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# Low partial pressure of end-tidal carbon dioxide predicts left ventricular assist device implantation in patients with advanced chronic heart failure

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ABSTRACT

*Background:* This study aimed to clarify the prognostic impact of partial pressure of end-tidal carbon dioxide ($PETCO_2$) in patients with advanced chronic heart failure (HF).
*Methods:* Forty-eight patients (mean age 43.1 ± 11.9 years, 32 males) with chronic HF (44 with non-ischemic and 4 with ischemic cardiomyopathy) were prospectively enrolled. Echocardiography, blood tests, pulmonary function testing, and $PETCO_2$ measurements were performed as noninvasive tests, whereas right heart catheterization and arterial blood gas analysis were conducted as invasive tests. The primary end point of this study was left ventricular assist device (LVAD) implantation or cardiac death.
*Results:* Eighteen patients underwent LVAD implantation at the Interagency Registry for Mechanically Circulatory Support (INTERMACS) profile 3 during the follow-up period, and no patient died. $PETCO_2$ was significantly lower in a stepwise manner with New York Heart Association functional class (class I or II, 34.2 ± 9.3 mmHg vs. class III or IV, 27.7 ± 2.5 mmHg; $p < 0.001$). Univariate and multivariate Cox proportional hazard models and time-dependent receiver operating characteristic curve analysis revealed that $PETCO_2 \leq 31$ mmHg is an independent noninvasive predictor of LVAD implantation. Univariable and multivariable linear regression analyses showed that pulmonary arterial pressure was independently and highly correlated with $PETCO_2$ ($r^2 = -0.512$, $p < 0.001$).
*Conclusions:* Among various noninvasive clinical parameters investigated, $PETCO_2$ was the independent predictor of LVAD implantation at the INTERMACS profile 3 in patients with chronic HF. Pulmonary congestion may significantly contribute to decreases in $PETCO_2$ in patients with HF.



## 1. Introduction

A left ventricular assist device (LVAD) is an alternative therapy for patients with advanced heart failure (HF) refractory to conventional guideline-directed therapies for HF. Successful LVAD therapy often requires appropriate timing of referral for LVAD implantation [1–3]. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profile, which stratifies the severity of advanced HF in patients with New York Heart Association (NYHA) functional class IIIb and IV disease into seven categories, has facilitated our understanding that patients with advanced HF should be considered for LVAD implantation when they have reached INTERMACS profile 3 or higher [4–6]. However, since the INTERMACS patient profile is relatively subjective, objective and noninvasive clinical parameters have been investigated.

Expired gas analysis is an essential technique to monitor the pathophysiology of HF that allows various insights into ventilation, circulation, and metabolism. Given the comprehensive nature of this monitoring technique, several clinical parameters derived from expired gas analysis, such as peak exercise oxygen consumption and ventilatory efficiency, have been recognized as reliable objective prognostic factors for death, re-hospitalization, LVAD implantation, and heart transplantation in patients with HF [7,8]. However, these parameters are measured during exercise; thus, many patients with advanced HF cannot be correctly evaluated using these examinations.

Partial pressure of end-tidal carbon dioxide ($PETCO_2$), which is mainly used in the fields of anesthesiology and critical care medicine, has been recently reported to be associated with the pathophysiology of HF and could thus be a prognostic factor in patients with HF [9,10]. However, the prognostic significance of $PETCO_2$ and the mechanisms of decreased $PETCO_2$ in patients with HF have not been completely elucidated.

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This study aimed to prospectively evaluate the prognostic impact of $PETCO_2$ at rest for cardiac events, such as LVAD implantation or cardiac death in patients with chronic HF, and elucidate the pathophysiological mechanisms that lead to decreased $PETCO_2$ in patients with HF.

