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NEDA PH-LHD predictive model: validation of diastolic markers of pulmonary hypertension with right heart catheterization

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Rationale/Background: Our group has developed a predictive model to diagnose pulmonary hypertension due to left heart disease (PH-LHD) using markers of diastolic function. This has been validated in a cohort of 302,746 echos (174,229 patients) and the model has an accuracy of 75%. The gold standard in the diagnosis of PH-LHD is a right heart catheterization (RHC).

Our objective is to establish the predictive value of our PH-LHD model in patients undergoing RHC.

Methods/Materials: Data were extracted for patients undergoing RHC from a tertiary cardiology center in addition to their most recent echo results. Diastolic markers of age, E' , E/e' , $E:A$ ratio, and indexed left atrial volume (LAVI) were used to apply our predictive model in patients with PH-LHD diagnosed on RHC (pulmonary capillary wedge pressure > 15 mmHg, mean pulmonary arterial pressure [mPAP] > 25 mmHg).

Results: A total of 887 patients with a mean (\pm SD) age of 68 (± 18) years, 56% male, mPAP of 31 (± 13) mmHg and mean pulmonary arterial systolic pressure (PASP) of 53 (± 18) mmHg. The incidence of PH on RHC was 68% (mPAP > 25 mmHg) vs. 50% on echo ePASP (> 40 mmHg). We applied our formula constant ($-6.649 + [0.035 \times \text{age}] + [0.072 \times E'] + [0.077 \times E/e'] + [0.509 \times E/A] + [0.03 \times \text{LAVI}]$) to establish the predictive value of our model in RHC diagnosis of PH-LHD. The AUC was 0.793 (95% CI 0.651–0.934, $P = 0.017$).

Conclusion: Using our predictive model, we are able to predict, with 80% accuracy, patients with PH-LHD previously diagnosed by RHC using Echo-derived diastolic markers of LHD.

Limiting the learning curve for pulmonary endarterectomy: an Australian single-center experience

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Rationale/Background: Despite advances in medical treatment, pulmonary endarterectomy (PEA) remains the most curative option for patients with chronic thromboembolic pulmonary hypertension (CTEPH). The majority of centers initiating a PEA service report a significant surgical learning curve. This study examines the outcomes of patients undergoing PEA for CTEPH in a single institution with initial surgical mentoring and double evaluation of patient suitability with an established high-volume center.

Methods/Materials: Forty-three patients (21 women, 22 men; average age 61.1 ± 14.7 years) with surgically amenable CTEPH underwent PEA between November 2010 and July 2017. Functional (New York Heart Association [NYHA] class, 6-minute walk test [6MWT]), hemodynamic (right heart catheterization) and survival outcomes were examined after 12 months. Eleven of the 43 patients (25.6%) had a preoperative pulmonary vascular resistance (PVR) of > 1000 dynes.

Results: Significant post-PEA improvements were observed in NYHA class (pre 3.0 ± 0.5 vs. post 1.7 ± 0.6 , $P < 0.01$), 6MWT (pre 329.7 ± 112.1 m vs. post 451.7 ± 95.6 , $P < 0.01$), mean pulmonary artery pressure (pre 49.3 ± 12.4 mmHg vs. post 31.1 ± 10.0 , $P < 0.01$), PVR (pre 795.6 ± 326.7 dynes vs. post 276.1 ± 115.0 , $P < 0.01$), and cardiac output (pre 4.1 ± 1.2 L/min vs. post 5.4 ± 1.2 , $P < 0.01$). The one-year mortality rate was 2.3%.

Summary/Conclusions: PEA remains an effective treatment for CTEPH with significant improvements demonstrated in pulmonary hemodynamics and functional outcomes. Furthermore, instituting a PEA service in conjunction with an established center can mitigate the learning curve, associated with significant mortality, and produce comparable results to those from high-volume centers.



