Effect of 7.2% Hypertonic Saline/6% Hetastarch on Left Ventricular Contractility in Anesthetized Humans

Axel W. Goertz, M.D.,* Tobias Mehl, M.D.,† Karl H. Lindner, M.D., Michael G. Rockemann, M.D.,* Uwe Schirmer, M.D.,* Bernhard Schwick, M.D., Michael Georgiell, M.D.§

Background: Although a positive inotropic effect of hypertonic saline has been demonstrated in isolated cardiac tissue as well as in animal preparations, no information exists about a possible positive inotropic action of hypertonic saline in humans. The aim of this investigation was to determine whether a clinically relevant positive inotropic effect can be demonstrated in humans.

Methods: Twenty-six patients without cardiovascular disease were randomized to receive 4 ml/kg of either 7.2% hypertonic saline/6% hetastarch or 6% hetastarch (control) at a rate of 1 ml·kg⁻¹·min⁻¹ while under general endotracheal anesthesia. Transesophageal echocardiography was used to evaluate left ventricular function. Arterial pressure, heart rate, and left ventricular end-systolic and end-diastolic diameter, area, and wall thickness were measured immediately before and after administration of either solution. Fractional area change, end-systolic wall stress, and the area under the end-systolic pressure-length relationship curve (ESPLRarea) were calculated. ESPLRarea was used to assess left ventricular contractility.

Results: Administration of hypertonic saline/hetastarch resulted in a significant decrease of mean arterial pressure and end-systolic wall stress from 77 ± 14 (mean ± SD) to 64 ± 17 mmHg (P < 0.01) and from 52 ± 14 to 32 ± 11 (P < 0.01), respectively. End-diastolic area and fractional area change increased from 16.5 ± 2.9 to 21.7 ± 3.3 cm² (P < 0.01) and from 0.53 ± 0.05 to 0.70 ± 0.06 (P < 0.01), respectively, whereas there was only a minor change of ESPLRarea from 38 ± 13 to 44 ± 13 mmHg · cm (P < 0.05).

Conclusions: The apparent improvement of left ventricular systolic function in response to hypertonic saline/hetastarch is caused mainly by the combined effect of increased left ventricular preload and reduced left ventricular afterload. A possible positive inotropic action of hypertonic saline/hetastarch is not likely to be clinically relevant. (Key words: Anesthesia; general. Heart: contractility; end-systolic pressure-length relationship; isotropic state. Measurement techniques: echocardiography. Saline solution: hypertonic.)

HYPERTONIC saline given in small volumes has been shown to be effective in the treatment of hypovolemic shock in various animal species1-3 and in humans. In addition to its use in the care of traumatized patients, hypertonic saline has been proposed for intraoperative volume replacement.4-13 The hemodynamic effect of hypertonic saline is based on osmotic translocation of extracellular and intracellular water into the vascular compartment,15 on peripheral vasodilation,16 and on improvement of regional blood flow.17 Furthermore, an increase of myocardial contractility has been demonstrated in isolated cardiac tissue,16 isolated hearts,10 and animal preparations.18 However, no data are available about the influence of hypertonic saline on left ventricular contractility in humans and about the possible clinical relevance of such influence. This lack of clinical data is due to the multiple sites of action of hypertonic saline and the complex interaction of preload, afterload, and contractility. In particular, it is difficult to assess changes in left ventricular contractility in a clinical setting with changes in afterload occurring at the same time.

In this study, we used a modification of the end-systolic pressure-length relationship (ESPLR) as an index of left ventricular contractility. Left ventricular dimensions were obtained using transesophageal echocardiography. All measurements were performed in anesthetized patients without cardiovascular disease and under normovolemic conditions. Normovolemia was chosen because hypovolemic and hypotensive states...
may be associated with impaired left ventricular contractility on the basis of impaired myocardial perfusion or based on possible effects of circulating negative inotropic mediators. Correction of these states per se could result in improved left ventricular performance.

Materials and Methods

Study Population

After approval by the Ethics Committee of our institution and written informed consent was received, 26 patients of either sex scheduled for minor elective abdominal or orthopedic surgery were enrolled in the study. All subjects were ASA physical class status 1 or 2 adults. Exclusion criteria were any kind of cardiovascular or neurologic disorder, any electrolyte imbalance, or any contraindication to transesophageal echocardiography, such as esophageal or gastric pathology. Two of the patients were excluded during the course of the study because of a poor quality of the echocardiographic recordings.

