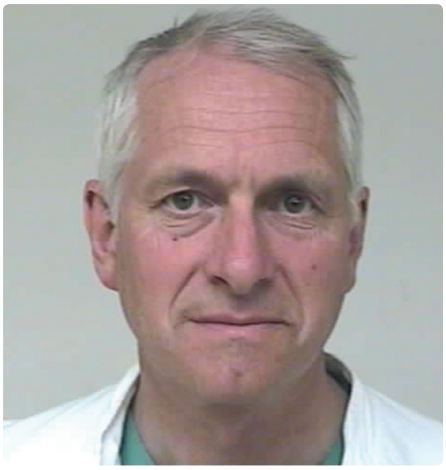
# Caring for cold hearts



**Professor Torkjel Tveita**'s experiments and experience with accidental and induced hypothermia highlight the need for adjusted approaches to treatment of heart failure patients with low internal body temperatures



**Your group has spent almost two decades conducting experimental research on accidental hypothermia. What types of work have you carried out during this time?**

Primarily we have conducted preclinical work, that is, studies using intact experimental animals and *in vitro* organ and cellular models, aimed at elucidating pathophysiologic factors related to 'rewarming shock' or 'rewarming collapse', which may appear during or after rewarming accidental hypothermia patients. From our experimental studies, we have defined 'hypothermia-induced acute heart failure' which is an important contributing factor to circulatory dysfunction which can end in circulatory collapse during or after rewarming from experimental hypothermia.

**Could you explain the term 'rewarming shock'?**

Rewarming shock is an ill-defined clinical term for a feared complication of circulatory dysfunction during rewarming with high mortality – 80 per cent. The exact cause remains unknown, but from our research we have detected pathophysiology in the heart – hypothermia-induced acute heart failure – as well as in the peripheral vasculature, particularly the capillaries.

We have discovered that calcium ions, which are essential to make heart muscle cells contract during a heartbeat, accumulate during hypothermia, inducing calcium overload, and this essentially explains life-threatening cardiac dysfunction during rewarming.

**What specific aspects of hypothermia are you investigating at the moment?**

In recent years, we have realised more and more that our research is relevant to challenges met when applying hypothermia therapeutically. Over the last decade, induced therapeutic hypothermia has been increasingly used to reduce cerebral damage in patients after resuscitation from sudden cardiac arrest. However, after return of spontaneous circulation (ROSC), these patients often suffer from acute heart failure and need inotropic cardiac support to resume adequate circulatory function after hypothermia where core temperature has been deliberately lowered to 32-34 ºC and maintained for 24-48 hours.

With great interest, we learned that after resuscitation and coronary stenting, more than 50 per cent of survivors suffer acute heart failure and need pharmacological intervention to elevate blood pressure and support heart function. At 37 ˚C, these drugs appear effective in elevating heart function and blood pressure to improve organ perfusion, but written guidelines for such pharmacologic interventions at reduced core temperatures are missing.

**Have your studies performing extended cardiopulmonary resuscitation (CPR) on a hypothermic pig model revealed any findings?**

From clinical work we have experienced patient survival after pre-hospital CPR in accidental hypothermia victims with cardiac arrest performed for up to six hours; and resuscitation from accidental hypothermia of 13.7 ˚C with circulatory arrest. This is essentially in contrast to the limited time of effective CPR in normothermic cardiac arrest patients.

Therefore, in ongoing studies using an intact pig model of hypothermia-induced cardiac arrest at 25 ˚C, we have been investigating oxygen transport and organ blood flow during prolonged CPR. Preliminary results indicate that CPR provides oxygen transport which is close to 100 per cent of that during spontaneous circulation at the same temperature. This contrasts with the 30 per cent of spontaneous oxygen transport during optimal CPR in patients with 37 ˚C core temperature, which also explains the limited 'window of therapy' for CPR during normothermia. Therefore our hypothesis is that due to hypothermia-induced reduction in metabolism in hypothermic patients, adequate CPR performed on these patients is more sufficient than in patients at normal core temperatures.

