CHEST

Official publication of the American College of Chest Physicians

Misclassification of Pulmonary Hypertension Due to Reliance on Pulmonary Capillary Wedge Pressure Rather Than Left-Ventricular End-Diastolic Pressure

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Chest; Prepublished online March 2, 2009;
DOI 10.1378/chest.08-2784

WORD COUNT: 2,858
ABSTRACT WORD COUNT: 250

MISCLASSIFICATION OF PULMONARY HYPERTENSION DUE TO RELIANCE ON PULMONARY CAPILLARY WEDGE PRESSURE RATHER THAN LEFT-VENTRICULAR END-DIASTOLIC PRESSURE

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SUPPORT and DISCLOSURE: This work was supported by an American Thoracic Society Fellows Career Development Award to Dr. Halpern. Drs. Halpern and Taichman have each received support from Actelion Pharmaceuticals to conduct other research related to pulmonary hypertension. The authors have no other involvement with organizations with a financial interest in the subject matter.

Abstract

Background: Pulmonary arterial hypertension is typically distinguished from pulmonary venous hypertension by documenting a pulmonary capillary wedge pressure (PCWP) ≤ 15mmHg. However, PCWP has uncertain utility in establishing pulmonary venous hypertension. We sought to determine the calibration, discrimination, and diagnostic accuracy of PCWP, using simultaneously measured left-ventricular end-diastolic pressure (LVEDP) as the gold standard.

Methods: We examined hemodynamic data from the 11,523 unique patients undergoing simultaneous right- and left-heart catheterization at a large academic center from 1998 – 2007.

Results: Among 4,320 patients (37.5%) with pulmonary hypertension (mean pulmonary artery pressure ≥ 25mmHg), hemodynamic data were complete for 3,926 (90.9%). Of these, 580 (14.8%) met criteria for pulmonary arterial hypertension with a PCWP ≤ 15mmHg, but 310 (53.5%) of these patients had an LVEDP > 15mmHg. Such discrepancies remained common among patients with a pulmonary vascular resistance > 3 Wood units and those being catheterized specifically to evaluate pulmonary hypertension. PCWP provided moderate discrimination between patients with high vs. normal LVEDP (area under the receiver-operating characteristic curve = 0.84, 95% confidence interval = 0.81 – 0.86) but was poorly calibrated to LVEDP (Bland-Altman limits of agreement: – 15.2mmHg to 9.5mmHg; Hosmer-Lemeshow goodness-of-fit χ^2 statistic: 155.4, $p < 0.0001$).

57 **Conclusions:** Roughly half of patients presumed to have pulmonary arterial hypertension based
58 on PCWP may be found to have pulmonary venous hypertension based on LVEDP. Reliance on
59 PCWP may result in the dangerous or cost-ineffective use of pulmonary vasodilators for patients
60 with left-heart disease. Furthermore, without assessing LVEDP, investigators may include
61 patients with left-heart disease in therapeutic trials of PAH drugs, thereby limiting their ability to
62 detect beneficial drug effects.

KEY WORDS: pulmonary hypertension, left-heart disease, pulmonary capillary wedge pressure, hemodynamic assessment, cardiac catheterization

ABBREVIATION LIST

AUROC, area under the receiver-operating characteristic curve

LVEDP, left-ventricular end-diastolic pressure

mPAP, mean pulmonary artery pressure

PAH, pulmonary arterial hypertension

PCWP, pulmonary capillary wedge pressure

PVH, pulmonary venous hypertension

PVR, pulmonary vascular resistance

TPG, transpulmonary gradient

WHO, World Health Organization

Introduction

In approaching a patient with pulmonary hypertension, it is crucial to distinguish between pulmonary arterial hypertension (PAH) and other causes of elevated pulmonary pressures, including pulmonary venous hypertension (PVH) due to left-sided heart disease. The World Health Organization (WHO) emphasizes the importance of such a differentiation in its classification system that separates PAH (Group 1) from other forms of pulmonary hypertension (e.g., Group 2 patients with left heart dysfunction).[1-3] Patients with PAH may benefit from recently approved prostacyclin analogues, endothelin receptor-antagonists, or phosphodiesterase inhibitors.[4] By contrast, in patients with PVH these same therapies are not indicated, may be harmful, and initial management is best focused on amelioration of left-heart dysfunction.[5, 6]

Differentiation of PAH from PVH is most commonly accomplished by documenting a pulmonary capillary wedge pressure (PCWP) of $\leq$ 15mmHg at the time of diagnostic right-heart catheterization.[7, 8] This diagnostic approach is predicated on the assumption that a normal PCWP measurement adequately excludes left atrial hypertension. Indeed, rather than having intrinsic value, the utility of the PCWP resides primarily in its ability to rule in or out disease states characterized by an elevated left-ventricular end-diastolic pressure (LVEDP).

