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Noninvasive Cardiac Output Measurements in Patients with Pulmonary Hypertension

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Abstract:

Background: Pulmonary hypertension (PH) is characterized by a progressive decline in cardiac output (CO) and right heart failure. NICOM® is a bioreactance-based technology that has been broadly validated, but its specific application in right heart failure and PH is unknown.

Methods: Cardiac catheterization was performed in 50 consecutive patients with PH. CO measurements were performed using three different methods (thermodilution(TD), Fick, and NICOM) at baseline and after vasodilator challenge. We compared the precision (coefficient of variation) and accuracy of NICOM compared to TD and Fick.

Results: The mean CO (L/min) at baseline as measured by the three methods was 4.73±1.15 (NICOM), 5.69±1.74 (TD), and 4.84±1.39 (Fick). CO measured by NICOM was more precise than by TD (3.5±0.3% vs. 9.6±6.1%, $p<0.001$). Bland-Altman analyses comparing NICOM to TD and Fick revealed bias and 95% limits of agreement that were comparable to those comparing Fick to TD. All three CO methods detected an increase in CO in response to vasodilator challenge.

Conclusions: CO measured via NICOM is precise and reliably measures CO at rest and changes in CO with vasodilator challenge in patients with PH. NICOM may allow for the noninvasive hemodynamic assessment of patients with PH and their response to therapy.

Abbreviation List:

Cardiac output (CO)

Noninvasive measurement of cardiac output (NICOM)

Oxygen consumption (VO2)

Pulmonary arterial hypertension (PAH)

Pulmonary hypertension (PH)

Pulmonary vascular resistance (PVR)

Stroke volume (SV)

Thermodilution (TD)

Tricuspid regurgitation (TR)

World Health Organization (WHO)

Introduction:

Pulmonary arterial hypertension (PAH) is a disease characterized by an elevated pulmonary vascular resistance (PVR) that ultimately results in a progressive decline in cardiac output (CO) due to right ventricular failure[1]. Whereas the severity of pulmonary artery pressure elevation does not reliably predict mortality, the status of the right ventricle as measured by CO has consistently been shown to be among the strongest predictors of outcomes in this fatal disease[2, 3]. From a clinical perspective, the ability to measure and serially follow the CO response to treatment is of significant value, perhaps even more so than serial measurements of pulmonary artery pressure. However, the measurement of CO has traditionally required a cardiac catheterization, which has inherent risks and expense[4]. Thus, the ability to serially measure CO noninvasively in patients with PAH is clinically attractive.

Transthoracic bioreactance is a recently introduced technology that allows for the noninvasive measurement of CO (NICOM®) [5, 6]. The bioreactance signal is determined by measuring blood flow-dependent changes in the phase shifts between an oscillating electrical current applied across the thorax and the resulting voltage signal. This signal has been shown to be directly proportional to aortic blood flow[5]. Importantly, this technology differs from bioimpedance, which relies on the detection of changes in voltage signal amplitude which has been shown to be limited by factors such as body habitus, pleural effusions, and body motion[7-9]. Because bioreactance is generally unaffected by these factors, it yields a favorable signal-to-noise ratio[5]. The accuracy and precision of the NICOM device has been validated against invasive

measurements of CO in several different clinical settings[6, 10]. However, the ability of NICOM to reliably measure CO in patients with pulmonary hypertension (PH) and right heart failure has never been evaluated. Therefore, since it is unknown how changes in pulmonary blood flow may affect the measurement of CO with NICOM, we tested the accuracy of NICOM to measure CO as compared to the reference standards of thermodilution (TD) and the indirect Fick method in a consecutive cohort of patients with PH.

Methods:

The current study was approved by the University of Chicago Institutional Review Board (IRB # 10-179-B). Written informed consent was obtained from all patients.

We enrolled 50 consecutive patients referred to the cardiac catheterization laboratory for a hemodynamic assessment of presumed or previously confirmed PH. We included patients from all five World Health Organization (WHO) PH Groups, but excluded patients who carried a diagnosis of WHO Group 1 PAH secondary to congenital heart disease to eliminate technological issues with all three methods that may be affected by the presence of an intracardiac shunt. With each patient lying quietly and supine on the catheterization table, venous access was achieved with an 8 French sheath placed in either the internal jugular or femoral vein. A 7.5 French Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA) was inserted, followed by measurements of right atrial, right ventricular, pulmonary artery and pulmonary capillary wedge pressures. After the pressure measurements were performed, we measured CO as close to simultaneously as

possible according to the NICOM, TD, and indirect Fick methods (see below). The same clinical investigator, expertly trained and experienced in the performance of cardiac catheterization, performed every measurement in this study.

