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Effects of Hypertonic Saline (7.5%) on Haemodynamics and Extracellular Water Volumes after Coronary Artery Bypass Grafting and before Spinal Anaesthesia

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ACADEMIC DISSERTATION

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for public discussion in the auditorium of Finn-Medi,
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To my loved ones

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LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following communications, referred to in the text by their Roman numerals.

I **Järvelä K, Kaukinen S**: Hypertonic saline (7.5%) after aortocoronary bypass surgery. Eur J Anaesthesiol 2001;18:100-107.

II **Järvelä K, Koskinen M, Kaukinen S, Kööbi T**: Effects of hypertonic saline (7.5%) on extracellular fluid volumes compared with normal saline (0.9%) and 6% hydroxyethylstarch after aortocoronary bypass surgery. J Cardiothorac Vasc Anesth 2001;15:210-215.

III **Järvelä K, Kaukinen S**: Hypertonic saline (7.5%) decreases perioperative weight gain in cardiac surgery. J Cardiothorac Vasc Anesth (accepted).

IV **Järvelä K, Honkonen SE, Järvelä T, Kööbi T, Kaukinen S**: The comparison of hypertonic saline (7.5%) and normal saline (0.9%) for initial fluid administration before spinal anesthesia. Anesth Analg 2000;91:1461-1465.

V **Järvelä K, Kööbi T, Kauppinen P, Kaukinen S**: Effects of hypertonic saline 75 mg/ml (7.5%) on extracellular water volume when used for preloading before spinal anaesthesia. Acta Anaesthesiol Scand (accepted).

ABBREVIATIONS

BSA	body surface area
CABG	coronary artery bypass grafting
CI	cardiac index
CO	cardiac output
CPB	cardiopulmonary bypass
CPP	cerebral perfusion pressure
CVP	central venous pressure
ECW	extracellular water
HES	hydroxyethylstarch
HR	heart rate
HS	hypertonic saline
ICG_{WB}	whole-body impedance cardiography
ICP	intracerebral pressure
ISW	interstitial water
LCWI	left cardiac work index
MAP	mean arterial pressure
MPAP	mean pulmonary arterial pressure
NS	normal saline
PACWP	pulmonary artery capillary wedge pressure
PV	plasma volume
PVRI	pulmonary vascular resistance index
SAP	systolic arterial pressure
SV	stroke volume
SVRI	systemic vascular resistance index
TD	thermodilution

INTRODUCTION

Saline solution is a mixture of permeant water molecules and nonpermeant sodium and chloride ions, and the cellular membranes are semipermeable, allowing only water but no solute to pass through (Guyton and Hall 2000). Sodium is mainly an extracellular electrolyte due to an active transport mechanism on cellular membranes (Na^+-K^+ pump), which moves three Na^+ ions to the exterior for every two K^+ ions to the interior (Guyton and Hall 2000). Sodium is also the most important electrolyte in the regulation of water distribution. It is responsible for most of the extracellular osmolality, which is the driving force for water distribution. Water diffuses freely through cellular membranes along the osmotic gradient until a new osmotic balance is reached.

Administration of hypertonic saline (HS) intravenously causes an initial rapid fluid influx into the vasculature. This is due to the sudden hypertonic state of plasma caused by the infusion of HS in a relatively short time. Water is shifted from the intracellular spaces, first from the erythrocytes and endothelial cells and then from the tissue cells, into the extracellular compartment (Mazzoni et al. 1988). Shrinkage of the endothelium has beneficial microcirculatory effects due to the reduced resistance of the capillaries (Mazzoni et al. 1988). Interstitial water also moves into the intravascular compartment by the osmotic gradient.

Hypertonic saline expands intravascular volume by mobilising fluid that is already present in the body; intracellular and interstitial fluid is shifted into the intravascular space. Plasma volume expansion is therefore achieved with less free water administration than with isotonic plasma expanders.

Reductions of 5.5 to 7.5% in blood volume have been observed after open heart surgery and cardiopulmonary bypass (CPB) (Karanko et al. 1987). Meanwhile, post-CPB increase in total body water is common (Stone et al. 1983). This extra water may have adverse effects on cardiorespiratory functions; especially on the heart recovering from surgery (Foglia et al. 1978, Laks et al. 1977).

The effect of HS on plasma volume is transient since the fluid will shift from the intravascular space back to the extravascular space. Spinal anaesthesia causes sympathetic blockade, which leads to vasodilatation and relative hypovolaemia. In this situation the need for plasma volume expansion is transient. Large volumes of extra water retained in the body after spinal anaesthesia may be harmful to the patients with compromised heart condition. Therefore, HS may be a beneficial plasma volume expander before spinal anaesthesia.

The purpose of the present study was to evaluate the effects of hypertonic saline solution on hypotension in different anaesthetic situations, namely rewarming after coronary artery bypass grafting (CABG), and spinal anaesthesia. In both situations hypotension is caused by insufficient circulating intravascular volume. The effects of HS on haemodynamics were measured and compared with those of normal saline (NS) and hydroxyethylstarch (HES). Changes in different extracellular water compartments, including plasma volume and interstitial water volume, were also evaluated because HS causes rapid changes in them. The increase of plasma volume after HS infusion was measured in the rewarming phase after (CABG). This is a situation where vascular permeability is increased. 7.5% saline was chosen to avoid as much unnecessary free water administration as possible.

REVIEW OF THE LITERATURE

Hypertonic saline

Small-volume resuscitation

Small-volume resuscitation with hypertonic saline was first introduced by Velasco and colleagues (1980). They demonstrated successful resuscitation of severely haemorrhaged (40 ml/kg) dogs by infusing hypertonic saline (7.5%, 1283 mmol/l NaCl) in a volume of 4 ml/kg, which is equal to only 10% of shed blood. HS infusion caused an immediate improvement in haemodynamics and increased survival up to 100%. This small-volume principle clearly shows its advantages when compared with fluid volumes of 4-5 times the blood volume deficit required, when isotonic crystalloid solutions are infused instead, in the treatment of hypovolaemia or shock.

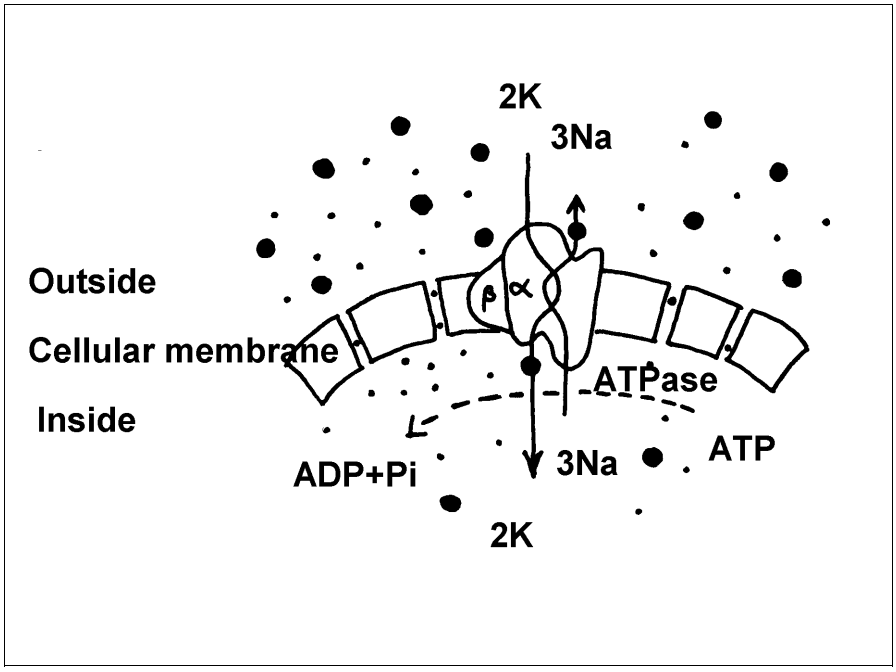
The addition of colloid (dextran or hydroxyethylstarch) together with hypertonic saline has been described later (Smith et al. 1985). This hyperosmotic-hyperoncotic crystalloid-colloid combination has a longer duration of plasma expansion than hyperosmotic colloid (Kramer et al. 1989). The present review and study, however, concentrate on the effects of pure HS alone.

Compared with artificial plasma expanders and human plasma, HS is inexpensive and presents no risk of allergic reactions. In addition, it is readily available and imposes no risk of transmission of infectious agents (Vassar et al. 1990).

Mode of action

Cellular membranes are semipermeable, allowing only water but no solute to pass through (Guyton and Hall 2000). Sodium is mainly an extracellular electrolyte due to an active transport mechanism; sodium-potassium (Na^+-K^+) pump moves sodium ions outward through the cell membrane and at the same time pumps potassium ions from the outside to the inside. In this active transport, the energy is derived directly from the breakdown of adenosine triphosphate. One of the most important functions of the Na^+-K^+ pump is to control the fluid volume of the cells. Sodium is the most important electrolyte in the regulation of water distribution. It is responsible for most of the extracellular osmolality, which is the driving force for water distribution. Figure 1 shows the structure of the Na^+-K^+ pump on the cellular membrane.

Figure 1. Sodium-potassium pump at a cell membrane (based on figures by Guyton and Hall, 2000).



The initial rapid influx of water into the vasculature, after the HS infusion, is due to the sudden hypertonicity of plasma caused by the infusion of HS in a relatively short time. Water is shifted from the intracellular spaces, first from the erythrocytes and endothelial cells and then from the tissue cells, into the extracellular compartment (Mazzoni et al. 1988). Shrinkage of the endothelium has beneficial microcirculatory effects due to the reduced resistance of the capillaries (Mazzoni et al. 1988). Interstitial fluid also moves into the intravascular compartment by the osmotic gradient.