Although the assumption that PCWP is a useful surrogate marker for LVEDP has both strong historical roots and substantial face validity,[9] there is scant evidence regarding the abilty of PCWP to establish the presence or absence of left-sided heart disease among patients with pulmonary hypertension. Thus, when both PCWP and LVEDP are available in a patient with pulmonary hypertension, the LVEDP is generally considered to be the gold standard.

In a preliminary report of a study involving 131 patients with pulmonary hypertension, Soto and colleagues found that PCWP has poor operating characteristics when tested against the standard of LVEDP.[10] Given the potential importance of such findings to the management of pulmonary hypertension patients, we sought to determine the calibration, discrimination, and accuracy of mean PCWP compared with the gold standard of LVEDP among a large cohort of patients with pulmonary hypertension.

Methods

Patients

All patients undergoing right-heart catheterization at Penn-Presbyterian Medical Center – a large, community-based, academic hospital and regional referral center for pulmonary vascular disease affiliated with the University of Pennsylvania Health System – from January 1, 1998 – December 31, 2007 were included. This study was deemed exempt from review by the University of Pennsylvania Institutional Review Board because it used previously collected, de-identified data.

Patients were considered ineligible for the study if they had a diagnosis of mitral stenosis (identified by an International Classification of Diseases – 9 code between 394.0 and 396.8 on the catheterization record) or if tachycardia (>130 beats per minute) was present during catheterization because these phenomena are known to cause discrepancies between PCWP and LVEDP.[12] Among the 2,763 patients who underwent multiple catheterizations during the study period, only the first catheterization was included.

Eligible patients were grouped according to whether they had a combined right- and left-heart catheterization (the "combined catheterizations" group) or a right-heart catheterization alone. Because patients in whom physicians order combined catheterizations may differ from those in whom only right-heart catheterization is ordered, hemodynamic measurements were compared between these groups to determine whether selection bias may have influenced the results.

In both groups, patients were considered to have pulmonary hypertension (PH) if their mean pulmonary artery pressure (mPAP) (calculated as 2/3 pulmonary artery diastolic pressure + 1/3 pulmonary artery systolic pressure) was $\geq$ 25mmHg at rest.[1] Patients were excluded if data were missing for mPAP, PCWP, or LVEDP (among patients undergoing combined catheterization) (Figure 1).

Hemodynamic Measurements

Catheterizations were performed by 10 interventional cardiologists, all of whom were board-certified and members of the University of Pennsylvania faculty. Hemodynamic parameters were recorded directly into electronic spreadsheets and stored in a computerized database.

Physicians performing the catheterizations followed standard protocols for measuring hemodynamic values. Hemodynamic values from both right- and left-heart catheterizations were obtained prior to the injection of contrast for left ventriculography or coronary angiography. For PCWP, values for the A-wave pressure, V-wave pressure, and mean pressure were recorded at end-expiration. The mean PCWP was used for analyses. Among patients who underwent left-

heart catheterization, LVEDP was recorded simultaneously with PCWP using a pigtail catheter placed in the left ventricle.

Pulmonary vascular resistance (PVR) was calculated as (mPAP – PCWP) / cardiac output (measured using the estimated Fick method), and patients were classified as having elevated PVR if the value was > 3 Wood units.[1] Transpulmonary gradient (TPG) was calculated as mPAP – PCWP, and patients were classified as having elevated TPG if the value was ≥ 12.[13]

Statistical Analysis

The accuracy of a mean PCWP ≤ 15mmHg vs. > 15mmHg in distinguishing between WHO Groups 1 and 2 PH (i.e. PAH versus PVH) was assessed by calculating the proportion of patients that would be reclassified by instead using LVEDP of ≤ 15mmHg vs. > 15mmHg.

The calibration of PCWP to LVEDP was assessed using a Bland-Altman analysis[14] and the Hosmer-Lemeshow goodness-of-fit test.[15] When conducting the goodness-of-fit test, LVEDP was dichotomized as ≤ 15mmHg vs. > 15mmHg; sensitivity analyses were performed using LVEDP cut-points from 10 to 20mmHg.

