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NORMOTHERMIA IN CARDIAC SURGERY WITH EXTRACORPOREAL CIRCULATION

A REVIEW

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A b s t r a c t

Hypothermia was introduced in cardiac surgery with extracorporeal circulation in the past in order to protect organs against hypoperfusion and hypoxia. At hypothermia, organs and tissues have lower metabolic requirements while their tolerance to hypoxia is enhanced. However, hypothermia is associated with many adverse effects on the organism, which results in impairment of organ and systemic functions, a potential development of serious post-operative complications and increased mortality. Normothermia, on the other hand, is more in agreement with the physiology of the human organism, is less harmful to organs and systemic functions and, consequently, there are less post-operative complications. Its use has resulted in a shorter operative time, including the duration of extracorporeal circulation, a better post-operative outcome, a decrease in the need of mechanical ventilation and a shorter intensive care unit and hospital stay. There has been a reduction in morbidity and mortality and a decrease in overall hospital costs. In this review, the trend in gradual conversion from hypothermia to normothermia, even in surgical procedures requiring circulatory arrest, is demonstrated on the clinical results achieved in the Centre of Cardiovascular Surgery and Transplantation in Brno over the 25 years of its existence.

K e y w o r d s

Normothermia, Hypothermia, Extracorporeal circulation, Cardiopulmonary bypass, Systemic inflammatory response syndrome, Multiorgan system failure

INTRODUCTION

Rapid progress in cardiac surgery in the middle of the last century brought about the requirement for a method that would permit surgery on an arrested and open heart. Therefore, intensive research was carried out on the use of an extracorporeal circulation (ECC) system. This was first introduced in cardiac surgery in 1951. The initial trials were not successful and the first patients died of serious complications during the procedure or in the early post-operative period. The first successful outcome with the use of ECC was achieved by John Gibbon of Massachusetts, USA, in March 1953.

Hypothermia has been an integral part of any cardiac operation involving extracorporeal circulation since the pioneer era of cardiac surgery (*1, 2*). It was introduced to protect organs against the effects of low-flow perfusion, a consequence associated with the use of early ECC systems that were unable to provide sufficient blood flow. One of the first devices used in the 1950s is shown in *Fig. 1*. Hypothermia served as a means of reducing tissue metabolism, decreasing tissue oxygen consumption and protecting the brain against hypoperfusion and hypoxia. Since its adoption, further development of ECC techniques has been possible.

However, in addition to these advantages, hypothermia also has several disadvantages. The temperature of a human body is maintained almost constant throughout life. Any deviation from its physiological value, including artificially induced systemic hypothermia, is always a pathological state and a harmful factor. Hypothermia has an adverse effect on many functions at the cellular to the organ level. It changes membrane stability, glucose utilisation, mitochondrial oxidation, hydrogen ion regulation, enzymatic reactions, tissue water content, exchange of blood gases and blood clotting mechanisms; it affects vascular tonus, microvascular circulation, microvascular vasomotor activity and vascular permeability (*3*). Therefore, efforts have been made to find more physiological conditions for the use of extracorporeal circulation, which also included a more frequent application of normothermia.

Recent advancements in ECC technologies have changed the situation (*Fig. 2*). The currently used pumps are more efficient and are able to provide sufficient blood flow under normothermic conditions, present-day oxygenators have a much larger oxygenating capacity; the biocompatibility of the whole ECC system has been increased, which results in reduced adverse effects on the patient's organism (*4,5,6*). Because of high reliability of all components of the ECC system, a defect of the device or oxygenator is a very rare event. More effective cardioplegic solutions and techniques have been evolved. These changes have influenced approaches to this issue as well as ways of thinking. Hypothermia preferred in the past is gradually losing its role (*5,6*).

However, there are still some disadvantages of normothermia that should be kept in mind. During normothermia, there is a shorter time reserve for potential technical problems or poorer protection of the myocardium against heat transfer from the surrounding tissues; requirements for blood flow and pressure during ECC are higher and, consequently, there is more bleeding from the operating field. Peripheral vasoconstriction, no longer induced by systemic hypothermia, must be maintained by vasoconstrictve drug therapy.

Fig. 1
Mark III heart-lung machine (USA, 1958). It was used in Brno during the 1959–1961 period for 270 cardiac surgery procedures.

Fig. 2
Stocker S3 heart-lung machine (Stockert Instrumente Munchen, Germany), the currently used system.

RESULTS FROM THE CENTRE OF CARDIOVASCULAR SURGERY AND TRANSPLANTATION IN BRNO

In the Centre of Cardiovascular Surgery and Transplanation, established in 1978, the approach to the necessity of using hypothermia during surgery with cardiopulmonary bypass was re-evaluated in 1988 and normothermia began to be preferred. It was initially used for diagnoses that had before been indicated for cardiac surgery with ECC at mild hypothermia (28–30 °C); in the first years this included mostly patients with ischaemic heart disease. Since 1991, normothermia has been used in patients with valvular disease and in those treated by combined surgical procedures. Since 2001 even procedures such as surgical repair of the ascending aorta or aortic arch, which require cardiopulmonary bypass with circulatory arrest, have been performed at deep hypothermia only occasionally.

