**Prognostic Value of Pulmonary Hypertension in Ambulatory Patients With Non-Ischemic Dilated Cardiomyopathy**

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**Background:** Pulmonary hypertension (PH) because of left-sided heart disease carries a poor prognosis. We investigated whether non-ischemic dilated cardiomyopathy (DCM) with PH is associated with poor prognosis.

**Methods and Results:** A total of 256 consecutive DCM patients were enrolled. We measured the ratio of the maximum first derivative of left ventricular pressure (LV\(dP/dt_{\text{max}}\)) to systolic blood pressure and pressure half-time (\(T_{1/2}\)) as cardiac function. Patients were allocated to 2 groups on the basis of mean pulmonary arterial pressure (mPAP), namely DCM without PH group (mPAP <25 mmHg; n=225) and DCM with PH group (mPAP ≥25 mmHg; n=31). We followed all patients for a mean of 4.3 years for the occurrence of cardiac events, defined as cardiac death or hospitalization for worsening heart failure. Cardiac events were significantly more frequent in the DCM with PH group than in the DCM without PH group (\(P<0.001\)). Multivariate Cox regression analysis revealed that mPAP ≥25 mmHg and LV end-systolic volume index were significant independent risk factors for cardiac death. Incidence of cardiac death was significantly higher in patients with DCM with PH than in those without PH [hazard ratio 11.79 (3.18–43.7), \(P<0.0001\)].

**Conclusions:** The presence of PH was independently associated with an increased incidence of cardiac death in ambulatory patients with DCM. *(Circ J 2014; 78: 1245–1253)*

**Key Words:** Dilated cardiomyopathy; Prognosis; Pulmonary hypertension

Pulmonary hypertension (PH) resulting from left-sided heart disease (LHD) carries a poor prognosis.\(^1\)\(^2\) It is classified in group 2 of the Dana Point 2008 classification\(^7\) and is believed to be the most common form of PH.\(^3\) It can be caused by passive downstream elevation of left-sided heart pressure or by a combination of that and pulmonary arterial pathologies.\(^4\)\(^5\) Indeed, post-capillary PH (pc-PH) is a risk factor for poor prognosis in patients with chronic heart failure (HF).\(^4\) PH because of LHD is defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg and mean pulmonary arterial wedge pressure (mPAWP) >15 mmHg.\(^5\) Although group 2 of the Dana Point 2008 classification includes PH caused by LHD with primary valvular disease, systolic dysfunction, diastolic dysfunction, or congenital or acquired left-sided inflow/outflow tract obstruction, here we focus on non-ischemic dilated cardiomyopathy (DCM) with PH. The presence of PH is a predictor of morbidity or mortality in patients with ischemic or idiopathic DCM.\(^5\) Moreover, moderate to severe functional tricuspid regurgitation (TR) is independently associated with cardiac events in patients with left ventricular (LV) systolic dysfunction and functional mitral regurgitation (MR).\(^6\)

To our knowledge, there are no published studies on whether the presence of PH in the non-ischemic heart with a reduced ejection fraction (EF) affects hemodynamic parameters and clinical outcome. We used cardiac catheterization with a micromanometer to investigate the relationship between PH and cardiac function, as well as the association between PH and clinical outcome, namely cardiac death or hospitalization for worsening HF, in ambulatory patients with DCM.

**Methods**

**Study Population**
A total of 256 consecutive ambulatory patients with DCM (195 men and 61 women; mean age±SD, 52±13 years) between December 2000 and October 2011 were retrospectively enrolled in the study at Nagoya University Hospital, Japan. All patients were on optimal pharmacological therapy according to current guidelines for the treatment of HF.\(^7\) Individuals who had suffered an episode of acute HF within the previous 3 months,
who had renal dysfunction [estimated glomerular filtration rate (eGFR) <30 ml·min⁻¹·1.73 m⁻²], or who had received implanted cardiac resynchronization therapy or an implantable cardioverter defibrillator before cardiac catheterization were excluded from the study. To exclude coronary artery disease, we subjected all patients to coronary angiography. DCM was defined by the presence of both an LVEF <50% (as revealed by contrast left ventriculography) and a dilated LV cavity in the absence of coronary artery stenosis >50% (as determined by coronary angiography), valvular heart disease, arterial hypertension, and secondary cardiac muscle disease attributable to any known systemic condition. No patients had histories of acute viral myocarditis or familial DCM, or evidence of immune triggers. The study protocol complied with the Declaration of Helsinki, and written informed consent was given by each study patient. The study protocol was approved by the Ethics Review Board of Nagoya University School of Medicine (approval no. 359).