The area under the receiver-operating characteristic curve (AUROC)[16] was calculated to determine the ability of PCWP to discriminate patients with LVEDP ≤ 15mmHg vs. > 15mmHg. Wilcoxon rank-sum tests were used to compare hemodynamic values between patients who underwent combined catheterizations vs. right-heart catheterization alone. Stata 9.2 (Stata Corp., College Station, Texas) was used for all analyses.

Results

There were 12,744 eligible unique patients who underwent right-heart catheterization at our institution from 1998 – 2007. Of these, 11,523 had combined catheterizations, and 4,320 (37.5%) of these patients had PH (Figure 1).

Disease classification

Among 3,926 patients (90.9%) with PH and complete data, 580 (14.8%) met criteria for PAH based on a low PCWP (≤ 15mmHg). However, 310 (53.5%) of these patients would be classified as having PVH if LVEDP were used instead (Table – Panel A and Figure 2). By contrast, among the 3,346 patients classified as having PVH using PCWP, only 152 (4.5%) would meet criteria for PAH if LVEDP were used instead.

To determine rates of misclassification among patients who might be considered to have "pulmonary hypertension out of proportion to left-heart disease,[5, 6]" we restricted our analyses to those patients with either a PVR > 3 Wood units (1,116 patients) or a TPG ≥ 12 (1,300 patients). Among patients with an elevated PVR, 361 (32.4%) would be classified as PAH using PCWP, but 148 of these (41.0%) would be reclassified as PVH based upon the LVEDP (Table – Panel B). Among patients with an elevated TPG, 494 (38.0%) would be classified as PAH using PCWP, but 247 of these (50.0%) would be reclassified as PVH based upon the LVEDP (Table – Panel C).

Compared with patients undergoing right-heart catheterization alone, the patients who underwent combined catheterizations had a lower PVR (median = 2.1 Wood units, interquartile range 1.4 – 3.3 vs. median = 3.2 Wood units, interquartile range 1.9 – 5.9; $p < 0.0001$) and TPG (median = 9.8, interquartile range 6.7 – 14.0 vs. median = 13.3, interquartile range 8.0 – 24.3; $p < 0.0001$). However, the two groups had similar PCWP (median = 22.0mmHg, interquartile range 14.0 – 30.0 vs. median = 22.0mmHg, interquartile range 18.0 – 27.0; $p = 0.31$).

Disease classification among patients catheterized specifically for evaluation of PH

To more specifically address the utility of left-heart catheterization among patients being evaluated for PH, we restricted analyses to the 604 patients who were referred for catheterization by PH specialists as part of their initial evaluation of PH. Of these, 340 (56.3%) had a combined catheterization, and 282 (83.9%) of these patients had PH. Of the 265 patients with documented PH, who had been referred for combined catheterization as part of their PH evaluation, and for whom LVEDP was measured, 164 (61.9%) met criteria for PAH by virtue of having a PCWP ≤ 15mmHg, but 34 of these patients (20.7%) had an LVEDP > 15mmHg.

Calibration

In the complete sample of patients with PH and combined catheterizations, Bland-Altman analysis revealed that on average, PCWP underestimated LVEDP by 2.9 mmHg (95% CI = 2.7 – 3.0) (Figure 3). In 39.0% of patients, the absolute difference between PCWP and LVEDP was > 5mmHg; in 11.3% it was > 10mmHg. The 95% limits of agreement were -15.2 mmHg to 9.5mmHg, indicating that even after excluding the 5% of patients with the most discrepant

values between PCWP and LVEDP, the PCWP underestimated LVEDP by as much as 15.2 mmHg and overestimated LVEDP by as much as 9.5 mmHg.

Using LVEPD ≤ 15mmHg vs. > 15mmHg as a dichotomous outcome in a logistic regression model, the calibration of PCWP was poor, as indicated by a Hosmer-Lemeshow χ^2 statistic of 155.4 ($p < 0.0001$). The goodness-of-fit test remained significant (indicating poor calibration) for all cutpoints of LVEDP between 10mmHg and 20mmHg.

Because the large sample size could account for the statistical significance of the goodness-of-fit test, we performed 1000 iterations of bootstrap resampling with 20% random samples of the total (785 patients each). The goodness-of-fit test remained significant in 72.4% of these samples, confirming the poor calibration.

