Efficacy of Goal-Directed Therapy Using Bioreactance Cardiac Output Monitoring after Valvular Heart Surgery

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Purpose: We compared the efficacy of postoperative hemodynamic goal-directed therapy (GDT) using a pulmonary artery catheter (PAC) and bioreactance-based noninvasive cardiac output monitoring (NICOM) in patients with atrial fibrillation undergoing valvular heart surgery. **Materials and Methods:** Fifty eight patients were randomized into two groups of GDT with common goals to maintain a mean arterial pressure of 60–80 mm Hg and cardiac index ≥ 2 L/min/m^2: the PAC group (n=29), based on pulmonary capillary wedge pressure, and the NICOM group (n=29), based on changes in stroke volume index after passive leg raising. The primary efficacy variable was length of hospital stay. Secondary efficacy variables included resource utilization including vasopressor and inotropic requirement, fluid balance, and major morbidity endpoints. **Results:** Patient characteristics and operative data were similar between the groups, except that significantly more patients underwent double valve replacement in the NICOM group. The lengths of hospital stay were not different between the two groups (12.2±4.8 days vs. 10.8±4.0 days, p=0.239). Numbers of patients requiring epinephrine (5 vs. 0, p=0.019) and ventilator care >24 h (6 vs. 1, p=0.044) were significantly higher in the PAC group. The PAC group also required significantly larger amounts of colloid (1652±519 mL vs. 11430±463 mL, p=0.004). **Conclusion:** NICOM-based postoperative hemodynamic GDT showed promising results in patients with atrial fibrillation undergoing valvular heart surgery in terms of resource utilization.

Key Words: Pulmonary artery catheterization, goal directed therapy, non-invasive cardiac output monitoring, atrial fibrillation, valvular heart surgery

INTRODUCTION

In the current era of critical care, increasing evidence supports the adoption of hemodynamic goal-directed therapies (GDT) to improve patient outcomes.[1,2] For a hemodynamic GDT to be beneficial, objective feedback from reliable assessments of cardiac output and a patient's status on the Frank-Starling curve seem mandatory, as only half of hemodynamically unstable patients are fluid responders and fluid excess may actually lead to dismal prognosis.[3,4]

Despite technical advances, the postoperative course following cardiac surgery

in the intensive care unit (ICU) is often complicated by hemodynamic perturbations, alarming the need for an effective GDT. However, appropriate preload assessment can be especially challenging in patients after valvular heart surgery, as it invariably accompanies various degrees of myocardial and vasomotor dysfunction and changes in loading conditions of the heart related to surgery and cardiopulmonary bypass (CPB).[5,6]

In the cardiac surgical setting, pulmonary artery catheters (PAC) have been traditionally used to guide hemodynamic management. However, it is now widely accepted that invasive cardiac filling pressures derived from PACs are no longer valid in predicting fluid responsiveness, and the role of PACs in high-risk patients has been constantly questioned.[7,8] In contrast, dynamic preload indices derived from arterial pressure waveforms have emerged as accurate predictors of fluid responsiveness over the last decade.[9] However, these indices cannot be applied to patients with spontaneous breathing efforts or arrhythmia, limiting their postoperative use after cardiac surgery.[10]

The totally Noninvasive Cardiac Output Monitoring device (NICOM™, Cheetah Medical, Portland, OR, USA) is based on thoracic bioreactance and measures the phase shift in voltage across the thorax created by pulsatile ejection of the left ventricle.[11] While its accuracy and reliability have been validated in various clinical settings, including in patients with arrhythmia, it has also been shown to accurately predict fluid responsiveness when coupled with a passive leg raising (PLR) maneuver in critically ill patients, regardless of the presence of spontaneous breathing efforts.[12-15] Therefore, the aim of this study was to compare the efficacy of two different postoperative GDTs based on conventional PAC derived parameters versus NICOM derived parameters coupled with PLR in patients with atrial fibrillation undergoing valvular heart surgery in a randomized trial.

