Glucose dilution can detect fluid redistribution following phentolamine infusion in dogs

A. Matsui
H. Ishihara
A. Suzuki
E. Hashiba
T. Fukushi
A. Matsuki

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Abstract Objective: We have recently reported that the initial distribution volume of glucose (IDVG) reliably measures the central extracellular fluid (ECF) volume in the presence of fluid gain or loss. However, it is not clear if IDVG consistently reflects central-ECF volume when redistribution of fluid occurs in the absence of fluid gain or loss. This study was designed to investigate changes in fluid volumes during phentolamine infusion in dogs.

Design: Prospective animal study.

Setting: Institutional animal research laboratory.

Subjects: Fourteen anesthetized and ventilated mongrel dogs.

Interventions: Anesthetized animals were mechanically ventilated and received infusions of normal saline (n = 7) or phentolamine (10 μg kg min) (n = 7). Plasma volume was estimated using the indocyanine green (ICG) dilution method (PV-ICG) and IDVG was calculated using a one-compartment model by simultaneous administration of ICG 0.5 mg/kg and glucose 100 mg/kg before, during, and after infusion of either drug.

Measurements and results: PV-ICG during infusion was not different between groups. However, IDVG significantly decreased (P < 0.05) following phentolamine infusion when compared with normal saline infusion.

Conclusion: Our results suggest that IDVG rather than PV-ICG consistently measures central extracellular fluid volume, even when redistribution of fluid occurs.

Key words Phentolamine · Measurement techniques · Glucose · Indocyanine green · Fluid redistribution

Introduction

Routine hemodynamic variables such as arterial pressure, cardiac filling pressures, and hematocrit, do not consistently indicate blood volume adequately [1, 2], leading to inadequate pharmacological support of circulation instead of fluid administration or restriction. Consequently, reduced oxygen supply to several important organs such as kidneys and gastrointestinal tract can occur from reduced blood flow or increased interstitial edema, resulting in significant increases in morbidity and mortality as well as in length of hospital stay in critically ill patients [3, 4]. Thus, evaluation of blood volume status is important for fluid management in critically ill patients. However, redistribution of blood from the central to the peripheral compartment can occur in various diseases of critically ill patients, resulting in central hypovolemia and peripheral blood pooling, even though circulating blood volume is normal. Some authorities recommend assessment of central blood volume (CBV), namely, intrathoracic blood volume, rather than total or circulating blood volume for decision making for therapeutic interventions of critically ill patients [5, 6]. Although cardiac filling pressures are routinely used as an indicator of CBV – a major determinant of cardiac preload – these pressures do not reliably indi-
cate CBV in critically ill patients [7]. Thus, an alternative simple and reliable variable is required as a measure of CBV.

Glucose does not remain in the intravascular compartment and rapidly distributes throughout the intracellular and extracellular compartments when administered intravenously. Radioisotopic studies demonstrate that insulin does not affect extracellular glucose distribution kinetics or volumes [8, 9], and that size of the interstitial compartment can be derived mathematically from plasma glucose data only [10]. We have previously reported that initial distribution volume of glucose (IDVG) correlates with plasma volume estimated using the indocyanine green (ICG) dilution method (PV-ICG) [11, 12], and is essentially identical to the central extracellular fluid (ECF) volume in hypo- and hypervolemic dogs [13, 14]. Central ECF volume consists of the interstitial fluid volume of highly perfused tissues including heart, lungs, liver, brain, and kidneys in addition to plasma volume [8]. Moreover, IDVG was found to correlate with cardiac output (CO) in critically ill patients whether or not they were receiving continuous infusions of insulin and/or vasoactive drugs [15]. Although various mechanisms including cardiac preload, afterload, and myocardial contractility can affect CO, our previous study demonstrated that patients with congestive heart failure had a relatively larger IDVG than those without it [16]. These findings would allow speculation that IDVG reflects CBV, the main factor of cardiac preload, and thus indirectly affects CO. However, it is not clear whether IDVG consistently reflects the state of central-ECF volume even when redistribution of fluid occurs in the absence of fluid gain or loss. As indicated by a report where application of positive end-expiratory pressure induced a considerable decrease in CO, but did not affect PV-ICG [17], dilution volumetry cannot consistently mirror redistribution.

