THE EFFECTS OF CARDIAC OUTPUT ON THE INITIAL DISTRIBUTION VOLUME OF GLUCOSE IN THE ABSENCE OF FLUID GAIN OR LOSS IN PIGS

（循環体液量を変化させない心拍出量変化のブドウ糖初期分布用量への影響の検討）

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Abstract

Initial distribution volume of glucose (IDVG) has been reported to be a surrogate marker of a cardiac preload. However, the relationship between cardiac output and IDVG measurement is not fully understood. We have investigated the effects of cardiac output on IDVG in the absence of fluid gain or loss in pigs.

Material and Methods

Thirteen pigs were anesthetized and allocated to the modified cardiac output group (m-CO group, n=10) and the control group (control group, n=3). In the m-CO group CO was sequentially modulated from high CO (high CO) to two grades of low CO (low CO-1 & low CO-2) with dobutamine and propranolol with lidocaine, respectively in the absence of apparent changes in basal fluid volume status. Thermo-dilutional, CO and IDVG at each CO condition were measured. IDVG was measured with 2 g glucose, based on a one-compartment model as previously reported. The same parameters were measured in the control group, at the same time schedule as m-CO group without inotropes under a stable CO state. Thereafter, 250 ml of 10% dextran was infused over 15 minutes to confirm the effects of preload-dependent increase in CO on IDVG measurents, as a comparison to the pharmacological modification of CO. Data were expressed as mean ± SD. Statistical analysis was performed with repeated measures of ANOVA, followed by Dunnett's test. Pearson's correlation test was used for the correlation test. P value

less than 0.05 were considered as significant.

Results

IDVG did not change with the modification of CO in m-CO group, where CO increased to 147.2±26.7 % of the baseline CO values in high CO state and decreased to 65.9±11.0 % and 37.3±14.4 % of the baseline CO values in low CO-1 state and in low CO-2 state, respectively. IDVG significantly increased in response to the volume loading of dextran in the control group. There was no correlation between IDVG and CO in m-CO group in the absence of fluid gain or loss ($r = 0.097$, $n=40$, $P=0.554$), but IDVG was correlated well with CO in control group with volume loading ($r = 0.764$, $n=18$, $P=0.0002$).

Conclusion

This study suggests that IDVG is dependent on the central extracellular fluid volume and not on cardiac output. (364words)

Introduction

The surviving sepsis campaign guidelines recommended that quantitative resuscitation with the fluid volume load targeting central venous pressure (CVP) of more than 8-12 mm Hg, ScvO2 of 70% and normalization of lactate is achieved in the early phase of severe sepsis [1]. However, static cardiac filling pressures such as CVP and PCWP are known to limit to access intravascular volume status and fluid responsiveness [2-4]. Unnecessary fluid will cause or exacerbate edema in lungs, heart, gut, skin, brain and other tissues, which may create clinically obvious organ failure, such as respiratory failure, abdominal compartment syndrome [5], or, cerebral edema and herniation [6]. It has also been demonstrated that positive fluid balance was correlated with reduced survival in ARDS [7,8] and sepsis [9]. Assessments of adequate fluid volume status, indicating the cardiac preload, are important in critically ill patients, and it may lead to a decrease in mortality and morbidity in septic patients.

The Initial distribution volume of glucose (IDVG) has been reported to be a useful indicator of central extracellular fluid [10, 11] and is well correlated with the cardiac output (CO) in animals with fluids volume removal and loading [12, 13] and in critically-ill patients without heart failure [14]. In esophageal cancer surgery, IDVG showed refilling of the extracellular fluid and correlated with cardiac output better than the plasma volume or blood volume [15]. IDVG

was also demonstrated to predict hypovolemic hypotension early after abdominal aortic surgery [16]. Moreover, IDVG had an inverse correlation with pulse pressure variation and the Pleth Variability Index [17,18]. Therefore, based on these results IDVG may be considered to express the status of the cardiac preload and it can be used as a surrogate marker of cardiac preload, even though the concept of dilution volumetry is different from the exact concept of cardiac preload.