## MATERIALS AND METHODS

Patients and management protocol

This study protocol was approved by the Institutional Review Board of the Yonsei University Health System (4-2012-0735), Seoul, Korea, and conducted in accordance with the Declaration of Helsinki. Between January 2013 and May 2014, 64 patients diagnosed with valvular heart disease having atrial fibrillation were enrolled into this prospective randomized study, and written informed consent was ob-

tained from every patient. Exclusion criteria comprised patients with left ventricular ejection fraction <35%, congestive heart failure (New York Heart Association functional class ≥3), and end-stage renal disease. Patients who were already on pharmacologic/mechanical hemodynamic support or requiring emergency surgery were also excluded.

According to a computer generated randomized table, patients were allocate to one of two hemodynamic monitoring groups: a conventional PAC group (n=32) and the NICOM group (n=32). Among them, 6 patients (3 patients in each group) who had converted to sinus rhythm after operation were excluded. In the conventional PAC group (n=29), hemodynamic and fluid management was primarily based on mean arterial pressure (MAP), cardiac index (CI), and pulmonary capillary wedge pressure (PCWP) (Fig. 1). In the NICOM group (n=29), management was targeted according to the MAP, CI, PLR maneuver, and stroke volume index (SVI) (Fig. 2). The primary difference between the two GDTs was that fluid challenge (colloid; 6% hydroxyethyl starch 130/0.4, Voluven; Fresenius Kabi, Graz, Austria) was done based on PCWP and changes in SVI after PLR in the PAC and NICOM groups, respectively, to maintain a CI≥2.0 L/min/m^2 and a MAP of 60–80 mm Hg (details of the GDTs are shown in respective figures).

Vasopressors and inotropics were used in a stepwise additive fashion as follows. The primary vasopressor used was norepinephrine up to 0.5 μg/kg/min, after which vasopressin (up to 4 IU/hr) was added when the desired MAP could not be achieved. The primary inotrope used was dobutamine (up to 10 μg/kg/min) [milrinone (up to 0.7 μg/kg/min) in patients who received β-blockers]. When the targeted hemodynamic goals could not be achieved (either in terms of MAP or CI), epinephrine was added starting at 0.02 μg/kg/min.

