Title Page

Title: Corrected right ventricular end-diastolic volume and initial distribution volume of glucose correlate with cardiac output after cardiac surgery

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Abstract Page

Purpose: Appropriate adjustment of cardiac preload is essential to maintain cardiac output (CO) especially in patients after cardiac surgery. This study was intended to determine whether index of right ventricular end-diastolic volume (RVEDVI), corrected RVEDVI using ejection fraction (cRVEDVI), index of initial distribution volume of glucose (IDVGI) or cardiac filling pressures are correlated with cardiac index (CI) following cardiac surgery in the presence or absence of arrhythmias.

Methods: Eighty-six consecutive cardiac surgical patients were studied. Patients were divided into two groups; the non-arrhythmia (NA) group (n=72) and the arrhythmia (A) group (n=14). Three sets of measurements were performed: on admission to the ICU and daily on the first 2 postoperative days. The relationship between each cardiac preload variable and CI was evaluated. A p value less than 0.05 indicated statistically significant differences.

Results: Each studied variable was not different between the two groups immediately after admission to the ICU. cRVEDVI had a linear correlation with CI in both group (NA group: r=0.67, n=216, p<0.001; A group: r=0.77, n=42, p<0.001), but RVEDVI had a poor correlation with CI (NA group: r=0.27, n=216, p<0.001; A group: r=0.19, n=42, p=0.036). IDVGI had a linear correlation with CI (NA group: r=0.49, n=216, p<0.001; A group: r=0.61, n=42, p<0.001), Cardiac filling pressures had no correlation

with CI.

Conclusion: Our results demonstrated that cRVEDVI and IDVGI were correlated with CI in the presence or absence of arrhythmias. cRVEDVI and IDVGI have a potential as an indirect cardiac preload marker following cardiac surgery.

Introduction

Appropriate adjustment of cardiac preload is essential to maintain cardiac output (CO) especially in patients following cardiac surgery, but the evaluation is not easily performed, since either impairment of cardiac function [1-3] or internal bleeding may occur following cardiac surgery. Cardiac preload is traditionally assessed by its filling pressures, but edema or focal ischemia of myocardium after cardiac surgery may affect ventricular compliance, leading to poor correlations between these pressures and the end-diastolic volume, which makes these preload variables unreliable [4]. There is interest in pulmonary artery catheter (PAC) that allows continuous measurements of CO and right ventricular end-diastolic volumes (RVEDV) on the basis of thermodilution technique [5], since RVEDV has been reported to reflect cardiac preload better than pulmonary artery wedge pressure (PAWP) and central venous pressure (CVP) [6]. However, RVEDV has also been shown to have a poor correlation with CO following cardiac surgery [7]. Considering that RVEDV is related to patients' individual state of contractility by determining the difference between the estimated right ventricular ejection fraction (RVEF), corrected RVEDV (cRVEDV) modified by RVEF has been proposed to promote the reliability of this method [8]. Thus, it remains unclear whether RVEDV or cRVEDV can reliably reflect cardiac preload following cardiac surgery.

The presence of arrhythmias also makes RVEDV difficult to assess cardiac preload, since RVEDV is calculated from stroke volume (SV) divided by RVEF and SV is not constant under arrhythmia condition. However, it has not been studied adequately whether RVEDV or cRVEDV indicated cardiac preload in the presence of arrhythmias following cardiac surgery.

Initial distribution volume of glucose (IDVG) has been proposed as a marker of the central extracellular fluid (ECF) volume [9-12] using a small amount of glucose. The central extracellular fluid volume consists of the intravascular volume and the interstitial fluid volume of highly perfused organs such as brain, heart, lung, liver and kidneys. Previous studies reported that IDVG rather than plasma volume has a better correlation with CO during early postoperative days of esophagectomy and that IDVG can predict the occurrence of subsequent hypovolemic hypotension early after major surgical procedures [13, 14]. Additionally, IDVG has been demonstrated to have a linear correlation with CO during hemodynamically unstable states early after esophagectomy, after percutaneous coronary intervention for acute myocardial infarction and after major burns [11, 12, 15]. These results would allow us to speculate that IDVG has a potential as an alternative preload variable in critical ill patients, even though the concept of dilution volumetry is different from that of cardiac preload. Furthermore, considering the

concept of IDVG measurement, IDVG would not be affected significantly, even in the presence of arrhythmia, unless its cardiovascular state changes obviously during measurement.

Additionally, decreased cardiac function after cardiac surgery may yield to changes in the relationship between cardiac preload and CO on the ascending part of the Frank-Starling curve, and easily reach its descending part. Furthermore, a large variability of fluid volume status, from hypovolemia to hypervolemia, may be present in each individual patient following cardiac surgery. Assuming that each tested variable has a linear correlation with CO even in such heterogenous conditions, it would be clinically relevant as a cardiac preload marker following cardiac surgery.

