Non-invasive algorithms for the diagnosis of pulmonary hypertension

Diana Bonderman1; Paul Wexberg2; Harald Heinzl3; Irene M. Lang1

1Department of Cardiology, Medical University of Vienna, Austria; 2Second Medical Department, Krankenanstalt Rudolfstiftung, Vienna, Austria; 3Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Austria

Summary
Precapillary pulmonary hypertension (PH) is diagnosed when mean pulmonary arterial pressure (mPAP) equals or exceeds 25 mmHg and the pulmonary capillary wedge pressure (PCWP) is equal or lower than 15 mmHg. Because both parameters can only be derived from invasive hemodynamic assessment, right heart catheter (RHC) is still a gold standard for the diagnosis of PH. Severe precapillary PH corresponds to pulmonary vascular disease and carries a poor prognosis. Unfortunately, due to a generally low specificity of non-invasive estimates of systolic pulmonary pressure, at least 50% of patients with suspicion of PH need to undergo invasive RHC for exclusion of precapillary PH. Therefore, and also in order to manage the growing number of postcapillary PH due to heart and lung disease in the general population, pulmonary and cardiologic diagnostic algorithms combining multiple parameters have been developed. Recent disease scores are reviewed, and an outlook is given on emerging evidence from the DETECT clinical study holding the promise to non-invasively predict precapillary PH in vulnerable patients. These diagnostic trees help limit unnecessary procedures and help differentiate the current categories of PH. However, one has to keep in mind that the diagnosis of PH is still made by hemodynamic assessment.

Keywords
Diagnosis management, cardiology, clinical studies

Introduction
Precapillary pulmonary hypertension (PH) is a fatal condition leading to right heart failure and death within 2–3 years after diagnosis, if left untreated (1). While idiopathic and familial pulmonary arterial hypertension (PAH) are rare, drug-and-toxin induced PAH as well as associated forms of PAH are more common and may be triggered by connective tissue disease, human immunodeficiency virus infection, portal hypertension, congenital heart disease, schistosomiasis or chronic haemolytic anaemia. Moreover, precapillary PH may occur as sequelae of chronic lung disease and/or hypoxia, such as chronic obstructive pulmonary disease, interstitial lung disease or sleep-disordered breathing (2). Medical conditions, including infection, immune disorders, inflammatory bowel disease and permanent venous catheters predispose to chronic thromboembolic pulmonary hypertension (CTEPH) (3–5).

Right heart catheter (RHC) is a gold standard for PH diagnosis (2). It must be performed in order to make the correct diagnosis and implement an appropriate treatment plan. Despite its invasive nature, in experienced hands RHC is safe with an overall procedure-related mortality of 0.055% (6). Precapillary PH is diagnosed when mean pulmonary arterial pressure (mPAP) equals or exceeds 25 mmHg and the pulmonary capillary wedge pressure (PCWP) is equal or lower than 15 mmHg. Both parameters can only be derived from invasive haemodynamic assessment. Moreover, RHC is critical in order to obtain reliable measurement of cardiac output and calculation of pulmonary vascular resistance (PVR). Thus, it is the only diagnostic method at hand allowing to trace back haemodynamic changes underlying pressure elevations in the pulmonary vasculature, e.g. high cardiac output states, elevated left-sided filling pressures with or without additional pulmonary vascular disease. Ultimately, invasive diagnostic work-up with acute vasodilator testing is necessary to assess candidacy for calcium channel blocker therapy.

Transthoracic echocardiography (TTE) is the recommended screening tool in patients at risk and in those who present with signs and symptoms compatible with precapillary PH. However, it has become increasingly apparent that the use of Doppler echocardiography for the diagnosis of PH is unreliable (7, 8). Current European practice guidelines acknowledge that despite a strong correlation of the tricuspid regurgitation velocity and tricuspid regurgitation pressure gradient, Doppler-derived pressure estimation may be inaccurate in the individual patient. In patients with severe tricuspid regurgitation use of the simplified form of the Bernoulli equation may lead to underestimation of sPAP, also overestimations by >10 mmHg are common. PH cannot be reliably defined by a cut-off value of Doppler-derived sPAP. Moreover, estimation of PAP based on Doppler TTE measurements is not suitable for screening for mild, asymptomatic PH (2). Other non-invasive diagnostic tools, such as serum biomarkers of heart failure, electrocardiogram (ECG) signs of pulmonary heart disease or lung function tests are currently used to complement TTE, but...
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Bonderman et al. Diagnostic algorithms in PH prediction... additional echocardiographic variables suggestive of PH