Ventilator weaning was performed when the patients were awake with alert mentality and upon recovery of normal skeletal muscle power, when they were hemodynamically stable without tachy- or brady-arrhythmias or mediastinal bleeding, and when blood gas analysis values were within the normal range. All patients who achieved successful extubation were transferred to the general ward on the morning of postoperative day one or two according to hemodynamic status. The criteria for hospital discharge included stable vital signs without fever, no rhythm disturbance, no wound complications, and achievement of target international normalized ratio level.
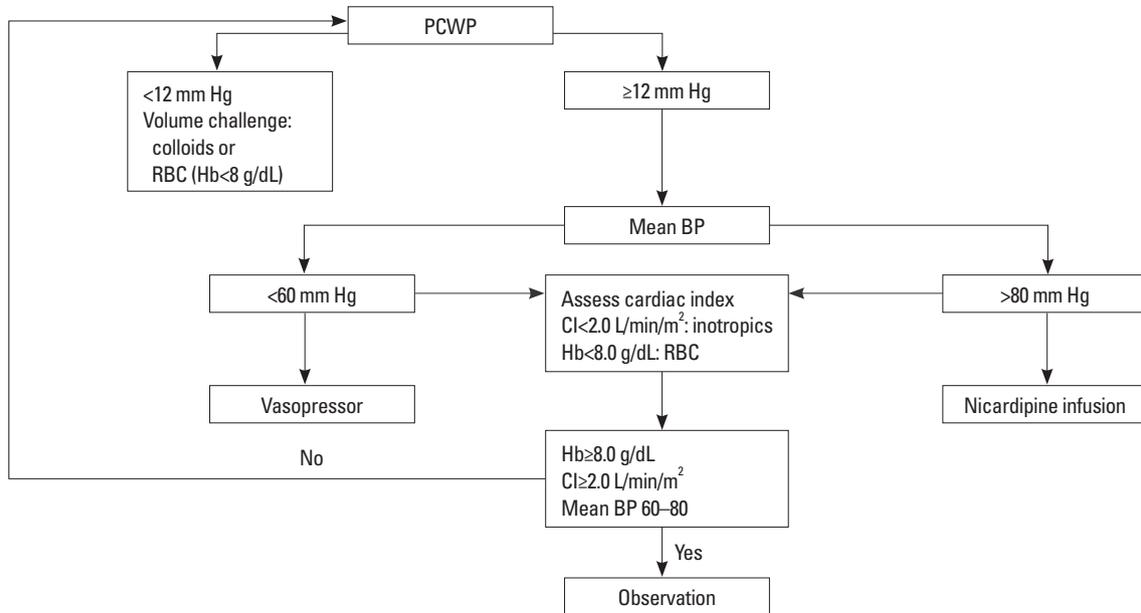
Fig. 1. Goal directed therapy algorithm based on pulmonary artery catheters. PCWP, pulmonary capillary wedge pressure; RBC, red blood cell; BP, blood pressure; CI, cardiac index; Hb, hemoglobin.
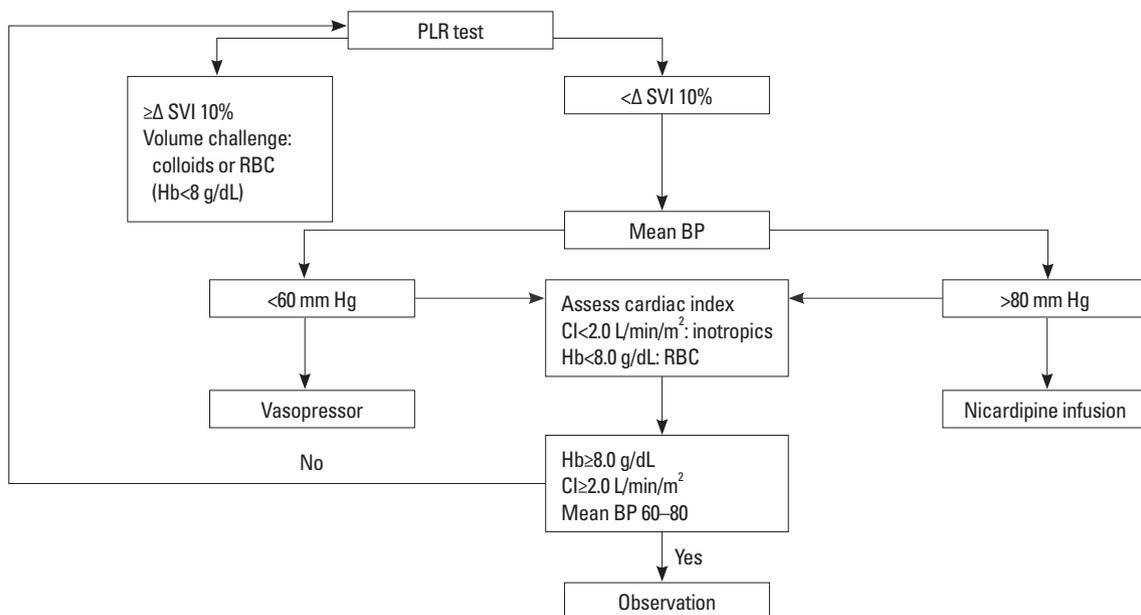
Fig. 2. Goal directed therapy algorithm based on Noninvasive Cardiac Output Monitoring system. PLR, passive leg raise; SVI, stroke volume index; RBC, red blood cell; Hb, hemoglobin; BP, blood pressure; CI, cardiac index.

Assessed variables

The assessed preoperative variables included patient demographic data, comorbidities (hypertension, diabetes, chronic renal insufficiency, chronic obstructive pulmonary disease, cerebrovascular disease, coronary artery disease, and logistic EuroSCORE), position of diseased valve (mitral, aortic, or both), and echocardiographic data (left ventricular ejection fraction, left atrial, and ventricular dimensions, right ventricular systolic pressure). Operative data included duration of operation, duration of CPB and aortic cross clamp,

and type of valvular surgery. In all patients, postoperative hemodynamic parameters were monitored continuously, and recorded on an hourly basis in stable situations. If patients became hemodynamically unstable, the management was changed to a different GDT guideline in each patient group.