### Study Protocol

Physical examination, laboratory measurements, echocardiography, overnight simplified respiratory polygraphy (LS-300 device, Fukuda Denshi, Tokyo, Japan), 24-h continuous electrocardiography, and biventricular catheterization were performed within 3 days of study enrolment. All patients were in a stable condition at the time of testing. The eGFR in adult males was calculated by using an equation modified for the Japanese population, namely eGFR (ml/min) = 194 × (serum creatinine) −1.094 × (age in years) −0.287. To adjust for female sex, the following equation was used:

\[
eGFR_{female} = 194 \times (\text{serum creatinine}) - 1.094
\]

Table 1. Study Patients Clinical Characteristics

|                     | DCM without PH | DCM with PH | P value |
|---------------------|----------------|-------------|---------|
| **Age (years)**     | 52±13          | 47±13       | 0.029   |
| **Male (n, %)**     | 175 (78)       | 20 (65)     | 0.105   |
| **BMI (kg/m²)**     | 24.1±4.2       | 23.6±3.2    | 0.154   |
| **NYHA class 1/2/3/4** | 120/88/17/0   | 5/18/8/0    | <0.001  |

**Medications**

|                     | DCM without PH | DCM with PH | P value |
|---------------------|----------------|-------------|---------|
| Diuretics (n, %)    | 137 (61)       | 29 (93)     | 0.003   |
| ACEIs/ARBs (n, %)   | 182 (81)       | 30 (96)     | 0.284   |
| β-blockers (n, %)   | 149 (66)       | 24 (78)     | 0.204   |
| Statins (n, %)      | 45 (20)        | 9 (30)      | 0.264   |
| Amiodarone (n, %)   | 18 (8)         | 5 (15)      | 0.284   |
| Spironolactone (n, %)| 90 (40)       | 25 (81)     | <0.001  |

**Laboratory data**

|                     | DCM without PH | DCM with PH | P value |
|---------------------|----------------|-------------|---------|
| BNP (pg/ml)         | 138 (27–165)   | 540 (153–829)| <0.001  |
| eGFR (ml·min⁻¹·1.73m⁻²) | 72±22        | 74±15       | 0.687   |
| Hb (mg/dl)          | 14.1±1.6      | 13.9±2      | 0.590   |
| TC (mg/dl)          | 194±37        | 192±46      | 0.818   |
| TG (mg/dl)          | 166 (83–197)  | 152 (80–163)| 0.644   |
| HbA1c (%)           | 5.82±1.19     | 5.78±0.84   | 0.890   |
| TP (g/dl)           | 6.77±0.41     | 6.9±0.14    | 0.551   |
| Alb (g/dl)          | 3.84±0.42     | 3.88±0.47   | 0.895   |
| Na (mEq/L)          | 139±1.76      | 141±5.45    | 0.433   |
| hs-CRP (mg/L)       | 0.17±0.32     | 0.22±0.42   | 0.159   |
| hs-Troponin T (ng/ml)| 0.0141±0.015 | 0.0169±0.013| 0.477   |

**Echocardiography**

|                     | DCM without PH | DCM with PH | P value |
|---------------------|----------------|-------------|---------|
| LAD (mm)            | 38.1±7.3       | 44.2±7.3    | <0.001  |
| LVDd (mm)           | 60.9±8.4       | 66.4±11.5   | 0.001   |
| LVDs (mm)           | 49.5±9.8       | 57.9±11.7   | 0.001   |
| LV mass index (g/m²)| 156±57         | 173±62      | 0.126   |
| MR (0/1/2/3)        | 123/78/22/2    | 6/9/9/7     | <0.001  |
| E wave (cm/s)       | 62.9±23        | 97.9±36.6   | <0.001  |
| A wave (cm/s)       | 64.3±20.8      | 53.7±30     | 0.055   |
| DcT (ms)            | 192.2±58.2     | 149±48.8    | 0.004   |
| E/e'                | 15.08±8.28     | 23.69±15.63 | 0.002   |

**ECG, Holter recording, SDB and pulmonary function**

|                     | DCM without PH | DCM with PH | P value |
|---------------------|----------------|-------------|---------|
| QRS duration (ms)   | 113.1±24.4     | 113.8±26.0  | 0.890   |
| VPC (%)             | 1.19±2.76      | 1.25±2.42   | 0.938   |
| AH1 (l/h)           | 14.3±15        | 14.2±14.6   | 0.978   |
| DLoO (ml·min⁻¹·mmHg⁻¹)| 107.7±25.3    | 96.1±12.2   | 0.412   |