Normothermia is currently used in surgical treatment of ischaemic heart disease, in valve replacement, valve reconstruction or discission, in combined procedures, involving revascularisation with valvular surgery or surgical intervention on several valves, the left ventricle or the ascending aorta, and in surgery for mild congenital defects in children and adults.

During the 25 year's existence of our Centre, over 14 800 surgical procedures using extracorporeal circulation have been performed. Of these, more than 10 400, i.e., about 70%, have been carried out with the use of normothermia. In the first period (1978 to 1987), the proportion of patients operated on at normothermia was low (17%). This included children with mild congenital defects not requiring a long operative time, e.g., patent foramen ovale, atrial septal defects and some forms of ventricular septal defects. In adults, less complicated revascularisation procedures, such as aorto-coronary single bypass surgery, were performed with the use of normothermia. In the 1988–1990 period, normothermia began to be used for most of the patients undergoing surgery for ischaemic heart disease and this accounted for about 40% of all procedures. Since 1991, when the indication criteria were extended to include valvular disease and combined procedures, the proportion of patients undergoing normothermic cardiopulmonary bypass has been stable; in the last period it reached 89% of all cardiac surgery procedures with ECC. In the whole period, i.e., from January 1, 1978 to October 31, 2003, out of the 14 830 patients treated in our Centre, 10 476 patients were operated on at normothermia. Exact figures are given in the table below, in which the numbers of patients operated on at normothermia are shown in relation to the total numbers of patients (in brackets).

With the routine use of normothermia, both the morbidity and mortality of our patients has decreased; mortality in recent years has been one third of that before 1988. The need for cardiac defibrillation after aortic declamping has decreased, spontaneous onset of sinus rhythm has been more frequent, duration of ECC has been significantly reduced and fewer problems associated with weaning from ECC

Cardiac surgery with cardiopulmonary bypass at normothermia in the period from January 1978 to October 2003

Period	No. and % of patients undergoing surgery at normothermia				Total no. and %
	Ischaemic heart disease	Valvular disease	Combined defects	Congenital defects	
1978–1987	0 (455) 0%	0 (1063) 0%	0 (61) 0%	537 (1457) 36.8%	537 (3036) 17.7%
1988 – 1990	336 (354) 94.9%	12 (316) 3.8%	25 (224) 11.2%	96 (424) 22.6%	522 (1318) 39.6%
1991–2003	4429 (4911) 90.2%	2720 (2976) 91.4%	2018 (2377) 84.9%	182 (212) 85.8%	9349 (10476) 89.2%

have been encountered. The duration of post-operative mechanical ventilation is now shorter, requirements for pharmacological or mechanical cardiac support are reduced and post-operative blood losses are lower; manifestations of central nervous system dysfunction are also significantly lower. A reduced severity of systemic inflammatory response syndrome has resulted in a decreased occurrence of organ dysfunctions or multiorgan system failures, which has improved the general post-operative outcome. There is a lower need for post-operative haemofiltration and haemodialysis and a lower number of patients require a prolonged stay in the intensive care unit. The duration of hospital stay, in the absence of complications, has recently been reduced to 7–10 days and thus hospital costs have decreased.

Our patients undergoing cardiac surgery with ECC at hypothermia showed significantly elevated plasma levels of TNF-alpha in all blood samples in the period from aortic declamping to the second post-operative day. Plasma IL-6 levels were significantly increased at 2 days after surgery and IL-8 levels were high throughout the duration of ECC. On the other hand, in patients with normothermia, at 2 post-operative days, the plasma levels of anti-inflammatory IL-10 were significantly elevated and this corresponded with lower levels of pro-inflammatory cytokines (THF-alpha, IL-6 and IL-8).

DISCUSSION

The issue of using either normothermia or hypothermia in patients undergoing cardiac surgery with cardiopulmonary bypass has been discussed since the early clinical use of ECC in 1953. Each method has its advocates who compare its advantages and disadvantages. In the past, the main argument in favour of hypothermia was seen in that the body organs have higher tolerance to the reduced oxygenation of tissues due to a decrease in blood flow (*5*). At present, both methods are commonly used and regarded as equal and to decide which will be used is the responsibility of the surgeon. Recently, normothermia has been reported to be preferred by an increasing number of authors (*5, 6, 7*)