However, patients with heart failure, or patients immediately after cardiac surgery, showed relatively higher values of IDVG, compared with patients without these [19,20]. It seemed that IDVG can be measured relatively independently of the CO even in patients with low cardiac output. In one patient with a low cardiac index (approximately 1.6 l/min/m^2), due to a right ventricular myocardial infarction following pulmonary thromboembolism, IDVG reflected the fluid volume loading to increase the cardiac preload [21]. As the distribution of an indicator is theoretically dependent on the blood circulation, the relationship between IDVG and CO is unclear. Therefore, the aim of this study was to investigate the effects of changes in CO on IDVG measurements without apparent changes in the basal fluid volume status.

Material and Methods

1) Preparation of the experiments

The study was completed following ethical approval by our institutional Animal Experiment Committee. Thirteen pigs were used in this study. Ten pigs weighing 14.5~26.3kg were allocated to the modified cardiac output group (m-CO group) and three pigs weighing 11.5~15.3 kg were allocated to the control group (control group). The anesthesia was induced with intramuscular injection of ketamine (1500 mg) and kept with a continuous infusion of pentobarbital (100-200 mg/hr), remifentanil (0.2-0.4 μg/kg/min) and vecronium bromide (2-4mg/hr). Tracheotomy was established and the lung was mechanically ventilated with a mode of synchronized intermittent mandatory ventilation with pressure support (fraction of inspiratory oxygen = 0.5, target tidal volume = 8～10ml/kg, Respiratory rate = 20~25 b.p.m.) to maintain PaCO2 around 40 mmHg. The right common carotid artery was cannulated with 20G in-dwelling catheter for blood sampling and continuous monitoring of blood pressures. A flow directed pulmonary arterial catheter (Swan-Ganz catether, 744HF75; Baxter Healthcare, Irvine, CA, USA) was also inserted through the right external jugular vein and the tip of the catheter was placed in the pulmonary artery to measure Cardiac output (CO), pulmonary artery wedge pressure (PAWP) and central venous pressure (CVP), using a Vigilance Monitor system (Baxter Health care, Irvine, CA, USA). Physiological saline was infused at the rate of 4ml kg^{-1} hr^{-1} as a maintenance fluid infusion.

2) Modulation of cardiac output

Cardiac output was sequentially modulated from high to low output without apparent changes in the basal fluid volume status in m-CO group (n=10). Dobutamine (5-10 μg kg^{-1} min^{-1}) was used to increase CO around 150% of the baseline CO value which was the CO measured after the experimental preparation and obtaining the hemodynamic stability (high CO). Continuous intravenous infusion (civ.) of dobutamine was started 20 min before the injection of glucose and continued during the blood samplings. The total fluid volume of the infused dobutamine was between 2ml and 8ml. The CO in two grade (low CO-1 and low CO-2), was decreased sequentially. The targeted CO values of low CO-1 and low CO-2 were 75% and 50% of the baseline CO values which was the CO following the experimental preparation, respectively. To obtain a low CO-1 state propranolol (10 mg), a bolus injection of 7 mg kg^{-1} of 4% lidocaine followed by a civ. of 20mg kg^{-1} hr^{-1} was administered. To obtain a low CO-2 state, a bolus injection of 20 mg kg^{-1} of 4% lidocaine followed by a civ. of 40$mg^{-1}kg^{-1}hr^{-1}$ was administered a few minutes prior to each glucose injection for IDVG measurement. The induced high or low grade CO states were kept during the IDVG measurements. Total fluid volume of propranolol and lidocaine used for each low CO states were between 12ml and 14ml.The intervals of each CO modulation were more than 30~40 minutes, as IDVG has been demonstrated to be accurate

if repeatedly measured in 30 minutes interval [22].

hree pigs were allocated to a control group where intentional CO modulations with inotropes were not induced. The first-four measurements of the experimental parameters were performed at the same time schedule as the m-CO group, with administration of the same amounts of saline, to investigate the stability of basic fluid volume status under a stable CO state. Thereafter, in the control group, 250 mL of 10% low molecular weight dextran 40 (Otsuka Pharmaceutical Factory Inc., Tokyo, Japan) was administered over 15 minutes, to investigate the effects of preload-dependent increase in CO on IDVG measurements, as a comparison to the pharmacological modification of CO.