(Table 1 continued the next page.)
Cardiac Catheterization

| Cardiac Catheterization | DCM without PH (n=225) | DCM with PH (n=31) | P value |
|-------------------------|------------------------|--------------------|---------|
| PAWP (mmHg)             | 10.2±4.5               | 23.7±6.5           | <0.001  |
| Systolic PAP (mmHg)     | 24.8±6.3               | 53.8±33.9          | <0.001  |
| Diastolic PAP (mmHg)    | 9.8±3.6                | 24.8±9.2           | <0.001  |
| Mean PAP (mmHg)         | 14.6±4                 | 33.2±8.4           | <0.001  |
| PVR (dyne·s⁻¹·cm⁻³)     | 77.1±70.4              | 225.9±233.1        | <0.001  |
| Systolic RVP (mmHg)     | 27±6.6                 | 47.1±12.6          | <0.001  |
| RAP (mmHg)              | 5.2±2.9                | 8.1±3.3            | <0.001  |
| SvO₂ (%)                | 70.6±5.8               | 62.6±6.9           | 0.002   |
| TPG (mmHg)              | 4.4±4.2                | 9.4±2.0            | <0.001  |
| DPG (mmHg)              | −1.1±4.6               | 4.6±1.9            | <0.001  |
| Heart rate (beats/min)  | 75.2±13.6              | 86.8±18.2          | <0.001  |
| Cardiac output (L/min)  | 5.0±1.34               | 4.27±1.26          | 0.002   |
| Cardiac index (L·min⁻¹·m⁻²) | 2.93±0.67           | 2.49±0.63          | 0.001   |
| Systolic BP (mmHg)      | 127±21                 | 120±42             | 0.192   |
| Diastolic BP (mmHg)     | 74±16                  | 75±17              | 0.629   |
| LVEDP (mmHg)            | 11.5±7.2               | 22.6±9.6           | <0.001  |
| LVEDVI (ml/m²)          | 108.4±41.8             | 165.3±66.8         | <0.001  |
| LVESVI (ml/m²)          | 70.5±36.3              | 125.4±62.9         | <0.001  |
| LVEF (%)                | 38.2±12.7              | 27.0±13.1          | <0.001  |
| LVdP/dtmax/systolic BP (mmHg/s) | 9.70±3.83       | 9.54±1.95          | 0.114   |
| T₁/₂ (ms)               | 40.1±7.9               | 46.4±8.9           | 0.001   |

Data are presented as mean±SD and medians (interquartile range or n (%)). ACEI, angiotensin-converting enzyme inhibitor; AHf, apnea-hypopnea index; Alb, albumin; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; DcT, deceleration time; DLCO, diffusion capacity of the lung for carbon monoxide; DPG, diastolic pulmonary vascular gradient; E/e‘, ratio of early transmitral velocity to tissue Doppler mitral annular velocity during early diastole; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; hs-Troponin T, high-sensitivity troponin T; LAD, left atrial diameter; LVdD, left ventricular diastolic diameter; LVdPs, LV systolic diameter; LVdPFP, LV end-diastolic pressure; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVI, LV end-systolic volume index; LVEDP, LV end-diastolic pressure; LVEDP, LV end-diastolic pressure; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVP, right ventricular pressure; SDB, sleep-disordered breathing; SvO₂, mixed venous oxygen saturation; T₁/₂, pressure half-time; TC, total cholesterol; TG, triglyceride; TP, total protein; TPG, transpulmonary pressure gradient; VPC, ventricular premature contraction.

We measured the maximum first derivative of LV pressure (LVdP/dtmax) and then used the ratio of LVdP/dtmax/systolic blood pressure (SBP) as an index of contractility that adjusted the influence of BP. To evaluate LV isovolumic relaxation function, we determined the pressure half-time (T₁/₂) directly, instead of the LV relaxation time constant, Tₑ, which is defined as the time required for the LV cavity pressure at LVdP/dtmax to be reduced by 1/e, as previously described. 16 Endomyocardial biopsy was performed in all patients to exclude myocarditis (according to the Dallas criteria) and specific heart muscle disease. Biopsy specimens were obtained from the septal wall of the right ventricle (RV) with a 6F bioprobe.

Diagnosis of PH

PH was defined as mPAP ≥25 mmHg during measurements at rest, without inhalation of nitric oxide and oxygen. pc-PH was defined as mPAP ≥25 mmHg and mPAWP >15 mmHg. All patients who had DCM with PH also had pc-PH. We subdivided pc-PH into (1) “passive” PH, with mPAP ≥25 mmHg, mPAWP >15 mmHg, and transpulmonary pressure gradient (TPG) ≤12 mmHg, and (2) “reactive” PH, with mPAP ≥25 mmHg, mPAWP >15 mmHg, and TPG >12 mmHg. mPAP, mean right atrial pressure, mPAWP, and the respective oxygen saturations, together with those in the inferior and superior venae cava, were measured. Cardiac output was assessed by thermodilution.

× (age in years)⁻⁰·²⁸⁷ × 0.739. We followed up all patients for the occurrence of cardiac events, which were defined as cardiac death or hospitalization for worsening HF. For survival analysis, the follow-up time was calculated from the date of catheterization until the date of the last clinical visit or contact by telephone, or the date of death. Patients were followed up for an average of 4.3 years (range, 0.7–12.6 years).