Study endpoints

The primary endpoint of this study was to compare the length of hospital stay between the groups. Secondary endpoints were to compare resource utilization (requirement of

inotropic and/or vasopressors, and administration of colloids and blood product); mortality; major morbidity endpoints, including ventilator care >24 h, permanent stroke, acute kidney injury, reoperation, deep sternal wound infection, and myocardial infarction; and the use of an intra-aortic balloon pump or extracorporeal membrane oxygenation.

Statistical analysis
According to our institutional data regarding patients undergoing valvular heart surgery,[16] a sample size of 29 patients each was required to detect a 3-day difference in the length of hospital stay between the groups [standard deviation (SD) 4 days], with 80% power at an alpha level of 0.05. Considering a 10% drop out rate, 32 patients in each group were enrolled.

All data are expressed as mean±SD, frequency, or percentage. In case of a normal distribution, we used Student's t-test for intergroup comparisons and categorical variables were compared using the χ^2 or Fisher exact test as appropriate. For all tests, p-values<0.05 were considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) statistical software package, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics and operative data are described in

Table 1. The patients' characteristics including the EuroSCORE were all similar between the groups, except for history of cerebral infarction, which was significantly more prevalent in the NICOM group than the PAC group. The incidence of diabetes mellitus also showed a trend towards being higher in the NICOM group. Operative data including the duration of CPB were all comparable between the groups, except that significantly more patients required double valve replacement (aortic and mitral) in the NICOM group than the PAC group.

Baseline hemodynamic data after surgery before ICU admission were similar between the two groups (data presented in the order of PAC and NICOM group): central venous pressure 8.7±2.9 mm Hg vs. 8.5±2.8 mm Hg, p=0.798; mean pulmonary arterial pressure 24.0±6.2 mm Hg vs. 23.5±5.3 mm Hg, p=0.729; MAP 70±10 mm Hg vs. 69±11 mm Hg, p=0.586; and CI 2.8±0.6 L/min/m^2 vs. 2.6±0.8 L/min/m^2, p=0.194.

Postoperative data in the ICU regarding fluid balance and resource utilization are shown in Table 2. The amount of chest tube drainage for 24 h showed a trend towards being larger in the PAC group, compared with the NICOM group. PAC group required significantly larger amounts of colloid than the NICOM group. Inotropic and vasopressor requirements in terms of number of patients and duration were all larger in the PAC group than the NICOM group without statistical significance. The number of patients requiring epinephrine was significantly larger in the PAC group than the

Table 1. Patient Characteristics and Operative Data

Variables	PAC group (n=29)	NICOM group (n=29)	p value
Age (yrs)	60.2±12.6	62.6±11.4	0.449
Male:Female	8:21	6:23	0.929
BSA (m^2)	1.61±0.18	1.63±0.29	0.734
LVEF (%)	60.0±10.3	59.9±5.4	0.987
EuroSCORE	4.86±1.87	5.00±1.91	0.782
Hypertension	11 (38%)	15 (52%)	0.291
Diabetes mellitus	3 (10%)	8 (28%)	0.094
Chronic kidney disease	2 (7%)	4 (14%)	0.389
Cerebrovascular accident	0 (0%)	6 (21%)	0.01
Chronic obstructive pulmonary disease	4 (14%)	6 (21%)	0.487
Type of surgery			
Aortic valve	24 (83%)	19 (66%)	0.230
Mitral valve	4 (14%)	1 (3%)	0.352
Aortic+mitral	1 (3%)	9 (31%)	0.012
Duration of operation (min)	209.0±46.2	194.2±59.7	0.296
Duration of CPB (min)	110.9±26.7	100.8±27.8	0.164
Duration of ACC (min)	78.2±20.3	76.3±20.9	0.722

PAC, pulmonary artery catheter; NICOM, non-invasive cardiac output monitoring; BSA, body surface area; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; ACC, aortic cross clamp.

Table 2. Fluid Balance and Resource Utilization

Variables	PAC group (n=29)	NICOM group (n=29)	*p* value
Inotropic agents			
Number of patients	23 (79.3%)	20 (69%)	0.368
Duration of use (days)	2.8±4.6	1.6±2.1	0.097
Vasoactive agents			
Number of patients	15 (51.7%)	10 (34.5%)	0.185
Duration of use (days)	1.7±0.9	1.1±0.4	0.147
Chest tube drainage for 24 hrs (mL)	658.3±431.0	465.9±363.7	0.071
Colloid (mL)	1652.4±783.7	1143.0±463.3	0.004
Crystalloid (mL)	1307.6±519.1	1364.1±515.9	0.679
Packed erythrocytes (mL)	248.3±310.1	131.0±228.5	0.107

PAC, pulmonary artery catheter; NICOM, non-invasive cardiac output monitoring.