**Why are the effects of drugs such as adrenaline significantly diminished when used on patients with hypothermia?**

Relatively few studies have explored the pharmacologic effects of adrenaline treatment during hypothermia.

Studies on the effects of adrenaline used to convert hypothermic cardiac arrest to ROSC during CPR in pigs show diverse effects. In clinical practice it is recognised that in the acutely failing heart, postoperatively or after resuscitations in patients with normal body core temperature, only drugs such as adrenaline support heart function and blood pressure. In our lab we found that adrenaline, if given in doses that support heart function without elevating blood pressure during normothermia, gave rise to a significant increase in blood pressure but failed to support heart function when given during hypothermia.

In a situation like this, adrenaline will increase the burden of the failing heart; that is, the failing hart will have to fight an elevated blood pressure, in addition to dealing with other challenges, to support the organs' gradually increasing need for more and more oxygen as temperature rises during rewarming.

# A framework for hypothermia treatment

Investigations into the cellular and physiological processes responsible for the high risk of mortality during resuscitation after hypothermia at the **University of Tromsø** have identified safer procedures for medical practice

**IN COLD WEATHER** or in cold water, when a person's internal body temperature cools rapidly from the norm of 37 ºC to below 35 ºC, hypothermia sets in and brings about progressive loss of mental and physical function; left untreated, it can lead to heart and respiratory failure and, ultimately, death. Someone with hypothermia is usually unaware of the danger they are in, as sleepiness, apathy and confusion grow. If their core temperature drops below 28 ºC, cardiac arrest follows.

Hypothermia is sometimes induced in patients undergoing heart surgery, to prevent heart failure and to increase chances of survival and improve neurological outcomes. It is also used on patients in a coma after cardiac arrest. When the supply of oxygen to brain tissue is reduced, brain function can be maintained for longer at lower temperatures than normal. In such cases and in accidental hypothermia where heart failure is indicated, adrenaline is administered to increase heart function and improve oxygen transport by the blood. However, adrenalin's efficacy is temperature-dependent; at low temperatures, its side-effects become dominant: it raises the blood pressure but does not improve heart function to the same degree as in patients with normal body temperatures.

In the event of a major disaster, such as an aeroplane crash or shipping accident, where many people are suddenly plunged into cold water or exposed to very cold weather, there is a need for emergency services from widespread medical facilities to attend. Generally, the treatment for hypothermia is warming of the trunk of the body and administration of drugs, such as adrenaline, to restart the heart. In many cases, however, if hypothermia is severe, the chances of full recovery are slight. It is only if the attending emergency medical staff are properly aware of the need for gentle and careful rewarming, and the limitations of conventional techniques, that the outcomes of such interventions will be consistently successful. However, at present there is no general guidance available in Norway.

To address this gap, Professor Torkjel Tveita, Chair of the Anesthesic and Critical Care Research group at the University of Tromsø, which includes the University Hospital of North Norway, was recently given a mandate to develop regional health authority guidelines for the treatment of accidental hypothermia. In addition, he and his team are about to take on the task of writing national guidelines for the rescue and treatment of hypothermia patients, in close collaboration with the Norwegian Directorate of Health and the other national University Hospitals.

## FIRST FINDINGS

Tveita's research group has investigated the processes in hypothermia that lead to heart failure and fatality for more than 15 years. Their focus is on the treatment of hypothermia en route to hospital and then in the hospital setting, combining preclinical experiments and clinical procedures: "We investigate changes in physiological function and systems in the circulatory system induced by hypothermia which have major consequences for resuscitation and survival during and after rewarming," he explains.

Research is carried out under the heading of 'Arctic Physiology and Medicine'. This encompasses three main themes: hypothermia and medicine, occupational health and comparative medicine, and is directed to the challenges arising from expanding activity in the Arctic region in the forms of tourism and oil, shipping, aquaculture and fisheries enterprises.