Cardiac Catheterization

All patients initially underwent diagnostic right and left heart catheterization. Patients were in a stable condition at the time of catheterization was performed. For hemodynamic assessment, a 6F Swan-Ganz catheter (Goodman Biosensors, Tokyo, Japan) was inserted using a jugular approach. Coronary angiography and left ventriculography via the right radial artery were also performed. A 6F fluid-filled pigtail catheter with a high-fidelity micromanometer (CA-61000-PLB Pressure-tip Catheter; CD Leycom, Zoetermeer, The Netherlands) was positioned in the left ventricle to measure LV pressure. Micromanometer pressure signals and standard electrocardiograms were recorded continuously with a multichannel recorder online. LV pressure signals were digitized at 3-ms intervals and were analyzed throughout the procedure with software developed in-house and a 32-bit microcomputer system. LV pressure and heart rate were determined as averages for at least 15 consecutive beats.
and was expressed in liters per minute. TPG was calculated by subtracting mPAWP from mPAP; pulmonary vascular resistance (PVR) was calculated by dividing TPG by cardiac output. Diastolic pulmonary vascular pressure gradient (DPG) was calculated as the difference between diastolic pulmonary artery pressure and mPAWP during a pull-back.

Statistical Analysis
Data are presented as mean±SD. Variables were compared between the DCM with PH and DCM without PH groups by Student’s t-test for unpaired data. The chi-squared test was used to assess the significance of differences between dichotomous variables. Correlations were performed by using Pearson correlation coefficients. Cumulative cardiac event-free survival estimates were calculated by using the Kaplan-Meier method. Differences between survival curves were assessed by log-rank test. Receiver-operator characteristic analysis was performed to assess the usefulness of mPAP in distinguishing between cardiac and non-cardiac events. The effect of mPAP on outcome was analyzed by using the presence or absence of PH at baseline as a categorical determinant of adverse events. A logistic regression model was used to investigate the association of the presence or absence of PH with important clinical and hemodynamic parameters, such as age, sex, body mass index (BMI), HbA1c, eGFR, hemoglobin, plasma brain natriuretic peptide (BNP) level, left atrial diameter, ratio of early transmitral velocity to tissue Doppler mitral annular velocity during early diastole (E/e’), heart rate, cardiac index, SBP, LV end-diastolic volume index, LV end-systolic volume index, LVEF, PVR, mPAWP, LVdP/dtmax/SBP, and T1/2. Model building proceeded with stepwise backward elimination, requiring P<0.05 for significance and starting with a model that contained all variables. Other baseline predictors of events were determined by performing univariate Cox proportional hazard regression analysis with age, BMI, QRS duration, left arterial diameter, LV mass index, E/e’, SBP, LV end-diastolic pressure, mPAP, mPAWP, TPG, PVR, cardiac index, LV end-diastolic volume index, LV end-systolic volume index, LVEF, mixed venous oxygen saturation (SvO2), LVdP/dtmax/SBP, and T1/2 as potential determinants. The hazard ratio and 95% confidence interval (CI) were defined. To confirm their independent predictive value, variables with P<0.1 were tested in a multivariate model. All analyses were performed with the SPSS 17.0 software package (SPSS, Chicago, IL, USA). A P value <0.05 was considered statistically significant.

Results
Patients Clinical and Hemodynamic Characteristics
The mean age of the cohort was 52 years, and 76% were male; 125 patients were classified as New York Heart Association (NYHA) functional class 1, 106 were class 2, and 25 were class 3. At the time of cardiac catheterization, β-blockers were used by 67% of all patients, angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) by 83%, diuretics by 65%, and spironolactone by 55%. The mean plasma BNP level was 190 pg/ml, the mean mPAP value was 16.9 mmHg, and the mean LVEF was 36.7%.

Clinical characteristics and important hemodynamic parameters for all patients are shown in Table 1. Subjects were allocated to 1 of 2 groups on the basis of the absence (DCM without PH group, n=225) or presence (DCM with PH group, n=31) of PH. PH was present in 12% of patients with DCM, and the median (25th, 75th percentile) mPAP for all DCM patients was 15.5 (12.0, 19.3) mmHg. DCM patients with PH were younger than those without PH (P=0.029). There were no significant differences in sex or BMI. DCM patients with PH had a significantly more severe NYHA class. Diuretics, and spironolactone specifically, were used significantly more frequently in DCM with PH patients than in those with DCM without PH, but there were no differences in the use of ACEIs or ARBs and β-blockers at the time of cardiac catheterization. Although plasma BNP...
MR caused by tethering was significantly more severe in DCM with PH. The E wave was significantly higher in DCM with PH patients and, consequently, E/e’ was also significantly higher in them.

There were no significant differences between the 2 groups in eGFR and serum hemoglobin levels did not differ between the 2 groups. On echocardiography, left atrial dimension, LV diastolic dimension, and LV systolic dimension were significantly larger in the DCM with PH group than in DCM without PH.

levels were significantly higher in the DCM with PH group, eGFR and serum hemoglobin levels did not differ between the 2 groups. On echocardiography, left atrial dimension, LV diastolic dimension, and LV systolic dimension were significantly larger in the DCM with PH group than in DCM without PH.