Immunological effects

Together with an improvement in haemodynamics, some potentially beneficial immunological effects of HS resuscitation on trauma outcome have been documented: HS resuscitation prevents the shock-induced increased lung permeability and reduces neutrophil infiltration in the lung (Rizoli et al. 1998, Junger et al. 1997). This effect may be mediated through the prevention of trauma-induced immunosuppression (Junger et al. 1997). Reduction in neutrophil-mediated tissue damage, after HS administration, has been attributed to its interference with intracellular signal transduction (Ciesla et al. 2001).

Cardiovascular effects

In anaesthetised dogs HS has been shown to increase myocardial contractility (Kien et al. 1991a), which may have a favourable effect on cardiac lymph flow (Utley 1982). The increase in myocardial contractility and relaxation combined with a coronary vasodilatation is related to the hypertonicity of HS, and calcium influx through the

sarcolemma could be the major mechanism of this effect (Mouren et al. 1995). Plasma activity of a myocardial depressant factor was significantly lower after HS resuscitation compared to NS resuscitation of cats and rats in haemorrhagic shock (Bitterman et al. 1987). These factors may contribute to its beneficial effect on CO. On the other hand, Welte and colleagues (1997) have shown that in the presence of a flow-limiting coronary stenosis, initial fluid resuscitation with 7.2% saline/10% dextran 60 failed to restore perfusion pressure, redistributed myocardial blood flow in favour of normally perfused myocardium, and did not reverse ischaemia in post-stenotic myocardium.

HS causes modest coronary vasodilatation (Crystal et al. 1994) and decreases systemic vascular resistance (Ramires et al. 1992). It induces direct unspecific vasodilatation mediated by hypertonicity (Rocha e Silva et al. 1986). HS also causes direct renal vasodilatation and increases glomerular filtration rate (Fujita et al. 1991). Saline infusion is associated with elevated serum sodium and lowered blood aldosterone levels (Drummer et al. 1992). These lead to increased diuresis after HS infusion.

The haemodynamic support prior to, and following, aortic declamping in pigs was more efficient with HS than with NS; lactate clearance and restitution of high energy phosphagen levels in skeletal muscle were faster and more profound in the HS group (Waagstein et al. 1997). HS also attenuates postischaemic microvascular disturbances elicited by ischaemia-reperfusion, presumably through the reduction of postischaemic leukocyte-endothelium interaction and capillary swelling (Nolte et al. 1992). This was seen as a minor decrease in capillary perfusion and a minor increase in macromolecular leakage when HS was infused before reperfusion but as significant changes in the NS group.

Clinical use

HS solutions of varying concentrations (1.8 to 7.5%) have been investigated as plasma expanders in different clinical situations, but the most commonly used concentrations are the most hypertonic solutions (7.2-7.5%). These most effective hypertonic saline solutions can be used safely in a fixed dose of 4 ml/kg or 250 ml (Vassar et al. 1990). Another approach is the use of more dilute solutions titrated to physiologic end-points as larger amounts of these solutions can be administered without danger of acute hypernatraemia.

Hypertonic saline was described and used in the treatment of haemorrhagic shock in dogs by Velasco and colleagues in 1980. In a clinical trial reported in the same year, HS (7.5%) reversed the shock in 11 out of 12 patients in terminal hypovolaemic shock who had not responded to vigorous volume replacement and dopamine infusions. The immediate effects of HS injections (100-400 ml) were a moderate rise in arterial pressure, the resumption of urine flow, and recovery of consciousness (De Filippe et al. 1980). Small-volume (4 ml/kg) infusion of HS (7.5%) also induced an important haemodynamic improvement in six patients with cardiogenic shock due to right ventricular infarction (Ramires et al. 1992).

Trauma patients often require rapid restoration of circulating volume to ensure tissue perfusion. Even within the most favourable prehospital conditions, it is difficult to infuse sufficient amounts of crystalloid solutions to replace the blood loss of severely injured trauma patients. Prehospital infusion of 250 ml of 7.5% saline increased blood pressure and survival to hospital discharge. Patients with low baseline Glasgow Coma Scale scores seemed to benefit the most from HS resuscitation (Vassar et al. 1993). Cardiovascular resuscitation of patients having surgery for acute severe injuries can be achieved with one half of the cumulative fluid requirements using 3% saline compared to isotonic fluids (Holcroft et al. 1987).

Burn injuries involve wide vascular and tissue damage, which causes the loss of large amounts of fluid through the burn wound. Vigorous fluid resuscitation is needed to avoid shock. Together with low intravascular volume, tissue perfusion may be compromised due to cellular oedema after administration of large amounts of crystalloids. Resuscitation with hypertonic lactated saline (HLS) resulted in a better electrolyte balance with lower fluid load, reducing tissue oedema and complication rate than with lactated Ringer's in this situation (Bortolani et al. 1996). HLS may be associated with ameliorated respiratory function not only because of less volume loading during resuscitation, but also because the PV/ISW ratio is less than after an administration of lactated Ringer's (Shimazaki et al. 1991). However, results to the contrary have also been reported: Huang and colleagues found no reduction in the total resuscitation volume required in the HS group (290 mmol/l Na) compared with the Ringer's group (130 mmol/l Na) (1995). Furthermore, HS resuscitation of patients with major burns was associated with an increased incidence of renal failure and death (Huang et al. 1995).

Cerebral perfusion pressure (CPP) is dependant on mean arterial pressure (MAP) and intracranial pressure (ICP): CPP=MAP-ICP. Patients with severe head injury often have cerebral oedema or space-occupying haematomas, both of which can increase ICP. Fluid restriction, because of fear that fluid administration can enhance cerebral oedema, may lead to hypotension and decreased CPP. Conventional emergency treatment of elevated ICP is an intravenous infusion of hypertonic mannitol, which decreases brain water content and reduces ICP (Smith et al. 1986). HS solutions also decrease brain water and ICP while temporarily increasing mean arterial pressure leading to increased CPP (Freshman et al. 1993, Qureshi et al. 1998, Sheikh et al. 1996, Simma et al. 1998, Suarez et al. 1998). 7.5% HS is also as efficacious as 20% mannitol in reducing both brain bulk and the cerebrospinal fluid pressure during neurosurgical procedures under general anaesthesia (Gemma et al. 1997). Not all studies, however, support these findings (Shackfod et al. 1998).

Use of hypertonic saline (7.5%) immediately after aortic unclamping during surgical treatment of aortic aneurysms leads to higher PAP, PACWP and CI, and lower SVR and PVR values than when isotonic saline is used (Auler et al. 1987). Improved haemodynamics after HS infusion during the immediate postoperative period have also been demonstrated in patients who have undergone mitral valve repair (Sirieix et al. 1999). Patients undergoing aortic reconstruction and receiving HS have been shown to have less positive intraoperative fluid balance (Auler et al. 1987, Shackford et al. 1987) without any long-lasting changes in serum sodium values or osmolality (Shackford et al. 1987). Perioperative fluid balance may even be negative when hypertonic saline is used: Cross and colleagues compared hypertonic saline (1.8%) with isotonic saline titrated to physiologic endpoints (HR, SAP and PACWP) in postoperative CAGB patients, and also found decreased third-space losses (1989). Besides less positive perioperative fluid balance due to a larger diuresis, Mazhar and colleagues showed better cardiorespiratory recovery with shorter extubation time in the group receiving HS after cardiac surgery compared to the group receiving gelatin (1998). No improvement in cardiorespiratory recovery was, however, demonstrated by Auler's group who found no significant changes in respiratory system mechanics after HS infusion in patients submitted to coronary artery bypass (1992).

HS has successfully been used for fluid preloading before regional anaesthesia to prevent hypotension caused by lumbar extradural anaesthesia (Veroli and Benhamou 1992) and spinal anaesthesia (Baraka et al. 1994, Wang et al. 1997).

Studies on perioperative use of pure hypertonic saline are summarised in table 1.