Tveita's experience of clinical practice and his experimental hypothermia and rewarming research, especially studies of the effects of cardiopulmonary resuscitation (CPR) on oxygen transport in the blood during hypothermia, place him in a uniquely qualified position to come up with the Norwegian recommendations and guidelines for pharmacological treatment of patients at low core temperatures. Tveita and his group have found that the heart cells suffer from an overload of calcium on prolonged exposure to hypothermia which then damages the mitochondria in particular. The effect is a negative impact on circulation, which adds to the risk of heart failure during patient rewarming. They have also found that signalling within heart cells is disrupted, which then impedes the ability of the heart to beat; and that the immune system also begins to attack the damaged heart cells.

Interestingly, the research has also revealed that if circulation is supported blood haemoglobin continues to transport and upload oxygen even

during deep hypothermia. This is a key finding, as it means that CPR performed even at very low body temperatures is likely to succeed. In fact, Tveita is certain that CPR should be performed for a greatly extended period of time (hours), during the transport of a patient to hospital and then the patient should be connected to a heart/lung machine during rewarming at the hospital: "Findings from our experiments will have great impact on the recommendations and guidelines for treatment of accidental hypothermic patients," he muses.

## MODEL PATIENTS

For experiments related to hypothermia and rewarming based on water immersion, as well as core cooling and rewarming, Tveita's group has established animal models based on the pig. One of these allows his group to study the effects of extracorporeal circulation using a heart/lung machine during body rewarming. Involving 3-5 hours of CPR on pigs with a core body temperature of 25 ºC, the researchers aim to discover how well chest compressions transport oxygen to the organs and cells in the body; afterwards, the pigs are rewarmed following the same sort of procedures found in an operating theatre for humans: "Our models of experimental hypothermia and rewarming often display great similarities with aspects of rewarming shock in patients," Tveita elucidates.

The University Hospital of North Norway holds the record for successful rewarming of a human patient from the lowest body core temperature ever recorded. He attributes their success to procedural measures: "We think that prolonged pre-hospital CPR and 'careful' bypass rewarming were two important factors".

The researchers are currently in the process of applying to the Norwegian health authorities for permission to initiate research investigating the effects of drugs given to support heart function in patients treated with therapeutic hypothermia after the return of spontaneous circulation in intensive care.

## PRODUCTIVE PARTNERSHIP

Since 2004, Tveita and his group have worked closely with Dr Gary C Sieck from the Department of Physiology and Biomedical Engineering at the Mayo Clinic in Minnesota, which is another centre of excellence in research in hypothermia. Tveita initially worked with Sieck on two sabbaticals and their collaboration has expanded ever since, including graduate and doctorate student exchanges. Over the last year, this tight collaboration between the Mayo Clinic and the University in Tromsø has expanded.

In the future, Tveita plans to further investigate the effects of hypothermia and rewarming on the processes inside heart cells, especially the effects of calcium overload on sub-cellular functions, to find ways to eliminate or mitigate the harm such changes cause during patient rewarming: "By increasing our knowledge of pathophysiological processes initiated under hypothermia, we may add factors to future rewarming techniques which can prevent them worsening and perhaps even be able to fight them and cure them".

### KEY PUBLICATIONS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## INTELLIGENCE

### EFFICACY OF PROLONGED CARDIOPULMONARY RESUSCITATION DURING ACCIDENTAL COLD WATER HYPOTHERMIA

### OBJECTIVES

The research group has conducted experimental research on accidental hypothermia with a focus on pre-hospital as well as intra hospital treatment and rewarming of hypothermia victims, in addition to preclinical research on experimental hypothermia and rewarming. In experimental hypothermia, work has focused on heart function and circulation during hypothermia and rewarming using intact animal models.

### KEY COLLABORATORS

**Dr Gary C Sieck**, Mayo Clinic, US • **Dr Godfrey Smith**, University of Glasgow, UK • **Dr Hannu Rintamäki**, Finnish Institute of Occupational Health, Finland

### FUNDING


Northern Norway regional Health Authority • Norwegian Air Ambulance Foundation • The Laerdal Foundation • The Norwegian Ministry of Foreign affairs (Barents 2020) • The Research Council of Norway (Petromax) • University of Tromsø


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