To examine these hypotheses, we measured cardiac preload variables including RVEDV, cRVEDV, IDVG, PAWP and CVP as well as CO immediately after admission to the ICU and daily during the first 2 postoperative days following cardiac surgery in the presence or absence of arrhythmias. Additionally, we evaluated the effect of volume loading on each tested variable and CO when volume loading is clinically required during the first 24 hours after admission to the ICU.

Materials and methods

The study was approved by our institutional Ethics Committee of the Hirosaki University Graduate School of Medicine, and each patient gave written informed consent. Eighty six consecutive patients were enrolled into the study. Patients who underwent cardiac surgery including off-pump coronary artery bypass (OPCAB) and major thoracic aortic surgery were prospectively included, and each patient had a thermodilution pulmonary artery catheter placed in the operating room. Patients with hyperglycemia (> 250 mg/dL), neurologic illness, apparent tricuspid regurgitation (diagnosed by transesophageal echocardiography during surgery) and mechanical cardiac support including intra-aortic balloon pumping and/or percutaneous cardiac pulmonary support were excluded from the study.

A pulmonary artery catheter (Swan-GanzCCOmbo CCO/SVO2, 744HF75; Baxter Healthcare Corporation, Irvine, CA) was inserted into the right internal jugular vein and connected to a Vigilance Monitor system (Vigilance Ⅱ Monitor, Model VG00765; Baxter Health care Corporation, Irvine, CA), and arterial pressure, PAWP, CVP, continuous CO (CCO), RVEDV and RVEF were recorded. A 3 to 5-minute running average of CO determinations (CCOaverage mode) was used to record daily CO and RVEDV [16]. For volume loading study they were determined every 30 seconds (CCOstat mode).

On the basis of the presence or absence of arrhythmia, patients were divided into two groups, the non-arrhythmia (NA) group (patients who had normal sinus rhythm; $n = 72$) and the arrhythmia (A) group (patients who had atrial fibrillation, supraventricular premature contraction, ventricular premature contraction and/or pacemaker with heart's native electrical rhythm; $n = 14$). Three sets of measurements were performed: on admission to the ICU and daily at 10 AM on the first 2 postoperative days. IDVG was determined immediately after cardiovascular variables (CCOaverage, RVEDV, PAWP, CVP, RVEF, HR and mean arterial pressure (MAP)) and other routine clinical variables were recorded. The corrected value of index of RVEDV (cRVEDVI) was also calculated using the following formula [8]

$$cRVEDVI = RVEDVI / \exp (2.74 \times (0.4 - RVEF (\%) \times 0.01)$$

To calculate IDVG, a bolus of 10 ml of 50% glucose (5 g) was injected through the proximal port of the pulmonary artery catheter. Heparinized blood samples were obtained from an arterial catheter immediately before and at 3 min after the completion of glucose injection for measurement of approximated IDVG. The reported difference between the approximated IDVG and original IDVG using repeated samplings through 7 min after injection was -0.05 ± 0.54 (SD) L[17]. Plasma was separated immediately for glucose measurement and plasma glucose levels were measured using glucose oxidase

method (glucose analyzer GA-1151; ARKRAY Co. Ltd., Kyoto, Japan). Plasma glucose levels were measured in duplicate and averaged. The coefficient of variation was less than 2% for repeated glucose measurements at a glucose concentration of 70 - 249 mg/dL. IDVG was calculated according to the following formula: IDVG (L) = 24.4 × $\exp^{(-0.03 \times \Delta gl)}$ + 2.7 (Δgl (mg/dL) is increase in glucose concentration) [18].

During the first 24 postoperative hours after admission to the ICU, volume loading was performed in the NA group, when a diagnosis of hypovolemic hypotension was clinically made by attending ICU physicians not related to this study. Cardiovascular variables and IDVG were also measured immediately before volume loading and 10 min after completion of volume loading with 250 mL of 5% albumin over 20 min.

Statistical analysis

Calculated values are presented on the basis of the reported basal body weight before the surgery. They are also indexed to body surface area when compared with cardiac index (CI). All data were presented as mean and standard deviation (SD) because all variables were normally distributed in *ad hoc* testing. Daily variables were assessed using a one-way analysis of variance for repeated measures. *Post hoc* testing was performed using Dunnett's test. Changes in variables before and after volume loading

were assessed using the paired Student's *t* test, and comparisons between the NA and the A groups were assessed using the unpaired Student's *t* test. The Pearson product moment correlation using either actual values or changed values was performed. Actual values were defined as current values at each testing point. Changed values were defined as current values minus previous values. A *p* value less than 0.05 indicated statistically significant differences.