Table 3. Postoperative Outcomes

Variables	PAC group (n=29)	NICOM group (n=29)	*p* value
Duration of ventilator care (hrs)	27.4±32.3	19.7±17.9	0.263
Length of ICU stay (days)	2.4±1.9	2.2±1.7	0.717
Length of hospital stay (days)	12.2±4.8	10.8±4.0	0.239
In-hospital mortality	0 (0%)	0 (0%)	
Major morbidity endpoints			
Reoperation	2 (6.9%)	0 (0%)	0.150
Acute kidney injury	2 (6.9%)	2 (6.9%)	1.000
Ventilator care>24 hrs	6 (21%)	1 (3%)	0.044
Permanent stroke	0 (0%)	0 (0%)	
Deep sternal wound infection	0 (0%)	0 (0%)	
Myocardial infarction	0 (0%)	0 (0%)	
IABP or ECMO	0 (0%)	0 (0%)	

PAC, pulmonary artery catheter; NICOM, non-invasive cardiac output monitoring; ICU, intensive care unit; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation.

NICOM group (5 vs. 0, *p*=0.019).

Data regarding postoperative outcomes are shown in Table 3. There was no in-hospital mortality in either group and the incidences of the major morbidity endpoints were all similar between the two groups, except the number of patients requiring ventilator care >24 h, which was significantly higher in the PAC group than the NICOM group. The length of hospital stay was 1.5 days shorter in the NICOM group than the PAC group without statistical significance (12.2±4.8 days vs. 10.8±4.0 days, *p*=0.239).

DISCUSSION

In this prospective, randomized trial comparing the efficacy of PAC- and NICOM-based postoperative hemodynamic GDT in patients with atrial fibrillation undergoing valvular heart surgery, NICOM-based GDT coupled with PLR was associated with significant reductions in resource utilization (colloid and epinephrine requirement). These beneficial influences led to significantly fewer patients requiring ventilator care >24 h, without any significant difference in length of hospital stay, compared with the conventional PAC group.

Despite pharmacologic and technical advances aimed to reduce systemic inflammation and myocardial injury during CPB, approximately 10% of patients experience hemodynamic instability or multiple organ dysfunctions following cardiac surgery.[6,17] CPB with cardioplegic arrest inevitably results in various degrees of myocardial injury and edema, resulting in both systolic and diastolic dysfunction, not to mention that valvular heart surgery alone causes significant changes in the loading conditions of the heart. The postoperative course is also frequently complicated by severe vasodilation as a result of systemic inflammatory response. As the systemic inflammatory response persists for several hours to days after surgery,[18] clinicians are confronted with hemodynamic perturbations in the ICU, mandating the need for hemodynamic GDTs based on proper feedback of the he-

modynamics and volume status. Indeed, studies of GDTs at any time point during the perioperative period have shown benefits, although a variety of different surgical patients, algorithms, and goals have been assessed.[1,2]

To ensure optimal oxygen delivery to the tissues, maintenance of sufficient cardiac output and perfusion pressure is imperative. Before advancing to vasopressors and/or inotropes, preload optimization by fluid resuscitation is often considered as the first line of therapy. However, it has been consistently reported that only 50% of the critically ill patients are fluid responsive and fluid excess may actually worsen these patients' outcomes.[3,4]

While cardiac filling pressures derived by PAC are no longer considered to be valid preload indices,[7] dynamic indices derived from arterial pressure waveforms, such as pulse pressure variation, have emerged as useful and accurate predictors of fluid responsiveness over the last decade.[9] Albeit exhibiting almost a 90% power in predicting fluid responsiveness, these indices require mechanical ventilation and sinus rhythm, and thus, cannot be applied to patients with spontaneous breathing efforts or atrial fibrillation.[10] Also, the validity of these devices in terms of cardiac output measurement may be compromised in patients with arrhythmia.[19]