Discrimination

The AUROC was 0.84 (95% CI = 0.81 – 0.86) (Figure 4). This indicates that among all randomly selected pairs of patients in which one has an LVEDP ≤ 15mmHg and the other has an LVEDP > 15mmHg, the patient with the higher LVEDP would have a higher PCWP in 84% of cases. These results were similar using LVEDP cut-points of 10mmHg or 20mmHg (Figure 4).

Comparison with patients without pulmonary hypertension

Among 7,117 patients who underwent combined catheterizations and did not have pulmonary hypertension, complete data were available in 6,551 (92.0%) patients. Misclassification was also evident among these patients, as 2,253 of 5,454 patients with PCWP ≤ 15mmHg (41.3%) had LVEDP > 15mmHg. A Bland-Altman analysis of calibration in this group revealed that PCWP

underestimated LVEDP by 4.7 mmHg (95% CI = 4.6 – 4.8), with 95% limits of agreement from -14.5mmHg to 5.1mmHg. Finally, the ability of PCWP to discriminate patients with high or low LVEDP among patients without pulmonary hypertension, as assessed by the AUROC, was 80% (95% CI = 79% – 81%).

Discussion

This study of a large number of patients undergoing sequential measurement of PCWP and LVEDP suggests that PCWP frequently underestimates LVEDP, that it is poorly calibrated to LVEDP, and that it has a moderate ability to discriminate between patients with normal or elevated LVEDP. Perhaps most importantly, these results suggest that approximately half of all patients who meet hemodynamic criteria for PAH on the basis of PCWP measurements may, in fact, have elevated left-ventricular filling pressures.

This degree of misclassification was robust even when we restricted the sample to patients with an elevated PVR or TPG, groups hypothesized to be more homogenous and reflective of true PAH patients.[5] These results emphasize the importance of avoiding the conclusion that a patient has "pulmonary hypertension out of proportion to left heart disease" without evaluating the LVEDP.

Although many of the patients in our study underwent cardiac catheterization for reasons other than evaluation of PH, disease misclassification remained common even among patients specifically referred for catheterization by PH specialists as part of their PH evaluation. Among

259 such selected patients, one fifth of those who would be classified as having PAH by PCWP
260 would instead be classified as having PVH by LVEDP.
261
262 Bias resulting from the selective referral of certain patients for combined catheterization is
263 unlikely to have influenced these results. First, discrepancies between PCWP and LVEDP
264 persisted even among patients with elevations in PVR or TPG. Second, the median PCWP did
265 not differ between patients undergoing combined catheterization versus those undergoing right-
266 heart catheterization.
267
268 The clinical consequences of mistakenly classifying patients as having PAH when left-heart
269 disease is present are incompletely understood. However, the potential for PAH-specific
270 therapies such as pulmonary vasodilators to precipitate the acute deterioration of patients with
271 PVH is well described.[5, 6, 17] Even if frank deterioration occurs infrequently following use of
272 PAH therapies for patients with PVH, there are no high-quality data to suggest that patients with
273 PVH would benefit from these therapies. It is thus critical to make the correct diagnosis prior to
274 instituting therapies that are inappropriate, potentially harmful, and tremendously expensive.
275
276 In addition to these clinical considerations, disease misclassification due to reliance on PCWP
277 may influence the results of clinical trials. For example, the modest mean treatment effects
278 noted in most randomized trials of approved treatments for PAH may be attributable, in part, to
279 the enrollment of heterogeneous patient populations. If only some enrolled patients are afflicted
280 with diseases likely to respond to these therapies, summary treatment effect estimates would be

biased toward the null and would not reflect the treatment benefits that true PAH patients might achieve.

The implications of this study depend, in part, on the mechanisms that account for the poor correspondence between PCWP and LVEDP in patients with pulmonary hypertension. One possibility is that the observed measurement errors are attributable to fundamental alterations of the pulmonary vascular bed among patients with pulmonary hypertension that make it difficult to obtain an accurate PCWP.[5] However, this explanation seems unlikely because the poor calibration and moderate discrimination of PCWP were similarly evident among patients without pulmonary hypertension.