Results

Demographic data of 86 studied patients are shown in Table 1. All but five patients required a continuous infusion of vasoactive drugs such as noradrenaline and dobutamine during the study period without changes in an infusion rate during measurement.

Daily hemodynamic and volumetric variables are shown in Table 2. In the NA group, index of RVEDV (RVEDVI), cRVEDVI and index of IDVG (IDVGI) were increased along with CI on the second postoperative day when compared with the operative day ($p < 0.05$, respectively). However, PAWP, CVP as well as body weight remained unchanged throughout the study period.

In the NA group, actual RVEDVI had a poor correlation with actual CI ($r = 0.27$, $n =$

216, $p < 0.001$) (Figure 1A), but actual cRVEDVI had a linear correlation with actual CI ($r = 0.67$, $n = 216$, $p < 0.001$ for the latter, respectively) (Figure 1C). IDVGI also had a linear correlation with actual CI ($r = 0.49$, $n = 216$, $p < 0.001$) (Figure 1E). Neither actual PAWP nor actual CVP had a correlation with actual CI ($r = 0.10$ for the former and $r = -0.09$ for the latter, respectively). Changes in RVEDVI (ΔRVEDVI) had an only poor correlation with those in CI ($r = 0.22$, $n = 144$, $p = 0.007$) (Figure 2A), but those in cRVEDVI (ΔcRVEDVI) had a linear correlation with CI ($r = 0.48$, $n = 144$, $p < 0.001$) (Figure 2C). Changes in IDVGI (ΔIDVGI) also had a linear correlation with ΔCI ($r = 0.54$, $n = 144$, $p < 0.001$) (Figure 2E).

In the A group, all studied variables remained unchanged throughout the study period. Between the NA and the A groups, all tested variables were not different on each postoperative day. In the A group, actual cRVEDVI, but not RVEDVI, had a linear correlation with actual CI ($r = 0.77$, $n = 42$, $p < 0.001$ for the former and $r = 0.19$, $n = 42$, $p = 0.22$ for the latter, respectively) (Figure 1D and 1B). Actual IDVGI had a linear correlation with actual CI ($r = 0.61$, $n = 42$, $p < 0.001$) (Figure 1F). Actual CVP also had an inverse correlation with actual CI ($r = -0.41$, $n = 42$, $p = 0.007$), but actual PAWP did not. Only ΔcRVEDVI had a moderate correlation with ΔCI ($r = 0.58$, $n = 28$, $p = 0.001$) (Figure 2D).

Volume loading was done in 14 patients. A small, but statistically significant increase was observed in actual CI, cRVEDVI, IDVGI, CVP and MAP after volume loading ($p < 0.01$ except for cRVEDVI, $p < 0.05$ for cRVEDVI) (Table 3). However, only actual cRVEDVI had a linear correlation with actual CI ($r = -0.48$, $n = 28$, $p = 0.009$).

Using all actual daily data, the IDVG/CO ratio was 1.66 ± 0.33 ($n = 216$) for the NA group and 1.73 ± 0.29 ($n = 42$) for the A group. Between both groups, the ratio was not different ($p = 0.17$).

Discussion

The present results confirmed that cardiac filling pressures were unreliable in evaluating cardiac preload following cardiac surgery, since changes in cardiac compliance may have a significant impact on the pressure and cardiac preload relationship. In contrast, this study demonstrated that actual daily cRVEDVI and IDVGI had a positive linear correlation with actual CI regardless of the presence or absence of arrhythmias, supporting the notion that these two variables can be used as a cardiac preload marker following cardiac surgery, since changes in cardiac compliance may have a negligible effect on the volume and cardiac preload relationship, even though volume loading in this study has only a limited effect due to a small increase in CI after volume loading.

Although, two clinical studies reported that RVEDVI was useful as a cardiac preload marker after cardiac surgery [6, 15], a poor correlation between RVEDVI and CI was found in both groups in this study, indicating that RVEDVI is not a reliable marker of cardiac preload following cardiac surgery. Inaccurate RVEDVI determinations have been reported when patients had a low RVEF, since RVEDVI is calculated as the quotient of SV and RVEF [19-20]. Diebel et al. stated that RVEDV was reliable only when RVEF was 38 ± 9% [5].The RVEF in this study was 29 ± 7 % (n=216) which was similar

to the previous study (31 ± 10 %; normal RVEF range 40 - 60 %) [19]. A lower RVEF in this study would be responsible for the inaccuracy of RVEDVI measurement following cardiac surgery. To overcome the limitation of RVEDVI management, cRVEDVI modified by RVEF has been proposed [16]. In fact, cRVEDVI had a better correlation with CI regardless of the presence or absence of arrhythmias in this study. Malbrain et al. also revealed that changes in cRVEDVI had a good correlation with changes in CI even in which RVEFs (21-23 %) were lower than those in this study [16]. Therefore, cRVEDVI can be used as a reliable cardiac preload marker after cardiac surgery, even if patients have lower RVEF in the presence of arrhythmia. Although the RVEDV value is not shown on the monitor display when severe irregular rhythm developed, cRVEDVI in the presence of arrhythmias might be as reliable as cRVEDVI without arrhythmia as long as the RVEDV value is shown on the monitor display.