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Left atrial dilatation is common in scleroderma: implications for the assessment of dyspnea and pulmonary hypertension

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Rationale/Background: Pulmonary arterial hypertension (PAH) and pulmonary hypertension (PH) secondary to interstitial lung disease (ILD) are recognized complications of scleroderma, but the possibility of PH being secondary to left heart disease in scleroderma has received relatively little attention. The aim of this study was to identify individuals with scleroderma who had the potential for either a left heart cause or contribution to PH or dyspnea based on an echocardiogram performed for either screening or investigation of symptoms.

Methods/Materials: Diastolic function and left atrial (LA) pressure were assessed using American Society of Echocardiography (ASE) 2016 criteria which included consideration of LA volume index (LAVI), transmitral E, E/A, mitral annular tissue Doppler velocity (e'), calculated E/e' , and whether the tricuspid regurgitation (TR) velocity was >2.8 m/s. A LAVI of >34 mL/m² was assumed to indicate chronic elevation of LA pressure. Elevation of pulmonary artery pressure (PAP) was assumed if the TR velocity was ≥ 3.0 m/s. Right heart catheterization was performed on symptomatic patients in which PAH was suspected.

Results: There were 194 individuals (30 men; age 58 ± 15 years); three had atrial fibrillation, three had pacemakers, and four had a reduced left ventricular ejection fraction (40–50%). LA dilatation (LAVI >34 mL/m²) was present in 88/194 and a LAVI >40 mL/m² was present in 56/194. Only 100 participants were classed as having normal diastolic function. The TR velocity could not be obtained in 20 individuals and was ≥ 3.0 m/s in 23 participants, of whom ten had a dilated left atrium and 11 met the ASE criteria for elevation of LA pressure.

Summary/Conclusions: LA dilatation is a common finding in scleroderma, implying that PH can be secondary to left heart disease in scleroderma and that PAH and PH secondary to ILD could also have a PH component secondary to LA pressure elevation. Furthermore, individuals with LA dilatation but a normal LA pressure at rest are likely to have a lower threshold for subsequent symptomatic elevations of LA pressure.

Comparison of pulmonary capillary wedge pressure measured on right heart catheterization and pulmonary capillary wedge pressure calculated from Nagueh's formula application to same-day echocardiograms in patients with pulmonary hypertension

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Rationale/Background: Mitral E velocity, when corrected for ventricular relaxation by E/E' , has been found to correlate well to mean pulmonary capillary wedge pressure (PCWP) through Nagueh's formula $PCWP = 1.9 + 1.24(E/E')$. Echocardiographic PCWP calculation in pulmonary hypertension (PH) patients may assist in pre-capillary or post-capillary PH classification.

Methods/Materials: Consecutive right heart catheterization (RHC) PCWP measurements from May 2013 to February 2017 were compared with same-day echocardiograph (ECHO)-derived PCWP calculations in ten patients with ECHO right ventricular systolic pressure (RVSP) ≥ 35 mmHg or RHC PCWP ≥ 25 mmHg referred for PH investigation. PCWP >15 mmHg suggested the presence of post-capillary PH.

Results: Classification concordance, with both RHC and ECHO-derived PCWP concurring in pre-capillary or post-capillary PH class, was observed in all patients with $E/E' \leq 6.44$ or $E/E' \geq 16.32$. E/E' readings in the range of 7.36–12.54 appeared more likely to result in classification discordance (3/4 patients).

Summary/Conclusions: ECHO-derived PCWP calculation could be considered in patients with $E/E' < 6.45$ or > 16.31 . Our results suggest that Nagueh's formula estimation of PCWP in pre- or post-capillary PH classification may be more rigorous at either ends of the range of E/E' readings as described. E/E' readings falling in the mid-range may be less reliable for PH classification through Nagueh's formula estimation. Larger studies are warranted to determine the value of this technique in differentiating pre-capillary from post-capillary PH.

A potential role for PDE-5 inhibitors for pulmonary hypertension due to lung disease/hypoxia

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Rationale/Background: Pulmonary hypertension (PH) secondary to lung disease/hypoxia is common, particularly related to end-stage lung disease, and when present, reduces exercise tolerance, dyspnea, and quality of life. Beyond disease-specific therapy for lung disease and correction of hypoxemia, there is

little published evidence that disease-specific PH therapy has a role in these patients.