Table 1. Perioperative use of HS

Reference	Con-centration	Dose	Surgery	Control solution	Effects	n=
Shackford et al. 1983	1.5%	Phys. end-points	Aortic reconstruc-tion	Ringer's	less fluid Qs/Qt↓	58
Shackford et al. 1987	1.5%	Phys. end-points	Aortic reconstruc-tion	Ringer's	less fluid	52
Auler et al. 1987	7.5%	4 ml/kg	Aortic reconstruc-tion	NaCl-isotonic	CI↑, PAWP↑, SVR↓, less fluid	10
Cross et al. 1989	1.8%	Phys end-points	Cardiac	NaCl-isotonic	30% less fluid	20
Croft et al. 1992	1.8%	Phys end-points	Aortic reconstruc-tion	Ringer's	less fluid, less LVEDV drop	28
Auler et al. 1992	7.5%	4 ml/kg	Cardiac	NaCl-isotonic	Cardiores-piratory recovery (ns)	21
Veroli et al. 1992	5%	2.3 ml/kg	Preloading before spinal anaesthesia	NaCl-isotonic Ringer's	less fluid, MAP (ns)	30
Baraka et al. 1994	3%	7 ml/kg	Preloading before spinal anaesthesia	NaCl-isotonic	less hypotension and vasopressor	33
Wang et al.1997	3%	7 ml/kg	Preloading before spinal anaesthesia	Ringer's	less hypotension	60
Gemma et al. 1997	7.5%	2.5 ml/kg	Neurosurge-ry	Mannitol 20%	CSFP↓ (ns)	50
Mazhar et al. 1998	7.2%	5 ml/kg	Cardiac	Polygeline	less positive fluid balance	20
Sirieix et al. 1999	7.2%	250 ml	Cardiac	HES, HS-HES	LVEDA↑, SVR↓, EF↑, CI↑	26

HES=hydroxyethylstarch; HS-HES=hypertonic saline-hydroxyethylstarch
Qs/Qt=intrapulmonary shunt; CI=cardiac index; PACWP=pulmonary artery capillary wedge pressure; SVR=systemic vascular resistance; PVR=pulmonary vascular resistance; LVEDVI=left ventricular end diastolic volume; MAP=mean arterial pressure; CSFP=cerebrospinal fluid pressure; LVEDA=left ventricular end diastolic area; EF=ejection fraction

Safety of hypertonic saline

The use of hypertonic saline solutions is limited by the possible complications they may cause if not administered with caution. A rapid increase in plasma sodium concentration and osmolality could cause central pontine myelinolysis to chronically debilitated patients with pre-existing hyponatraemia (McKee et al. 1988). Osmotic demyelination syndrome is likely to follow the correction of chronic hyponatraemia by more than 12 mmol per litre per day (Sterns et al. 1986). On the other hand, neurological and SSEPs improvement of a 14-year-old boy with vasospasm of the intracranial vertebral arteries and ischaemic brain stem damage, following head trauma, has been reported after an infusion of hypertonic saline (Gemma et al. 1996). The serum sodium concentration and osmolality should, however, be carefully monitored to avoid adverse effects after hypertonic saline infusion, even though these changes resolve rapidly (Shackford et al. 1987).

Rapid intravascular volume expansion without concomitant potassium replacement could produce hypokalaemia (Shackford et al. 1987), leading to arrhythmias. Therefore, the serum potassium level should be monitored closely and replaced aggressively. If hypertonic saline chloride is used instead of hypertonic saline lactate, hyperchloraemia may occur leading to hyperchloraemic acidosis (Vassar et al. 1990). This is not usually a problem. Despite an initial, transient acidaemia, which is primarily due to a hyperchloraemic, hypokalaemic, metabolic acidosis with normal anion gap and decreased inorganic strong ion difference, the acid-base status may be improved more effectively with hypertonic-hyperoncotic solution than with isotonic saline due to its beneficial effect on haemodynamics (Moon and Kramer 1995).

HS does not have anticoagulant activity at the usual small volume necessary to produce haemodynamic improvement. Nevertheless, significant deteriorations in clotting tests and platelet aggregation developed when 10% or more of plasma was

replaced by HS (Reed et al. 1991). The anticoagulant effect needs to be taken into consideration with ongoing clotting factor losses or with the addition of dextran or hydroxyethylstarch. HS does not interfere with crossmatching of blood either (Vassar et al. 1990).

When no chronic hyponatraemia pre-exists, hypertonic saline is likely to have a favourable risk-to-benefit ratio in small-volume plasma volume expansion (Shackford et al. 1987, Vassar et al. 1990). HS is a safe fluid in a setting of limited volume resuscitation when used with care and in justified indications.

Rewarming hypovolaemia

Effects of cardiopulmonary bypass

Patients undergoing open heart surgery with cardiopulmonary bypass (CPB) and often also hypothermia are prone to acute changes of body fluid compartments. CPB dilutes serum proteins and reduces plasma colloid osmotic pressure, especially when Ringer's solution is used for priming (London 1988). CPB also increases capillary permeability: Contact of the blood with foreign surfaces activates the kinin pathway, and the extracorporeal circulation further promotes the formation of C3a and C5a anaphylatoxins, all leading to increased vascular permeability (Pang et al. 1979, Chenoweth et al. 1981). This, in turn, causes leakage of intravascular volume into the extravascular space resulting in tissue oedema formation.

In spite of myocardial protection during open heart surgery, the immediate recovery of myocardial function is not optimal. Moderate hypothermia (32°C) used in CPB promotes haemodynamic (Czer et al. 1983) and left ventricular (Gray et al. 1979) dysfunction during the rewarming period after CABG even in uncomplicated cases.

Further, myocardial oedema, which reduces cardiac compliance, may occur after the use of crystalloid primes (Foglia et al. 1978, Laks et al. 1977). Other contributing factors which depress myocardial function include residual myocardial disease, anaesthetics, acid-base and electrolyte imbalance.

Rewarming phase

When the aortic crossclamp is removed at the end of the CPB, the first phase of gradual warming starts. The core temperature reaches normothermia by the end of the CPB, followed by a decrease in SVR and an increase in CO. Redistribution of the heat to the periphery causes a fall in the core temperature, followed by an increase in SVR and MAP together with a reduction in CO (Sladen 1982, Estafanous 1985). After about a 2 to 4 hour latent period, the second phase of warming of the body starts. This is followed by a new fall in SVR and MAP. This latter warming of the patient is referred to as 'the rewarming phase'. Postoperative volume loading is often required to maintain preload and to prevent hypoperfusion during the rewarming period in the intensive care unit (ICU) (Ivanov et al. 1984). Reductions of 5.5 to 7.5% in blood volume have been observed after open heart surgery (Karanko et al. 1987). Meanwhile, post-CPB increase in total body water is common (Stone et al. 1983).

Even if most cases of postoperative hypotension can be managed with fluid therapy, patients with hypotension, high CI, and a low SVRI require vasopressor therapy to stimulate α-adrenergic receptors. Inotropes with or without vasodilator are needed to treat ventricular failure. Catecholamines, through β_1-receptor stimulation, and phosphodiesterase inhibitors, through inhibition of the breakdown of intracellular cyclic adenosine monophosphate, increase intracellular calcium and may be used to improve myocardial contractility (Levy et al. 1999).

Haemodynamic effects of spinal anaesthesia

Spinal anaesthesia produces sympathetic nervous blockade causing arterial and venous vasodilatation (McCrae and Wildsmith 1993). This leads to pooling of the intravascular blood volume in the skeletal muscle and skin at the expense of the intrathoracic blood volume, which also decreases because of the supine position (Arndt et al. 1985). Besides decreased systemic vascular resistance, venous return is reduced by the lack of pumping action of the muscles during spinal anaesthesia. This will lead to decreased cardiac output, since according to the Frank-Starling law venous return determines cardiac output. Cardiovascular instability is expressed as arterial hypotension and bradycardia during spinal anaesthesia. These cardiovascular side effects requiring treatment may occur at any time during spinal anaesthesia (Arndt et al.1998).

Treatment of hypotension may be either preventive, including correction of hypovolaemia, avoidance of high levels of blockade, use of a slight head-down tilt for better venous return and treatment of overactivity with sedatives, or on-demand treatment. The definition of hypotension which requires treatment varies in the literature: SAP<100 mmHg or <90 mmHg and 20-30% decrease from baseline have been used. Treatment regimens consist of fluids to increase plasma volume and vasopressors to stimulate □- and/or □-receptors. Preloading with either crystalloid or colloid solution is not necessarily associated with any lesser degree of hypotension compared with no prehydration at all (Buggy et al. 1997). The most commonly used vasopressors, ephedrine and etilefrine, used in central Europe and Scandinavia, are equally effective in restoring systolic pressure (Taivainen 1991). Other possible vasopressors include methoxamine, phenylephrine, dihydroergotamine, mephentermine, metaraminol, dopamine, dobutamine and adrenaline. Mechanical methods of compressing the lower limbs, in order to improve venous return, have not

been proven effective (Lee et al. 1987). In the obstetric patients, the use of left-lateral tilt plays an important role in the prevention of hypotension (Ekstein and Marx 1974).

AIMS OF THE STUDY

The purpose of the present study was to evaluate the effects of hypertonic saline (7.5%) on haemodynamics and extracellular water volumes when used in the treatment of rewarming hypovolaemia after CABG and when used for fluid preloading before spinal anaesthesia. In addition, a comparison with normal saline and hydroxyethylstarch was undertaken.

The specific objectives were:

1. to compare the haemodynamic effects of hypertonic saline (7.5%) and normal saline (0.9%) in the treatment of rewarming hypovolaemia after CABG (**I**).

2. to compare the effects of hypertonic saline (7.5%), normal saline (0.9%) and hydroxyethylstarch (6%) on extracellular water volumes (plasma volume, interstitial volume) (**II**).

3. to compare the effects of hypertonic saline (7.5%) and normal saline (0.9%) on perioperative weight gain during CABG (**III**).

4. to compare the clinical effects of hypertonic saline (7.5%) and normal saline (0.9%) containing the same amount of sodium when used for fluid preloading before spinal anaesthesia (**IV**).

5. to evaluate the effects of hypertonic saline (7.5%) on extracellular water volume and haemodynamics when used for fluid preloading before spinal anaesthesia (**V**).

PATIENTS AND METHODS

Patients and study designs

One hundred and twenty-eight patients participated in these studies. Eighty-eight of them were operated on for myocardial revascularisation (I, II and III) and forty of them had a lower limb orthopaedic operation (IV and V). Study III includes patients receiving HS or NS solutions from both studies I and II. Studies IV and V share the same patient cohort. The exclusion criteria were: left ventricular ejection fraction below 0.4; serum creatinine above 130 µmol/l; or hepatic disease (I, II and III) and any contraindication to spinal anaesthesia (IV and V). All the studies were carried out at Tampere University Hospital.

Summary of study settings are presented in table 2.