Protocol

The patients were studied before surgery under general anesthesia. All received 20 mg chloralhydrate diphosphate per os the night before surgery and again 2–4 h before surgery. On arrival in the operating room, a 14-G cubital vein cannula, a 20-G radial artery catheter, and electrocardiogram leads were placed. General anesthesia was induced using midazolam (0.1 mg/kg) and fentanyl (5 μg/kg) intravenously. Neuromuscular block was performed using vecuronium (0.1 mg/kg) intravenously. The trachea was intubated, and respiration was controlled by intermittent positive pressure ventilation. The respiratory rate was 10 breaths/min. We used 40% O2 in nitrous oxide. Tidal volume and, therefore, minute volume was adjusted to achieve normocapnia (PETCO₂ 35–45 mmHg). Additional doses of fentanyl were administered when the patients reacted to laryngoscopy with an increase of heart rate or mean arterial pressure by more than 20% of the preinduction values. The echocardiographic probe then was inserted, and the patient left with no stimulation for 10 min.

The patients were randomized to receive either 4 ml/kg of a 7.2% hypertonic saline/6% hetastarch 200/0.5 (molecular weight/degree of substitution) solution (group HS-HES) or the same volume of 6% hetastarch 200/0.5 (HAES-steril, group HES, control). (Both solutions were provided by Fresenius, Bad Homburg, Germany.) Each solution was given as an intravenous infusion over 4 min (1 ml·kg⁻¹·min⁻¹) via cubital vein cannula. Hemodynamic measurements were performed immediately before start of either infusion (baseline) and just after termination of infusion.

Hemodynamic Measurements and Calculations

An Ultramark 9 ultrasound system with a 5-MHz transducer (Advanced Technology Laboratory, Bothwell, WA) was used to perform the echocardiographic studies. The transducer was advanced to a position where cross-sectional images of the left ventricle at the level of the midpapillary muscle could be obtained. The two-dimensional registrations were displayed with an electrocardiogram lead II curve and were recorded on VHS-format videotape. Arterial pressure curve and an electrocardiography tracing were recorded simultaneously using a strip chart recorder (Siredec 220, Siemens, Erlangen, Germany) at a speed of 25 mm/s. Care was taken to synchronize the video and the strip chart recorder (by using event markers) to facilitate analysis of the data on a beat-to-beat basis.

The following parameters were measured from the echocardiographic recordings: left ventricular end-systolic and end-diastolic diameter (ESD, EDD), end-systolic and end-diastolic cross-sectional area (ESA, EDA), and end-systolic wall thickness (ESWT). Encompassing and pericardial lines were identified according to the leading edge method. End-diastole was indicated by the peak of the R-wave. End-systole was defined as the smallest systolic endocardial area. Wall thickness was measured at the anterior wall of the left ventricle. The following parameters were calculated:

Fractional area change:

\[
FAC = \frac{(EDA - ESA)}{EDA}
\]

End-systolic meridional wall stress:

\[
ESWS = \frac{1.332 \times SAP \times ESD}{4 \times ESWT \times (1 + ESWT/ESA)} \times [10^3 \times \text{dyne} \times \text{cm}^2]
\]

According to Reichek et al., we included (peak) systolic arterial pressure in our calculation of end-systolic wall stress, which has been shown to correlate well with invasively measured wall stress in a variety of clinical conditions.

Left ventricular contractility was assessed using the concept of end-systolic pressure-length relation-

![Fig. 1. Schematic of the end-systolic pressure-length curve.](image)

Table 1. Demography

<table>
<thead>
<tr>
<th>Group</th>
<th>(HS/HES)</th>
<th>(HES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>(HS/HES)</td>
<td>(HES)</td>
</tr>
</tbody>
</table>

Data are absolute value.

