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

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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 (ESPLRₐuv) were calculated. ESPLRₐuv 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 dyne/cm² (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 ± 0.07 to 0.70 ± 0.06 (P < 0.01), respectively, whereas there was only a minor change of ESPLRₐuv, from 58 ± 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 species and in humans. In addition to its use in the care of traumatized patients, hypertonic saline has been proposed for intraoperative volume replacement. The hemodynamic effect of hypertonic saline is based on osmotic translocation of extracellular and intracellular water into the vascular compartment, on peripheral vasodilation, and on improvement of regional blood flow. Furthermore, an increase of myocardial contractility has been demonstrated in isolated cardiac tissue, and animal preparations. 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 hypertensive 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 transthoracic 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 clorazepate dipotassium *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 electrocardiogram tracing were recorded simultaneously using a strip chart recorder (Sirecrod 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). Endocardial 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**:
  
  \[
  \text{FAC} = \frac{(\text{EDA} - \text{ESA})}{\text{EDA}}
  \]

- **End-systolic meridional wall stress**:
  
  \[
  \text{ESWS} = \frac{1.332 \times \text{SAP} \times \text{ESD}}{4 \times \text{ESWT} \times (1 + \text{ESWT}/\text{ESD})} \times [10^3 \times \text{dyne} \times \text{cm}^2]
  \]

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.
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![Diagram](image)

**Fig. 1. Schematic illustration of the method used to obtain end-systolic pressure-length relationship area (ESPLR<sub>area</sub>).** The linear relationship between end-systolic pressure (P) and left ventricular end-systolic diameter (D) is characterized by its slope (E<sub>max</sub>) and its length axis intercept (D<sub>0</sub>). The minimum (D<sub>min</sub>) and maximum (D<sub>max</sub>) end-systolic left ventricular diameters measured during the baseline period served as the limits of integration to calculate the area beneath the curve (ESPLR<sub>area</sub>, dark shaded area). After positive inotropic intervention, the curve is shifted up or to the left of baseline. ESPLR<sub>area</sub> of this curve (total shaded area) is obtained using D<sub>min</sub> and D<sub>max</sub> of the control period.

Instead of end-systolic pressure, which is difficult to obtain under clinical conditions, we used peak-systolic pressure, which has been demonstrated to correlate with end-systolic dimension in a linear fashion. In addition to the slope of the linear relationship (maximal elastance, E<sub>max</sub>) and the length axis intercept (D<sub>0</sub>) we calculated the area under the curve between defined limits (ESPLR<sub>area</sub>), which has been suggested to be more reliable in assessing changes in contractility than either E<sub>max</sub> or Vo. According to Crotogini et al., we calculated the area under the ESPLR-curve as the area of a trapezoid. The limits of the area on the x-axis were given by the highest and lowest end-systolic diameter obtained during baseline:

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

with P<sub>0</sub> 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.

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.

**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 (n/n)   | ASA (II) (n/n) | Age (yr)        | 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/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).

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body surface area between the two groups. However, body weight was greater in group HES compared to group HS-HES ($P = 0.05$).