Table 2. Binary Logistic Regression Analysis for the Presence of Pulmonary Hypertension

|                     | Univariate analysis | Multivariate analysis |
|---------------------|---------------------|-----------------------|
|                     | B       | Wald | OR   | 95% CI | P value | B       | Wald | OR   | 95% CI | P value |
| Age (years)         | –0.032  | 4.61  | 0.97  | 0.940–0.997 | 0.032   |         |       |       |        |         |
| Sex (M/F = 0/1)     | 0.655   | 2.57  | 1.92  | 0.865–4.284 | 0.109   |         |       |       |        |         |
| BMI (kg/m²)         | –0.074  | 2.02  | 0.93  | 0.839–1.028 | 0.155   |         |       |       |        |         |
| HbA1c (%)           | –0.031  | 0.02  | 0.97  | 0.632–1.488 | 0.889   |         |       |       |        |         |
| eGFR (ml·min⁻¹·1.73m⁻²) | 0.004  | 0.16  | 1.00  | 0.986–1.022 | 0.685   |         |       |       |        |         |
| Hb (mg/dl)          | –0.064  | 0.29  | 0.94  | 0.744–1.182 | 0.588   |         |       |       |        |         |
| BNP (pg/ml)         | 0.004   | 24.3  | 1.00  | 1.002–1.005 | <0.0001 |         |       |       |        |         |
| LAD (mm)            | 0.112   | 16.4  | 1.12  | 1.059–1.181 | <0.0001 |         |       |       |        |         |
| E/e’                | 0.065   | 6.19  | 1.07  | 1.014–1.124 | 0.013   |         |       |       |        |         |
| Heart rate (beats/min) | 0.059  | 18.5  | 1.06  | 1.033–1.089 | <0.0001 |         |       |       |        |         |
| Cardiac index       | –1.353  | 13.9  | 0.26  | 0.127–0.526 | <0.0001 |         |       |       |        |         |
| Systolic BP (mmHg)  | –0.011  | 1.71  | 0.99  | 0.972–1.006 | 0.191   |         |       |       |        |         |
| LVEDVI (ml)         | 0.020   | 25.8  | 1.02  | 1.013–1.029 | <0.0001 |         |       |       |        |         |
| LVESVI (ml)         | 0.023   | 27.8  | 1.02  | 1.015–1.032 | <0.0001 |         |       |       |        |         |
| LVEF (%)            | –0.077  | 17.0  | 0.93  | 0.893–0.960 | <0.0001 |         |       |       |        |         |
| PVR (dyne·s⁻¹·cm⁻²) | 0.014   | 25.4  | 1.014 | 1.009–1.020 | <0.0001 |         |       |       |        |         |
| PAWP (mmHg)         | 0.434   | 38.2  | 1.54  | 1.346–1.772 | <0.0001 | 0.486   | 26.7  | 1.625 | 1.352–1.954 | <0.0001 |
| LVEDP/systolic BP (mmHg/s) | –0.163 | 5.452 | 0.850 | 0.742–0.974 | 0.020   |         |       |       |        |         |
| T1/2 (ms)           | 0.082   | 10.4  | 1.09  | 1.033–1.141 | 0.001   |         |       |       |        |         |

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Table 3. Univariate Analysis of Cardiac Events

|                     | HR     | 95% CI  | P value |
|---------------------|--------|---------|---------|
| Age (years)         | 0.990  | (0.97–1.01) | 0.254   |
| Sex (M/F = 0/1)     | 1.540  | (0.85–2.83) | 0.206   |
| BMI (kg/m²)         | 1.022  | (0.97–1.08) | 0.433   |
| QRS duration (ms)   | 1.001  | (0.99–1.01) | 0.792   |
| LAD (mm)            | 1.085  | (1.05–1.12) <0.0001 |
| LV mass index (g/m²) | 1.003 | (1.001–1.005) | 0.0008  |
| E/e’                | 1.001  | (0.96–1.04) | 0.927   |
| Systolic BP (mmHg)  | 0.993  | (0.98–1.00) | 0.192   |
| LVEDP (mmHg)        | 1.059  | (1.03–1.09) <0.0001 |
| LVEDVI (ml/m²)      | 1.008  | (1.003–1.01) | 0.001   |
| LVESVI (ml/m²)      | 1.010  | (1.006–1.02) <0.0001 |
| LVEF (%)            | 1.007  | (1.002–1.01) | 0.001   |
| mPAP (mmHg)         | 1.081  | (1.06–1.11) <0.0001 |
| mPAWP (mmHg)        | 1.088  | (1.05–1.12) <0.0001 |
| TPG (mmHg)          | 1.094  | (1.03–1.16) | 0.003   |
| DPG (mmHg)          | 1.047  | (0.99–1.11) | 0.141   |
| Cardiac index (L·min⁻¹·m⁻²) | 0.622 | (0.42–0.92) | 0.016   |
| PVR (dyne·s⁻¹·cm⁻²) | 1.004  | (1.00–1.01) | 0.0001  |
| mPAP ≥25 (mmHg)     | 6.203  | (2.61–14.7) <0.0001 |
| SvO₂ (%)            | 0.962  | (0.89–1.04) | 0.337   |
| LVEDP/systolic BP (mmHg/s) | 0.862 | (0.783–0.947) | 0.002   |
| T1/2 (ms)           | 1.049  | (1.02–1.08) | 0.0007  |