In our study, actual IDVGI had a linear correlation with actual CI in the presence or absence of arrhythmias following cardiac surgery, since the initial volume of distribution of several drugs is determined by several factors including CO [21]. As CO depends on cardiac preload based on the Frank-Starling relationship, the better the filling of the heart, the better the resulting forward output. In fact, our previous experimental and clinical studies showed a relatively good correlation coefficient

between IDVG and CO ranging from 0.71 to 0.89 [8, 9, 22]. However, an excessive fluid volume loading (60 ml/kg) in dogs yielded a decrease in CO despite an increase in IDVG [23]. Additionally, IDVGI and CI did not consistently move together toward the same direction, as shown in Figure 2F of this study and as described in non-surgical critically ill patients [24]. These findings allow us to speculate that IDVGI only correlates with CI when cardiac preload is on the ascending part of the Frank-Starling curve, but not on its descending part, and that IDVGI itself is not consistently affected by CI, but rather reflects the central extracellular fluid volume status. Presumably, excessive increase in cardiac preload, decrease of myocardial contractility and changes in cardiac afterload may also have a significant impact on the relationship between IDVGI and CI early after cardiac surgery. Furthermore, all but five patients required a continuous infusion of vasoactive drugs such as noradrenaline and dobutamine during the study period. These vasoactive drugs would change myocardial contractility and cardiac afterload, and have a significant impact on the relation between IDVGI and CI. Nevertheless, actual IDVGI had a linear correlation with actual CI in our study. Therefore our results suggest that IDVGI is a reliable indirect cardiac preload marker even following cardiac surgery. Furthermore, a regression line between actual IDVGI and actual CI in the A group was close to that in the NA group. Therefore, this result

suggests that IDVGI is not affected even in the presence of arrhythmias.

In the A group, no liner correlation was found between changes in each tested variable and ΔCI. However, the mean ΔCI in this group was only 0.02 ± 0.51 L/min/m^2. Biancofiore et al. reported that a small change in CO (ΔCO) should be excluded to assess the accuracy of CO measurement [25]. According to a report of Critcheley et al. a minimal ΔCO is required 0.5 - 1.0 L/min for this purpose [26]. Applying this value into this study, about 68% of data in the A group was included in the ΔCO exclusion criteria. Accordingly, in the A group, daily ΔCI was too small to assess the correlation between changes in cardiac preload variables and ΔCI. Further studies are needed to evaluate the relationship between them in the presence of arrhythmias.

Similarly, an increase in CI after volume loading in this study was only small, but significant (mean ΔCI = 0.3 L/min/m^2), since the amount of volume loading was relatively small (250ml of 5% albumin solution) compared to the other fluid loading studies [25, 27], as data obtained for this study was collected during routine postoperative ICU management, rather than in a controlled research-oriented management situation, resulting in insufficient effect for evaluation of fluid loading. Additionally, the time interval between IDVG measurements before and after fluid loading was only 30 min in this study. Rose et al. calculated IDVG using a one-compartment model with repeated

sampling and the bias of repeated IDVG measurements was only 0.08 ± 0.32 L at a 30-min interval in hemodynamically stable states [28], IDVG in this study was calculated from one-point incremental plasma concentration [18]. Therefore, one-point sampling as well as hemodynamically unstable states might affect the result that IDVGI has a poor correlation with CI at least partly, when fluid loading was performed. Nevertheless, cRVEDVI, IDVGI, CVP and MAP, but not RVEDV and PAWP, were increased after volume loading, even though no correlation was found between each tested variable and CI. Further studies are required to determine whether IDVGI can be correlated with CI in the fluid loading study.

To our knowledge, there have been two clinical reports describing the relationship between IDVG and fluid responsiveness after cardiac surgery. van Tulder et al. reported that IDVG was insensitive to volume loading during the early postoperative period after cardiac surgery [29]. However, they did not measure CO, even though they used a pulmonary artery catheter. Interestingly, their arterial pressure remained statistically unchanged despite an increase in CVP after volume loading. Harvey et al. also reported that neither IDVG, systolic area variability nor systolic blood pressure variability were predictive of preload responsiveness after cardiac surgery [30]. Accordingly, evaluation of fluid responsiveness during hemodynamically unstable states early after cardiac

surgery should be cautiously performed, since internal bleeding, temperature change, alternations in vasomotor tone, or fluid shift between compartments during the measurements may have a significant impact on the result [31].