Over recent years, several diagnostic algorithms have been developed to rule in or rule out PH in various patient populations at risk for precapillary PH, such as patients with a history of pulmonary embolism, patients with chronic lung disease, left heart disease, or systemic sclerosis. However, only few algorithms were calibrated by RHC, which is the gold standard for PH diagnosis. For example, Klok et al. (12) reported 82 consecutive patients with confirmed CTEPH and 160 consecutive patients with a history of pulmonary embolism who were at risk for CTEPH, but in whom CTEPH was not ruled out (Table 2). A diagnostic rule including ECG criteria and N-terminal brain natriuretic peptide (NT-proBNP) levels had a sensitivity of 94% (95% confidence interval [CI] 86–98%) and a specificity of 65% (95% CI 56–72%).

Methodology of diagnostic algorithms

In general, algorithms may rely on various statistical methodologies. Most common techniques utilised for the development of prediction models or rules are univariate or multivariable analyses, e.g., logistic regression, and classification and regression tree (CART) analyses.

The use of multiple logistic regression models will usually result in prediction scores, which can be used to calculate the probability of a particular endpoint. A prediction score provides an individualised estimate of the predicted probability of the diagnosis of interest, which is entirely based on the individual’s disease characteristics (11).

In contrast to a multiple regression model, CART does not result in a complicated formula. CART intends to identify distinct population subgroups with regard to the diagnosis of interest in a simple hierarchical manner. Binary splits of the data set and its subgroups are based on single covariates and their respective predictive performance. Both, the chosen covariates and the order in which they are chosen, are well determined by the underlying mathematical algorithm.

The choice of a CART decision tree for statistical analysis is usually triggered by at least one of two intentions: an efficient handling of complex nonlinear or interactive relationships in the data set, and the need for a clinically adequate and easy-to-use decision tool. A CART provides both by offering great model-fitting flexibility and a decision making structure that physicians frequently use in clinical situations (12). However, the hierarchical nature of CART hampers the assessment of how an individual covariate affects the endpoint of interest.

Overview of non-invasive diagnostic algorithms for the diagnosis of PH

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Table 2: Overview of published non-invasive diagnostic algorithms for pulmonary hypertension that were calibrated by right heart catheterisation. *DETECT clinical study (ClinicalTrials.gov number NCT00706082); PFT=pulmonary function tests; ECG=electrocardiography; TTE=transthoracic echocardiography; NT-proBNP=N-terminal brain natriuretic peptide; CTPA=CT pulmonary angiography; IF=P=idiopathic pulmonary fibrosis; SpO2=resting room air pulse oximetry-derived arterial oxygen saturation; FVC=forced vital capacity; DLCO=diffusing capacity for carbon monoxide; precap. PH=precapillary pulmonary hypertension.

Information about algorithm development:

**Table 3:** Validated sensitivities, specificities, positive and negative predictive values of non-invasive diagnostic algorithms for pulmonary hypertension, taking into account various pulmonary pressure thresholds. a) Algorithms and thresholds considered by Zisman et al. (17). b) Algorithm analysed by Bonderman et al. (10). RHC=right heart catheter; PPV=positive predictive value; NPV=negative predictive value; mPAP=mean pulmonary arterial pressure; sPAP=systolic pulmonary arterial pressure.

<table>
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<td>decision tree</td>
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(mild, moderate or severe) or absence of tricuspid regurgitation was assessed. A threshold of CT/TTE composite index ≥28, or the presence of at least mild tricuspid regurgitation produced a sensitivity of 100%, specificity of 63%, PPV of 87% and NPV of 100%.

