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The haemodynamic effects of bolus versus slower infusion of intravenous crystalloid in healthy volunteers☆

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ABSTRACT

Purpose: This pilot study aimed to characterise the haemodynamic effect of 1L of IV normal saline (NS) administered as a rapid versus slow infusion on cardiac output (CO), heart rate (HR), systemic blood pressures, and carotid blood flow in six healthy volunteers.
Materials and methods: Six healthy male volunteers aged 18–65 years were randomized to receive 1L NS given over 30 min or 120 min. On a subsequent study session the alternate fluid regimen was administered. Haemodynamic data was gathered using a non-invasive finger arterial pressure monitor (Nexfin®), echocardiography and carotid duplex sonography. Time to micturition and urine volume was also assessed.
Results: Compared to baseline, rapid infusion of 1 L of saline over 30 min produced a fall in Nexfin®-measured CO by 0.62 L/min ($p < 0.001$), whereas there was a marginal but significant increase during infusion of 1L NS over 120 min of 0.02 L/min ($p < 0.001$). This effect was mirrored by changes in HR and blood pressure (BP) ($p < 0.001$). There were no significant changes in carotid blood flow, time to micturition, or urine volume produced.
Conclusions: Slower infusion of 1L NS in healthy male volunteers produced a greater increase in CO, HR and BP than rapid infusion.

1. Introduction

The administration of crystalloid fluid bolus therapy (FBT) in response to hypotension is one of the most frequent therapeutic interventions in intensive care and anaesthesia. It is predicated upon the expectation that increasing cardiac output (CO) by either correcting hypovolaemia, or increasing preload and stroke volume by the Starling mechanism will restore mean arterial pressure (MAP). Despite the ubiquitous use of this intervention, there is a surprising paucity of studies that aim primarily to describe the magnitude, duration, or reproducibility of the effect of a typical bolus of intravenous (IV) crystalloid on haemodynamics in man. Even fewer have assessed the effect of varying the infusion rate [1,2]. Indeed, to our knowledge, while several studies report changes in haemodynamics with FBT, only one study specifically assessed the effect of an IV crystalloid bolus on CO and its determinants in healthy volunteers [3-8].

Beyond the amount, the rate of fluid administration may influence the haemodynamic response. The same volume of fluid given more slowly may lead to a more sustained increase in CO and/or MAP. Several studies based on haemoglobin (Hb) dilution techniques and mathematical modelling of volume kinetics support this theory. In particular, these studies show that the plasma volume effects of a fixed volume of IV fluid vary considerably with the rate of fluid infusion [9-11]. Moreover, observational data obtained from non-anaesthetised female volunteers after an IV crystalloid load have demonstrated that the plasma volume expansion produced by the same volume of IV crystalloid is greater and more prolonged with longer duration of infusion [11]. Thus, although important, it remains uncertain how best to administer a given quantity of fluid to maximize its systemic hemodynamic effects, and no studies have compared the systemic haemodynamic effects of a typical (1 L) bolus of normal saline (NS) in healthy volunteers when given rapidly (30 min) versus more slowly (120 min).

Accordingly, we conducted a proof of concept study in human volunteers. We aimed to measure the effect of 1 L of IV NS administered as a bolus over 30 min versus continuous infusion over 120 min on CO, heart rate (HR), blood pressure (BP), carotid arterial flow velocities, and mitral valve inflow rate and annular tissue velocities in six healthy volunteers. We hypothesized that a slower infusion given over 120 min

☆ This study was conducted at the Austin Hospital, Heidelberg VIC, Australia.

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would produce a more sustained increase in CO and MAP when compared to a rapid bolus given over 30 min.

2. Methods

The study design and protocol were approved by the Human Research Ethics Committee of the Austin Hospital (Heidelberg, Melbourne), a large teaching hospital, where the study was also performed.

Six healthy male volunteers who provided written informed consent were included in this study. Volunteer attendance was required on two separate occasions at least 24 h apart in order to complete both arms of the protocol, with random allocation to rapid or slow infusion as the first treatment and subsequent crossover to the alternative regimen. Volunteers were allowed their usual dietary intake but no caffeine prior to commencing the protocol. The bladder was emptied immediately prior to starting the study and participants were then placed semi-recumbent in an intensive care bed.

A 20-gauge IV cannula was inserted into a dorsal hand vein and a 10-min period of baseline observations was recorded, followed by baseline transthoracic echocardiography and carotid artery Doppler flow assessment. A further 10-min period of observation was allowed before commencing infusion of 1 L NS over 30 min or 120 min. Infusion of 1L NS over 30 min was used for the rapid bolus protocol as this has previously been demonstrated to be consistent with clinicians' views of what constitutes a typical fluid bolus [1]. Additionally, this regimen comprised part of the inclusion criteria for three major randomized controlled trials of septic patients [12-14]. Volunteers were allowed to void as desired and urinary volume was recorded. Repeat echocardiography and carotid flow Doppler assessment was performed at the end of the observation period.

2.1. Haemodynamic data

Cardiac output, MAP and HR data were obtained using the Nexfin® (BMEYE, Amsterdam, Netherlands) non-invasive finger arterial pressure monitor at baseline, during IV NS administration, and up to 120 min after commencement of the infusion [15,16].