* M = male; F = female
* P < 0.05 versus control
HYPERTONIC SALINE AND CARDIAC CONTRACTILITY

![Diagram of end-systolic pressure-length relationship area (ESPLRarea)](image)

*Fig. 1. Schematic illustration of the method used to obtain end-systolic pressure-length relationship area (ESPLRarea). The linear relationship between end-systolic pressure (P) and left ventricular end-systolic diameter (D) is characterized by its slope (E_max) and its length axis intercept (D_o). The minimum (D_min) and maximum (D_max) end-systolic left ventricular diameters measured during the baseline period served as the limits of integration to calculate the area beneath the curve (ESPLRarea, dark shaded area). After positive inotropic intervention, the curve is shifted up or to the left of baseline. ESPLRarea of this curve (total shaded area) is obtained using D_min and D_max of the control period.*

The area on the x-axis were given by the highest and lowest end-systolic diameter obtained during baseline:

$$\text{ESPLR}_{\text{area}} = \frac{2P_0 + E_{\text{max}} (D_{\text{max}} - D_{\text{min}})}{2}$$

with $P_0$ being the pressure axis intercept (fig. 1). To avoid baroreceptor reflex-mediated influences in response to blood pressure increase, we confined the measurement of corresponding pressure-diameter values to the beginning of the increase in arterial pressure, before any lengthening of the electrocardiogram RR-interval occurred.\(^{52}\)

Evaluation of the echocardiographic registrations was performed off line on an electronic device (Cardio 200, Kontron Instruments, Germany) by two independent investigators. Interobserver variability, which was assessed before a series of studies, was reported with an earlier publication.\(^{15}\)

Statistical Analysis

Statistical evaluation was performed using a personal computer-based program (StatView IV, Abacus Concepts, Berkeley, CA). All hemodynamic data and the numeric biometric data in groups HS-HES and HES were compared using the Wilcoxon's U test. Analysis between the groups was performed at baseline and after treatment. The effect of both treatments in each group was analyzed using Wilcoxon's signed-rank test. The chi-square test was used to evaluate the category characteristics of both groups. All data are given as mean ± SD. A value of $P < 0.05$ indicated statistical significance.

Results

The biometric characteristics in groups HS-HES and HES are presented in table 1. There was no significant difference in sex, ASA physical status, age, height, and

| Table 1. Demographic Data in Group 1 (HS/HES) and Group 2 (HES, Control) |
|------------------|--------|----------------|--------|----------------|--------|----------------|
|                  | M/F    | ASA (III) (n) | Age (y) | Weight (kg)   | Height (cm) | BSA (m²)   |
| Group 1 (HS/HES) | 4/7    | 5/6           | 40 ± 12 | 67 ± 15*      | 170 ± 13    | 1.77 ± 0.25 |
| Group 2 (HES)    | 9/4    | 6/7           | 44 ± 11 | 80 ± 14       | 172 ± 9     | 1.93 ± 0.19  |

Data are absolute numbers (n/%) and arithmetic means ± SD, respectively.

M = male; F = female; ASA = American Society of Anesthesiologists physical status group; BSA = body surface area.

* $P < 0.05$ versus control (Group 2, HES).

Anesthesiology, Vol 82, No 6, Jun 1995
Table 2. Hemodynamic Data before and after Administration of HS/HES (Group 1) or HES (Group 2, Control)

<table>
<thead>
<tr>
<th></th>
<th>SAP (mmHg)</th>
<th>DAP (mmHg)</th>
<th>HR (beats/min)</th>
<th>EDA (cm²)</th>
<th>ESA (cm²)</th>
<th>FAC</th>
<th>ESWS (10¹¹ dyne/cm²)</th>
<th>Emax (mmHg/cm)</th>
<th>D₀ (cm)</th>
<th>ESPLRmax (mmHg/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HS/HES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>109 ± 15</td>
<td>61 ± 15</td>
<td>51 ± 8</td>
<td>16.5 ± 2.9</td>
<td>7.9 ± 2.1</td>
<td>0.53 ± 0.07</td>
<td>52 ± 14</td>
<td>58 ± 15</td>
<td>1.1 ± 1.0</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>After</td>
<td>93 ± 21†</td>
<td>50 ± 15†</td>
<td>60 ± 9†</td>
<td>21.7 ± 3.3†</td>
<td>6.5 ± 1.6†</td>
<td>0.70 ± 0.06††</td>
<td>32 ± 11††</td>
<td>66 ± 16††</td>
<td>1.3 ± 0.9</td>
<td>44 ± 13††</td>
</tr>
<tr>
<td><strong>HES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>112 ± 8</td>
<td>62 ± 7</td>
<td>56 ± 9</td>
<td>19.3 ± 4.1</td>
<td>10.2 ± 3.6</td>
<td>0.49 ± 0.09</td>
<td>59 ± 11</td>
<td>51 ± 16</td>
<td>1.2 ± 0.7</td>
<td>34 ± 13</td>
</tr>
<tr>
<td>After</td>
<td>112 ± 10</td>
<td>60 ± 9</td>
<td>55 ± 9</td>
<td>21.9 ± 6.1*</td>
<td>12.8 ± 5.4*</td>
<td>0.44 ± 0.09</td>
<td>71 ± 11*</td>
<td>51 ± 15</td>
<td>1.4 ± 0.8</td>
<td>34 ± 17</td>
</tr>
</tbody>
</table>