Table 2. Study design

Study	Design	Groups	Main variables	Number of patients
I	prospective, randomised	HS and NS, 4 ml/kg	CI, MAP	40
II	prospective, randomised, double-blind	HS, NS and HES, 4 ml/kg	PV, ECW	48
III	prospective, randomised	HS and NS, 4 ml/kg	weight gain	72
IV	prospective, randomised, double-blind	HS 1.6 ml/kg and NS, 13 ml/kg	CI, MAP	40
V	prospective, randomised, double-blind	HS 1.6ml/kg and NS, 13 ml/kg	ECW	40

HS=hypertonic saline; NS=normal saline; HES=hydroxyethylstarch; CI=cardiac index; MAP=mean arterial pressure; PV=plasma volume; ECW=extracellular water

Randomisation was achieved according to a list of random digits. A sealed envelope was opened after obtaining written informed consent from the patient.

Before the trial, a power calculation for a 0.5 l/min/m² difference in CI or 15 mmHg difference in MAP (1 SD in previous studies in similar situations) with a probability level of 0.05 and a power of 0.80 (1-□) yielded a sample size of 15-16 patients. Accordingly, 20 (I, IV and V) and 16 (II) patients were enrolled in each group. Using a two-sided □ of 0.05, a 1.0 kg difference in perioperative weight gain could be detected with 95% power with 26 patients in both study groups. Accordingly, 36 + 36 patients was a large enough sample size (III).

Anaesthesia

General anaesthesia and cardiopulmonary bypass (I, II and III)

For premedication all patients received lorazepam, morphine and scopolamine. Anaesthesia was induced with lorazepam or midazolam, fentanyl and thiopentone, and maintained with fentanyl or sufentanil and isoflurane. Muscle relaxation was achieved with pancuronium. After endotracheal intubation, the patients were ventilated with oxygen in air (FiO_2 0.4-0.5) maintaining normocarbia. The cardiopulmonary bypass circuit was primed with Ringer-Acetate solution with heparin. No mannitol or albumin was included in the priming solution. CPB with nonpulsatile perfusion flow 2.0-2.4 l/min/m^2 was conducted using a membrane oxygenator. Nasopharyngeal temperature was kept at 32□C during the perfusion. For myocardial protection, cold blood ante/retrograde cardioplegia was given intermittently, with a final warm cardioplegia infusion at the end of the cross-clamping period. In all patients, the internal thoracic artery was used as a graft, in addition to

saphenous vein grafts. Before weaning from CPB, all patients were rewarmed to 37□C nasopharyngeal temperature and volume loaded to PACWP of 12 mmHg. If vasoactive medication was needed for successful weaning from CPB (CI over 2 l/min/m²), the required infusion rate was maintained at the same level until the patient was normothermic. The rest of the cardiotomy reservoir fluid was administered after successful weaning.

After the operation, the patients were attended to the intensive care unit and their lungs were mechanically ventilated for at least four hours. Adequate oxygenation was adjusted and normocarbia maintained on the basis of intermittent blood gas analyses. Sedation and analgesia were achieved with i.v. incremental doses of 2.5 mg midazolam and/or 3 mg oxycodone administered by the intensive care nurse caring for the patient (I, III) or with i.v. infusions of midazolam 0.05-0.10 mg/kg/h and sufentanil 0.5 μg/kg/h (II, III). The ICU nurses did not collect any data for this study. All the data was collected by the investigators.

Regional anaesthesia (IV and V)

If premedication was needed, 1 ml of fentanyl was administered iv after the insertion of a peripheral venous cannula. Spinal anaesthesia was induced immediately after the end of the study fluid infusion. A 27-gauge Quinke-type spinal needle (Spinocan, B. Braun, Melsungen, Germany) was inserted at the L2-3 or L3-4 intravertebral space. The patients were in lateral decubitus position with the operative side dependent. All patients received 10 mg of 0.5% bupivacaine (hyperbaric). The patients were kept in lateral decubitus position for 5 min and then repositioned in the supine position. The surgical procedure was started when the level of sensory block was satisfactory for the operation.

Fluid therapy

Treatment of rewarming hypovolaemia

In the intensive care unit 5% glucose/0.3% saline solution was given at the rate of 1 ml/kg/h, as maintenance fluid until the first postoperative morning. Volume loading was commenced when the patient fulfilled at least two of the following criteria: a) A decrease of PACWP to 10 mmHg or below, b) A decrease of CVP greater than 2 mmHg and c) A decrease of SAP 20 mmHg or more. The patients were given, according to the randomisation, either HS or NS as a single dose of 4 ml/kg into the central venous line over 30 minutes (I, III). The infusion was discontinued if SAP exceeded 170 mmHg. After a follow-up of one hour, 4% albumin was given if additional plasma volume expansion was needed to maintain CI at 2.5 l/min/m² or higher. After the follow-up of two hours, packed red cells were transfused if the haematocrit value was below 0.30. In study II the patients received, according to randomisation, either HS (NaCl 7.5%), NS (NaCl 0.9%) or HES (6% hydroxyethylstarch 120/0.7) as a single dose of 4 ml/kg for volume loading.

Preloading before spinal anaesthesia

For fluid preloading over 10-15 min, the patients received either 1.6 ml/kg of HS (NaCl 7.5%) or 13 ml/kg of NS (NaCl 0.9%) according to randomisation, through a 16-gauge cannula inserted in a peripheral vein in the cubital fossa. All patients received the same amount of sodium (2 mmol/kg) in this preloading, which was given by the anaesthesia nurse caring for the patient in the operating room. The investigators were blinded to the infusion. After the fluid preloading, 0.45% saline infusion was started as maintenance fluid at the rate of 2 ml/kg/h.

Monitoring

Haemodynamic monitoring

Before the induction of anaesthesia, a radial artery catheter for measuring blood pressure, and a pulmonary artery catheter (BOC Ohmeda Criticath Pacing Model SP5537 catheter, Ohmeda Pte Ltd, Singapore, Malaysia) for measuring CVP, PAP and PACWP were introduced (I, II and III). CO was measured by the thermodilution method with a Hewlett Packard Merlin M1046-9149E monitor (Hewlett-Packard S.A., Geneva, Switzerland) using cold saline timed to end expiration (I). If the difference between two successive measurements was greater than 10%, a third measurement was performed. The mean of these measurements was calculated. Derived variables (cardiac index, systemic and pulmonary vascular resistance indexes) were calculated: CI=CO/BSA; SVRI=80x(MAP-CVP)/CI; PVRI=80x(MPAP-PACWP)/CI.

A commercially available whole-body impedance cardiograph CircMon™ B202 (7.51) (JR Medical Ltd, Tallinn, Estonia) was used for the measurement of impedance derived heart rate (HR), cardiac index (CI=CO/BSA), left cardiac work index (LCWI=0.0144x(MAP-PACWP)xCI) and systemic vascular resistance index (SVRI=80x(MAP-CVP)/CI) (II, IV and V). An example of recordings is presented in figure 2. As a non-invasive method the CircMon™ B202 uses average normal values of CVP and PACWP for these calculations. Deviation from the actual values has a similar effect on results in all study groups and therefore comparison between the groups is possible. Disposable electrocardiograph electrodes (Blue sensor type R-00S, Medicotest A/S, Ølstykke, Denmark) were used. A pair of electrically connected current electrodes was placed on the distal parts of the extremities, just proximal to the wrists and ankles. Voltage electrodes were placed proximal to the current electrodes, with the distance between the centers of the electrodes being 5 cm

(Kööbi et al. 1997a). Electrode placement is presented in figure 3. Measurements were taken with patients in the horizontal position, and the patient's limbs were isolated from the trunk to prevent surface contact and an electrical connection during the bioimpedance measurements. Arterial blood pressure was measured noninvasively using Accutorr 4 (Datascope Corp, Montvale, NJ, USA) which was included in the CircMon™ B202 (II, IV and V).

Figure 2. Schematic presentation of CircMon B202™-recordings: ECG, whole-body impedance plethysmogramme and impedance plethysmogramme recorded from the calf.