Second, it is possible that PCWP systematically underestimates LVEDP in all patients. This conclusion is supported by the consistent underestimation noted in our study among patients with and without pulmonary hypertension, as well as by smaller studies showing that PCWP underestimates LVEDP in the contexts of acute myocardial infarction[18] and generalized critical illness.[19] However, the width of the limits of agreement in the Bland-Altman analysis and the consistently poor fit of the regression slope between PCWP and LVEDP suggest that systematic bias is not the only problem. Thus, clinicians cannot overcome this problem simply by adding a set value to the PCWP to better estimate LVEDP or by using a different PCWP cutpoint.

Rather, the observed measurement variability suggests that PCWP is genuinely unreliable in estimating left-ventricular filling pressure, that physicians err in measuring PCWP or LVEDP, or that both of these explanations are true. These hypotheses have been offered previously in

attempts to explain the consistently negative or null effects of right-heart catheterization to guide therapy in many critically ill populations,[20-25] including patients with left-ventricular disease.[24]

The present study is limited by our inability to directly review the hemodynamic tracings from the catheterizations because they were not routinely stored during the study period. Thus, we cannot exclude the possibility that although PCWP was recorded as a mean pressure, LVEDP may have been recorded following the A wave in some patients. This could cause PCWP to underestimate LVEDP. Other measurement errors, however, are unlikely to explain our results. Contrast injection for ventriculography or coronary angiography might artificially elevate the LVEDP, but LVEDP was measured before contrast injection in this study. Additionally, although physicians did not routinely confirm proper wedge position by measuring pulmonary venous saturation with the balloon inflated,[5] difficulties obtaining a proper wedge position in patients with pulmonary hypertension should cause PCWP to *overestimate* LVEDP, whereas we found the opposite. Furthermore, because these "wedge saturations" are not routinely performed in most settings, our results may reflect current practice more generally.

A second limitation of this study is that the use of deidentified data precluded assessment of whether discrepancies between PCWP and LVEDP were particularly common when the catheterizations were performed by specific physicians. However, the validity and generalizability of our results are supported by the similar findings of Soto and colleagues[10] at a different institution.

Third, we were unable to evaluate whether specific subgroups of patients were particularly likely to have discrepant PCWP and LVEDP values. Patients with left ventricular diastolic dysfunction (e.g., older patients with long-standing systemic hypertension), may be particularly likely to have PVH despite a low PCWP measurement.[17] Because the de-identified nature of our data precluded confirmation of this hypothesis, future studies are needed to determine whether certain patient characteristics can be used to help clinicians determine when discrepancies between PCWP and LVEDP are likely to be present.

Conclusions

Some might conclude from our results that LVEDP should be measured routinely among all patients referred for catheterization as part of an evaluation for pulmonary hypertension. However, this approach carries increased risks and inconveniences for patients as well as increased costs and resource utilization. We therefore suggest a more conservative approach in routine practice in which clinicians obtain left-heart hemodynamic measurements whenever there are reasons to suspect left-heart disease based on the patient's history or physical exam, whenever the diagnosis is uncertain following right-heart catheterization, and when patients do not show favorable responses to initial therapy. If future studies identify types of patients who are particularly likely to have discrepancies between PCWP and LVEDP, then combined catheterization may represent a prudent initial diagnostic approach in such patients.

Ultimately, a randomized trial may be needed to determine whether treatment guided by combined catheterizations leads to improved patient-centered outcomes such as quality of life, symptom control, or mortality; such evidence would provide the strongest possible justification

for routinely measuring LVEDP. Indeed, such an approach may prove to be cost-effective or even cost-saving if it helps prevent the needless and potentially dangerous prescription of expensive PAH therapies.

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418

Legend to Figure 1

RHC, right-heart catheterization; LHC, left-heart catheterization; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure.

Legend to Table

Percentages reflect proportions within rows. PAH, pulmonary arterial hypertension; PVH, pulmonary venous hypertension; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; TPG, transpulmonary gradient.

427 **Legend to Figure 2**

428 PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure.

Legend to Figure 3

*Difference represents PCWP – LVEDP, Average represents (PCWP + LVEDP)/2. Larger circles represent identical observations among multiple patients. Mean bias = -2.9 mmHg (95% CI = -3.0 – -2.7); Limits of agreement = -15.2 – 9.5 mmHg. PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure.

Legend to Figure 4

Area under receiver-operating characteristic curve (AUROC) = 0.84 (95% CI = 0.81 – 0.86) using a cutpoint of LVEDP of ≤15 mmHg to indicate PAH. If a cutpoint of LVEDP ≤ 10 mmHg were used, the AUROC would be 0.86 (95% CI = 0.82 – 0.91). If a cutpoint of LVEDP ≤ 20 mmHg were used, the AUROC would be 0.81 (95% CI = 0.80 – 0.83). Sens, sensitivity for the outcome of LVEDP > 15 mmHg; Spec, specificity for the outcome of LVEDP > 15 mmHg; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure.