3） Experimental measurements

Blood pressure (Bp), heart rate (HR), CVP, CO, systemic vascular resistance (SVR) and IDVG were measured during this study. CO was measured by a bolus injection of 5 ml chilled saline, based on a thermodilution method. An averaged CO value of triplicate measurements was established. IDVG was measured with a 2g glucose injection (4ml of 50% glucose) through the external jugular vein, based on the one-compartment model as described in a previous report (Takamura ITM 1997). Blood samples were taken to measure plasma levels of glucose immediately before and at 3, 4, 5, 7 minutes after the injection. Each blood sampling volume

was 2ml and approximately the same volume of physiological saline was injected through the direct arterial pressure line. Total sampling volumes for m-CO group and control group were 40ml and 60ml, respectively. Plasma glucose levels were measured using the glucose oxidase method (glucose analyzer GA-1151; ARKRAY, Kyoto, JAPAN). Each blood sample was measured twice and averaged. IDVG is calculated by following the two formulae using a least square regression technique to find the line of the best fit:

$$IDVG = Dose/C0,\ C0 = (Ct-Cb)/\exp(-kt)$$

where Dose = amount of glucose administered, C0 = the initial plasma glucose concentration at time zero extrapolating the line of the best fit to time 0, Ct = the measured plasma glucose concentration at time t, Cb= the baseline plasma glucose concentration before glucose injection and k =the disappearance rate of glucose from plasma.

Akaike's Information Criterion (AIC) was calculated to evaluate the exponential term of the pharmacokinetic model [23].

$$AIC = -2\log(L1) + 2np,$$

where L1 is the maximum likelihood and np is the number of parameters. Convergence was assumed when AIC was less than -10.

After the obtaining a stable state of hemodynamic parameters, following the experimental preparation, the hemodynamic parameters and IDVG in the m-CO group and in the control group were measured. The same parameters were measured in the m-CO group, in the baseline control state, in the high CO state, in the low CO-1 state and in the low CO-2 state without apparent changes in the basal fluid volume status. In the control group, these parameters were measured 4 times, at the same time schedule as m-CO group, with administration of the same amounts of saline instead of the inotropes, to investigate the stability of basic fluid volume status. Furthermore, in control group a volume loading of 250ml of 10% dextran was infused over 15 minutes, following the above 4-times measurements, as a comparison with the modification of CO, by increasing cardiac preload, to investigate the effects of volume loading on hemodynamic parameters and IDVG. The parameters were measured at 30 minutes and 60 minutes after the initiation of volume loading. All blood samples were stored in ice until the glucose measurements were completed.

4) Statistical analysis

Data were expressed as mean ± SD. Statistical analysis was performed with repeated measures of ANOVA, followed by Dunnett's multiple comparison test to compare the variables with each baseline values. Pearson's correlation test was used for the correlation test. P values less than 0.05 were considered as significant.

Results

1) The results of hemodynamic changes in m-CO group and control group

In the m-CO group, the baseline CO values after the experimental preparation was 2.3±0.6 L/min. The CO increased to 3.2 ± 0.6 L/min (147.2 ± 26.7 % of the baseline CO values) in high CO state ($P<0.01$) and decreased to 1.5 ± 0.4 L/min and 0.8 ± 0.3 L/min (65.9±11.0 % and 37.3±14.4 % of the baseline CO values) in low CO-1 state and in low CO-2 state, respectively ($P<0.01$) (table 1 & fig. 1A). The CO did not change significantly within the 4-times measurements in the control group with the CO values of 1.8 ± 0.1 L/min, 1.8 ± 0.2 L/min, 1.6 ± 0.1 L/min and 1.7 ± 0.2 L/min, respectively, before the volume loading (table 2 & fig. 1B). The CO significantly increased to 3.0 ± 0.3 L/min and 2.6 ±0.3 L/min (169.1 ± 13.3 % and 144.3 ± 15.0 % of the baseline CO values 30min and 60min after the initiation of 250ml of dextran infusion, respectively ($P<0.01$) (table 2 & fig. 1B). Mean BP and HR increased significantly with dobutamine administration and those decreased with propranolol and

lidocaine administration in m-CO group ($P<0.05$) (Table 1). CVP significantly increased with negative inotropes in m-CO group ($P<0.05$). However, in control group those hemodynamic parameters did not change before the volume loading (table2). SVRs just before the IDVG measurements did not changed significantly in m-CO group and within the 4times measurements in the control group (table 1 and 2). SVRs following the dextran loading significantly decreased, compared with the baseline SVR value ($P<0.01$) (table 2).