HR, hazard ratio; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary artery wedge pressure. Other abbreviations as in Table 1.
QRS duration, ventricular premature contraction, apnea hypopnea index, or mean percent predicted diffusion capacity of the lung for carbon monoxide. On cardiac catheterization, the systolic, diastolic, and mean PAPs, as well as PVR, systolic right ventricular pressure, right arterial pressure, heart rate, and cardiac index were significantly higher in DCM with PH patients than in those without PH, whereas SvO₂ was significantly lower in the former group. Both TPG and DPG were significantly higher in DCM with PH patients than in those without PH. In contrast, there were no significant differences between the 2 groups in systolic or diastolic BP, LV end-diastolic pressure, LV end-diastolic volume index, and LV end-systolic volume index were significantly higher, and LVEF was significantly lower, in the DCM with PH group. There was a significant correlation between mPAP and mPAWP in both groups (Figure 1). Binary logistic regression analysis showed that only mPAWP was independently associated with the presence of PH in the multivariate analysis (Table 2).

Prognosis

With regard to the univariate analysis of cardiac events, the clinical characteristics of the study population at index evaluation are shown in Table 3. In the univariate Cox regression analysis, mPAP, mPAP ≥25 mmHg category classification, cardiac index, LV end-systolic volume index, LV end-diastolic volume index, mPAWP, PVR, left atrial dimension, LV mass index, LV end-diastolic pressure, LVEF, TPG, LV dP/dt/diastolic/SBP, and T1/2 were associated with the occurrence of cardiac events. The cumulative probability of cardiac event-free survival was calculated for both groups by the Kaplan-Meier method (Figure 2A). The probability of cardiac event-free survival was lower in the DCM with PH group than in the DCM without PH group (P<0.001). The 5-year cardiac event-free survival rate was 77% for DCM without PH and 51% for DCM with PH. Similarly, rates of cardiac death (Figure 2B) and hospitalization for worsening HF (Figure 2C) were significantly more frequent for DCM with PH. Cardiac death occurred in 15 (sudden cardiac death, 6; death from HF, 9) patients (6.7%) with DCM without PH and in 9 (sudden cardiac death, 1; death from HF, 8) patients (29%) with DCM with PH during the follow-up period. In addition, 50 patients (22%) with DCM without PH and 15 patients (48%) with DCM with PH were hospitalized for worsening HF.

Multivariate Cox regression was used to determine independent risk factors for cardiac events (Table 4). Presence of PH and the LV end-systolic volume index were significant independent risk factors for cardiac death. PAWP and T1/2 were significant independent risk factors for hospitalization for worsening HF, LV end-systolic volume index, PAWP, and T1/2 were independent risk factors for cardiac events overall. Table 5 shows the results of a univariate Cox proportional hazard analysis of DCM with PH vs. DCM without PH. The incidence of

Figure 2. Kaplan-Meier analysis of cardiac events, cardiac death, and hospitalization for worsening heart failure in all patients. (A) Cardiac events (cardiac death + hospitalization for worsening heart failure)-free survival curves. (B) Cardiac death-free survival curves. (C) Curves for freedom from hospitalization for worsening heart failure. PH, pulmonary hypertension.
Here, we report for the first time that the presence of PH was an independent and important prognostic indicator in patients with DCM, despite optimized treatment. The presence of PH (i.e., mPAP $\geq 25$ mmHg) was an independent predictor of cardiac death, whereas high PAWP was a useful predictor of hospitalization for worsening HF. This suggests that both PH and PAWP are useful for assessing the treatment and prognosis of individual patients with non-ischemic DCM. These findings underscore the importance of the presence of PH as a marker of cardiac death in patients with DCM.

Cardiac death was significantly higher in the DCM with PH group than in the DCM without PH group: univariate analysis revealed a hazard ratio of 11.79 (95% CI 3.18–43.7; $P<0.0001$). Similarly, the incidence of hospitalization for worsening HF was significantly higher in the DCM with PH group than in the DCM without PH group (hazard ratio, 6.749; 95% CI, 2.81–16.2; $P<0.0001$), as was the incidence of cardiac death and hospitalization for worsening HF combined (hazard ratio, 6.023; 95% CI, 2.61–14.7; $P<0.0001$).