The largest effort that has ever been undertaken to date to develop a non-invasive screening algorithm for the diagnosis of precapillary PH (Table 2) has been the DETECT cross-sectional clinical study. This contemporary study which was performed between October 2008 and November 2011 is combining various non-invasive screening tests to construct a predictive algorithm for precapillary PH in patients with systemic sclerosis. A total of 466 adult patients with systemic sclerosis, which represents one of the strongest risk factors for precapillary PH, underwent multiple screening tests followed by RHC. Patients could be included if systemic sclerosis, dated from onset of first non-Raynaud feature, had been diagnosed more than three years prior to enrollment and had a diffusion capacity of the lung for carbon monoxide (DLCO) <60% of predicted (ClinicalTrials.gov number NCT00706082). Publication of main study results is pending and is expected later in 2012. However, data from this study will primarily be applicable to patients with advanced systemic sclerosis and cannot be easily extrapolated to the general population of patients who present to their physicians with shortness of breath.

To date, only two of the published non-invasive diagnostic algorithms for the diagnosis of PH were validated in separate patient cohorts (Table 2). Zisman et al. (14) developed a prediction formula for mPAP using standard lung function measurements to screen for PH in patients with idiopathic pulmonary fibrosis (IPF). PH frequently complicates advanced IPF and is associated with poor outcome (15, 16). The authors reviewed data of 61 patients with IPF who underwent RHC to establish non-invasive predictors of PH (14). Based upon pulmonary function tests, including forced vital capacity (FVC) and DLCO, as well as resting room air pulse oximetry (SpO2) an equation [predicted mPAP = -11.9+0.272 x SpO2+0.0659 x (100- SpO2)2 + 3.06 x (% FVC/% DLCO)] was developed that reliably predicted the presence of PH, defined as mPAP >25 mmHg. The sensitivity, specificity, PPV and NPV of model-predicted PH were 71% (95% CI: 50–89%), 81% (95% CI: 68–92%), 71% (95% CI: 51–87%) and 81% (95% CI: 68–94%), (Table 2). In a second step, the equation was externally validated in a sample of 60 IPF patients (17). Diagnostic abilities, including sensitivity (63% (95% CI: 38–84%), specificity (85% (95% CI: 70–94%), PPV (67% (95% CI: 36–86%) and NPV (83% (95% CI: 63–89%) were rather low, but still superior to those obtained by TTE in the same patients. When the pulmonary artery pressure threshold for PH diagnosis was decreased to 21 mmHg, sensitivity improved at the cost of specificity (Table 3a). Unfortunately, in non-IPF patients at risk or under clinical suspicion of PH this algorithm is not applicable. Another limiting factor for its clinical applicability is that it has been validated solely on its ability...
to detect mPAP >25 mmHg, not considering left-sided filling pressures, cardiac output and PVR calculations.

At our tertiary referral centre, we developed and validated a diagnostic decision tree based on standard non-invasive diagnostic procedures to reliably identify or exclude precapillary PH in patients referred for clinical suspicion of PH and echocardiographic sPAP ≥36 mmHg. We used a retrospective data set of 251 consecutive individuals and constructed a simple non-invasive diagnostic algorithm. Because of the prognostic implications of a delayed precapillary PH diagnosis and treatment (1), a false negative diagnosis was assumed to have far more serious consequences than a false positive one. Therefore, the class assignment rule was chosen in a way that the percentage of false negative predictions did not exceed 4% (one out of 25) of the true positive cases.

Relying on the CHAID (Chi-Squared Automatic Interaction Detection) procedure, two out of 28 clinical, echocardiographic or ECG parameters were automatically identified (right ventricular strain pattern [RVS] on ECG defined as ST-segment deviation and T-wave inversion in leads V1-V3 [18] and NT-proBNP with a cutoff of 80 pg/ml), in the absence of which precapillary PH could be safely excluded. Although a biomarker threshold that is below the upper limit of reference appears to be of limited value, the validity of the decision tree was confirmed in a prospective cohort (Fig. 1) comprising 121 patients referred for clinical suspicion of precapillary PH and echo sPAP ≥36 mmHg (Table 3b). According to current practice guidelines all patients with sPAP ≥36 mmHg and a suspicion of PH are referred to RHC. Therefore, the sensitivity of TTE is 100%, and the specificity is 0.0%. When incorporating the decision-tree algorithm in the non-invasive diagnostic work-up of patients, sensitivity was unchanged (100% vs. 100%, p=1.0), while specificity had improved from 0.0% according to current clinical practice, to 19.3% (p=0.0009).

