environment. Neither of these situations presents a risk for a bout of Malignant Hyperthermia Syndrome but there is probably a small increased risk of Exercise Rhabdomyolysis.

While this is accepted, it should also be noted that aircrew performance is degraded by fatigue and heat stress and that efforts are constantly being made (airconditioned accommodation, briefing areas, crew vans etc) to reduce aircrew exposure to high physical workload and high thermal workload environments.

The possible on-ground operations of an RAAF pilot have the potential to lead to a bout of Exercise Rhabdomyolysis in susceptible individuals. The probability of this happening is very low. This probability can be reduced by the susceptible individual maintaining a high level of physical fitness, good hydration, and good heat acclimatisation.

As with the in-flight considerations above any further rhabdomyolysis attacks, however unlikely, would probably present as an easily detected gradual deterioration in well being. An acute incapacitation is extremely unlikely.

### **Escape, evasion, and capture.**

Escape, evasion, and capture scenarios have the potential to expose military aircrew to unpredictable and extreme environments under adverse circumstances. RAAF Combat Survival training attempts to train aircrew to cope with such situations.

Exercise rhabdomyolysis occurs in non Malignant Hyperthermia Trait individuals in sufficiently hot, physically demanding environments. It is probable that susceptible, Malignant Hyperthermia Trait, individuals have an increased chance of Exercise Rhabdomyolysis in such adverse circumstances.

There is the potential for exposure to a variety of psychoactive drugs during interrogation procedures. Many drugs have been reported as producing rhabdomyolysis (16-27). There is no data or suggestion that Malignant Hyperpyrexia Trait individuals are more likely to suffer rhabdomyolysis upon drug exposure. Exposure to certain anaesthetic agents could precipitate Malignant Hyperthermia Syndrome in a MHT individual (see below).

Physical trauma and torture produce rhabdomyolysis (28-30). There is no data or suggestion that Malignant Hyperpyrexia Trait individuals are more likely to suffer rhabdomyolysis upon receipt of physical trauma.

### **Emergency and elective anaesthesia.**

Individuals with MHT are much more likely to suffer Malignant Hyperthermia Syndrome during an anaesthetic where volatile anaesthetic agents (including halothane, enflurane, and isoflurane) and/or depolarising muscle relaxants (suxamethonium, suxethonium, and decamethonium) are used. It is, however, possible for a MHT individual to undergo many general anaesthetics, employing these agents, without suffering MHS (12, 13).

Prior to the use of Sodium Dantrolene the mortality rate for anaesthetic induced MHS was approximately 80% (3, 11). Now that Dantrolene is available and anaesthetists are more aware of Malignant Hyperthermia the mortality has dropped to approximately 20% (3, 11). There may also be a role for Dantrolene usage in a prophylactic manner to prevent MHS in at-risk anaesthetics (31).

While an anaesthetic using either the volatile agents or the depolarising muscle relaxants is potentially fatal for a MHT individual a wide variety of anaesthetic agents can be employed without the risk of MHS. These agents include all of the narcotics, all non-depolarising muscle relaxants, all local anaesthetic agents, nitrous oxide, and adrenaline (32). No deaths from Malignant Hyperthermia Syndrome have occurred in previously diagnosed individuals when the anaesthetics team have been aware of their malignant Hyperthermia Trait (3).

Given the range of drugs that can be used, with relative safety, for anaesthetising an MHT individual there is no reason that elective, or emergency, anaesthesia cannot be provided to XXXXXXXX should the need arise. It is imperative that any MHT individual's medical documents be clearly marked and that some form of permanent record (eg. a MedicAlert bracelet or neckchain) be worn by the patient. It has been suggested, in jest but not without some validity, that MHT individuals might consider having a tattoo on their chest or arm to advise possible future emergency anaesthetists of their condition.

While an elective or emergency anaesthetic is possible in an MHT individual it is not without risk. In the emergency situation anaesthetic induction and intubation, using non-depolarising muscle relaxants, presents the anaesthetists with a higher risk of regurgitation and inhalation of vomitus. This is primarily due to the slower onset of action of the non-depolarising muscle relaxants.

Should an inappropriate anaesthetic be given to a MHT individual and an episode of MHS be triggered it is possible to treat the latter condition with Sodium Dantrolene. However Dantrolene does not have good storage characteristics and is not likely to be held by every ADF medical facility at all times.

### **Discussion.**

XXXXXXXXXX's medical condition presents this CAMFB with a number of difficult considerations. His medical condition is rare and not thoroughly understood. His medical condition has the potential to afflict him with any of several dramatic complications although this is very unlikely.

This CAMFB believes that XXXXXXXXXX's medical condition is compatible with all of the flying duties of a military pilot. We accept that there is a risk of a recurrence of Rhabdomyolysis or another complication of his Malignant Hyperthermia Trait and that such an event has the potential to lead to acute incapacitation. The chances of such a complication occurring are extremely low and if it did occur the chances of it actually resulting in an acute incapacitation are also very low. The overall probability of an acutely incapacitating complication of his condition during military flight is, in the opinion of this CAMFB, infinitesimally low.

This CAMFB acknowledges that there are probably higher risks attached to XXXXXXXXXX's non-flying duties of a military pilot (On-ground operations; escape, evasion, and capture; emergency and elective anaesthesia.) than to his flying duties. He is probably at risk of a recurrence of Rhabdomyolysis during heavy work in a hot environment, during escape and evasion, or during rigorous physical interrogation. There is probably a low - very low chance of such a Rhabdomyolysis relapse. This risk can probably be further reduced through the maintenance of a high level of physical fitness and heat acclimatisation. He is at risk of Malignant Hyperthermia Syndrome if administered an inappropriate anaesthetic agent. The chances of such an inappropriate agent being given are very low while the chances of him being afflicted are probably moderate.

It is also possible that he could suffer a mild bout of Malignant Hyperthermia syndrome precipitated by stress or anxiety. This relationship is postulated in the literature but far from confirmed. The chances of this occurring are felt to be extremely low.

XXXXXXXXXX's condition presents an unusual situation where this CAMFB believes he has less of a risk of problems during military flight than during some of the non-flight aspects of his duties. The risks of problems are all quite low but some of the sequelae are potentially quite dramatic, including death.

### **Recommendations.**

This CAMFB recommends that:

XXXXXXXXXX is fully fit for all military flying (A1).

XXXXXXXXXX is fit for all ground duties associated with being a military pilot (G1). This recommendation assumes that the risks of complications and their sequelae, as discussed above, is acceptable to the ESC. If these risks are not acceptable XXXXXXXXXX is probably Medically Unfit For Further Service.

XXXXXXXXXX requires no zonal restrictions (Z1).

XXXXXXXXXX should, at all times, wear some device suitable to advise medical carers of his Malignant Hyperthermia Trait (eg. MedicAlert bracelet or neckchain).

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