Phentolamine is a competitive α-adrenergic antagonist and has similar affinities for α-1 and α-2 receptors [18]. Infusion reduces splanchnic blood perfusion [19], inducing redistribution of blood, central hypovolemia, and peripheral blood pooling associated with a decrease in cardiac preload and/or afterload. Assuming that IDVG consistently measures central-ECF volume even during redistribution of blood, phentolamine infusion should produce a decrease in cardiac preload, IDVG and CO without considerable changes in PV-ICG. This study was therefore designed to investigate changes in IDVG and PV-ICG simultaneously before, during, and after phentolamine infusion in dogs and to test whether IDVG rather than PV-ICG has potential as an indicator of CBV.

**Methods**

This study was approved by our institutional Animal Experiment Committee. Fourteen mongrel dogs of either sex weighing 6.5–17.5 kg were randomly allocated into the following two groups: (1) saline group: normal saline infusion; and (2) phentolamine group: phentolamine infusion 10 μg/kg/min. Following an intravenous injection of pentobarbital 30 mg/kg, all dogs were intubated and mechanically ventilated with a Servo 900C ventilator (Siemens-Elema, Stockholm, Sweden) to maintain the end-tidal carbon dioxide equivalent to approximately 40 mmHg throughout the procedure. Anesthesia was maintained with an infusion of pentobarbital 2 mg/kg/h and pancuronium bromide 0.06 mg/kg/h.

The right femoral artery was catheterized for continuous blood pressure monitoring and blood sampling. A pulmonary artery catheter (Model 93A-741H-7.5F, Baxter Healthcare, Irvine, Calif., USA) was inserted through the right femoral vein and the tip was placed in the pulmonary artery. CO was measured by a CO computer (American Edwards Laboratories, Santa Ana, Calif., USA) using 5 ml of chilled normal saline solution. An infusion of lactated Ringer’s solution was continued at a rate of 4 ml/kg/h, and the urinary bladder was catheterized.

A period of 60 min was allowed for establishment of a stable circulatory state. Prior to the first glucose and ICG infusions, mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), blood temperature, and urine volume were recorded. CO was measured in duplicate and averaged randomly during the ventilation cycle. Measurements of hematocrit, total plasma protein and plasma albumin concentrations, and arterial blood gas analysis (pH, PaO2, PaCO2) were made. When these measurements were completed, both glucose 100 mg/kg (0.5 ml/kg) and ICG 0.5 mg/kg (0.2 ml/kg) (Daichi Pharmacol, Tokyo, Japan) were simultaneously infused through the central venous line over 30 s. Each 2.5 ml of arterial blood sample was drawn for determination of plasma glucose and ICG concentrations, immediately before, and at 1, 2, 3, 4, 5, 7, 9, 11, 15, 20, and 30 min following glucose and ICG infusions. These data served as the pre-infusion values.

In the phentolamine group a bolus of 0.1 mg/kg i.v. was administered followed by an infusion of 10 μg/kg/min. Phentolamine was diluted with normal saline to achieve a concentration of 2.5 mg/ml. In the saline group, the same volumes of normal saline were infused. Ninety minutes after commencing phentolamine or saline infusion, the second series of measurements and blood samplings were performed as described previously [15, 16]. These data served as the during-infusion values.

Phentolamine or normal saline infusion was terminated after 120 min. Ninety minutes later, the third series of measurements and blood samplings were conducted as previously described. These data served as the post-infusion values.

Blood samples were centrifuged immediately and plasma glucose concentrations were determined using the glucose oxidase method (GA-1150 Glucose Auto and Stat, Kyoto Daiichi Kagaku, Tokyo, Japan). Plasma ICG concentrations were determined according to a spectrophotometric technique (U3200 Spectro-photometer, Hitachi, Tokyo, Japan). IDVG and the PV-ICG were calculated from plasma decay curves using a one-compartment model (OCM) with incremental values above pre-infusion from 3 to 7 min post-infusion for the former and 3 to 11 min for the latter, as described in previous reports [11, 12, 13, 14, 15, 16, 20, 21, 22, 23, 24, 25].

In an OCM, the volume of distribution (Vd) is calculated as follows:

\[ Vd = \frac{\text{Dose}}{Co} \]