Our previous study showed that patients with congestive heart failure (CHF) had a higher IDVG/CO ratio compared with patients without CHF; the ratio 1.68 ± 0.47 for the former vs. 1.16 ± 0.40 for the latter, respectively [24]. When applying this ratio in the present study, the result is comparable with the ratio observed in patients with CHF and suggests that the patients following cardiac surgery have either decreased cardiac function or relative fluid accumulation in the central extracellular compartment. Considering that actual IDVGI in NA group in this study was 4.2 ± 0.5 L/m^2 (n = 216) and reported IDVGI in 16 healthy volunteers was 4.0 ± 0.5 L/m^2 [32], the former was not apparently increased, and thus high IDVG/CO ratio in this study may reflect decreased cardiac function rather than relative fluid accumulation in the central ECF compartment, even though some patients possibly had fluid accumulation. Considering our previous study, the normal IDVG range is approximately from 110 to 130 ml/kg. When decision making of fluid management is required, even in the presence of high IDVG/CO ratio, a large IDVG (> 130 ml/kg) indicates fluid removal to overcome excess fluid. On the other hand, small IDVG (< 110 ml/kg) indicates a low cardiac preload and we should

take into consideration of volume loading.

In nearly one fourth (55/216) of our studied points, a low CO state (CI < 2.2 L/min/m^2) was present. A low CO state might yield underestimation of IDVG, because the mixing of administered glucose would not be completed in the central extracellular compartment within 3 min postinfusion in a low CO state. However, Hashiba et al. reported an unusual extremely larger IDVGI following volume loading in a patient with right ventricular myocardial infarction, even though a low CI (approximately 1.6 L/min/m^2) remained unchanged despite extensive volume loading [33]. As judged by the fact that the velocity of glucose transfer across capillary membrane is about 50 times greater than the linear capillary blood flow [34], a low CO state itself would have a minimal effect on IDVG determination. Accordingly, we believe that IDVG values in this study are reliable even in a low CO state, even though further studies are required regarding the accuracy of IDVG determination in an extremely low CO state such as less than 1.5 L/min/m^2.

Limitations

Firstly, dynamic variables such as stroke volume variation and pulse pressure variation were not assessed in this study, because reliable measurement of dynamic variables

consistently require a relatively large tidal volume (> 8 ml/kg) without spontaneous breathing activity under heavy sedation, as well as regular sinus rhythm [35]. Measurement immediately after admission to the ICU may meet these essential underlying conditions for dynamic variables, but not thereafter. However, He et al. recently showed an inverse correlation between IDVG and pulse pressure variation (r = -0.65) without volume loading in neurosurgical patients after induction of anesthesia [36]. Further studies associated with volume loading are required to elucidate the relationship between them, even though the interpretation of the result should be cautiously carried out early after cardiac surgery [31]. Therefore, the relationship between IDVG and dynamic variables remains unclear.

Secondly, we did not simultaneously measure echocardiography. Left ventricular end-diastolic area derived from transesophageal echocardiography (TEE) was reported as a useful predictor of cardiac preload and fluid responsiveness in critically ill [37, 38]. However, after admission to the ICU, the use of TEE for cardiac preload assessment is not routinely performed because of its invasiveness requiring heavy sedation. Thus, it is difficult to assess cardiac preload repeatedly using TEE following cardiac surgery, especially in the early postoperative days.

Conclusion

Our results demonstrate that cRVEDVI and IDVGI had a positive linear correlation with CI following cardiac surgery regardless of the presence or absence of arrhythmias. These findings suggest that both cRVEDVI and IDVGI has a potential as an indirect cardiac preload marker following cardiac surgery.

Competing interests

The author(s) declare that they have no competing interests.

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References

1. De Hert SG, Rodrigus IE, Haenen LR, De Mulder PA, Gillebert TC. Recovery of systolic and diastolic left ventricular function early after cardiopulmonary bypass. Anesthesiology. 1996;85:1063-75.
2. Mangano D. Biventricular function after myocardial revascularization in humans:

Deterioration and recovery patterns during the first 24 hours. Anesthesiology. 1985;62:571-7.

3. Breisblatt WM, Stein KL, Wolfe CJ, Follansbee WP, Capozzi J, Armitage JM, Hardesty RL. Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. J Am Coll Cardiol 1990;15:1261-9.