As part of a larger Cochrane review—PDE-5 inhibitors for Pulmonary Hypertension—we sought to determine whether PDE-5 inhibitors (PDE5i) improved outcomes in PH due to lung disease.

Methods/Materials: Searches for randomized and quasi-randomized controlled studies on CENTRAL, MEDLINE, EMBASE, CINAHL, and Web of Science to August 2017 were performed.

Results: Seven trials with 427 participants were included. Six trials included those with PH secondary to chronic obstructive pulmonary disease and one trial secondary to idiopathic pulmonary fibrosis. Six trials used sildenafil and one trial used tadalafil, compared with placebo, for a mean duration of 12 weeks (range = 1–6 months). There was a significant difference in improvement in WHO functional class (odds ratio = 44.33, 95% confidence interval [CI] = 4.78–410.93; $P = 0.0008$), and 6-min walk distance (MD = 24.22 m, 95% CI = 15.70–32.74; $P < 0.0001$), favoring PDE5i compared to placebo. There was no significant difference in terms of hemodynamics, quality of life, or adverse events.

Summary/Conclusions: There may be some evidence for PDE5i for PH due to lung disease, although this data should be interpreted with caution due to the small number of studies and short treatment duration. Further studies with PH-specific therapy in PH due to different lung diseases are warranted.

PDE-5 inhibitors for pulmonary hypertension due to left heart disease: potential benefit?

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Rationale/Background: Pulmonary hypertension due to left heart disease (PH-LHD) is common, and when present, results in reduced exercise tolerance, worse quality of life, and increased mortality. Beyond appropriate treatment for left heart disease, the role of PH-specific therapy is unclear.

As part of a larger Cochrane review—PDE-5 inhibitors for Pulmonary Hypertension—we sought to determine whether PDE-5 inhibitors (PDE5i) improved outcomes in PH-LHD.

Methods/Materials: Searches for randomized controlled studies on CENTRAL, MEDLINE, EMBASE, CINAHL, and Web of Science to August 2017 were performed.

Results: Four trials with 194 participants comparing sildenafil with placebo were identified. One additional trial was terminated early. Treatment duration was on average 12 weeks (range = 1–6 months). There was low risk of bias.

There was a significant improvement in 6-min walk distance in one trial (MD = 29 m, $P = 0.047$), and a significant

improvement in mean PAP, TPG, PASP, and dyspnea. There was no difference in WHO functional class, mortality, cardiac index, or clinical worsening, including heart failure.

Summary/Conclusions: These data suggest there may be a cautious role for PDE5i in PH-LHD. The conclusions are limited by the small number of trials and participants, and short-term treatment duration. Further large, multi-centered trials should assess PDE5i in terms of functional and patient-centered outcomes, hemodynamics, and adverse events including risk of heart failure.

Initial findings of top end pulmonary hypertension study

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Rationale/Background: Pulmonary hypertension (PH) is the final common manifestation of multiple diseases with different managements and prognoses. It is associated with significant morbidity and mortality; however, its epidemiology is poorly understood. The current report is the initial findings of a comprehensive study into the epidemiology of PH in the top end of Australia.

Methods/Materials: A retrospective cohort study of the echocardiographic database (NT Cardiac) and electronic medical records was conducted. Echocardiograms (echos) with recorded peak tricuspid regurgitation velocity (TRV) of $TRV \geq 2.75$ m/s were searched in the echo database. The underlying causes for PH was determined using the diagnostic algorithm from the latest European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.

Results: We found 2072 patients whose echos were consistent with PH ($TRV \geq 2.75$ m/s) within the six-years period (January 2010 to December 2015). We have initially studied 150 consecutive patients whose echos were performed in 2015. The majority, 58% ($n = 87$) were group 2 PH (left heart disease related). Group 1 (pulmonary arterial hypertension), Group 3 (PH due to lung diseases), and Group 4 (chronic thromboembolic PH) were made up of 5%, 12%, and 4% of patients. Further, 5% ($n = 7$) was due to a combination of left heart and lung diseases. Etiology could not be ascertained in 13% ($n = 19$) patients with the available data.