Figure 1: Flow diagram

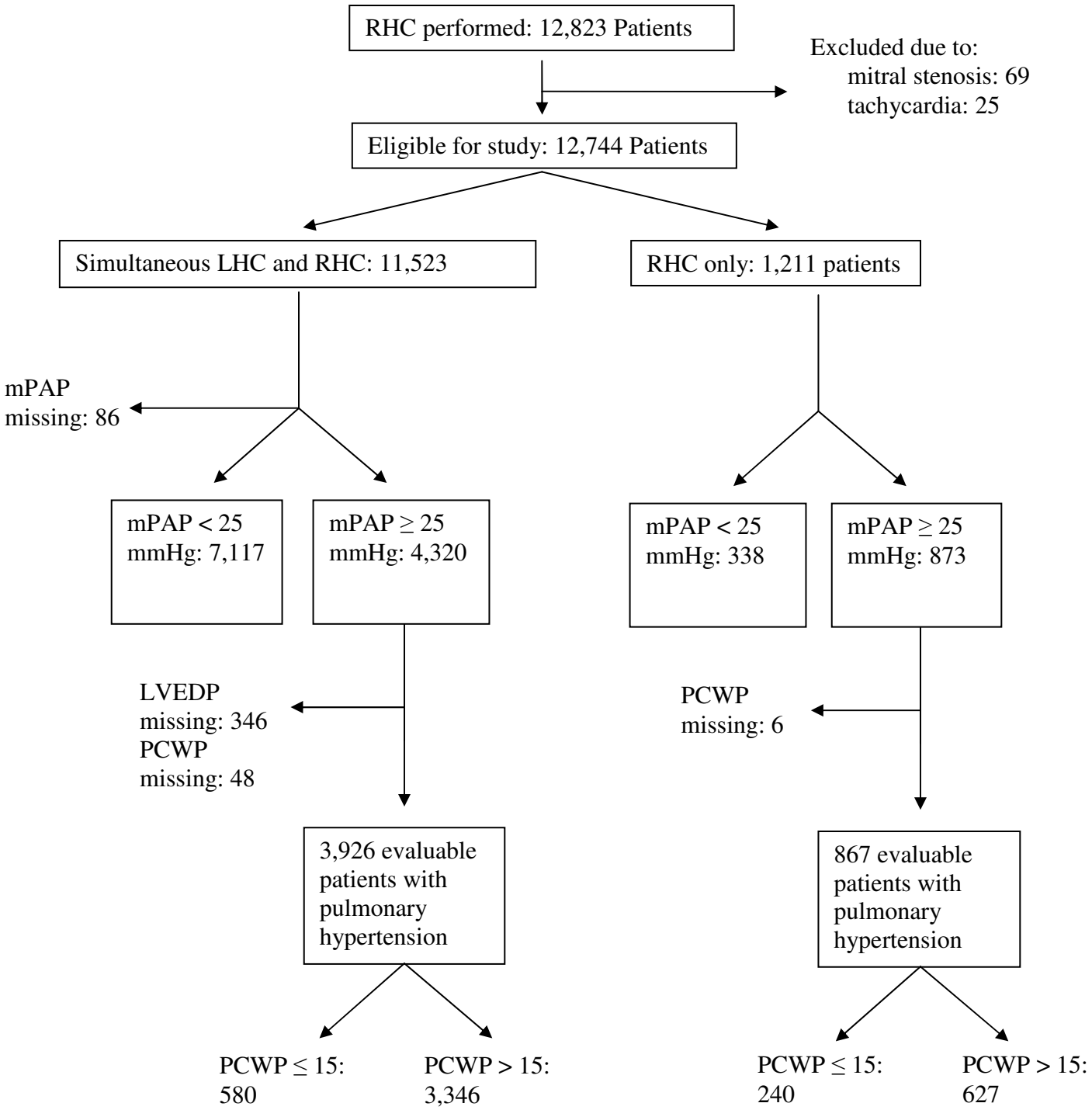

Table: Classification of PAH using PCWP or LVEDP

A. All patients with pulmonary hypertension

	PAH by LVEDP ≤ 15	**PVH** by LVEDP > 15	**Total**
PAH by PCWP ≤ 15	270 (46.5%)	310 (53.5%)	**580**
PVH by PCWP > 15	152 (4.5%)	3,194 (95.5%)	**3,346**
Total	**422**	**3,504**	**3,926**