NICOM:

Noninvasive bioreactance CO monitoring was performed using the NICOM system (Cheetah Medical Inc., Portland, OR, USA), the methodology of which has been described previously[5] (Table 1A). At the start of the preparation of each case, the NICOM device was connected to each patient by placing the four double electrodes on the patient's thorax, which were connected to the NICOM device by four wires. After the NICOM electrodes were applied, the device underwent a one minute auto-calibration and the patient was subsequently prepped and draped in sterile fashion for cardiac catheterization. The NICOM measured the CO continuously with average values displayed every minute throughout the procedure. The CO data were electronically stored within the monitor.

Thermodilution:

CO via TD was performed via the indicator-dilution technique[11]. For each patient, we confirmed the proper positioning of the Swan-Ganz catheter by documenting the presence of a right atrial pressure waveform from the proximal port of the Swan-Ganz catheter and fluoroscopic visualization of the distal tip of the catheter in the mid-pulmonary artery before every measurement. CO was measured by the injection of 10 ml of sterile, isotonic (0.9%) saline, injected through the proximal lumen of the catheter,

and the time course of change of temperature was recorded at the distal thermistor. Three consecutive bolus saline injections were performed for individual estimations of CO and the mean value of the three measurements used as the final value for CO.

Indirect Fick:

Total body oxygen consumption (VO2) was estimated via the formula of LaFarge-Miettinen[12] (Table 1B). Simultaneous blood samples were taken from the aorta and pulmonary artery for determination of the oxygen saturation and hemoglobin concentrations. CO was calculated according to the Fick equation (Table 1C).

Simultaneous CO Measurements:

In order to perform the CO measurements as nearly simultaneously as possible, the blood samples for the arterial saturations were drawn immediately prior to the initial TD bolus injection. Because the NICOM device is continuously sampling and providing a measured CO every minute, all NICOM measurements were determined based on the value displayed on the monitor as close as possible to each bolus TD injection. Thus, in each patient, we were able to consistently make the CO measurements according to each modality within approximately one to five minutes of one another. This was critical in order to best ensure that all measurements were obtained as simultaneous as possible, thus avoiding any significant changes in the clinical status of the patient during the course of the measurements.

Acute vasodilator challenge:

Vasodilator testing using intravenous adenosine was performed as clinically indicated (n=36). All vasodilator studies were initiated at a dose of 50 mcg/kg/min and up-titrated to a maximum dose of 150 mcg/kg/min or to the highest dose tolerated by the patient (whichever occurred first). After achieving a steady state at the final adenosine dose, hemodynamic measurements were repeated followed by a repeat of the near-simultaneous measurements of CO by NICOM, TD and Fick as described above.

Echocardiography:

The majority of patients in the study underwent cardiac imaging with 2D transthoracic echocardiography within 30 days of the cardiac catheterization (n=44). We tabulated the results of assessments made of overall RV size and function, presence and severity of tricuspid regurgitation (TR) and pulmonic insufficiency, respectively, to see if they affected the CO measurements by any of the techniques.

Statistical Analyses:

Baseline demographic and clinical variables were collected. Continuous variables are described as mean ±SD and categorical variables as percentages. Correlations between parameters of interest were determined according to the Pearson correlation method. A Student's t-test and/or a one-way repeated measure ANOVA with Bonferroni correction was performed to determine statistical significance of differences between continuous variables. A p-value <0.05 was considered statistically significant. Coefficient of variance was calculated to determine the precision of the NICOM and thermodilution methods, respectively. Bland-Altman analyses were performed to estimate the general

degree of agreement among the three methods. The mean bias and 95% limits of agreements were calculated. Sensitivity and specificity for directional change in response to adenosine vasodilator challenge for each CO method was calculated. A false positive directional change was considered to have occurred when an increase in CO of $\geq$10% was not detected by the remaining two modalities and a false negative change was considered to have occurred when the CO method did not detected the increase in CO of $\geq$10% while the other two methods did. All measured CO values were included in these analyses even when obvious outliers occurred.