2) The changes in IDVG and hemoglobin concentration

Each AIC value for IDVG calculations in this study indicated adequate convergence between the regression line and data points, as observed previously [10]. IDVG did not change, compared with the baseline IDVG values in m-CO group (fig. 1A and table 1). IDVG also did not change significantly within the 4-times measurements in the control group before the volume loading (fig.1B). However, as expected, IDVG significantly increased in response to the volume loading ($P<0.01$, fig. 1B and table 2). There was no correlation between IDVG and CO in m-CO group with stable basic fluid volume status ($r=0.097$, $n=40$, $P=0.554$), but IDVG was correlated well with CO in control group with volume loading ($r=0.764$, $n=18$, $P=0.0002$) (fig 2A and 2B).

Hemoglobin concentration (Hb) increased significantly to a high CO state and lost the

significance at low CO-1 and low CO-2 states, compared with the baseline Hb values in m-CO group. Hb also did not change significantly within the 4-times measurements in the control group before the volume loading (table 2). Hb significantly decreased in response to the volume loading ($P<0.01$, Table 2) in control group.

Discussion

This study demonstrated that the modulation of CO with positive and negative inotropes did not affect the measurement of IDVG as long as the basic fluid volume status was kept stable. It also demonstrated that IDVG was affected by the fluid volume loading in the same direction as the CO changes in the control group, and that IDVG showed a good correlation with CO. These results suggested that IDVG indicated previous fluid volume status which affected cardiac preload, with a relatively-independent manner to cardiac function.

IDVG has been demonstrated to be a good correlation with CO in several animal studies and clinical settings. Shimodate and the colleague measured IDVG before and after induced hemorrhage (-30ml/kg over 30 minutes) in 12 adult mongrel dogs and found that there was a good correlation between IDVG and thermodilution CO ($r=0.85$, $n= 24$, $P<0.001$) with negligible insulin response to the glycemic stimuli [12]. In the similar animal model, Koh *et al*

demonstrated that IDVG reflects plasma volume in normal and hypovolemic dogs again with a good correlation between IDVG and CO [24]. Furthermore, Iwakawa *et al* also reported that IDVG showed a good correlation with CO in dogs with volume loading following an induced hemorrhage ($r=0.93$, $n=36$, $P<0.001$) [13]. These results were consistent with our simple volume loading data in the control group with 10% dextran infusion.

In clinical setting, Ishihara *et al* obtained a good correlation between IDVG and CO in non-surgical, critically-ill patients without congestive heart failure ($r=0.89$, $n=27$, $P<0.001$) [14]. In esophageal cancer surgery, IDVG indicated the refilling of the extracellular fluid and correlated with CO better than the plasma volume and blood volume [15].

However, IDVG did not merely indicate CO. Miyahara *et al* investigated the relationship between IDVG and plasma volume even in hypervolemic state where volume loading of 30ml/kg of dextran was performed twice in adult mongrel dogs. In that study CO did not show a consistent change in response to volume challenges and IDVG correlated less with CO ($r= 0.48$, $n=30$, $P<0.01$), compared with plasma volume ($r=0.79$. $n=30$, $P<0.001$) [25]. This phenomenon was explained as the left ventricle would have reached near maximal size by the first volume challenge and the myocardium failed to increase its contractility in response to the second volume challenge, while the cardiac preload was on the descending part of the

Frank-Starling curve. This suggested that IDVG would show a good relationship with CO when the cardiac preload was on the ascending part of the Frank-Starling curve. That was also suggested by the study with patients with heart failure or patients immediately after cardiac surgery. Those kinds of patients showed relatively higher values of IDVG, compared with patients without them [19,20]. Together with the present results of t the m-CO group, it is clearly suggested that IDVG reflects the state of cardiac preload, relatively independent of CO.

The initial distribution volume of some indicators is determined by CO, regional blood flow and the characteristics of the particular indicator [26]. After intravenous injection, drug concentrations in blood may be higher in individuals with poor perfusion such as shock, than in individuals with better perfusion [27]. Water-soluble indicators such as sodium ions, chloride ions and glucose diffuse rapidly through inter-cellular pores in the capillary membrane. Regarding the capillary membrane permeability of glucose, the rate at which glucose molecules diffuse through the capillary membrane is approximately 50 times as great as the rate at which plasma itself flows linearly along the capillary [28]. Theoretically, the glucose molecules in the plasma are exchanged with glucose molecules in the interstitial fluid 50 times before the plasma can flow the entire distance though the capillary. Therefore, it has been speculated that CO itself has minimal effect on glucose distribution and IDVG can be determined even with low CO [10].