We then compared prognosis between passive (n=20) and reactive (n=11) pc-PH (Table 6). There were no significant differences between passive and reactive pc-PH in terms of baseline characteristics or hemodynamic variables [with the exception of PAP and PVR (mean PAP 29.6±5.3 mmHg and 40.6±9.0 mmHg, respectively, $P=0.004$; PVR 122.0±75.3 dynes·s$^{-1}$·cm$^{-5}$ and 348.5±207.9 dynes·s$^{-1}$·cm$^{-5}$, respectively; $P=0.007$)] or the incidence of cardiac events. In 5 passive pc-PH patients and 3 reactive pc-PH patients, cardiac death occurred within 2 years. Cardiac death occurred in 3 patients with reactive pc-PH and DPG $\geq 7$ mmHg but in no patients with reactive pc-PH and DPG <7 mmHg (Table 6).

### Table 4. Multivariate Analysis of Cardiac Events

| Cardiac death | Wald | Exp (B) | 95% CI | P value |
|---------------|------|---------|--------|---------|
| mPAP $\geq 25$ (mmHg) | 4.739 | 0.232 | (0.062–0.864) | 0.029 |
| LVESVI (ml/m$^2$) | 4.186 | 1.031 | (1.001–1.061) | 0.041 |
| LVEDVI (ml/m$^2$) | 3.844 | 0.975 | (0.951–1.000) | 0.050 |

### Table 5. Univariate Cox Regression Analysis of Dilated Cardiomyopathy (DCM) With Pulmonary Hypertension (PH) Compared With DCM Without PH

| Event | HR   | 95% CI | P value |
|-------|------|--------|---------|
| Cardiac death | 11.79 | (3.18–3.7) | $<0.0001$ |
| Hospitalization for worsening heart failure | 6.749 | (2.81–16.2) | $<0.0001$ |
| Cardiac death and hospitalization for worsening heart failure | 6.023 | (2.61–14.7) | $<0.0001$ |

### Table 6. Cardiac Death and Events in Patients With Dilated Cardiomyopathy (DCM) With Pulmonary Hypertension (PH) and Patients in Reactive and Passive Post-Capillary PH (pc-PH)

|               | DCM with PH (n=31) | Reactive pc-PH (n=11) | P value |
|---------------|-------------------|----------------------|---------|
|               | Passive pc-PH (n=20) | Reactive pc-PH (n=11) |         |
| Cardiac death | 5 | 3 | 0.89 |         |
| Cardiac events | 10 | 5 | 0.81 |         |

### Discussion

Here, we report for the first time that the presence of PH was an independent and important prognostic indicator in patients with DCM, despite optimized treatment. The presence of PH (i.e., mPAP $\geq 25$ mmHg) was an independent predictor of cardiac death, whereas high PAWP was a useful predictor of hospitalization for worsening HF. This suggests that both PH and PAWP are useful for assessing the treatment and prognosis of individual patients with non-ischemic DCM. These findings underscore the importance of the presence of PH as a marker of cardiac death in patients with DCM.

### Characteristics of DCM With PH

PH is common in patients with LHD and is associated with increased mortality. Over a decade ago, the presence of PH was found to predict morbidity or mortality in patients with ischemic or idiopathic DCM. The presence of moderate to severe MR is a predictor of PH development in patients with HF and LV systolic dysfunction; in other words, in end-stage HF patients and heart transplant candidates. Moderate or relatively functional TR is independently associated with worse survival and a high incidence of HF episodes in patients with DCM and...
functional MR. The DCM patients with PH in the present study were significantly younger than those without PH (P<0.029). DCM patients with PH had more severe symptoms, higher plasma BNP levels, advanced left atrial and ventricular remodeling, more severe MR because of tethering, severe diastolic dysfunction, and greater worsening of hemodynamic parameters, including a lower cardiac index and SvO2 and a higher PAWP.

These results suggest that the combination of reduced EF and younger age of onset is, at least in part, influenced by genetic factors, and that these patients develop refractory HF or early death.

On cardiac catheterization, although LVdP/dtmax/SBP was not significant, T1/2 was significantly longer in DCM with PH, suggesting that the presence of PH was influenced by LV diastolic function rather than LV systolic function. The time constant of ventricular relaxation is defined as the time required for the LV cavity pressure at LV dP/dtmax to be reduced by 1/e or 1/2. The factor 1/e has often been used because of the exponentiality of pressure-time data in general. We used T1/2 as LV isovolumic relaxation. However, the 2 parameters are not exactly the same, so these results of the present study should be interpreted with caution.