4. Kumar A, Anel R, Bunnnell E, Habet K, Zanotti S, Marshall S, Neumann a, Ali A, Cheang M, Kavinsky C, Parrillo JE. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med. 2004;32:691-9.

5. Diebel LN, Wilson RF, Tagett MG, Kline RA. End-diastolic volume: A Better Indicator of Preload in Critically Ill. Arch Surg. 1992;127:817-22.

6. Wiesenack C, Fiegl C, Andreas K, Laule S, Prasser C, Keyl C. Continuously assessed right ventricular end-diastolic volume as a marker of cardiac preload and fluid responsiveness in mechanically ventilated cardiac surgical patients. Crit Care. 2005;9:R226-33.

7. Godje O, Peyerl M, Lamm P, Mair H, Reichart B. Central venous pressure, pulmonary capillary wedge pressure and intrathoracic blood volumes as preload

indicators in cardiac surgery patients. Eur J Cardio Surg. 1998;13:533-40.

8. Malbrain ML, De Potter TJ, Dits H, Reuter DA. Grobal and right ventricular end-diastolic volumes correlate better with preload after correction for ejection fraction. Acta Anaesthesiol Scand. 2010;54:622-31.

9. Iwakawa T, Ishihara H, Takamura K, Sakai I, Suzuki A. Measurements of extracellular fluid volume in highly perfused organs and lung water in hypo- and hyper- volaemic dogs. Euro J Anaesthesiol. 1998;15:414-21.

10. Ishihara H, Suzuki A, Okawa H, Sakai I, Tsubo T, Matsuki A. The initial distribution volume of glucose rather than indocyanine green derived plasma volume is correlated with cardiac output following major surgery. Intensive Care Med. 2000;26:1441-8.

11. Ishihara H, Suzuki A, Okawa H, Ebina T, Tsubo T, Matsuki A. Comparison of the initial distribution volume of glucose and plasma volume in thoracic fluid accumulated patients. Crit Care Med. 2001;29:1532-8.

12. Ishihara H, Nakamura H, Okawa H, Yatsu Y, Tsubo T, Hirota K. Comparison of initial distribution volume of glucose and intrathoracic blood volume during hemodynamically unstable states early after esophagectomy. Chest. 2005;128:1713-9.

13. Orban JC, Blasin-Chadoutaud A, Zolfaghari P, Ishihara H, Grimaud D and Ichai C. Hypovolaemic hypotension after abdominal aortic surgery is predicted by initial distribution volume of glucose. Eur J Anaesthsiol. 2010;27:364-8.

14. Suzuki A, Ishihara H, Okawa H, Tsubo T, Matsuki A. Can initial distribution volume of glucose predict hypovolemic hypotension after radical surgery for esophageal cancer? Anesth Analg. 2001;92:1146-51.

15. Ishihara H, Otomo N, Suzuki A, Takamura K, Tsubo T, Matsuki A. Detection of capillary protein leakage by glucose and indocyanine green dilutions during the early post-burn period. Burns. 1998;24:525-31.

16. Ishida T, Lee T, Shimabukuro T, Niinami H. Right ventricular end-diastolic volume monitoring after cardiac surgery. Ann Thorac Cardiovasc Surg. 2004;10:167-70.

17. Ishihara H, Nakamura H, Okawa H, Takase H, Tsubo T, Hirota K. Initial distribution volume of glucose can be approximated using a conventional glucose analyzer in the intensive care unit. Crit Care. 2005;9:R144-9.

18. Hirota K, Ishihara H, Tsubo T, Matsuki A. Estimation of the initial distribution volume of glucose by an incremental plasma glucose level at 3 minutes after i.v. glucose in humans. Br J Clin Pharmacol. 1999;47:361-4.

19. Wagner JG, Leatherman JW. Right ventricular end-diastolic volume as a predictor

of the hemodynamic response to a fluid challenge. Chest. 1998;113:1048-54.

20. Rocca GD, Costa MG, Feltracco P, Biancofiore G, Beglopmini B, Taddei S, Coccia C, Pompei L, Di Marco P, Pietropaoli P. Continuous right ventricular end diastolic volume and right ventricular ejection fraction during liver transplantation: A multicenter study. Liver Transpl. 2008;14:327-32.

21. Ghoneim M, Pearson K: Pharmacokinetics of drugs administered intravenously. In: Scurr C, Feldman S, Soni N (eds) Scientific foundations of anaesthesia, 4th edn. Year Book Medical. Chicago: 1990. p.559-71.

22. Ishihara H, Shimodate Y, Koh H, Isozaki K, Tsubo T, Matsuki A. The initial distribution volume of glucose and cardiac output in critically ill. Can J Anaesth 1993;40:28-31.