## 2. Methods

### 2.1. Patient population

In this prospective observational study, we enrolled consecutive patients with chronic HF. These patients were admitted to our institution, the National Cerebral and Cardiovascular Center, for the evaluation of worsening HF from November 2013 to December 2015. All patients were followed up until January 2016. Since implantable continuous-flow LVAD implantation is only approved by the national insurance system as a bridge to transplantation in Japan, all study subjects were younger than 65 years in order to be potential candidates for heart transplantation based on the Japanese heart transplantation program guidelines. Patients with INTERMACS profiles 1 and 2 at the time of enrollment were excluded from the study. Administration of HF medications was encouraged in all patients according to the guidelines for chronic HF. Several patients had received continuous inotropic infusion. The end point of this study was LVAD implantation or cardiac death. All subjects enrolled in this study gave their informed consent. The present study was approved by the National Cerebral and Cardiovascular Center Institutional Review Board.

### 2.2. Clinical parameters

All enrolled patients underwent blood testing for albumin, total bilirubin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, total cholesterol (T-cho), creatinine (Cre), serum sodium, and brain natriuretic peptide (BNP); echocardiography with

**Table 1**
Baseline patient characteristics.

| | Overall ($n = 48$) | $PETCO_2 < 30$ mmHg ($n = 25$) | $PETCO_2 \geq 30$ mmHg ($n = 23$) | $p$ value |
|---|---|---|---|---|
| Age (years) | 43.1 ± 11.9 | 46.6 ± 11.3 | 39.4 ± 11.4 | 0.03 |
| Male sex [n (%)] | 32 (68.1) | 17 (68.0) | 16 (70.0) | 0.46 |
| Body mass index | 21.9 ± 4.1 | 21.6 ± 4.0 | 22.2 ± 4.3 | 0.66 |
| Body surface area ($m^2$) | 1.66 ± 0.24 | 1.6 ± 0.3 | 1.7 ± 0.2 | 0.36 |
| NYHA class (I/II/III/IV) | 3/21/20/4 | 0/3/18/4 | 3/18/2/0 | <0.001 |
| History of smoking [n (%)] | 26 (54.2) | 15 (60.0) | 11 (47.8) | 0.39 |
| Etiology [n (%)] | | | | 0.37 |
| DCM | 34 | 17 | 17 | |
| d-HCM | 4 | 2 | 2 | |
| ICM | 4 | 3 | 1 | |
| Post-myocarditis | 2 | 1 | 1 | |
| PPCM | 1 | 0 | 1 | |
| ARVC | 1 | 0 | 1 | |
| RCM | 2 | 2 | 0 | |
| Intravenous inotropic agents [n (%)] | 18 (37.5) | 12 (48.0) | 6 (26.1) | 0.11 |
| β-Blocker [n (%)] | 47 (98) | 25 (100) | 22 (96.7) | 0.22 |
| ACE inhibitor or angiotensin II antagonist [n (%)] | 44 (92) | 23 (92.0) | 21 (91.3) | 0.93 |
| Aldosterone antagonist [n (%)] | 44 (92) | 25 (100) | 19 (82.6) | 0.03 |
| Systolic blood pressure (mmHg) | 92.9 ± 12.7 | 89.4 ± 11.7 | 97.1 ± 12.7 | 0.03 |
| Heart rate (beats/min) | 72.1 ± 10.2 | 75.4 ± 11.7 | 69.6 ± 8.8 | 0.06 |
| Oxygen saturation (%) | 98 (97, 99) | 98.0 (96.5, 99) | 98 (97, 99) | 0.32 |