In the present study, the disappearance rate of glucose in Low CO_2 state was significantly lower than the baseline value in m-CO group, although the IDVG in low CO-2 state was not significantly different from than baseline value. There is a possibility that the much lower CO would affect IDVG measurements. However, in this study some of the animals died soon after the IDVG measurements in the low CO-2 state. It was found that the further modulation of low CO states with our pharmacological methods was impossible. Therefore, detecting a much lower CO, which really affects an IDVG measurement, is a future target of our study.

Practically, in a clinical case report IDVG reflected well the fluid volume status following volume loading in a patient with a severely low cardiac index (approximately 1.6 l/min/m2) due to the right ventricular myocardial infarction following pulmonary thromboembolism [21]. Together with the present-study results of m-CO group, IDVG can be measured with the minimum influence of CO, if the CO is around 40% of the baseline.

The hemoglobin concentration significantly increased in high CO state with dobutamine infusion and lost the significance at low CO-1 and low CO-2 state in m-CO group. It has been known that sympathetic stimulations like catecholamine infusion [29], exercise and mental

stresses induce hemoconcentration [30]. One of the explanations for this phenomenon is that the increased systemic pressure resulting from the increased sympathetic tones causes an increased capillary hydrostatic pressure with resultant increased filtration of fluid out of the plasma into the interstitial space. Additionally, as the stress-induced hemoconcentration would return to the pre-stress levels following the cessations of the stresses, it is also suggested that the hemoconcentration was due to reversible shifts in plasma volume, rather than dieresis [31], as seen in the present study. IDVG in high CO state did not change, compared with the baseline IDVG values, and did not reflect the hemoconcentration as IDVG measured plasma volume and highly perfused interstitial fluid volume [10].

Lidocaine was administered rapidly, in addition to propranolol, to obtain two-grade of low output. Propranolol is a nonselective β-adrenergic antagonist and has no capacity to activate β-adrenergic receptors, as known as intrinsic sympathomimetic activity. However, β-receptor blockade has relatively little effect on the normal heart at rest but has profound effects when sympathetic control of the heart is dominant, as during exercise or stress [32]. Even with high dose of propranolol, it was not possible to obtain an appropriate grade of low output of less than 75% of the control values in the preliminary experiment (data were not shown). Therefore, a high dose of lidocaine was administered, as lidocaine causes concentration-dependent decreases

in the contraction of myocardium [33]. This produced a grade two level of low CO with the values of 65.9±11.0 % and 37.3±14.4 % of the baseline CO values.

Limitation

Cardiac output was modulated with positive and negative inotropic agents and volume loading. The purpose of the modulation CO with those inotropes was to investigate the effects of rapid changes in cardiac function on measurements of IDVG. However, as lidocaine has vasodilative effects beside the negative contractive effects and CO is also dependent on cardiac afterload, the effects of changes in cardiac afterload on the IDVG measurements could not be excluded. In addition, there was no evaluation of the cardiac contractility itself using echocardiography during this study period. But, the main factor affecting the CO was considered to be the cardiac contractility or function due to the pharmacological effects of those inotropic drugs.

Clinical implication

The dynamic preload variables such as stroke volume variation have been reported to be better predictors of fluid responsiveness than commonly monitored static preload variables such as

cardiac filling pressures [34]. However, there were several clinical limitations for the dynamic preload indicators such as requiring mechanical ventilation (tidal volume >8 mL/kg) in the absence of spontaneous breathing and/or cardiac arrhythmias [35]. On the other hand, IDVG measurement is normally available in intensive care units which have a blood gas analyzer with the function of blood sugar measurement. IDVG can be a useful volumetric method intermittently to assess the cardiac preload, though the dynamic indicators show the cardiac preload continuously at every cardiac systole. According to the previous data [10] and the present data, low CO with a low IDVG value which is less than 110ml/kg suggests effectiveness of fluid volume loading and low CO with a high IDVG value which is more than 130ml/kg suggests usage of inotropes instead of volume loading.

Conclusion

This study suggests that IDVG can be assessed from high CO state to low CO state with the minimum influence of CO if the CO is more than 40% of the normal. IDVG is dependent on the central ECF volume and not on cardiac output.