Results:

Baseline demographics of the patient cohort are shown in Table 2 and key hemodynamic and echocardiographic data are shown in Tables 3A and 3B. The mean age of the patients was 54±15 years and the majority of patients had WHO Group 1 PAH. The majority of patients had moderate-to-severe PH as demonstrated by the elevated mean PA pressure (40.7±13.7 mm Hg) and PVR (6.0±4.3 Wood units) and most patients had at least moderate-to-severely reduced right ventricular function by echocardiography. Although almost all patients had some degree of TR, severe TR was relatively uncommon (n=5; 11.6%).

The mean CO at baseline as measured by the three methods was 4.73±1.15 L/min by NICOM, 5.69±1.74 L/min by TD, and 4.84±1.39 L/min by Fick. There was no difference in CO between NICOM and Fick ($p=0.58$), but CO according to TD was higher than CO measured by both NICOM and Fick ($p<0.01$ for both comparisons)

(Figure 1). NICOM measurements were significantly more precise than TD (coefficient of variation 3.5±0.3% vs. 9.6±6.1%, respectively; $p<0.001$) (Figure 2). The above findings were similar when we restricted our analyses to the subgroup of patients with WHO Group 1 PAH only.

A significant correlation was seen among all three CO methods: NICOM and TD ($r=0.60$, $p<0.001$), NICOM and Fick ($r=0.54$, $p<0.001$), TD and Fick ($r=0.83$, $p<0.001$). Bland-Altman analyses (Figure 3) revealed the following: NICOM compared to TD showed a mean bias of -0.81 with 95% limits of agreement of -3.54 to 1.92. NICOM compared to Fick showed a mean bias of 0.02 with 95% limits of agreements of -2.41 to 2.44. TD compared to Fick showed a mean bias of 0.83 with 95% limits of agreement of -0.98 to 2.63.

Similar findings were seen in those patients undergoing acute vasodilator challenge ($n=36$). Following vasodilator challenge, the mean CO was 5.53±1.46 L/min (NICOM), 7.02±1.84 L/min (TD), and 5.83±1.75 L/min (Fick). There was no difference in CO between NICOM and Fick ($p=0.22$) but CO measured by TD was higher than CO measured by both NICOM and Fick ($p<0.01$ for both comparisons). NICOM measurements were significantly more precise than TD (3.4±2.1% vs. 8.0±6.4%, $p<0.001$). All three CO methods detected a mean increase in CO: 18.8±16.8% (NICOM), 26.8±22.2% (TD), and 21.0±19.2% (Fick). Taken together, all three methods detected an increase in CO $\geq$ 10% of its baseline value in 24/36 cases. In 3/36 cases, all three methods determined that the CO did not increase by $\geq$ 10%. In the remaining cases

(n=9), there was disagreement in the directional change of similar magnitude (i.e. ≥ 10%). In 4 cases, NICOM did not detect the increase in CO but TD and Fick both did. In 4 cases, TD did not detect the increase in CO but NICOM and Fick both did. In one case, Fick did not detect the increase in CO but NICOM and TD both did. Thus, the sensitivity and specificity, respectively, of detecting a directional change in CO according to each method was: 88.9% and 100% for NICOM, 88.9% and 100% for TD, and 97.2% and 100% for Fick. There was not a single case where only one of the methods detected an increase in CO while the other methods did not.

Discussion:

We demonstrate that a noninvasive measurement of CO in patients with PH is feasible and produces results comparable to the existing invasive "reference standard" methods commonly used in clinical practice. Moreover, NICOM demonstrated superior precision to TD and reliably detects dynamic, directional changes in CO following vasodilator challenge. Among the many variables obtained during an invasive hemodynamic assessment, the CO has arguably the most prognostic relevance and impacts clinical decision strategies more than any other value in patients with PH[2, 13-15]. Accordingly, having the ability to easily measure and detect changes in CO noninvasively may have importance in the clinical care and assessment of treatments in patients with PH.

Numerous studies over the years have compared different technologies to measure CO against one another in a variety of clinical settings, though few studies have specifically addressed this question in patients with PH[16]. Despite the multitude of studies,

equipoise persists regarding the superiority (or lack thereof) of one particular method over another. While the "gold standard" of CO determination is the direct Fick method, this method is rarely used in the clinical setting because of the technical and logistical demands involved in directly measuring VO2, which makes this method impractical. As a result, the current reference standards most commonly employed in clinical practice in the evaluation of patients with PH, and the cardiac output methods employed in the largest PH registries, are the indirect Fick and TD methods, both of which are invasive and possess certain inherent limitations[2, 14, 15, 17]. For example, TD suffers from imprecision because of the potential influences from catheter migration, differences in injector technique (with intra- and inter-investigator variability), the influence of the different phases of the respiratory cycle, and other factors[18-21]. The lack of precision seen with TD also impacts the usefulness of using TD as a reference technique when comparing to other CO methods[22]. Some investigators have found TD to be less reliable in the setting of severe TR and/or low CO due to loss of indicator[23, 24], although others have not found this to be true[25-27]. These conditions are particularly common in patients with PH.