| Respiratory rate (breaths/min) | 13.7 ± 4.2 | 14.8 ± 4.8 | 12.7 ± 3.4 | 0.1 |
| $PETCO_2$ (mmHg) | 31 ± 4.4 | 27.5 ± 0.5 | 34.7 ± 0.5 | <0.001 |
| *Blood examination* | | | | |
| Albumin (g/dl) | 4.1 ± 0.4 | 4.0 ± 0.4 | 4.2 ± 0.3 | 0.06 |
| Total bilirubin (g/dl) | 0.9 ± 0.4 | 0.9 ± 0.5 | 0.9 ± 0.5 | 0.58 |
| GOT (IU/l) | 26.5 ± 11.7 | 25.2 ± 10.8 | 27.6 ± 12.5 | 0.5 |
| GPT (IU/l) | 24.5 ± 15.4 | 21.1 ± 14.3 | 29.3 ± 15.9 | 0.07 |
| Total cholesterol (mg/dl) | 165.5 ± 43.5 | 149.1 ± 41.6 | 181.7 ± 39.6 | 0.008 |
| Creatinine (mg/dl) | 0.9 ± 0.3 | 1.1 ± 0.3 | 0.83 ± 0.2 | 0.005 |
| Serum sodium (mEq/l) | 138.6 ± 3.0 | 137.5 ± 3.4 | 139.4 ± 2.6 | 0.03 |
| Brain natriuretic peptide (pg/ml) | 368 (171, 716) | 496 (361, 921) | 188 (75, 669) | 0.001 |
| *Blood gas analysis* | | | | |
| pH | 7.46 ± 0.03 | 7.47 ± 0.04 | 7.45 ± 0.03 | 0.07 |
| $PaO_2$ (mmHg) | 88.7 ± 11.9 | 86.1 ± 10.1 | 91.5 ± 13.1 | 0.11 |
| $PaCO_2$ (mmHg) | 35.1 ± 4.2 | 33.1 ± 3.3 | 37.3 ± 3.9 | <0.001 |
| Lactate (mmol) | 0.9 (0.8, 1.1) | 0.9 (0.8, 1.1) | 0.8 (0.8, 1.1) | 0.68 |
| *Echocardiographic parameters* | | | | |
| Left ventricular diastolic dimension (mm) | 67.5 ± 11.3 | 69.6 ± 11.8 | 65.1 ± 10.2 | 0.17 |
| Left ventricular systolic dimension (mm) | 59.0 ± 13.2 | 61.2 ± 13.5 | 56.6 ± 12.5 | 0.22 |
| Ejection fraction (%) | 22 (15, 30) | 20 (15, 29.5) | 23 (15, 31) | 0.34 |
| TRPG (mmHg) ($n = 42$) | 27 (19, 44) | 42 (27, 55) | 22 (16, 25) | <0.001 |
| *Pulmonary function test* | | | | |
| Tidal volume (l) | 0.62 (0.49, 0.77) | 0.6 (0.48, 0.77) | 0.62 (0.48, 0.81) | 0.79 |
| %VC (%) | 98.4 ± 19.4 | 94.2 ± 20.9 | 102.9 ± 16.4 | 0.12 |
| FEV1 (%) | 81.6 ± 10.1 | 77.8 ± 10.7 | 85.1 ± 8.3 | 0.01 |
| %DLco (%) | 74.3 ± 17.1 | 74.2 ± 16.7 | 74.3 ± 17.6 | 0.98 |
| *Hemodynamic parameters* | | | | |
| PCWP (mmHg) | 15.3 ± 9.0 | 20.4 ± 8.2 | 9.7 ± 6.1 | <0.001 |
| PAP (mmHg) | 22.9 ± 10.8 | 29.2 ± 10.2 | 16.0 ± 6.5 | <0.001 |
| RAP (mmHg) | 4 (2, 7.75) | 6 (3, 8) | 3 (2, 5) | <0.05 |
| Cardiac index (l/min/$m^2$) | 2.6 ± 0.5 | 2.4 ± 0.5 | 2.8 ± 0.5 | 0.06 |

NYHA, New York Heart Association; DCM, dilated cardiomyopathy; d-HCM, dilated-phase hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; PPCM, peripartum cardiomyopathy; ARVC, arrhythmogenic right ventricular dysplasia; RCM, restrictive cardiomyopathy; ACE, angiotensin-converting enzyme; $PETCO_2$, partial pressure of end-tidal carbon dioxide; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; $PaO_2$, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; TRPG, tricuspid regurgitation peak gradient; VC, vital capacity; FEV1, forced expiratory volume in the first second percent of normal value; DLco, diffusing capacity of the lung carbon monoxide; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary arterial pressure; RAP, right atrial pressure.

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