B. Patients with pulmonary hypertension and PVR > 3

	PAH by LVEDP ≤ 15	**PVH** by LVEDP > 15	**Total**
PAH by PCWP ≤ 15	213 (59.0%)	148 (41.0%)	**361**
PVH by PCWP > 15	65 (8.6%)	690 (91.4)	**755**
Total	**278**	**842**	**1,116**

C. Patients with pulmonary hypertension and TPG ≥ 12

	PAH by LVEDP ≤ 15	**PVH** by LVEDP > 15	**Total**
PAH by PCWP ≤ 15	247 (50.0%)	247 (50.0%)	**494**
PVH by PCWP > 15	61 (7.8%)	743 (92.2)	**806**
Total	**310**	**990**	**1,300**

Figure 2: Scatter plot of PCWP and LVEDP among 3,926 patients with pulmonary hypertension

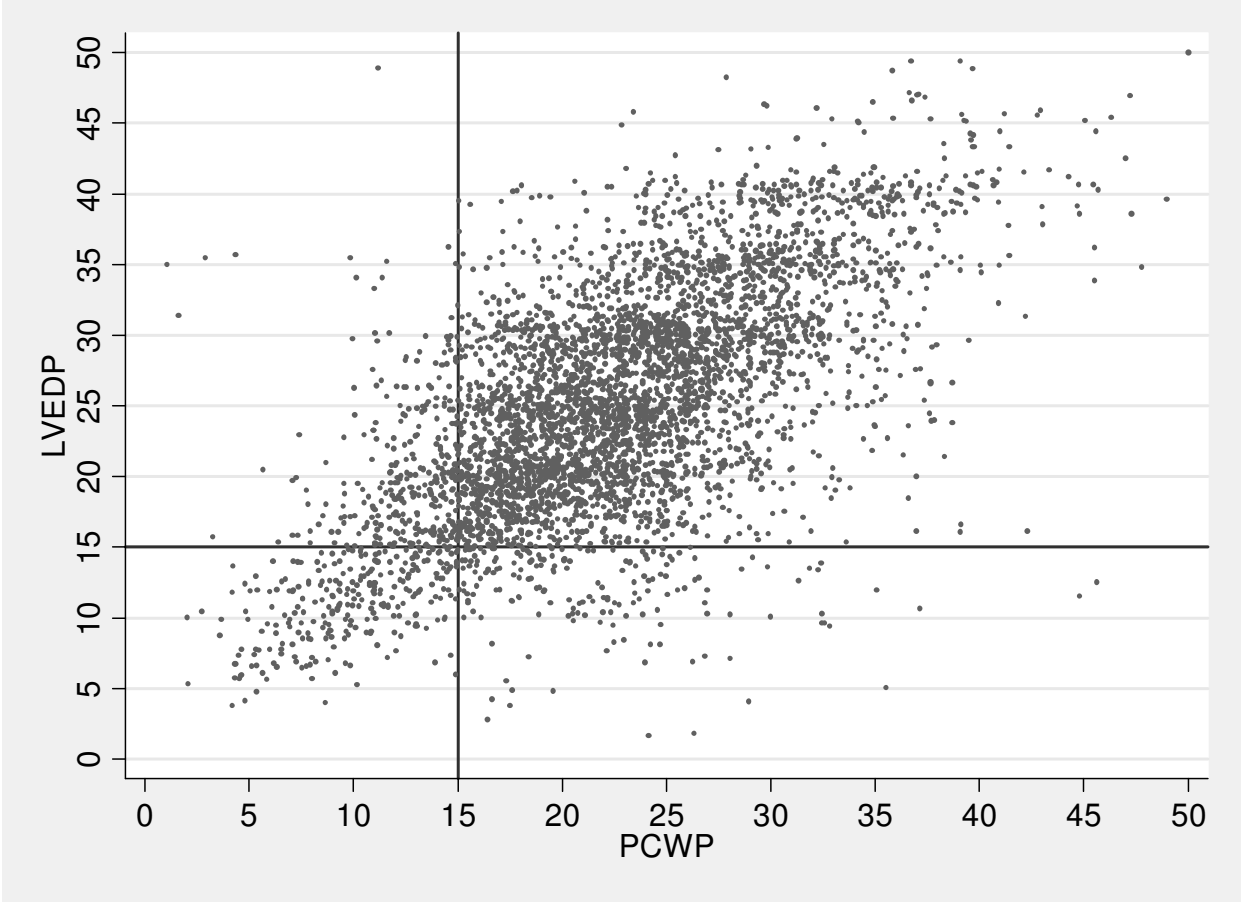

Figure 3: Bland-Altman plot of PCWP and LVEDP among 3,926 patients with pulmonary hypertension