The indirect Fick method also has limitations that may affect measurement accuracy, most notably the need to estimate VO2, which when estimated erroneously will lead to an error of the same magnitude in the estimation of CO. Other factors that may affect the Fick method include errors in the measurement of oxygen saturations and hemoglobin levels and the variable influence of bronchial and thebesian venous drainage on the mixed venous saturation[26, 28, 29]. The indirect Fick method, however, is likely to be

highly accurate and reliable in assessing percent changes in CO in response to an acute intervention, since the only value that often changes in response to the intervention is the mixed venous saturation and thus the other factors that go into the estimation will cancel out when calculating percent changes in CO. Hoeper et al[26] compared CO measured by TD and Fick, respectively, in a cohort of patients with PAH and found that both methods correlated well, and that the presence of TR did not appear to influence the CO as determined by either method. However, the wide limits of agreement as seen with Bland-Altman analyses led the authors of that study to conclude that TD and Fick should not be considered interchangeable. The findings in our study are similar to those by Hoeper et al in that all three methods of CO correlated with one another and all methods reliably detected a change in CO from drug challenge. However, while all three methods showed acceptable overall agreement, the 95% limits of agreement by Bland-Altman analyses were also sufficiently wide, that we too caution against assumption of the *interchangeability* amongst the methods[30]. In this study, although the vast majority of patients carried a diagnosis of WHO Group 1 PAH, we specifically included patients with PH from all five WHO Groups, including those with lung disease, left ventricular diastolic dysfunction, and obesity to ensure the ability to apply NICOM across the entire PH spectrum. Also, similar to the findings of Hoeper et al, the presence of severe TR did not seem to influence the CO measurements, although this should be interpreted with caution in our study as this subgroup of patients was small(11.6%).

Although no single CO method employed in current clinical practice can directly and precisely measure CO, the current reference standards (i.e. TD and indirect Fick) are still

heavily relied upon in the evaluation of the PH patient because they provide reasonably precise CO measurements and are able to consistently detect directional changes in CO; these two factors (i.e. precision and the ability to detect clinically relevant changes) are arguably the most important features of a CO methodology[31]. Because CO, as measured by either thermodilution or indirect Fick, is an important predictor of outcomes in PH[2, 14, 15], clinical PH specialists often track changes in CO over time to assess response to therapy or the need to escalate care. For example, McLaughlin et al showed that an improvement in cardiac index after initiation of epoprostenol therapy in patients with PAH predicted improved survival[13].

The purpose of the present study was not to validate the NICOM technique itself, as this technology has been previously validated against a variety of different CO methods in animals and in humans in the intensive care unit (ICU) and other clinical settings[6, 10, 32, 33]. Rather, this is the first study to assess its ability to measure CO in patients with PH and RV dysfunction. Similar to those studies, we show that NICOM in PH patients is more precise than TD and that all three methods show comparable sensitivity and specificity in detecting even small changes in CO in the majority of patients, thus potentially allowing the clinician to track response to therapy and disease progression in the ambulatory setting.

The success of the bioreactance technology used by NICOM to measure CO in comparison to the noninvasive bioimpedance technology is largely attributable to the more favorable signal-to-noise ratio favoring bioreactance. Whereas bioimpedance

measures changes in signal *amplitude*, bioreactance measures changes in signal *frequency* (analogous to the difference in signal strength in AM vs. FM radio)[5, 6]. As such, the precision of bioimpedance has been shown to be negatively impacted by any variable that affects the signal amplitude, including relative distance of electrode placement, the presence of pulmonary edema and/or pleural effusions, and body habitus[34]. The bioreactance technology on the other hand was developed specifically to overcome the limitations that hindered the use of bioimpedance, while retaining the simple and noninvasive nature of the CO measurement methodology, thus improving its clinical utility across many clinical settings[5]. While the bioreactance technology has helped overcome certain obstacles encountered by previous noninvasive technologies, it too has potential limitations. It should be noted that the system detects and mutes itself during periods of electrocautery when used continuously (i.e. in the operating room), and external pacemakers can potentially interfere with signal quality. Also, the device has not been tested in the setting of severe aortic insufficiency, which could theoretically result in an overestimation of the net forward CO (though this is rarely present in patients with PAH).