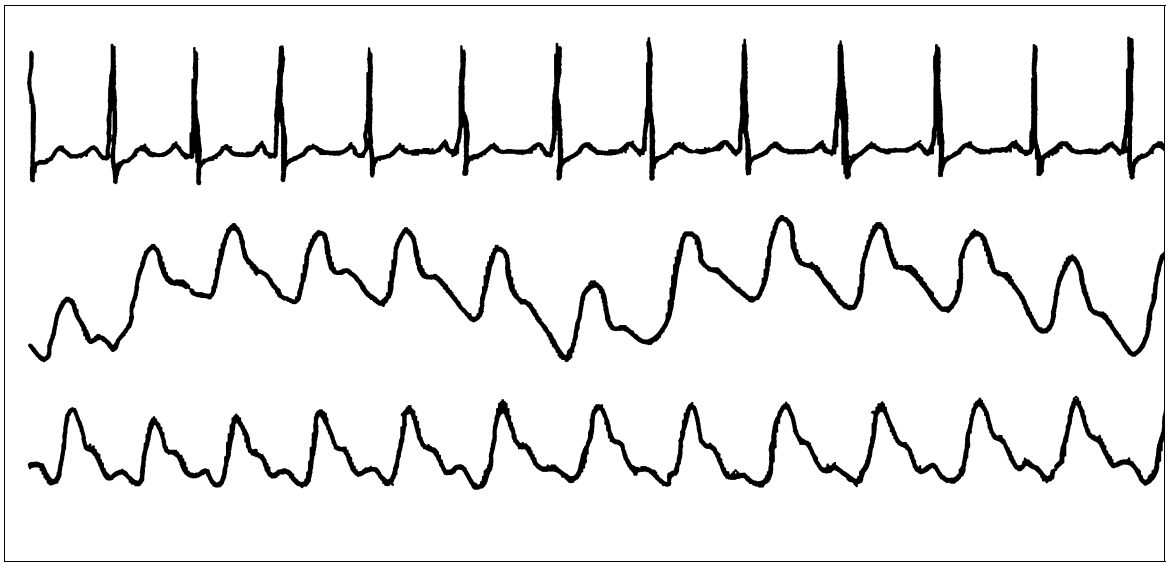
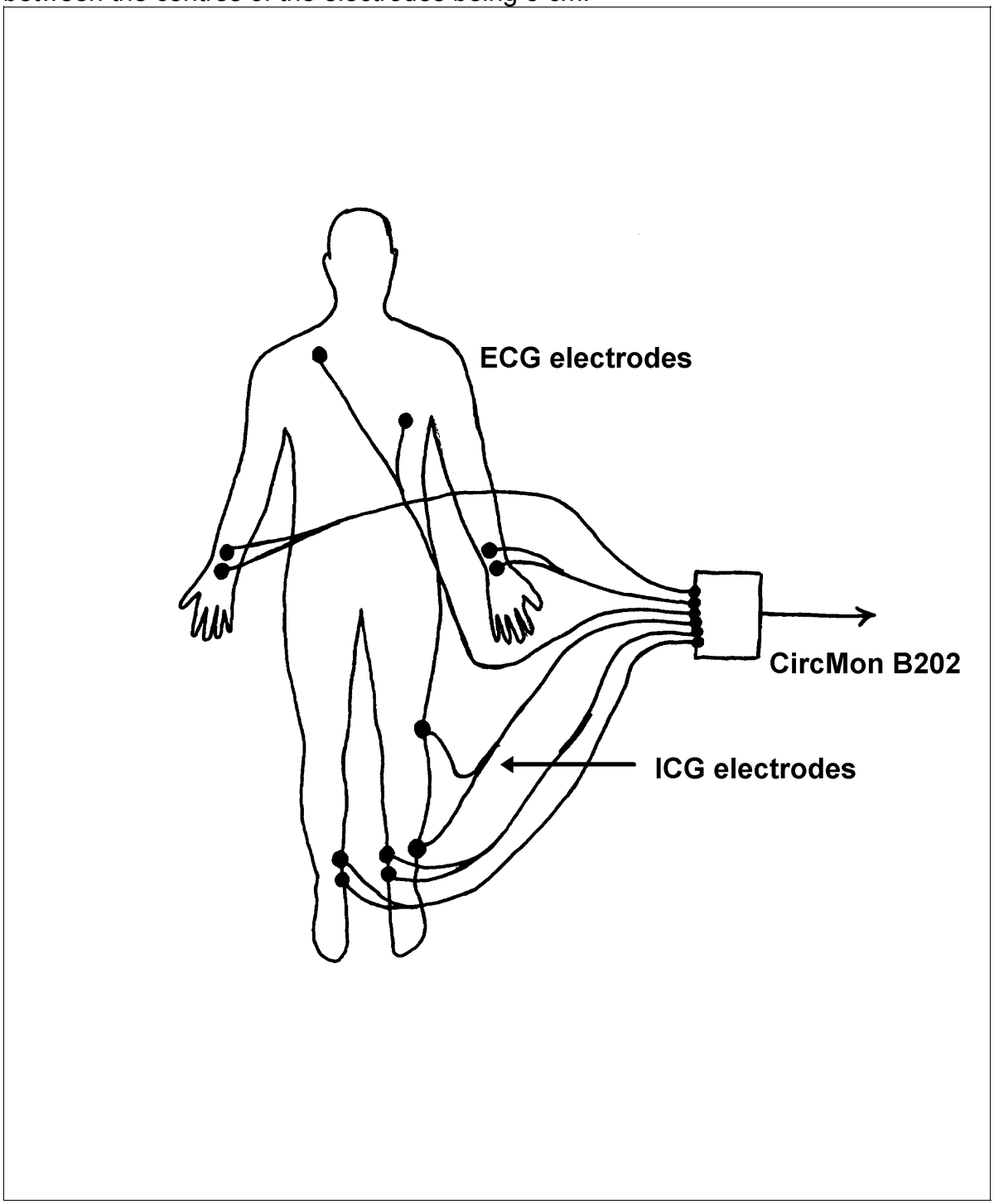


Figure 3. Schematic presentation of the electrode placement for the whole-body impedance cardiography. A pair of electrically connected current electrodes were placed on the distal parts of the extremities, just proximal to the wrists and ankles. Voltage electrodes were placed proximal to the current electrodes, with the distance between the centres of the electrodes being 5 cm.



Biochemical measurements

All the samples for biochemical measurements were sent to the Department of Clinical Chemistry, Tampere University Hospital, where they were analysed. Plasma levels of sodium, chloride and potassium together with serum osmolality were measured in both clinical situations: post-CABG (I) and during spinal anaesthesia (IV, V). The electrolyte levels were analysed using ion-specific electrodes with a direct method. Flame emission spectrophotometry was used for calibration and as reference. The analyses were made immediately after sample taking, and the results were used in the clinical care of the patients. Urine levels of sodium and potassium together with urine osmolality were measured in study I. Urine was collected from 0 to 60 min, from 61 to 240 min and from 241 min after the study fluid infusion to the first postoperative morning. The volume of urine was measured, and 10 ml of mixed urine for each collection period was used for the analyses of urine electrolyte levels with an ion-specific electrode and a direct method. 1 ml of serum and 10 ml of urine were used for the analysis of osmolality by measurement of the decrease in the freezing-point.

In studies I, II and V, blood samples for measurement of haematocrit were analysed with an automatic counter (Technicon H*3, ADVIA^{TM}120 hematology system and Coulter counter) or with a haematocrit -centrifuge. In study I, blood glucose was analysed with an enzymatic method.

Measurement of extracellular water volumes and weight gain

CircMon™ B202 (7.51) (JR Medical Ltd, Tallinn, Estonia) was used for the measurement of extracellular water (ECW). ECW (l) was calculated using the equation: $ECW=K\times H^2/R$, where H is the patient's height (cm); R is the resistive part of the whole-body bioimpedance (□); and K is the correction factor (K_{males}=0.078, $K_{females}$=0.095) (II and V).

Plasma volume was determined as the distribution volume of 125-I-labeled human serum albumin (125I-HSA) (Institute for Energy Technology, Kjeller, Norway) (II). A dose of 200 kBq was injected intravenously. The same dose was added into a standard bottle and mixed. In the recommended method, three samples (10, 20 and 30 minutes) and extrapolation to zero time are used to compensate the albumin leakage from the plasma volume (Maisey et al. 1991, International Committee for Standardization in Haematology 1980). Using only one 10-min sample a 1.5% reduction in the final result would be obtained (International Committee for Standardization in Haematology 1980). In this study, blood samples were taken through the radial artery catheter 15 and 20 minutes after the marker injection. Plasma was separated and the activity of 1.5 ml samples was measured on a LKB-Wallac 1272 Clinigamma counter (Wallac Oy; Turku, Finland). A total count above 10 000 was always used to assure statistical accuracy. The mean of the first two measurements (15 and 20 min) was considered the baseline value. New plasma samples were taken 30, 40 and 50 minutes after the injection (during the infusion) and 60, 70, 90 and 110 minutes after the injection (one hour follow-up time) to measure the changes in plasma volume. Interstitial water (ISW) was calculated using the equation: ECW-PV=ISW (II). This includes two independently measured factors and is suitable for assessing the changes caused by fluid administration.

The study patients were weighed with a calibrated scale before the operation and on the first postoperative morning (I and II), and daily thereafter until their hospital discharge (III).

Statistics

Statistical analysis was performed using the SPSS for Windows (version 6.1) (I) and (version 7.5) (II-V) (SPSS Inc., Chicago, Ill.). The results were analysed using analysis of variance for repeated measures with group as the factor, and time as the repeating factor. T-test for independent samples (intergroup comparison) and t-test for paired samples (intragroup comparison) were performed at different time points using the adequate Bonferroni-factor for post-hoc testing. Dichotomous variables were tested using the chi-square test. Mann-Whitney was used as a nonparametric test. Linear and logistic regression models were used in study V. A p values less than 0.05 was considered significant.

Ethical considerations

The study protocols were approved by the Ethical Committees of Tampere University Hospital, and by the National Agency for Medicines. Written informed consent was obtained from each patient investigated.

The partial use of the patient cohorts from studies I and II, in study III, may be problematic. Lack of power to find the difference between the smaller groups may, however, give reasons for such practise.