Summary/Conclusions: Heart disease was found to be the leading cause of PH, which was similar to the findings from previous studies. The current study may provide much needed insight into the burden of PH as well as the underlying diseases that lead to PH. In the future, we may also identify useful echo markers which can predict different causes of PH by incorporating and analyzing the automatically extracted echo data from NEDA (National Echo Database Australia).

Stress echocardiography allows reasonable estimation of RV contractile reserve compared to gold standard exercise magnetic resonance imaging

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Rationale/Background: Accurate estimation of contractility is important because it enables the clinician to identify the onset of right ventricular (RV) failure at an early stage independent of the confounding influence of raised afterload in patients with pulmonary hypertension (PH).

We sought to compare different echocardiographic measures of RV contractile reserve against a gold standard cardiac magnetic resonance (CMR) and invasive pressure-volume measure.

Methods/Materials: Twenty-nine participants (nine controls and 20 patients with chronic thromboembolic pulmonary hypertension [CTEPH]) underwent echocardiography and CMR both at rest and during incremental exercise. Three echocardiographic measures of RV contractile reserve (exercise-to-rest ratio of the RV pressure area relationship [RVESPAR], exercise-to-rest difference in peak longitudinal strain [Δ RV-LS], and exercise-to-rest difference in peak strain rate [Δ RV-SRs]) were compared with the exercise-to-rest ratio of the RV pressure volume relationship (RVESPVR) obtained from gold standard CMR volumes and direct invasive pressure measurements.

Results: Δ RV-LS ($R_2 = 0.46$, $P = 0.001$) and Δ RV-SRs ($R_2 = 0.45$, $P = 0.001$) correlated with RVESPVR to a similar extent (Fig. 1), perhaps surprisingly given the claim that SRs is less load-dependent than LS. RVESPAR ($R_2 = 0.69$, $P < 0.001$) tended to have the strongest correlation with RVESPVR, although the incremental improvement over RV-LS and RV-SRs was not significant ($P = 0.245$ and $P = 0.243$, respectively).

Summary/Conclusions: The strong correlation between RVESPAR and gold-standard estimates of RV contractility during exercise suggest that this is a good non-invasive surrogate measure. RVESPAR is the most promising echocardiographic measure for identifying early RV dysfunction in patients with increased RV afterload.

Effects of sildenafil on right ventricular function at rest and during exercise in chronic thromboembolic disease: an exercise cardiac magnetic resonance study

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Rationale/Background: It is unclear whether the beneficial effects of pulmonary vasodilator therapy in chronic thromboembolic pulmonary hypertension (CTEPH) also extend to patients with chronic thromboembolic disease without pulmonary hypertension (CTED). We compared the effects of sildenafil on exercise hemodynamics in patients with chronic thromboembolic pulmonary vascular disease with or without PH at rest.

Methods/Materials: Thirty participants (11 CTED and 19 CTEPH patients) underwent exercise cardiac magnetic resonance imaging with simultaneous registration of invasive pulmonary and systemic arterial pressures both before and after administration of a single dose of 50 mg sildenafil. As right ventricular (RV) function, expressed by RV ejection fraction (RVEF), is dependent on both afterload and RV contractility, the effects of sildenafil on the relationship between mean pulmonary artery pressure and cardiac output (mPAP/CO slope) as a measure of afterload and the ratio of peak-exercise to resting RV end-systolic pressure/volume relationship (RVESPVR) as measure of contractility were assessed.

Results: Sildenafil increased RVEF in both CTEPH (35.8% before vs. 40.4% after at peak exercise, $P < 0.001$) and CTED patients (65.6% before vs. 67% after at peak exercise, $P = 0.035$) although the increase was greater in CTEPH ($P < 0.001$ for the interaction sildenafil* group). This increase was explained by a significant decrease in the mPAP/CO slope in CTEPH patients (8.8 ± 4.0 before vs. 6.4 ± 3.4 after, $P = 0.025$), while only a trend towards reduction was noted in CTED patients (3.1 ± 1.7 before vs. 2.6 ± 1.7 after, $P = 0.135$, Fig. 2). RV contractility was not influenced by sildenafil in either CTEPH (1.36 before vs. 1.44 after, $P = 0.118$) or CTED patients (2.25 before vs. 2.13 after, $P = 0.339$, Fig. 3).