The results of this study suggest many possible clinical applications of NICOM in patients with PH. Because CO measured by NICOM can be performed quickly and noninvasively, it could be performed in the ambulatory setting, thus allowing for serial measurements of CO to track response to therapy and disease progression. Given the uncertainty over the use of multiple pulmonary vasodilators to treat PH patients[14] and the continued high mortality in patients with current treatments[15], NICOM has the

potential to favorably influence the clinical management of symptomatic patients, though this would need to be rigorously studied. It could also be applied to patients admitted to the ICU with acute decompensated RV failure because of its ability to provide rapid, continuous CO measurements, thus potentially avoiding invasive procedures in these very sick patients. Finally, another potentially useful application of NICOM would be during intravenous prostacyclin initiation, when close monitoring of CO is strongly advised[1].

Limitations:

This study has several important limitations. First, this was a single center study which may limit the generalizability of the findings. Second, in addition to TD, we also used the indirect Fick CO and thus did not directly measure VO2. However, this was not unintentional. The direct Fick method is cumbersome and generally impractical for daily use in busy clinical practices. Thus, because the technique is not widely used clinically in PH patients, we felt that a comparison of NICOM to the currently accepted reference standards (i.e. TD and indirect Fick) was most appropriate. Also, we performed the thermodilution CO measurements in triplicates. While this conforms with the practice of many clinicians and investigators, others suggest that taking the average of five measurements would yield more precise results. Finally, although we attempted to perform exactly simultaneous CO measurements to compare the three methods, the measurements were made within a few minutes of each other. Thus, although the patients remained stable and in the supine position, slight changes in CO may have occurred and produced disagreements in some of the measurements.

Conclusions:

The noninvasive measurement of CO with NICOM in PH patients is feasible, precise, and reliably detects clinically relevant changes. Although practice guidelines stress the importance of an initial cardiac catheterization to confirm the diagnosis of PH and assess response to vasodilators, this technology could minimize the need for serial invasive measurements to determine disease progression and response to therapy. While the use of the NICOM in the clinical management of patients with PH has not been studied, the noninvasive bioreactance technology should be added to the array of CO monitoring tools used in PH patients and further studies evaluating this promising technology in patients with PH are warranted.

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References:

1. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009; 53: 1573-1619.
2. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343-349.
3. Sandoval J, Bauerle O, Palomar A, Gomez A, Martinez-Guerra ML, Beltran M, Guerrero ML. Survival in primary pulmonary hypertension. Validation of a prognostic equation. *Circulation* 1994; 89: 1733-1744.
4. Matthay MA, Chatterjee K. Bedside catheterization of the pulmonary artery: risks compared with benefits. *Ann Intern Med* 1988; 109: 826-834.
5. Keren H, Burkhoff D, Squara P. Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance. *Am J Physiol Heart Circ Physiol* 2007; 293: H583-589.
6. Squara P, Denjean D, Estagnasie P, Brusset A, Dib JC, Dubois C. Noninvasive cardiac output monitoring (NICOM): a clinical validation. *Intensive Care Med* 2007; 33: 1191-1194.
7. Engoren M, Barbee D. Comparison of cardiac output determined by bioimpedance, thermodilution, and the Fick method. *Am J Crit Care* 2005; 14: 40-45.
8. Imhoff M, Lehner JH, Lohlein D. Noninvasive whole-body electrical bioimpedance cardiac output and invasive thermodilution cardiac output in high-risk surgical patients. *Crit Care Med* 2000; 28: 2812-2818.
9. Leslie SJ, McKee S, Newby DE, Webb DJ, Denvir MA. Non-invasive measurement of cardiac output in patients with chronic heart failure. *Blood Press Monit* 2004; 9: 277-280.
10. Raval NY, Squara P, Cleman M, Yalamanchili K, Winklmaier M, Burkhoff D. Multicenter evaluation of noninvasive cardiac output measurement by bioreactance technique. *J Clin Monit Comput* 2008; 22: 113-119.
11. Pavek K, Boska D, Selecky FV. Measurement of Cardiac Output by Thermodilution with Constant Rate Injection of Indicator. *Circ Res* 1964; 15: 311-319.
12. LaFarge CG, Miettinen OS. The estimation of oxygen consumption. *Cardiovasc Res* 1970; 4: 23-30.
13. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106: 1477-1482.
14. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and

Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164-172.
15. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jais X, Montani D, Souza R, Simonneau G. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156-163.
16. Reuter DA, Huang C, Edrich T, Shernan SK, Eltzschig HK. Cardiac output monitoring using indicator-dilution techniques: basics, limits, and perspectives. *Anesth Analg* 2010; 110: 799-811.
17. Bonderman D, Wexberg P, Martischnig AM, Heinzl H, Lang MB, Sadushi R, Skoro-Sajer N, Lang IM. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. *Eur Respir J* 2011; 37: 1096-1103.
18. Elkayam U, Berkley R, Azen S, Weber L, Geva B, Henry WL. Cardiac output by thermodilution technique. Effect of injectate's volume and temperature on accuracy and reproducibility in the critically Ill patient. *Chest* 1983; 84: 418-422.
19. Nishikawa T, Dohi S. Errors in the measurement of cardiac output by thermodilution. *Can J Anaesth* 1993; 40: 142-153.
20. Renner LE, Morton MJ, Sakuma GY. Indicator amount, temperature, and intrinsic cardiac output affect thermodilution cardiac output accuracy and reproducibility. *Crit Care Med* 1993; 21: 586-597.
21. Stevens JH, Raffin TA, Mihm FG, Rosenthal MH, Stetz CW. Thermodilution cardiac output measurement. Effects of the respiratory cycle on its reproducibility. *JAMA* 1985; 253: 2240-2242.
22. Cecconi M, Rhodes A, Poloniecki J, Della Rocca G, Grounds RM. Bench-to-bedside review: the importance of the precision of the reference technique in method comparison studies--with specific reference to the measurement of cardiac output. *Crit Care* 2009; 13: 201.
23. Cigarroa RG, Lange RA, Williams RH, Bedotto JB, Hillis LD. Underestimation of cardiac output by thermodilution in patients with tricuspid regurgitation. *Am J Med* 1989; 86: 417-420.
24. Hillis LD, Firth BG, Winniford MD. Analysis of factors affecting the variability of Fick versus indicator dilution measurements of cardiac output. *Am J Cardiol* 1985; 56: 764-768.
25. Buffington CW, Nystrom EU. Neither the accuracy nor the precision of thermal dilution cardiac output measurements is altered by acute tricuspid regurgitation in pigs. *Anesth Analg* 2004; 98: 884-890, table of contents.
26. Hoeper MM, Maier R, Tongers J, Niedermeyer J, Hohlfeld JM, Hamm M, Fabel H. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. *Am J Respir Crit Care Med* 1999; 160: 535-541.
27. Konishi T, Nakamura Y, Morii I, Himura Y, Kumada T, Kawai C. Comparison of thermodilution and Fick methods for measurement of cardiac output in tricuspid regurgitation. *Am J Cardiol* 1992; 70: 538-539.
28. Fakler U, Pauli C, Hennig M, Sebening W, Hess J. Assumed oxygen consumption frequently results in large errors in the determination of cardiac output. *J Thorac Cardiovasc Surg* 2005; 130: 272-276.

29. Kendrick AH, West J, Papouchado M, Rozkovec A. Direct Fick cardiac output: are assumed values of oxygen consumption acceptable? *Eur Heart J* 1988; 9: 337-342.
30. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999; 15: 85-91.
31. Squara P, Cecconi M, Rhodes A, Singer M, Chiche JD. Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices. *Intensive Care Med* 2009; 35: 1801-1808.
32. Marque S, Cariou A, Chiche JD, Squara P. Comparison between Flotrac-Vigileo and Bioreactance, a totally noninvasive method for cardiac output monitoring. *Crit Care* 2009; 13: R73.
33. Maurer MM, Burkhoff D, Maybaum S, Franco V, Vittorio TJ, Williams P, White L, Kamalakkannan G, Myers J, Mancini DM. A multicenter study of noninvasive cardiac output by bioreactance during symptom-limited exercise. *J Card Fail* 2009; 15: 689-699.
34. Moshkovitz Y, Kaluski E, Milo O, Vered Z, Cotter G. Recent developments in cardiac output determination by bioimpedance: comparison with invasive cardiac output and potential cardiovascular applications. *Curr Opin Cardiol* 2004; 19: 229-237.

Figure Legends:

Figure I: The mean resting cardiac output as measured by thermodilution tended to be slightly higher than both NICOM and Fick, respectively. On the other hand, there was no difference in resting cardiac output comparing NICOM with Fick.