RESULTS

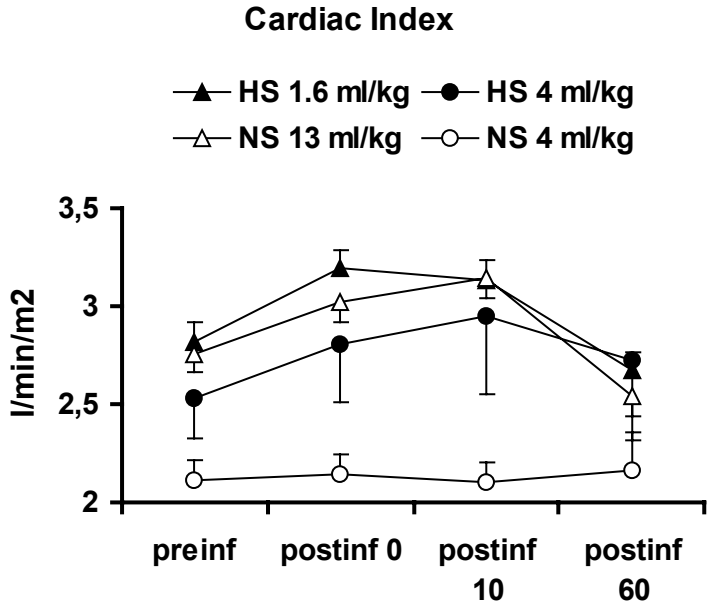
Demographic data

In study I, the age distribution differed significantly between the two groups (p=0.0197). In statistical analyses the two groups were divided in half according to age in order to exclude the influence of this factor on results. Haematocrit was lower in the older (62 years and older) age group than in the younger (under 62 years) (p=0.008). Age did not affect the results in any other variable. There were no differences between study groups with regard to weight, height**,** duration of anaesthesia and CPB-times (I, II, III) or duration and sensory level of spinal anaesthesia (IV, V).

Haemodynamic data

There were no statistically significant differences in baseline haemodynamics in any study. Hypertonic saline had positive haemodynamic effects (I, II, IV, V). CI increased after the HS infusion in both doses (1.6 ml/kg and 4 ml/kg) and was maintained at the higher level for about an hour (figure 4). MAP also increased following the trends in CI (I, II, IV, V). The treatment groups did not differ with regard to HR in any of the studies. Derived haemodynamic data were calculated in studies I, II and V. No significant changes in SVRI after the HS infusion were seen.

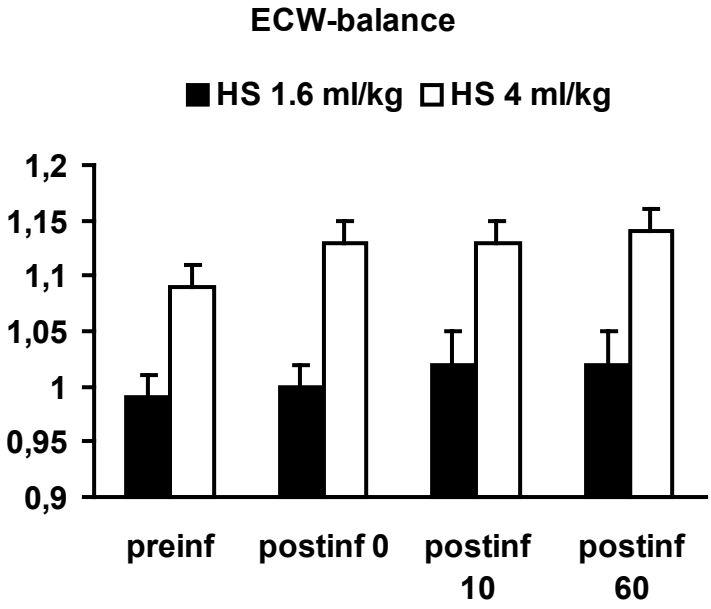
Figure 4. Cardiac Index (CI) (l/min/m^2) before and after HS and NS infusions of 1.6 ml/kg and 4 ml/kg measured with whole-body impedance cardiography (ICG).



Extracellular water volumes and weight gain

The increase in ECW after 4 ml/kg (II) and 1.6 ml/kg (V) of HS is presented in figure 5. There were no significant differences between the groups when using either HS or NS containing the same amount of sodium (V). The ECW change was significantly greater in the HS group than in the NS group at 40 and 50 minutes after the infusion ($p=0.041$ and $p=0.033$, respectively), when the same amount of fluid (4 ml/kg) was administered (II).

Figure 5. Extracellular water-balance (ECW-balance) after HS infusion of 1.6 ml/kg and 4 ml/kg measured with whole-body impedance cardiography. Preinf= before the infusion, postinf 0= after the infusion, postinf 10= 10 min after the infusion, postinf 60= 60 min after the infusion.



The plasma volume changes after infusion of 4 ml/kg of either HS, NS or HES are presented in figure 6. The HS group differed significantly from the NS group during the study fluid infusion ($p<0.001$). The HS group differed significantly from the HES group at 30 ($p<0.001$), 70 ($p=0.007$), 90 ($p<0.001$) and 110 ($p<0.001$) minutes. Changes in ISW after infusion of 4 ml/kg of either HS, NS or HES are presented in figure 7. The ISW change was greater in the HS group than in the NS and HES groups at 90 minutes ($p=0.022$) and at 90 and 110 minutes ($p=0.024$), respectively.

Figure 6. Plasma volume change from the baseline (%) after 4 ml/kg infusion of 0.9% normal saline (NS), 7.5% hypertonic saline (HS) and 6% hydroxyethylstarch (HES).

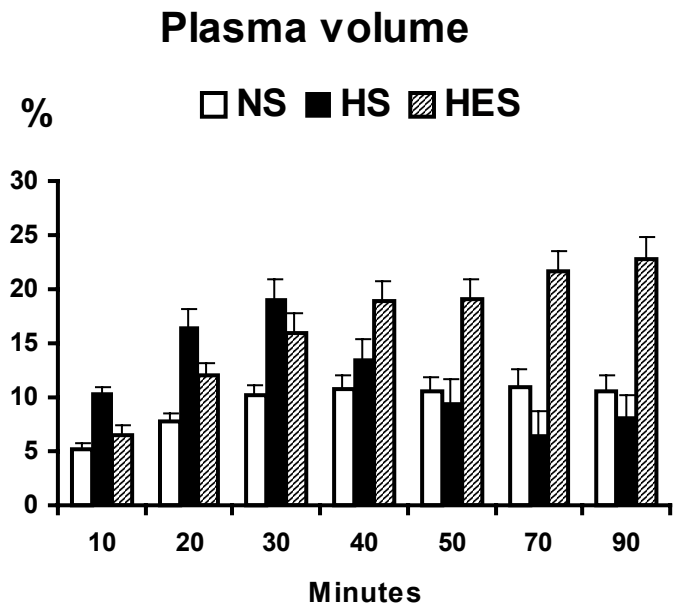
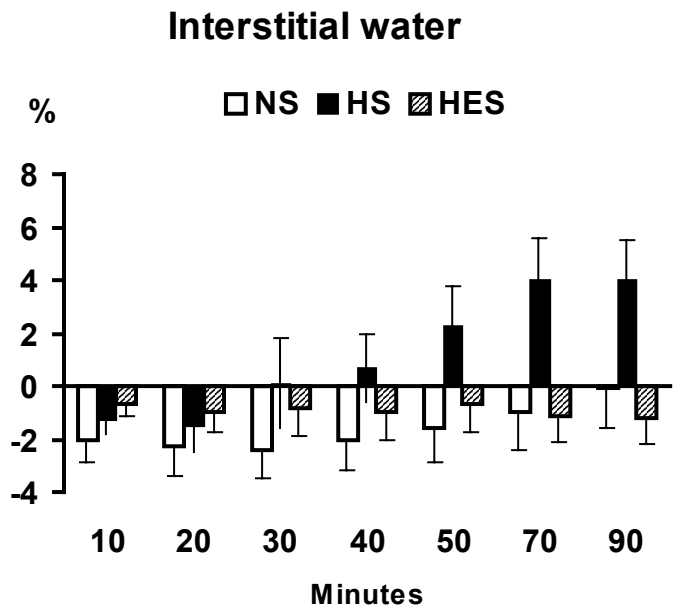


Figure 7. Changes in interstitial water volume (ISW) (%) after 4 ml/kg infusion of 0.9% normal saline, 7.5% hypertonic saline (HS) and 6% hydroxyethylstarch (HES).



Weight gain was measured in studies I and III. In study I, the difference in weight gain between the study groups did not reach statistical significance (1.0±1.1 kg vs. 1.7±1.7 kg in the HS group and NS group, respectively). Study I was not designed to evaluate the difference in weight gain. Therefore, the sample size may not be large enough. Whereas study III, which contained patients from studies I and II, was designed to evaluate weight gain. A statistically significant difference was found between the study groups ($p=0.005$) indicating a reducing effect of HS on weight gain. HS had a strong effect on one hour diuresis compared to the same amount of both NS ($p<0.001$) (III) and HES ($p=0.025$) (II).

Biochemical findings

HS elevated the levels of plasma sodium both in doses of 4 ml/kg (I) and 1.6 ml/kg (V) (figure 8). Plasma chloride followed the changes in plasma sodium. Also serum osmolality was raised by HS in both doses (I, V) (figure 9). No notable changes were seen in plasma potassium during spinal anaesthesia (V). Postoperative CABG patients had an elevated plasma potassium concentration in both groups, which is not, therefore, a result of HS infusion but a result of the potassium infusion that they had been given (I). Urine sodium, potassium and osmolality were measured and reported in study I.

Figure 8. Plasma sodium (P-Na) after HS infusion of 1.6 ml/kg and 4 ml/kg (mmol/l). Preinf= before the infusion, postinf 0= after the infusion, postinf 10= 10 min after the infusion, postinf 60= 60 min after the infusion.