Summary/Conclusions: Sildenafil significantly increases RV performance mainly due to a decrease in RV afterload and not by increased contractility. Although still significant, the observed benefits were less pronounced in CTED patients, potentially reflecting less small vessel vasculopathy.

Pulmonary arterial hypertension-related morbidity is prognostic for survival: insights from the SERAPHIN and GRIPHON studies

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Rationale/Background: Clinical and registry data suggest that pulmonary arterial hypertension (PAH) progression is indicative of poor prognosis.

Methods/Materials: The prognostic relevance of PAH-related morbidity was evaluated based on observations from randomized controlled trials SERAPHIN ($n=742$) and GRIPHON ($n=1156$). Both studies were double-blind, long-term, event-driven Phase III trials. In both, the primary endpoint was a composite of morbidity/mortality, prospectively defined and independently adjudicated. At three landmark time points—months 3, 6, and 12—the risk of all-cause death until end of study was assessed according to whether patients had experienced a primary endpoint morbidity event up to the landmark.

Results: At month 3, 720 SERAPHIN patients were at risk of death. Of those, 38 had experienced a morbidity event up to month 3. Within the median follow-up period of 27 months, patients had a more than threefold increased risk of death compared with the 682 patients who had not experienced a morbidity event up to month 3 (hazard ratio [HR] = 3.39, 95% confidence interval [CI] = 1.94–5.92). Similar observations were made in the GRIPHON population: 1127 patients were at risk of death at month 3; 62 patients had experienced a morbidity event up to month 3 and had a more than fourfold increased risk of death within the next 20 months (median follow-up) compared with the 1065 patients who had not (HR = 4.48, 95% CI = 2.98–6.73). In both studies, analyses at months 6 and 12 yielded similar findings.

Summary/Conclusions: These results confirm the prognostic relevance of PAH-related morbidity and the importance of its prevention in patients with PAH.

Pulmonary hypertension due to left heart disease: a predictive model using the National Echo Database of Australia (NEDA)

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Rationale/Background: Pulmonary hypertension due to left heart disease (PH-LHD) is common, but may be difficult to diagnose by echo in the absence of sufficient tricuspid regurgitation (TR). Once PH has progressed to moderate or severe disease, prognosis is poor.

Our objective is to create a predictive model using diastolic echo markers to diagnose PH, even in the absence of a measurable TR velocity.

Methods/Materials: A total of 302,746 echos (174,229 patients) were analyzed. Univariate analysis was used to establish significant diastolic markers of PH in 99,025 patients with sufficient TR (79,268 with PH vs. 19,767 with no PH). The whole cohort (including no measurable TR velocity) was randomized to two groups: Group A (151,373 echos) to perform multivariate regression analysis on the diastolic markers and to create a predictive model; and Group B to validate the predictive model (151,373 echos).

Results: Age, E', E/e', E:A, and indexed left atrial volume (LAVI) were identified in group A as markers of PH-LHD. A constant ($-6.649 + [0.035 \times \text{age}] + [0.072 \times E'] + [0.077 \times E/e'] + [0.509 \times E/A] + [0.03 \times \text{LAVI}]$) was developed and applied in group A to predict PH-LHD, with an area under the curve (AUC) of 0.746 (95% confidence interval [CI] = 0.729–0.762). We then validated this model on group B, with an AUC of 0.757 (95% CI = 0.741–0.773). TR is not measurable in 40% of echos. We have developed a new model that can predict PH-LHD with 75% accuracy, regardless of measurable TRV, using Age, E', E/e', E:A, and LAVI. Our model may be useful in echo software to automatically calculate a probability of PH-LHD.

Summary/Conclusions: TR is not measurable in 40% of echos. We have developed a new model that can predict PH-LHD with 75% accuracy, regardless of measurable TRV, using Age, E', E/e', E:A, and LAVI. Our model may be useful in echo software to automatically calculate a probability of PH-LHD.