Figure 1. Comparison of Simultaneous CO Measurements at Rest between NICOM, Thermodilution, and Fick in Patients with Pulmonary Hypertension.

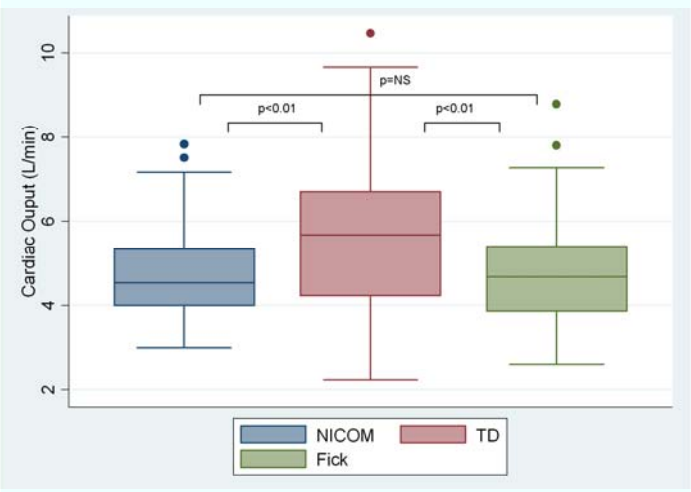

Figure II. Cardiac output measurements are significantly more precise with NICOM as compared to thermodilution.

Figure 2. Precision of Cardiac Output Measurements at Rest with NICOM Compared to Thermodilution in Patients with Pulmonary Hypertension.

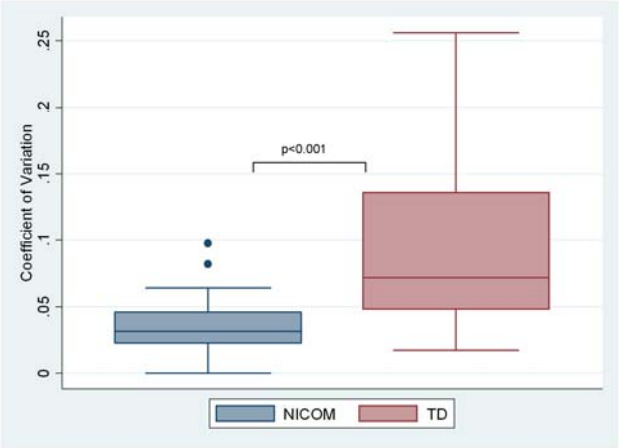

Figure III: Bland-Altman analyses revealed that thermodilution CO measurements tended to be higher than those measured by NICOM or Fick (mean bias of 0.81 L/min and 0.83 L/min, respectively) whereas a negligible difference was observed between NICOM and Fick (mean bias of 0.02 L/min). All three modalities demonstrated sufficiently wide 95% limits of agreement, thus cautioning against the interchangeability of one method with another in an individual patient.

Figure 3. Bland Altman Plots of (A) NICOM versus Thermodilution, (B) NICOM versus Fick, and (C) Thermodilution versus Fick in Patients with Pulmonary Hypertension.