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Figure legends

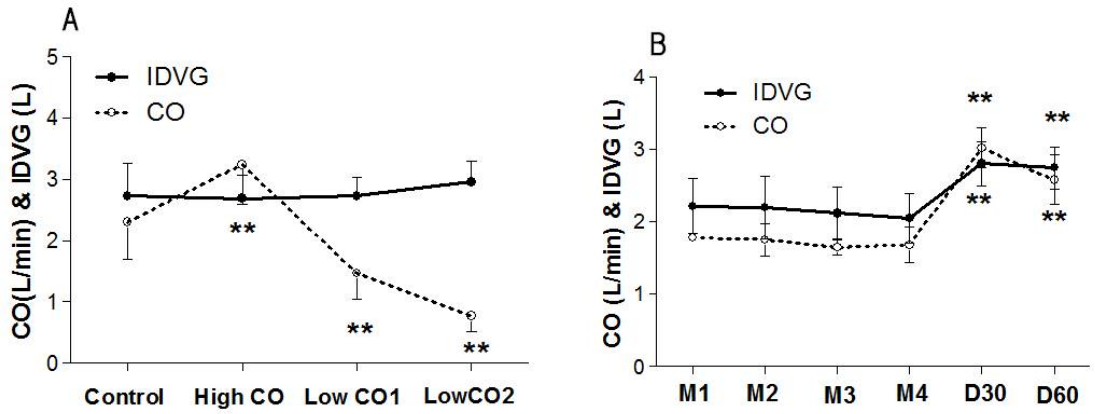

Fig. 1. Changes in IDVG and CO

Figure 1: Changes in IDVG and CO

A: The changes in the modified cardiac output group (n=10), where the CO was modulated from high to low with positive and negative inotropic agents with stable basic fluid volume status, CO: Cardiac output, IDVG: Initial Distribution Volume of Glucose, B: The changes in the control group where volume loading of 250ml of 10% dextran was performed following the 4 times measurements to confirm the stability of basic fluid volume status (n=3). M1~4: Data measurement at the same time schedule as m-CO group without inotropic drugs, D30 and D60 min: Data 30min and 60min after the volume loading of 250ml of dextran. Data are expressed as Mean ± SD. **P<0.01 vs. Control data or M1.

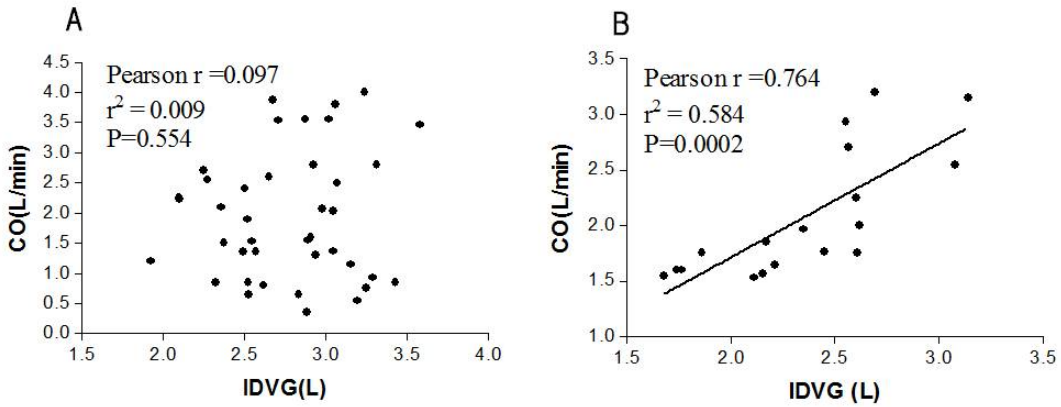

Fig. 2. The correlation between IDVG and CO in Pigs

Figure 2: The correlation between IDVG and CO in Pigs

A: The correlation in the modified cardiac output group (n=40), where the CO was modulated from high to low with positive and negative inotropic agents with stable basic fluid volume status, B: The correlation in the control group where volume loading of 250ml of 10% dextran was performed following the 4 times measurements to confirm the stability of basic fluid volume status (n=18).