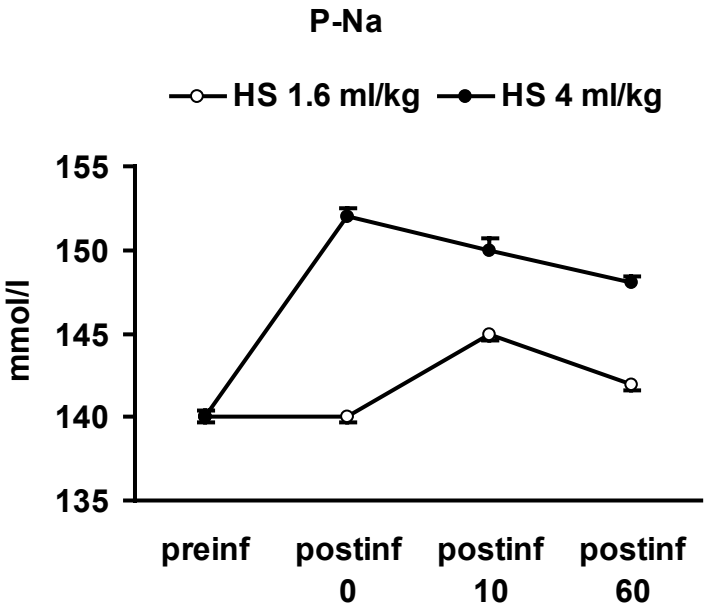
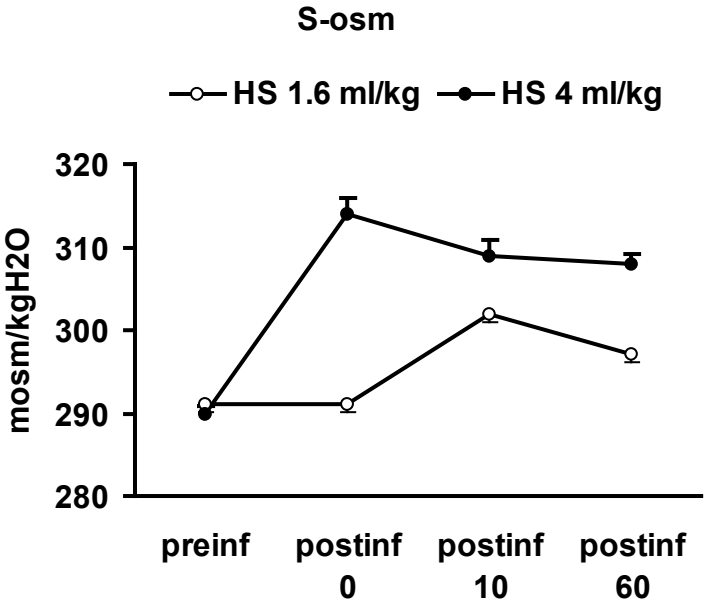
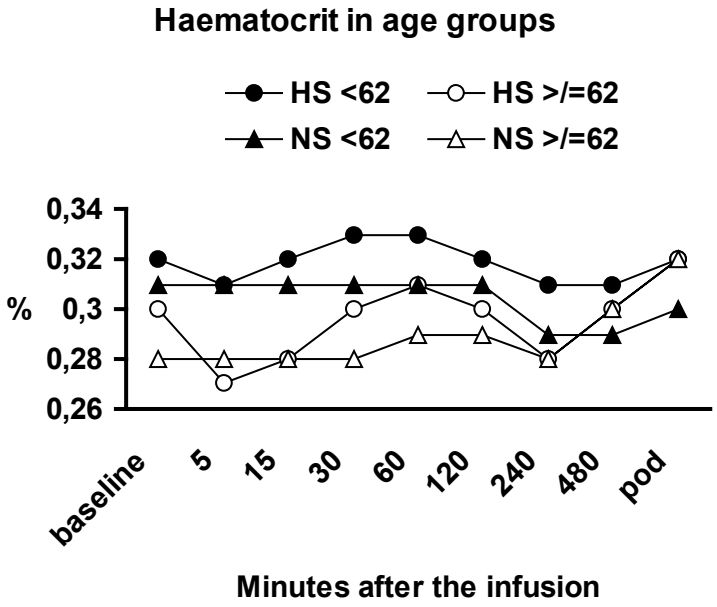


Figure 9. Serum osmolality (S-osm) after HS infusion of 1.6 ml/kg and 4 ml/kg (mosm/kgH2O). Preinf= before the infusion, postinf 0= after the infusion, postinf 10= 10 min after the infusion, postinf 60= 60 min after the infusion.



In study I, age influenced the results of haematocrit. The results after dividing the patients in age groups are presented in figure 10. A smaller dose of HS also lowered haematocrit level. The effect was comparable to that of a larger amount of NS containing the same amount of sodium (2 mmol/kg) (V).

Figure 10. Haematocrit values (%) in age-groups under 62 years and 62 years or older. Pod= first postoperative day.



Adverse events

In one patient SAP exceeded 170 mmHg after the 30 min infusion of 4 ml/kg of HS, and the HS-infusion was discontinued for five minutes (I). The infusion was then continued. No other adverse effects were seen during the studies in sedated postoperative CABG patients (I, II, III). Adverse effects, including sensation of heat and compression around the arm during the study fluid infusion and sensation of thirst, were more common in the HS group (75% of patients) than in the NS group (no adverse effects; $p<0.001$) in unsedated spinal anaesthesia patients (IV).

DISCUSSION

Methodological considerations

The thermodilution (TD) method has been shown to measure cardiac output accurately if flow is stationary (Jansen and Versprille 1995). Breathing causes temperature baseline fluctuations and therefore affects the repeatability of the TD method (Jansen et al. 1986). We have used the mean of two successive measurements with no greater than 10% difference between them and timed to end expiration.

Whole-body impedance cardiography (ICG_{WB}) has been shown to be a reliable method for the measurement of cardiac output. Comparison with the TD and direct Fick methods showed that the ICG_{WB} measures CO accurately in different conditions (in the supine position, during head-up tilt, after induction of anaesthesia, and after coronary artery bypass surgery) (Kööbi et al. 1997a, 1997b, 1999). The differences in CO values between the ICG_{WB} and TD methods were comparable to those between the direct Fick and TD methods, and the repeatability of ICG_{WB} was nearly twice as good as that of TD (Kööbi et al. 1997b, 1999). Therefore, ICG_{WB} can be considered an adequate method to estimate CO and its changes. The concern about accuracy of this method in patients with more than 15% of weight deviation (Van Der Meer et al. 1997) is not relevant in these studies, since appropriate body mass index (BMI) correction was used in all cases.

The exact volume of ECW in man remains unknown. The distribution space of substances used for ECW volume estimation ranges from about 15 (inulin and mannitol) to 23% (ions such as bromide, chloride) of body weight (Widdowson and

Dickerson 1964). Bioimpedance-derived ECW volume equations are usually fitted to some particular dilution method. The CircMon™ device calculates ECW volume on the basis of the equation derived by Kolesnikov and his group (Kööbi et al. 2000), which is fitted to thiosulphate space giving ECW values around 16% of body weight. The ECW values estimated in healthy adults using this equation (Kööbi et al. 2000) compare favourable with the reference values reported by Albert (1971). Slight overweightness may also explain the relatively low initial ECW values seen in some patients. In addition, patients undergoing an operation may have a relative ECW volume deficit after the preoperative fasting (Cohn and Angell 1971). Iodine-125-albumin was chosen for the measurement of plasma volume because this isotope distributes rapidly throughout its volume of distribution. Karanko and colleagues found approximately a 9% decrease in activity over two hours (1986). This is caused by gradual extravasation of the injected 125I-labeled albumin, and will lead to overestimation in PV at the end of the 110-minute study period. It can be assumed that the influence of albumin extravasation is similar in all treatment groups (Karanko et al. 1986), which makes comparison between them possible. The results of this study are also in agreement with the results obtained in an experimental setting (Nakayama et al. 1984). This indicator dilution technique in the measurement of plasma volume has been shown to be reproducible over 150 min in critically ill patients (Ernest et al. 1992).

Interstitial water volume was calculated using the equation: ISW=ECW-PV. This equation includes two independent factors and is, therefore, suitable for assessing the changes caused by fluid administration. Foster and Lukashi have reported good experimental correlations between whole-body bioimpedance and clinical findings related to ECW (1996). The solutions infused in this study have different conductivities which may influence the bioimpedance-derived ECW. It is difficult to estimate the significance of the conductivity-related errors, because the quantitative effects are complex and also involve varied physiological responses, including renal

excretion. Logically, the electrical conductivity of NS roughly equals the average conductivity of the human body having negligible effect on the results. As HS and HES are better conductors than NS, the bioimpedance-derived ECW may be slightly overestimated in these groups. The conductivities of HS and HES are approximately of the same magnitude. Therefore, no methodological bias is assumed between the ECW changes in these groups. As the ECW changes in the HS and NS groups were in agreement with the results obtained in previous studies using dilution techniques (Ernest et al. 1999, Onarheim 1995), it can be assumed that the differences in conductivity of the study fluids did not substantially alter the findings in the present study.