The Nexfin® device uses finger arterial pressure (FAP) employing a rapid pneumatic system that repeatedly inflates a finger cuff, and photoplethysmography to detect changes in finger arterial diameter during these inflations. A volume clamp method is used whereby rapid variations in the cuff pressure allow maintenance of a constant arterial diameter, using an automatic algorithm (Physiocal). The pressure within the cuff is therefore reflective of finger arterial pressure [17,18]. Beat-to-beat stroke volume and continuous CO can then be calculated using pulse contour analysis [19]. This approach to CO monitoring is of similar accuracy to other devices and is FDA-approved for cardiac output and blood pressure monitoring, previously marketed under the name of Nexfin® and, most recently, under the name of Clearsight® (Edwards Lifesciences, Irving, CA). The data from Nexfin® device were collected every second resulting in many thousands of data points for each subject.

Echocardiographic and carotid Doppler sonographic measurements protocol – Echocardiographic measures of CO, stroke volume (SV), mitral valve (MV) inflow rate, and mitral annular tissue velocity were obtained at baseline and at 120 min after commencement of the infusion. Measurements were recorded with subjects in the semi-recumbent position, and baseline measures occurred after a period of at least 5 min of quiet rest. Each parameter was measured three times and the mean of these recorded for analysis. Echocardiography was performed in accordance with the American Society of Echocardiography/European Association of Cardiovascular Imaging Guidelines and Standards [20].

Finally, Doppler sonographic assessment of carotid arterial flow velocities was performed at the same intervals and in the same position, using validated sonographic methodology [21-23]. An average of three measures was again calculated for each parameter. All echocardiography and Doppler sonography was performed by a single, experienced cardiac intensivist.

2.2. Statistics

Haemodynamic data obtained by Nexfin®, echocardiography, and carotid sonography were analysed using repeated measures ANOVA (RMANOVA), and the fluid infusion rate was assessed for interaction. Second-to-second data outputs by the Nexfin® were analysed using minutely averaging and are graphically presented as 10-minutely values for clarity. Non-parametric urine output and time to micturition data were analysed using the Wilcoxon signed-rank test. A two-sided p-value of 0.05 was used to indicate statistical significance with a Bonferroni adjustment applied to all results to account for multiple outcomes. All analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

We studied six healthy male volunteers aged 33–58 years (mean 40 years) with a body mass index (BMI) 20.6–32.8 $kg \cdot m^{-2}$ (mean 25.1 $kg \cdot m^{-2}$).

3.1. Cardiac output

Using Nexfin®-obtained CO (CO_{nexfin}), compared to the mean of the 10-min baseline period, the rapid infusion of 1L of saline over 30 min was associated an overall lower mean CO_{nexfin} by 0.62 (95% confidence interval [CI] −0.63 to −0.61) $L \cdot min^{-1}$ ($p < 0.001$) over the 120 min of observation.

In contrast, there was a small but significant increase in CO_{nexfin} during infusion of 1L NS over 120 min of 0.02 (95% CI 0.01–0.03) $L \cdot min^{-1}$ ($p < 0.001$). The difference in mean CO_{nexfin} between the two fluid regimens was also significantly different over the 120 min of observation with a higher CO_{nexfin} seen in the slower infusion group ($p < 0.001$) (Fig. 1, Table 1). However, by the end of the observation period, CO_{nexfin} had returned to similar values for both fluid therapy regimens (Fig. 1).

Echocardiographic assessment of CO (CO_{echo}), MV inflow rate and mitral annular tissue velocities post-infusion showed no significant change from baseline in either group (Tables 2 and 3). The average CO_{echo} was 4.8 (95% CI 3.6 to 6.2) $L.min^{-1}$ prior to rapid infusion and 4.9 (95% CI 3.5 to 6.1) $L.min^{-1}$ ($p > 0.99$) at 120 min post-infusion, while these values were 4.1 $L \cdot min^{-1}$ (95% CI 2.8 to 5.4) and 4.7 $L \cdot min^{-1}$ (95% CI 3.4 to 6.0) ($p < 0.99$) respectively with slower infusion. Carotid flow velocities also demonstrated no significant change from baseline at any time point with either rapid or slow infusion (Tables 2 and 3).

3.2. Heart rate

Rapid infusion of 1L NS produced a significant fall in mean HR with an overall 2.27 (95% CI −2.35 to −2.19) beats $\cdot min^{-1}$ lower mean HR post-infusion ($p < 0.001$). The group receiving the slow infusion of NS demonstrated a significant increase in mean HR of 0.47 (95% CI 0.37 to 0.58) beats $\cdot min^{-1}$ post-infusion ($p < 0.001$). A comparison of both groups found that those receiving the slow infusion had a significantly higher HR over the observation period ($p < 0.001$).

3.3. Blood pressure

A similar change to CO was seen in mean systolic blood pressure (SBP) with an average decrease of 1.64 (95% CI −1.74 to −1.53) mm Hg from the baseline period to 120 min of observation in the rapid infusion group compared to an increase of 5.64 (95% CI 5.52 to 5.76) mm Hg in the group that received the slower infusion (Fig. 2).