23. Miyahara A, Okawa H, Ishihara H, Matsuki A. Changes in the initial distribution volume of glucose and plasma volume following volume challenge in dogs. Infutionsther Transfusionsmed. 1995;22:274-9.

24. Ishihara H, Takamura k, Koh H, Iwakawa T, Tsubo T, Matsuki A. Does the initial distribution volume of glucose reflect the central extracellular fluid volume status in critically ill patients? Infusionsther transfusionsmed. 1996;23:196-201.

25. Biancofiore G, Critchley LA, Lee A, Biandi L, Bisa M, Esposito M, Meacci L,

Mozzo R, DeSimone P, Urbani L, Filipponi F. Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. Br J Anaesth. 2009;102:47-54.

26. Critchley L, Lee A, Ho AH. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg. 2010;111:1180-92.

27. Breukers RM, Sepehrkhouy S, Spiegelenberg SR, Groeneveld AB. Cardiac output measured by a new arterial pressure waveform analysis method without calibration compared with thermodilution after cardiac surgery. J Cardiothorac Vasc Anesth 2007;21:632-5.

28. Rose BO, Ishihara H, Okawa H, Panning B, Piepenbrock S, Matsuki A. Repeatability of measurements of the initial distribution volume of glucose in haemodynamically stable patients. J Clin Pharm Ther. 2004;29:317-23.

29. van Tulder L, Michaeli B, Chiolero R, Berger MM, Revelly JP. An evaluation of initial distribution volume of glucose to assess plasma volume during a fluid challenge. Anesth Analg. 2005;101:1089-93.

30. Harvey M, Voss L, Sleigh J. Preload response in patients after cardiac surgery: a comparison of systolic pressure and systolic are variability and initial distribution

volume of glucose. Crit Care Resusc. 2003;5:171-6.

31. Ishihara H. Initial distribution volume of glucose early after cardiac surgery. Anesth Analg. 2006;102:1904.

32. Ishihara H, Giesecke AH. Fluid volume monitoring with glucose dilution. Springer, Tokyo: 2007. p.23-37.

33. Hashiba E, Ishihara H, Tsubo T, Okawa H, Hirota K. Use of initial distribution volume of glucose to determine fluid volume loading in pulmonary thromboembolism and right ventricular myocardial infarction. J Anesth. 2008;22:453-6.

34. Guyton AC, Hall JE: Textbook of medical physiology, 10th edition. Saunders, Philadelphia, 2000:162-83.

35. Maguire S, Rinehart J, Vakharia S, Cannesson M. Respiratory variation in pulse pressure and plethysmographic waveform: Intraoperative applicability in a north American academic center. Anesth Analg. 2011;112:94-6.

36. He Z, Qiao H, Zhou W, Wang Y, Xu Z, Che X, Zhang J, Liang W. Assessment of cardiac preload status by pulse pressure variation in patients after anesthesia induction: comparison with central venous pressure and initial distribution volume of glucose. J Anesth 2011;25:812-7.

37. Scheuren K, Wente MN, Hainer C, Scheffler M, Lichtenstem C, Martin E, Schmidt J, Bopp C, Weigand MA. Left ventricular end-diastolic area is a measure of cardiac preload in patients with early septic shock. Eur J Anaesthesiol. 2009;26:759-65.

38. Tousignant CP, Walsh F, Mazer CD. The use of transesophageal echocardiography for preload assessment in critically ill patients. Anesth Analg 2000;90:351-5.

1 Tables

Table 1. Demographic data and types of operation

Demographic data	Non-Arrhythmia group	Arrhythmia group
Sex (M/F)	49 / 23	9 / 5
Age (years)	67 ± 12	70 ± 8
Height (cm)	159.2 ± 9.8	158.2 ± 10.0
Preoperative body weight (kg)	60.2 ± 10.6	58.9 ± 9.6
Body surface area (m^2)	1.59 ± 0.19	1.57 ± 0.18
Types of operation		
OPCAB	13	1
on-pump CABG	12	3
valve surgery	27	7
major vascular surgery with CPB	20	3

Number of patients and mean ± SD
OPCAB: off-pump coronary artery bypass; CABG: coronary artery bypass grafting;
CPB: cardiopulmonary bypass

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Table 2. Studied variables in the early postoperative days