Stress induced by cardiac surgery with ECC results in systemic inflammatory response syndrome. Its development is caused by the activation of several cascade systems, in which ECC plays an important role. This happens by contact of blood with foreign surfaces of the ECC device, as well as by release of activated leucocytes from the pulmonary blood stream after weaning from the device (*8,9*). The contact between blood and non-endothelial surfaces of the oxygenator, filters, tubes and other components of the ECC device brings about the activation of the complement system with subsequent activation of leukocytes, thrombocytes, blood clotting and fibrinolytic systems, vasoactive peptides and also the release of various mediators of systemic inflammation, which further activate the cytokine cascade (*9–13*). The intensity of this reaction depends on many factors, such as, patient's age, type of oxygenator, degree of biocompatibility of the oxygenator surface, involvement of heparin-coated parts of the ECC system, use of normothermia or hypothermia, blood flow and many other factors (*4,14,15,16*). Another agent activating the cytokine cascade is bacterial endotoxin which may penetrate into blood circulation through a mucosal barrier made dysfunctional by intra-operative ischaemia of the intestinal mucosa; the primary cause is hypoperfusion of the splanchnic region during cardiopulmonary bypass. Hypoxia of the gastric and intestinal mucosae can be assessed intra-operatively by measuring intra-mucosal pH (*17–19*). Endotoxin directly stimulates macrophages to synthesise TNF-alpha, which is regarded as one of the key mediators of systemic inflammatory response syndrome (*20*). TNF-alpha increases capillary permeability, induces hypotension and tachycardia and has a pyrogenic effect. It also stimulates macrophages and lymphocytes to produce more cytokines (*13*). Activated T-lymphocytes, granulocytes and macrophages in turn produce IL-10, which is an important anti-inflammatory cytokine. All these mediators are involved in the development of an overall inflammatory response of the organism to stress induced by surgery with ECC (*21*). An advanced systemic inflammatory response syndrome is characterised by increased levels of many cytokines that interact through complicated relationships not yet fully understood (*4,22,23*). Eventually, this results in endothelial impairment of the capillary bed of parenchymatous organs and impaired functions of these organs. The degree of these changes is probably directly related to the severity of multiorgan distress syndrome and is a limiting factor for healing in the patient.

In patients with elective surgery for ischaemic heart disease, the use of normothermia significantly reduced the systemic inflammatory response to extracorporeal circulation, as compared with the patients operated on at hypothermia. The normothermic patients had significantly lower levels of pro-inflammatory cytokines (THF-alpha, IL-6 and IL-8) and a higher level of anti-inflammatory interleukine (IL-10) in the early post-operative period than the hypothermic patients (*24, 25*). These results are in agreement with those of other authors who measured changes in cytokine levels in blood samples taken during and after surgery performed with the use of ECC (*26–28*).

The results of studies on cardiac surgery with ECC, including our observations, imply that hypothermia induces a higher production of cytokines and, consequently, a higher level of systemic inflammatory response than normothermia. Normothermic perfusion, which is close to the physiological conditions, is a less stressful factor for the patient than hypothermic perfusion. Therefore, in comparable surgical procedures, normothermic cardiopulmonary bypass is associated with less iatrogenic injury to the patients than hypothermic ECC (*5,6,29*).

It can be concluded that cardiopulmonary bypass at normothermia agrees with the body's physiology more than ECC at hypothermia. Both the patient and the surgical team benefit from it; its use is associated with advantages such as a shorter operative time and ECC duration, lower level of the systemic inflammatory response, better post-operative outcomes, less complications after surgery, decrease in morbidity and mortality and lower hospital costs. In addition, normothermic conditions can be used for any surgery not requiring circulatory arrest, even if this involves a long or complicated procedure. Normothermia is generally associated with a lower risk for the patients and, according to our experience over the last 15 years, it is suitable for most of the cardiac operations and can be recommended for routine use in every institution specialised in cardiac surgery.

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NORMOTERMIE U SRDEČNÍCH OPERACÍ V MIMOTĚLNÍM OBĚHU
PŘEHLEDNÝ ČLÁNEK

S o u h r n

Hypotermie při mimotělním oběhu byla v minulosti zavedena na ochranu orgánů před hypoperfuzí a hypoxií. V hypotermii se snižují metabolické nároky tkání a orgánů, zvyšuje se jejich tolerance k hypoxii. Hypotermie ale přináší mnoho negativních vlivů na organizmus. Výsledkem je narušení mnoha orgánových a systémových funkcí, které mohou způsobit závažné komplikace v pooperačním období a vyústit až v multiorgánové selhání s vysokou mortalitou. Normotermie lépe respektuje fyziologii homeotermního organizmu člověka, méně poškozuje orgánové a systémové funkce. S použitím normotermie je spojen pokles počtu i závažnosti pooperačních komplikací, zkrácení doby ECC i operace, zlepšení pooperačního průběhu, zkrácení doby arteficiální ventilace, pobytu na jednotce intenzivní péče i doby hospitalizace, snížení nákladů a pokles morbidity i mortality. Trend postupného přechodu od hypotermie k normotermii, v poslední době i u operací s nutností zástavy oběhu, je dokumentován na výsledcích Centra kardiovaskulární a transplantační chirurgie za 25 let jeho trvání.

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