Data are arithmetic means ± SD.

MAP = mean arterial pressure; HR = heart rate; EDA = left ventricular end-diastolic area; ESA = left ventricular end-systolic area; FAC = fractional area change; ESWS = left ventricular end-systolic wall stress; Emax = maximal elastance (slope of the linear end-systolic pressure-length relationship); D₀ = length-axis intercept of the end-systolic pressure-length relationship curve; ESPLRmax = area under the end-systolic pressure-length relationship curve between defined limits.

†P < 0.05 versus baseline (before).
††P < 0.01 versus baseline (before).
§P < 0.05 versus HES.
§§P < 0.01 versus HES.
*P < 0.001 versus HES.

Discussion

In this study, the subjects were divided into two groups: those with blood pressure between 110/70 and 139/89 mmHg (control group) and those with blood pressure between 140/90 and 160/100 mmHg (treated group). The treatment group received HES intravenously, while the control group received saline intravenously. The results showed that both groups had a decrease in arterial pressure and heart rate, but the treated group had a significantly greater decrease in arterial pressure and heart rate compared to the control group. The decrease in arterial pressure and heart rate was accompanied by a decrease in central venous pressure, indicating that the treatment had a significant effect on preload and afterload. The treatment group also had a significant increase in stroke volume, indicating that the treatment had a significant effect on cardiac output. The results suggest that HES is an effective treatment for hypertension, and that further studies are needed to determine the optimal dose and duration of treatment.

References


Hypertension is a chronic condition that affects millions of people worldwide. It is a major risk factor for cardiovascular disease, stroke, and kidney disease. The incidence of hypertension is increasing, especially in developing countries. The management of hypertension is important to reduce the risk of complications and improve quality of life. The treatment of hypertension is usually non-pharmacological and pharmacological. Non-pharmacological interventions include lifestyle modifications, such as dietary changes, exercise, and weight loss. Pharmacological interventions include the use of medications to lower blood pressure. The choice of medication depends on the patient's individual characteristics, such as age, gender, blood pressure level, and comorbidities.
developed signs of a volume overload. In addition, none of the subjects experienced thrombophlebitis as a result of hypertonic saline infusion.

Discussion

In this study, the predominant effect of hypertonic saline/hes gas was an increase of left ventricular preload, a decrease of left ventricular afterload, and an increase in left ventricular fractional area change. This apparent improvement of left ventricular systolic function appeared to be caused mainly by the decrease in afterload rather than by an enhancement of left ventricular contractility.

For each milliliter of hypertonic saline infused, plasma volume is known to increase by approximately 3 ml, which is the basis of the concept of “small volume resuscitation.” According to this, left ventricular preload could have been expected to be greater after infusion of hypertonic saline/hes than after equal volumes of hes alone. The fact that, in our study, both treatments increased left ventricular preload, measured as end-diastolic area, to a similar degree may be due to the interdependence of left ventricular preload, afterload, and systolic function. The decrease in left ventricular end-systolic wall stress that occurred after hypertonic saline/hes gas led to an increase in left ventricular stroke volume (which can be assessed by calculating the stroke area from left ventricular end-diastolic and end-systolic area), which is, in view of an unchanged or slightly increased heart rate, indicative of an increased cardiac output. As a consequence, the influence of a hypertonic saline-induced increase of systemic venous return on left ventricular preload was compensated in part by the increase of cardiac output that occurred at the same time.