	Non-arrhythmia group (n=72)			Arrhythmia group (n=14)		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
CI (L/min/m^2)	2.5±0.5	2.5±0.6	2.7±0.5*†	2.5±0.6	2.4±0.4	2.5±0.5
RVEDVI (ml/m^2)	114±23	111±22	119±22†	121±25	121±33	124±30
cRVEDVI (ml/m^2)	86±17	84±17	91±18†	91±26	91±14	92±24
IDVGI (L/m^2)	4.0±0.6	4.1±0.4*	4.4±0.5*†	4.1±0.6	4.2±0.3	4.3±0.4
PAWP (mmHg)	10±4	9±3	9±3	8±3	7±4	11±4
CVP (mmHg)	7±3	7±3	7±3	8±3	8±3	9, ±3
RVEF (%)	29±6	29±6	30±6	29±10	30±11	29±10
MAP (mmHg)	74±13	69±11*	73±11	72±12	71±15	71±14
HR (beats/min)	77±14	79±13	80±13	78±9	74±7	78±19
Body weight (kg)	61.3±10.6	61.5±10.6	61.4±10.6	59.8±8.9	60.0±9.0	60.5±8.9
IDVG/CO ratio	1.63±0.32	1.73±0.37	1.62±0.29†	1.67±0.33	1.75±0.29	1.78±0.28

Mean ± SD
*p<0.05 vs. Day 0
$^\dagger p$<0.05 vs. Day 1
CI: cardiac index; RVEDVI: indexed right ventricular end-diastolic volume; cRVEDVI: corrected RVEDVI, IDVGI: indexed initial distribution volume of glucose; PAWP: pulmonary artery wedge pressure; CVP: central venous pressure; RVEF: right ventricular ejection fraction; MAP: mean arterial pressure; HR: heart rate

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Table 3. Changes of variables before and after volume loading

	Before	After
CI (L/min/m²)	1.9 ±0.3	2.2 ±0.4*
RVEDVI (ml/m²)	106 ±12	108 ±18
cRVEDVI (ml/m²)	70±13	75±14**
IDVGI (L/m²)	3.4 ±0.4	3.6 ±0.5*
PAWP (mmHg)	7 ±4	8 ±2
CVP (mmHg)	6 ±3	7 ±4*
SvO_2 (%)	60 ±7	60 ±6
MAP (mmHg)	62 ±9	69 ±11*
HR (beats/min)	78 ±15	78 ±15

Mean ± SD
*p<0.01 compared with before volume loading
**p<0.05 compared with before volume loading
CI: cardiac index; RVEDVI: indexed right ventricular end-diastolic volume;
cRVEDVI: corrected RVEDVI; IDVGI: indexed initial distribution volume of glucose;
PAWP: pulmonary artery wedge pressure; CVP: central venous pressure;
SvO_2: mixed venous oxygen saturation; MAP: mean arterial pressure; HR: heart rate

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Figure legends

Fig 1. The relationship with actual cardiac index in the presence or absence of arrhythmias

A (top, left) RVEDVI vs. CI in the non-arrhythmia group ($r = 0.27$, $n = 216$, $p < 0.001$). B (top, right) RVEDVI vs. CI in the arrhythmia group ($r = 0.19$, $n = 42$ and $r = 0.22$). C (middle, left) cRVEDVI vs. CI in the non-arrhythmia group ($r = 0.67$, $n = 216$, $p < 0.0001$). D (middle, right) cRVEDVI vs. CI in the arrhythmia group ($r = 77$, $n = 42$, $p < 0.0001$). E (bottom, left) IDVGI vs. CI in the non-arrhythmia group ($r = 0.49$, $n = 216$, $p < 0.001$). F (bottom, right) IDVGI vs. CI in the arrhythmia group ($r = 0.61$, $n = 42$, $p < 0.001$).

Actual values were defined as current values at each testing point.

RVEDVI: index of right ventricular end-diastolic volume; CI: cardiac index, cRVEDVI; corrected RVEDVI; IDVGI: index of initial distribution volume of glucose

Fig 2. The relationship with changes in cardiac index in the presence or absence of arrhythmias

A (top, left) RVEDVI vs. CI in the non-arrhythmia group ($r = 0.22$, $n = 144$, $p = 0.007$). B (top, right) RVEDVI vs. CI in the arrhythmia group ($r = 0.37$, $n = 28$ and $p = 0.06$). C (middle, left) cRVEDVI vs. CI in the non-arrhythmia group ($r = 0.48$, $n = 144$, $p < 0.0001$). D (middle, right) cRVEDVI vs. CI in the arrhythmia group ($r = 0.58$, $n = 28$, $p = 0.0001$). E (bottom, left) IDVGI vs. CI in the non-arrhythmia group ($r = 0.54$, $n = 144$, $p < 0.001$). F (top, right) IDVGI vs. CI in the arrhythmia group ($r = 0.07$, $n = 28$ and $p = 0.70$).

Changed values were defined as current values minus previous values.

RVEDVI: index of right ventricular end-diastolic volume; CI: cardiac index; cRVEDVI: corrected RVEDVI; IDVGI: index of initial distribution volume of glucose