Treatment of rewarming hypovolaemia after CABG

Rewarming hypovolaemia after CABG was rapidly treated with 4 ml/kg of HS (I). CI and MAP increased significantly more with HS compared to the same dose of NS. The effect of HS lasted for about an hour. It is partly a result of the rapid dilution and re-extravasation of the HS solution in the circulation, and partly due to its intensive diuretic effect. This is also beneficial in this situation, since 800 ml/m^2 of fluid for each hour of CPB has been shown to be retained in the body (Utley et al. 1982). However, plasma volume expansion is often required because of reduced intravascular volume after open heart surgery (Karanko et al. 1986). If Ringer's solution is used for CPB priming, colloid osmotic pressure is reduced because of the dilution of serum proteins and the decrease in plasma sodium levels (Steele et al. 1997). HS is therefore beneficial not only because it increases osmolality (I) and shifts water from the extravascular space into the intravascular space thus expanding plasma volume (II) but also because it promotes the excretion of excessive fluid retained in the body after CPB thus reducing tissue oedema (Mazhar et al. 1998). Colloid solutions have comparable volume effect (II). In this situation, where vascular permeability is

increased, colloids may be lost in the interstitial space, and thus worsen tissue oedema. Elimination of colloids from the body is also more difficult than that of the HS solution; and the storage of hydroxyethylstarch in the reticulo-endothelial system can be particularly detrimental in patients prone to infections (Trop et al. 1992).

In our studies, HS did not decrease significantly the need for other fluid input in the ICU, but it decreased these patients' perioperative weight gain measured on the first postoperative morning (III). This was due to its strong diuretic effect. Cross and colleagues found a 30% reduction in additional fluid requirements after HS (1.8%) infusion in postoperative CABG patients, and their patients were in negative fluid balance after 8 hours (1989). HS solutions may therefore be beneficial in this situation where excess free water administration is not desired, and where tissue oedema may be detrimental to organ function.

Prevention of hypotension during spinal anaesthesia

Sympathetic blockade induced by spinal anaesthesia leads to peripheral vasodilatation and reduced systemic vascular resistance (V). Reduced cardiac preload decreases cardiac output, which is an important determinant of haemodynamic stability. Spinal anaesthesia eliminates the ability of the cardiovascular system to alter systemic vascular resistance in order to maintain adequate blood pressure and perfusion pressure to different organs (Marhofer et al. 1999). Another way that the body maintains blood pressure is by increasing cardiac output through higher heart rate or increased stroke volume. Patients with compromised heart conditions can not increase stroke volume. Tachycardia, on the other hand, is of limited value if the shortening of diastolic time leads to insufficient cardiac filling or coronary artery perfusion (McRae and Wildsmith 1993). Therefore, correction of the relative hypovolaemia and cardiac preload plays an important role in

prevention and treatment of hypotension during spinal anaesthesia.

The relatively small reduction in incidence of hypotension following crystalloid preload has challenged the investigators' perception of its value (Rout et al. 1993). Indeed, crystalloid preload with Ringer's solution in either smaller (8 ml/kg) or larger (16 ml/kg) doses had no effect on the incidence of hypotension after spinal anaesthesia in fit, elderly patients (Coe and Revanäs 1990). Colloid preloading with 6% hetastarch has been associated with lower incidence of spinal anaesthesia-induced hypotension compared to double volume of lactated Ringer's solution (Sharma et al. 1997). On the other hand, Buggy and colleagues found no difference on the effect of colloid preloading with polymerized gelatin on spinal anaesthesia-induced hypotension over preloading with crystalloid solution in a similar amount or no preloading at all (1997). This raises a question of the meaning of volume preloading in general. Ueyama and colleagues, however, suggest that the augmentation of blood volume with preloading, regardless of the fluid used, must be large enough to result in a significant increase in cardiac output for effective prevention of hypotension (1999). In the present study, HS (7.5%) increased cardiac output as effectively as eight times the volume of NS (0.9%), presumably by increasing preload, to maintain adequate arterial pressure during spinal anaesthesia (IV). Haemodilution, which indicates plasma volume increase, and exracellular water volume increase were similar in patients receiving 1.6 ml/kg of HS and in patients receiving 13 ml/kg of NS (V). The volume effect of HS was therefore achieved by redistributing the fluid that was already in the body, and thus without causing any marked fluid overload. The present results are in line with those obtained after using the same volume of hypertonic and isotonic fluids for prevention of spinal anaesthesia-induced hypotension (Baraka et al. 1994, Wang et al. 1997) and those obtained after using an equal amount of sodium in preloading before extradural anaesthesia (Veroli and Benhamou 1992).

Adverse events

In the present study, no notable adverse effects related to the HS infusion were seen in studies I, II and III. In one patient SAP exceeded 170 mmHg, and the HS-infusion was discontinued for five minutes. The infusion was then continued. HS had strong and rapid haemodynamic effects which increase mean arterial pressure rapidly to values of 100 mmHg or greater. This may not be advantageous in the early postoperative period of CABG patients with limited cardiac reserve. In these studies, the commonly used fixed dosage of 4 ml/kg body weight of HS-solution was used but it may not be an ideal dosage. Ellinger and colleagues have shown that 4 ml/kg of 7.5% saline/10% hydroxyethylstarch is too high in cardiac risk patients with slight hypovolaemia, and that it should be titrated individually (1995). The group of patients receiving 4 ml/kg of 7.5% saline without colloid did not have significantly higher PACWP values compared to the NS group. This could, however, be the case if HS was given as a 3 to 5 min bolus injection used in many animal studies. Infusion rate is therefore important. A 30 min infusion instead of a 3 to 5 min bolus injection was used to avoid side effects such as hypertension (both systemic and pulmonary) and arrhythmia (Kien et al. 1997). On the other hand, an initial period of hypotension has also been reported after rapid (3 ml/kg of HS in 1 min) infusion (Kien et al. 1991b). This initial decrease in arterial blood pressure was abrupt and transient (106±9 s) and was followed by a significant improvement in haemodynamics compared to the baseline values. Besides hypotensive episodes, sudden increases in PACWP, and ventricular arrhythmias have been reported after rapid infusion (250 ml in 15 mins) of HS (Sirieix et al. 1999). There is also evidence to the contrary; HS may also reduce pulmonary vascular resistance and decrease pulmonary hypertension (Nerlish et al. 1983). An ideal infusion rate in this setting could be around 30 minutes.

The patients investigated in studies IV and V were awake with no routine premedication. Fentanyl (50 μg) was given before spinal puncture. The patients in the HS group complained about the sensation of heat and compression around the arm during the HS infusion. These symptoms were well-tolerated and disappeared immediately after the completion of the HS infusion. Heat and pain are probably caused mainly by the high osmolality of the HS solution and cannot be eliminated totally (Himi et al. 1996). These unpleasant feelings were localised around the peripheral vein used for the infusion. A central infusion of hypertonic solution also causes heat and pain sensations (Tollofsrud et al. 1998). The patients of the HS group also felt thirsty until they were allowed to drink.

CONCLUSIONS

The following conclusions can be drawn from the studies:

1. In the treatment of rewarming hypovolaemia after CABG, hypertonic saline (7.5%) increased mean arterial pressure and cardiac output significantly more compared to normal saline (0.9%). The haemodynamic effects of HS lasted for about one hour.

2. Hypertonic saline (7.5%) changed the fluid volumes most rapidly: the increase in PV reached twice the infused volume of HS by the end of the infusion as did also the increase in ECW. ISW increased but more slowly. Normal saline (0.9%) increased the PV and ECW by its own volume but slightly decreased the ISW. Hydroxyethylstarch (6%) increased PV and ECW twice its own volume by the end of the study, and decreased ISW.

3. A single dose of 4 ml/kg of hypertonic saline (7.5%) compared to 4 ml/kg of normal saline (0.9%) reduces the weight gain by approximately half in CABG patients after the CPB.

4. The clinical effect of hypertonic saline (7.5%) was comparable to that of normal saline (0.9%) for preloading before spinal anaesthesia when the amount of sodium was kept unchanged. HS was effective in a small dose of 1.6 ml/kg.

5. A small dose of 1.6 ml/kg of hypertonic saline (7.5%) increases the extracellular water, plasma volume and cardiac output enough to maintain haemodynamic stability during spinal anaesthesia.

SUMMARY

The present study was conducted in order to investigate the effects of hypertonic saline 75 mg/ml (7.5%) on haemodynamics, extracellular water volumes and weight gain. Studies I, II and III were carried out in postoperative CABG patients during the rewarming period. Studies IV and V were carried out in patients undergoing lower limb orthopaedic surgery with spinal anaesthesia.

Cardiac output was measured using invasive thermodilution method and non-invasive whole-body bioimpedance cardiography. The whole-body bioimpedance cardiography was also used for the measurement of extracellular water volume, while plasma volume was determined as the distribution volume of 125-I-labeled human serum albumin (125I-HSA) in postoperative CABG patients.

Postoperative rewarming hypovolaemia of CABG patients was treated with 4 ml/kg of HS. HS was also compared with the same volume of NS and HES. The effect of HS on CI was significantly more positive than that of NS and HES, but it lasted only about an hour. The strong diuretic effect of HS may be a contributing factor to the short duration of action.

Compared to NS and HES, HS changed the extracellular fluid volumes most rapidly: the increase in PV reached twice the infused volume of HS by the end of the infusion. At the end of the study, however, the increase in PV was smaller than the infused HS-volume. ECW also increased rapidly, since the initial extra water in the circulation was most probably drawn from the intracellular space by the hyperosmotic influence of HS. The increase of ISW was slower. This could be due to the fluid shift from the intracellular to the extracellular compartment but partly also to the fluid efflux

from the intravascular space into the interstitial space after dilution of the hypertonic saline. HS also resulted in smaller perioperative weight gain by promoting the excretion of the excess fluid retained in the body after CPB.

HS is an alternative for preloading before spinal anaesthesia in situations where excess free water administration is not desired. It is effective in small doses of 1.6 ml/kg, which increase the extracellular water, plasma volume and cardiac output, and thus maintain haemodynamic stability during spinal anaesthesia.

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ORIGINAL COMMUNICATIONS