Summary and outlook

PH as a complication of heart and lung disease confers a poor prognosis across a spectrum of associated disorders (19–26). Current practice guidelines recommend RHC in any condition if echo sPAP exceeds 50 mmHg and precapillary PH is considered likely (Table 1). In the grey area of sPAPs between 36 mmHg and 50 mmHg, the diagnosis of precapillary PH is thought to be less likely but still possible, and a weaker recommendation exists with respect to RHC (2). Because of the malignant nature of the disease with rapid progression to right heart failure, and because effective therapies are available, most PH centres tend to proceed with an invasive RHC. In our clinical routine, patients with echo sPAP ≥36 mmHg, irrespective of other direct or indirect signs of precapillary PH, undergo RHC. However, due to a low specificity of currently recommended non-invasive screening tools, almost half of those with PH suspicion undergo RHC for exclusion of the diagnosis precapillary PH. To overcome inadequacies of non-invasive diagnostic methods, algorithms combining multiple parameters have been developed. For example, a prediction score for mPAP using standard lung function measurements can be used to screen for PH in IPF patients. However, due a relatively low sensitivity (Table 3) a strict translation into clinical routine may be inappropriate (14, 17). Owing to the serious implications of unrecognised and untreated precapillary PH, we propose to prioritise algorithms of high sensitivity (10). In our diagnostic work-up of patients with echo sPAP ≥36 mmHg we are currently relying on our ECG and NT-proBNP-based diagnostic decision tree. We were able to significantly reduce unnecessary RHCs in one out of five patients (10).

Taken together, our simple decision tree helps diagnose PH in a large group of patients, including those with lung disease and associated conditions (10). However, a limitation of the CART algorithm is that it only applies to the current technology and referral systems. In the future, it will have to be validated in more complex patients with mixed etiologies of PH, utilising emerging diagnostic tools.

General limitations of diagnostic algorithms

NPVs and PPVs are employed to characterise discriminative accuracies of diagnostic decision rules. Because in general, predictive values are strongly dependent on disease prevalence in a respective cohort, results may only be extrapolated to centres with similar patient populations. Thus, compared with tertiary referral centres, higher NPVs but lower PPVs are to be anticipated in primary or secondary care settings with a smaller prevalence of precapillary PH.

Taken together, the improved quality and broader use of non-invasive tests, as well as novel non-invasive tests (27–31) will allevi-
ate the decision on further invasive work-up of patients with suspected pulmonary vascular disease in the future. The integration of various non-invasive parameters derived from the 466-patient study DETECT is expected to allow classifying patients with suspicion of precapillary PH into a group in whom the disease can be safely excluded and another group in whom the likelihood of the diagnosis is very high. Of course, conditions with a high likelihood of precapillary PH, i.e. scleroderma or lung disease, will prompt early non-invasive diagnosis much easier and with a higher success rate than conditions with a low likelihood of precapillary PH, e.g. left heart disease. These conditions will remain a challenge, and will further the search for subset-specific risk factors in large multinational registries, combining interdisciplinarity efforts in the fields of cardiology, pulmonary medicine, vascular biology, immunology and thrombosis research.

Conflicts of interest
Diana Bonderman has consultancy relationships and/or has received research funding from Actelion, Bayer, United Therapeutics, AOP-Orphan and Pfizer. Paul Wexberg has consultancy relationships with Actelion, Novartis and Servier. Harald Heinzl has consultancy relationships and/or has received research funding from Actelion and Roche. Irene Lang has consultancy relationships and/or has received research funding from Actelion, Bayer, United Therapeutics, AOP-Orphan, Glaxo-SmithKline and Pfizer.

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