NICOM is a totally non-invasive method of measuring cardiac output, and is reported to have high accuracy in various clinical situations, compared with PAC or other devices using arterial waveform analysis.[12-14,20] The thoracic bioreactance system involves the application of a high-frequency electrical current across the chest, and measures changes in voltage via topical electrodes placed around the thorax. Pulsatile changes in thoracic blood volume result in changes in electrical impedance, and its rate of change during systole is measured, allowing a value of cardiac output to be derived.[12,21] Besides being totally non-invasive, other potential advantages of NICOM include that it provides accurate cardiac output measurement in patients with arrhythmia and has been validated to accurately reflect changes in stroke volume following PLR, and thereby, to reliably predict fluid responsiveness, even in patients who are breathing spontaneously.[15]

PLR causes a reversible increase in preload (200–300 mL), resulting in increases in stroke volume in potential fluid responders.[22] These changes need to detected within minutes.[23] Continuous cardiac output measurement, and thus stroke volume, by PAC requires 8 to 10 min of delay, whereas real-time intermittent bolus measurement is often not clinically feasible, as it requires stopping all pharmacologic agents delivered through central venous access. Moreover, at least three measurements are recommended for real-time intermittent thermodilution method using PAC, with its inherent problems regarding operator dependency and drift causing a discrepancy of up to 15%.[24,25]

Taken together, NICOM-based GDT coupled with PLR may have theoretical advantage over PAC or arterial waveform analysis devices in the immediate postoperative period, following valvular heart surgery in patients with atrial fibrillation, although it has not yet been validated.

In the current trial, the common goals of the applied hemodynamic GDTs were to maintain a MAP between 60–80 mm Hg and CI $\geq$2.0 L/min/m^2, starting with preload assessment based on PCWP or changes in SVI by PLR in the PAC and NICOM groups, respectively. Use of vasopressors and inotropics were standardized according to an institutional protocol in a stepwise additive fashion.

As our results indicate, NICOM-based GDT was associated with significantly less resource utilization in terms of the amount of colloid used and epinephrine requirement to meet the predefined hemodynamic goals despite that significantly more patients in the NICOM group received double valve replacement. Use of epinephrine is well known to be associated with increased lactic acidosis and mortality.[26,27] Thus, its use is usually not recommended as a first line of therapy for hemodynamic support, as was in the current trial.[28] Likewise, fluid excess in critically ill patients promotes tissue edema and congestion hindering the patients' recovery, thus exerting adverse influence on the patients' prognosis.[4] Apparently, these favorable influences led to significantly fewer patients requiring ventilator care >24 h. Although we did not observe any statistically significant differences in other major morbidity endpoints and length of hospital stay, NICOM-based hemodynamic GDT coupled with PLR showed favorable trends in all aspects regarding resource utilization.

The limitations of this trial are as follows. First, the primary endpoint of this trial was to assess whether NICOM-based hemodynamic GDT would exert any beneficial influence on the length of hospital stay, upon which the sample size calculation was performed. Although patients in the NICOM group were discharged 1.5 days earlier than the PAC group, this difference lacked statistical significance, clearly due to insufficient sample size, as opposed to our expectations, which merits further trials. However, statistically significant differences were noted in secondary end-points. Second, it may be argued that the observed difference in the use of colloids may be related to a trend observed in postoperative bl-

eeding amounts, which were higher in the PAC group without statistical significance. However, the mean difference in postoperative bleeding was less than 200 mL between the groups, while the difference in the amount of colloid was 500 mL. Moreover, considering the approximately 110 mL of difference in the amount of packed erythrocytes transfusion, its influence should be negligible. Third, despite being a randomized controlled trial adhering strictly to the respective GDT protocols, caregivers in the ICU could not be blinded due to differences in the nature of the monitoring systems.

In conclusion, appropriate preload assessment and hemodynamic management may be especially challenging after valvular heart surgery in patients with arrhythmia for the reasons described above. While conventional PAC or arterial waveform analysis devices have inherent limitations, our study demonstrates promising results regarding the application of NICOM-based hemodynamic GDT coupled with PLR in terms of resource utilization.

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