	Control	High CO	Low CO-1	Low CO-2
CO (L) **(%)**	2.3±0.6 (100)	3.2±0.6** (147.2±26.7)	1.5±0.4** (65.9±11.0)	0.8±0.3** (37.3±14.4)
Mean BP **（mmHg）**	85.3±14.5	98.5±16.9*	64.7±15.9*	40.4±8.4*
Heart rate **(bpm)**	118.8±24.4	161.5±33.2*	86.2±17.7*	62.0±11.6*
Mean PAP **(mmHg)**	20.2±3.6	21.1±2.8	22.3±5.5	19.8±4.1
CVP **(mmHg)**	8.8±2.6	7.9±2.2	10.4±2.5*	11.9±2.6*
SVR **(dynes▪sec▪cm^{-5})**	2766±816	2319±605	3108±1092	3082±1005
Hb(g/dl)	10.3±0.9	11.3±1.1*	10.3±0.9	9.9±1.1
IDVG(L) **（ml/Kg）**	2.73±0.53 （141.6±17.2）	2.69±0.38 (140.6±19.0)	2.72±0.30 (143.0±20.1)	2.96±0.33 (146.7±22.4)
Ke-Glu	0.091±0.016	0.085±0.027	0.092±0.015	0.058±0.024**
AIC-Glu	-26.3±6.3	-26.1±5.8	-25.9±6.5	-29.6±9.2

Table 1. The results of hemodynamic and volumetric parameters in a modified cardiac function group without basic fluid volume status in pigs (n=10)

High CO: measurement in a high output state more than 150% of the control CO values with dobutamine, Low CO-1 and Low CO-2: measurements in a low output state less than 75% and 50% of the control CO values with propranolol and lidocaine, respectively. IDVG: initial distribution volume of glucose, Ke-Glu and Ke-ICG: disappearance rate of glucose from plasma,

AIC-Glu : Akaike’s information criterionof glucose and ICG , PV: plasma volume, Data are expressed as mean ± SD.

*:P<0.05 and vs. control values, **P<0.01 vs control values.

	Measurement -1	Measurement -2	Measurement -3	Measurement -4	Dextran (30min)	Dextran (60min)
CO (L) (%)	1.8 ±0.1 (100)	1.8 ±0.2 (98.3±13.9)	1.6 ±0.1 (92.4±8.2)	1.7 ±0.2 (94.6±15.6)	3.0 ±0.3** (169.1±13.3)	2.6 ±0.3** (144.3±15.0)
Mean BP（mmHG）	77.7±10.0	75.0±1.0	75.7±7.2	79.3±2.9	82.0±6.0	70.0±4.4
Heart rate (bpm)	113.3±16.8	111.3±20.6	107.3±21.2	102.3±17.7	129.7±14.2*	120.3±11.7
Mean PAP (mmHg)	20.0±3.6	19.3±4.5	19.7±4.0	19.0±3.0	26.7±2.9**	22.0±3.0
CVP (mmHg)	9.3±2.1	8.7±2.3	9.0±1.7	9.3±3.1	14.3±2.1**	11.0±2.6*
SVR (dynes▪ sec▪cm^{-5})	3060±315	3064±387	3259±550	3385±622	1808±263**	1847±217**
Hb(g/dl)	9.3±1.1	9.2±1.0	8.9±0.9	9.1±0.9	6.3±0.4**	6.7±0.6**
IDVG(L)（ml/kg）	2.21±0.38 (167.6±6.4)	2.20±0.43 (172±12.3)	2.11±0.36 (163±8.9)	2.05±0.34 (160.4±9.7)	2.80±0.30** (221.4±9.5)	2.74±0.29** (215.3±12.9)
Ke-Glu	0.094±0.005	0.093±0.009	0.100±0.009	0.100±0.004	0.080±0.008*	0.083±0.009*
AIC-Glu	-30.9±2.4	-26.2±4.6	-24.3±1.5	-26.5±3.1	-31.8±6.7	-26.8±5.2

Table 2. The results of hemodynamic and volumetric parameters in control group with fluid volume loading in pigs (n=3)

Measurement 1~4: Data measurement at the same time schedule as modified cardiac output group without inotropic drugs, Dextran 30 and 60 min: 30 and 60 min after the volume loading of 250ml of dextran over 15min, IDVG: initial distribution volume of glucose, Ke-Glu: disappearance rate of glucose and indocyanine green from plasma, AIC-Glu : Akaike’s information criterion of glucose and ICG , Data are expressed as mean ± SD. *:P<0.05 and vs. Measuremrnt-1, **P<0.01 vs Measurement-1