Hemodynamic data obtained during the course of our measurements are presented in Table 2. At baseline, there were similar hemodynamic conditions in both groups with no significant difference between the groups for any of the hemodynamic parameters. The administration of hetastarch led to a significant change in blood pressure. In contrast, hypertonic saline/hetastarch caused a decrease of systolic and diastolic arterial pressure from 109 to 93 mmHg (arithmetic mean, $P = 0.008$) and from 61 to 50 mmHg ($P < 0.005$), respectively. For systolic and diastolic arterial pressure, this decrease resulted in a significant difference to group HES with $P = 0.005$ and 0.007, respectively. Some individuals showed a marked degree of arterial hypotension in response to hypertonic saline/hetastarch, with a lowest mean arterial pressure ranging from 45 to 108 mmHg. Heart rate was not altered in group HES, whereas there was a slight but significant ($P = 0.02$) increase after hypertonic saline/hetastarch administration. However, there was no difference in heart rate between the groups. There were similar increases of end-diastolic and end-diastolic area in response to hetastarch associated with an unchanged fractional area change. In group HS-HES, end-diastolic area increased ($P = 0.003$) despite insignificant changes of end-systolic area. As a consequence, fractional area change increased from 0.53 to 0.70 ($P = 0.003$) with a highly significant difference to group HES ($P < 0.0001$). Left ventricular afterload, measured as end-systolic wall stress, was influenced by both treatments in opposite directions. While HES increased end-systolic wall stress from 50 to 71 10$^{-3}\cdot$dyne$\cdot$cm$^{-2}$ ($P = 0.01$), there was a decrease from 52 to 32 10$^{-3}\cdot$dyne$\cdot$cm$^{-2}$ ($P = 0.004$) in response to hypertonic saline/hetastarch. Again the difference between the groups was highly significant ($P < 0.0001$). ESPLR$_{rea}$ was used to assess left ventricular contractility. Although there was no change of ESPLR$_{rea}$ in response to HES, a small but significant increase could be observed in group HS-HES ($P = 0.003$). Compared to group HES, however, any difference remained below the level of significance. $E_{max}$ appeared to be slightly higher in group HS HES compared to group HES after treatment ($P = 0.052$), but a significant change versus baseline could not be demonstrated.

We did not observe any complications during the course of our study. In particular, none of the patients developed signs of severe hypotension.

**Discussion**

In this study, the use of hypertonic saline/hetastarch, a dose which is commonly used in clinical practice, caused a significant decrease in systemic vascular resistance apparent immediately after infusion. This may indicate an afterload reduction, as the CRT was increased.

For each increment of plasma volume with saline, 10 ml, the volume required to increase peripheral resistance by a given amount after infusion of saline, was unchanged. This means that equal volume increments of saline may have been ineffective in the study, both in terms of left ventricular afterload. However, a decrease of left ventricular afterload, after hypertonic saline/hetastarch, may be due to an increase in left ventricular systolic pressure, by calculating $E_{max}$ as: left ventricular end-systolic area, systolic wall stress, $E_{max}$ = maximum pressure-volume relationship slope. $E_{max}$ and left ventricular end-systolic area were the two most important parameters in this study. However, despite the significant change in systolic wall stress, $E_{max}$ did not change significantly. Nevertheless, the decrease in left ventricular end-systolic area was highly significant ($P < 0.0001$).

Hypertonic saline/hetastarch had no significant effect on peripheral resistance and afterload in this study. However, this does not mean that hypertonic saline/hetastarch has no effect on peripheral resistance and afterload. There is still a need for further studies to determine the optimal dose of arterial hypertonic saline/hetastarch.

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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/hesastarch 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,15 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/hesastarch than after equal volumes of hesastarch 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.54 The decrease in left ventricular end-systolic wall stress that occurred after hypertonic saline/hesastarch 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/hesastarch. This phenomenon, based on peripheral vasodilation, has been attributed to increases of serum osmolality with or without changes in plasma sodium ion concentration.35,36,39 Although there is still discussion about the mechanism of this vasodilation,37,38,39 it generally is believed that the degree of arterial hypotension depends on the rate of administration of the hypertonic solution.35,39 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,2,24 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/hesastarch is associated with a clinically relevant improvement of left ventricular contractility. Although the slight increase of ESPVRmax from 38 to 44 mmHg·cm⁻¹·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.20 They used Emax of the ESPVR as a measure of left ventricular contractility and found an increase of Emax 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.19 They observed increasing dP/dtmax values with increasing perfusate sodium concentrations. In our study, possible influences from cardiovascular reflexes must be considered. There was a slight but significant cardioacceleration after hypertonic saline/hesastarch, 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 hypertensive 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 fenatyl 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/hetaspar 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/hetaspar 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 sympathetic activation of the heart or a direct action of hypertonic saline on the myocardium.

References


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