Arterial pressure decreased after administration of hypertonic saline/hes. This phenomenon, based on peripheral vasodilation, has been attributed to increases of serum osmolality with or without changes in plasma sodium ion concentration. Although there is still discussion about the mechanism of this vasodilation, it generally is believed that the degree of arterial hypotension depends on the rate of administration of the hypertonic solution. Although there are reports about the administration of hypertonic saline at a rate of 2 ml · kg⁻¹ · min⁻¹ as being effective and safe, the results of this study demonstrate that even infusion rates as low as 1 ml · kg⁻¹ · min⁻¹ may be associated with marked degrees of arterial hypotension.

The principal purpose of this study was to determine whether the administration of hypertonic saline/hes gas was associated with a clinically relevant improvement of left ventricular contractility. Although the slight increase of ESPVRmax from 38 to 44 mmHg · cm⁻² · min⁻¹ was statistically significant, it is unlikely to be clinically relevant. Furthermore, no statistical difference to the control group could be demonstrated. This is in contrast to the results from Kien et al. who studied the effect of 5 ml/kg of 7.5% hypertonic saline on left ventricular contractility and blood flow distribution in anesthetized dogs subjected to hemorrhage. They used ESPVRmax of the ESPLR as a measure of left ventricular contractility and found an increase of ESPVRmax by about 25% in response to hypertonic saline. Delayance et al. investigated the influence of hypertonic solutions with varying sodium concentrations (from 140 to 180 mmol/l) on myocardial performance in isolated blood-perfused rabbit hearts. They observed increasing dP/dtmax values with increasing perfuse sodium concentrations. In our study, possible influences from cardiovascular reflexes must be considered. There was a slight but significant cardiac acceleration after hypertonic saline/hes gas, which can be interpreted as baroreceptor reflex-mediated response to the decrease of arterial pressure. This, in turn, could indicate (besides a change of cardiac parasympathetic tone) an increase of efferent sympathetic outflow to the heart and, therefore, a positive inotropic action. As a consequence, the minor increase of ESPVRmax seen in this study could be the result of a baroreceptor reflex-mediated response to hypertonic saline-induced arterial hypotension rather than an intrinsic effect of hypertonic saline.

We recognize other limitations in our methods. We performed our study using patients without cardiovascular disease. Possible positive inotropic effects of hypertonic saline, with appeared to be clinically irrelevant in this study, could be more marked in subjects with impaired left ventricular function. We are not aware of information about hemodynamic effects of hypertonic saline in relation to the degree of left ventricular impairment. Normovolemia was chosen as a baseline condition because correction of hypovolemic and hypotensive states per se could result in an improvement of left ventricular contractility and, therefore, could interfere with an intrinsic effect of hypertonic saline. All measurements were performed in anesthetized patients. Although the influence of midazolam, fentanyl, and nitrous oxide on left ventricular contractility can be assumed to be minor (and equal

in both groups), the effect of all three agents on cardiovascular reflexes must be considered. It is well known that midazolam as well as fentanyl or nitrous oxide may cause a decrease of arterial baroreceptor reflex-sensitivity in a dose-dependent manner. As a consequence, the baroreceptor reflex-mediated cardiac stimulation that might have occurred in response to the hypertonic saline-induced drop in arterial pressure would have been more marked in awake subjects. Left ventricular pressure was not obtained in our patients. Instead we used peripheral artery pressure measured in the radial artery, which could have led to false high or low arterial pressure readings due to phenomena of resonance or damping, respectively.

We conclude that the administration of 7.2% hypertonic saline/hetastrach at the rate of 1 ml·kg⁻¹·min⁻¹ caused an increase of left ventricular preload and a decrease of left ventricular afterload, the latter leading to marked degrees of arterial hypotension in some patients. After hypertonic saline/hetastrach infusion, there was an improvement of left ventricular systolic performance, assessed as left ventricular fractional area change, which most likely was due to the changes in cardiac loading. The small positive inotropic effect that could be demonstrated could be the result of either baroreceptor reflex-mediated sympathic activation of the heart or a direct action of hypertonic saline on the myocardium.

References

HYPERTONIC SALINE AND CARDIAC CONTRACTILITY


31. Pagel PS, Kamptine JP, Schmelting WT, Wadler DC: Comparison of end-systolic pressure-length relations and preload recruitable stroke work as indices of myocardial contractility in the conscious and anesthetized, chronically instrumented dog. Anesthesiology 74:278-290, 1990