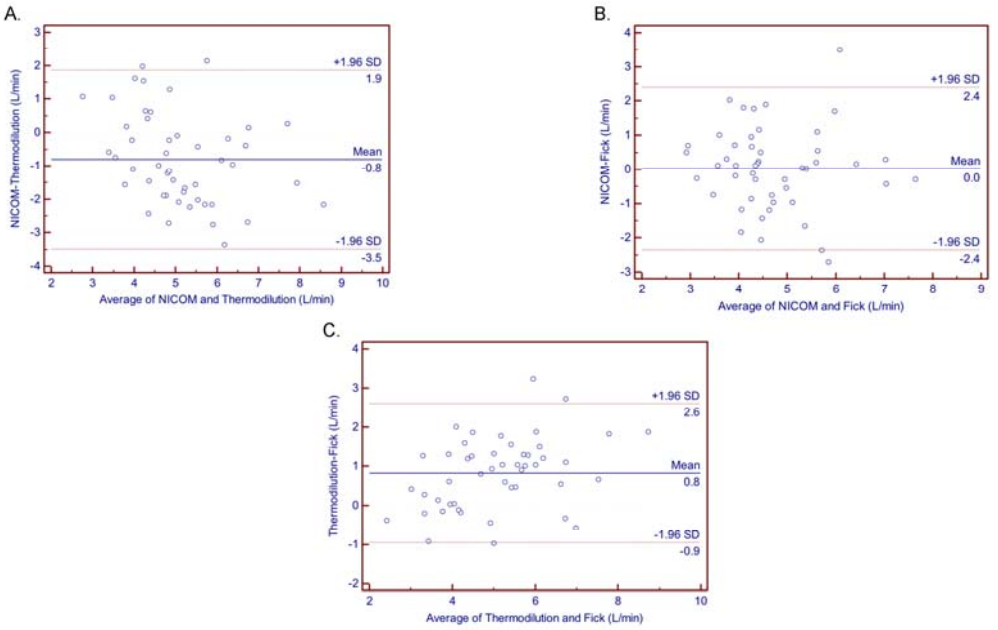

Table IA.

NICOM calculation of stroke volume (SV)
$SV=C \times VET \times \Delta\Phi / dt_{max;}$

where C is a constant of proportionality and VET is ventricular ejection time, which is determined from the NICOM and electrocardiogram signals. The value of C accounts for patient age, gender and body size[6]. Finally, CO is calculated as the product of SV and heart rate.

Table IB.

Oxygen consumption (VO2) estimated via the formula of LaFarge-Miettinen[12]
Females: $VO_2/BSA = (138.1 – 17.04 \times \ln(age) + 0.378 \times HR)/BSA(mL/\text{min})/m^2$
Males: $VO_2/BSA = (138.1 – 11.49 \times \ln(age) + 0.378 \times HR/BSA(mL/\text{min})/m^2$,

where VO2 is oxygen consumption in mL/min, age is presented in years, heart rate (HR) is in units of beats per minute, and BSA is body surface area in kg/m^2.

Table IC.

Calculation of cardiac output according to the Fick equation
$CO = VO_2/(CaO_2 – CvO_2)$

where CO is defined as CO in L/min, VO_2 is oxygen consumption in $L/min/m^2$, CaO_2 is arterial oxygen content in mg/L $(1.36 \times Hbg\ [g/L] \times SaO_2) + (PaO_2[mmHg] \times 0.003)$ and CvO_2 is defined as mixed venous oxygen content in mg/L $(1.36 \times Hbg\ [g/L] \times SvO_2) + (PvO_2[mmHg] \times 0.003)$.

Table II. Baseline Characteristics of the Pulmonary Hypertension Cohort

Characteristic	
Age (yrs)	54.4 ±15.1
Sex (% female)	56%
BSA	1.98
WHO PH Etiology n (%)	
Group 1	27 (54%)
Group 2	7 (14%)
Group 3	10 (20%)
Group 4	3 (6%)
Group 5	3 (6%)
PH-Specific Treatment n (%)	
No Treatment	29 (58%)
IV Prostanoid alone	4 (8%)
Sildenafil alone	12 (24%)
*Other	5 (10%)

BSA=Body Surface Area; IV=intravenous; WHO=World Health Organization;

*Other PH-specific treatments included: bosentan alone (n=1), bosentan + sildenafil (n=1), IV prostanoid + sildenafil (n=2), calcium channel blocker (n=1).

Table IIIA. Invasive Hemodynamic Measurements in the Pulmonary Hypertension Cohort

Hemodynamics (n=50)	
RA, mmHg	8.4 ± 5.6
PA systolic, mmHg	68.5 ± 24.3
PA mean, mmHg	40.7 ± 13.7
PVR, Wood units	6.0 ± 4.3
PCWP, mmHg	12.0 ± 4.7
PA saturation, %	63.0 ± 10.6
Arterial saturation, %	89.9 ± 8.9
Adenosine dose, mcg/kg/min	110.9 ± 35.3

PA=pulmonary artery; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RA=right atrial

Table IIIB. Echocardiographic Findings in the Pulmonary Hypertension Cohort

Echocardiographic Findings (n=44)	
Right Ventricular Function	
Normal	9 (20.5%)
Mildly reduced	11 (25.0%)
Moderately reduced	12 (27.3%)
Severely reduced	12 (27.3%)
Right Ventricular Size	
Normal	8 (18.2%)
Mildly enlarged	3 (6.8%)
Moderately enlarged	14 (31.8%)
Severely enlarged	19 (43.2%)
Tricuspid Regurgitation	
None	1 (2.3%)
Trace or Mild	24 (55.8%)
Moderate	14 (32.6%)
Severe	5 (11.6%)
Pulmonic Insufficiency	

None	10 (24.4%)
Trace	19 (46.3%)
Mild	9 (22%)
Moderate or greater	3 (7.3%)