**Prognosis of Ambulatory DCM Patients With PH**

It has been repeatedly demonstrated that the presence of PH in patients with HF is a predictor of all-cause death and hospital admission in cases of either systolic or diastolic dysfunction. In addition, elevated PVR is associated with early death and RV dysfunction after heart transplantation. To our knowledge, this is the first study to investigate the hemodynamic characteristics and prognosis in patients with PH caused by non-ischemic DCM treated with appropriate medications. In accordance with the findings of previous studies, it is reasonable to speculate that progression of PH can be caused by further LV remodeling and LV relaxation dysfunction, and, consequently, that the presence of PH in DCM reflects a higher incidence of cardiac events. Recently, monitoring using cardiac imaging of the LV structure has proved to be clinically useful for predicting the long-term clinical prognosis of DCM. In accordance with the previous study, the presence of PH and LV remodeling contributed to cardiac death in the present study’s DCM patients. In fact, our Kaplan-Meier curves suggested that cardiac events occurred frequently within 2 years in patients with DCM and PH. Our patients were ambulatory, and 90% of them were in NYHA class 1 or 2, whereas most previous studies have enrolled patients in class 3 or 4. Therefore, mPAP assessment can also help to stratify high-risk DCM patients with mild to moderate symptoms.

The incidence of cardiac death in patients with DCM with PH was more than 11-fold that in DCM patients without PH (Table 5). In the present study, sudden cardiac death accounted for only 1 (3%) among all DCM with PH patients. It remains unclear whether PH influence the cause of cardiac death. Further investigations are needed to confirm the association between DCM-PH and the causes of cardiac death.

In contrast, PAWP and T1/2 were significant independent risk factors for hospitalization for worsening HF. In addition, PAWP was also independently associated with the presence of PH. These parameters have repeatedly proven to be useful prognostic markers in patients with chronic HF. Unscheduled hospitalization for worsening HF can be prompted by multiple factors, such as changes in volume status and afterload.

LVdP/dtmax/SBP was a significant parameter in our univariate analysis, but not in the multivariate analysis, to predict the presence of PH and the incidence of cardiac events, respectively. On the other hand, T1/2 remained a significant predictor of cardiac events in the multivariate analysis. These results suggest that LV isovolumic relaxation dysfunction rather than LV systolic dysfunction contributes to the both the presence of PH and poor prognosis in ambulatory patients with DCM. Further studies are needed to confirm the details.

Patients with irreversible DCM with PH may need particularly strict follow-up. Reversible DCM with PH may be the cause of HF, because of inappropriate fluid retention; in that case, it would be possible to ameliorate the HF with medication. A change in mPAP after therapeutic intervention may provide independent prognostic information. Taken together, these findings suggest that evaluation of mPAP helps to identify a subset of high-risk DCM patients that need to be followed up carefully to ensure the timely use of non-pharmacologic strategies, including heart transplantation.

**Passive or Reactive Post-Capillary PH**

PH-LHD patients often present with 1 of 2 patterns of PH, namely passive PH or reactive PH. The mechanism of passive PC-PH is a simple backward transmission of elevated left atrial pressure, whereas reactive PC-PH is caused by functional or structural changes in the pulmonary arteries as a result of chronic elevation of pulmonary venous pressure. Generally, reactive PC-PH has a worse prognosis than passive PC-PH. We found no significant differences in clinical outcome between the 2 groups. The discrepancy could have been caused by the small sample size or by the fact that we studied only DCM patients. Patients with reactive PC-PH and DPG ≥7 mmHg had a high incidence of cardiac death, but again the 2 groups did not differ because of the small sample size. High DPG (≥7 mmHg) has previously been used to identify a high-risk group of patients with PH caused by LHD and with TPG >12 mmHg who suffered from pulmonary vascular disease. This new algorithm might be a useful predictor of cardiac events, but further investigations in this regard are needed.

**Therapeutic Strategy**

Currently, there is no specific therapy for PH caused by LHD. A number of drugs (including diuretics, nitrates, ACEIs, β-blockers, and inotropic agents) or interventions (implantation of devices to assist the LV, valvular surgery, resynchronization therapy, and heart transplantation) may lower PAP more or less rapidly through a drop in left-sided filling pressures. More than 80% of the DCM with PH patients were taking various combinations of diuretics (including spironolactone) and ACEIs/ARBs; in addition, >70% of them were taking β-blockers at the time of cardiac catheterization; we therefore considered that these DCM patients with PH were optimally medicated. Nevertheless, the occurrence of cardiac death within a relatively short follow-up period was significantly more frequent in DCM patients with PH than in those without PH.

Amelioration or reversibility of what was previously considered to be fixed PH by using LV assist device therapy has also been described. Therapeutic interventions targeting pulmonary abnormalities and the development of RV failure in DCM with PH could be important priorities for the future.

**Study Limitations**

This was a retrospective study in a single center with a relatively small sample size. Moreover, hemodynamic diagnosis by challenge tests such as exercise and acute pulmonary vasoreactivity testing was not performed. In addition, we did not check the right ventricular diameter or function by echocardiography. Finally,
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The use of single time-point measurements did not allow us to assess the time-dependence of PAP in the Cox regression analysis and may have led us to underestimate the prognostic significance of PH.

Conclusions

The presence of PH was associated with an increased incidence of cardiac death in ambulatory DCM patients. DCM patients with PH had worse clinical and hemodynamic parameters than those without PH. The potent effect of mPAP on mortality lends support to therapies aimed at PH in DCM.

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Disclosures

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