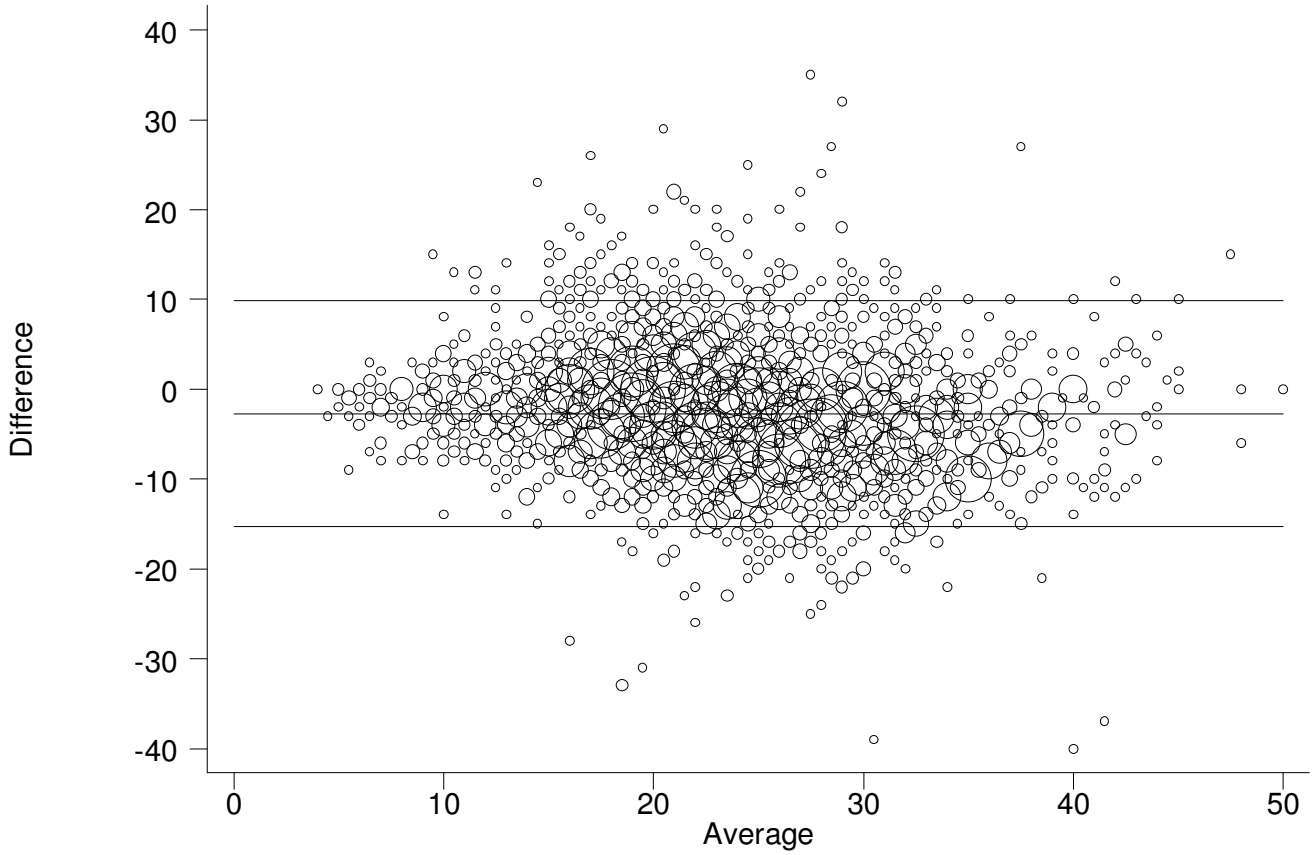

Figure 4: Receiver operating-characteristic curve of PCWP against LVEDP among 3,926 patients with pulmonary hypertension

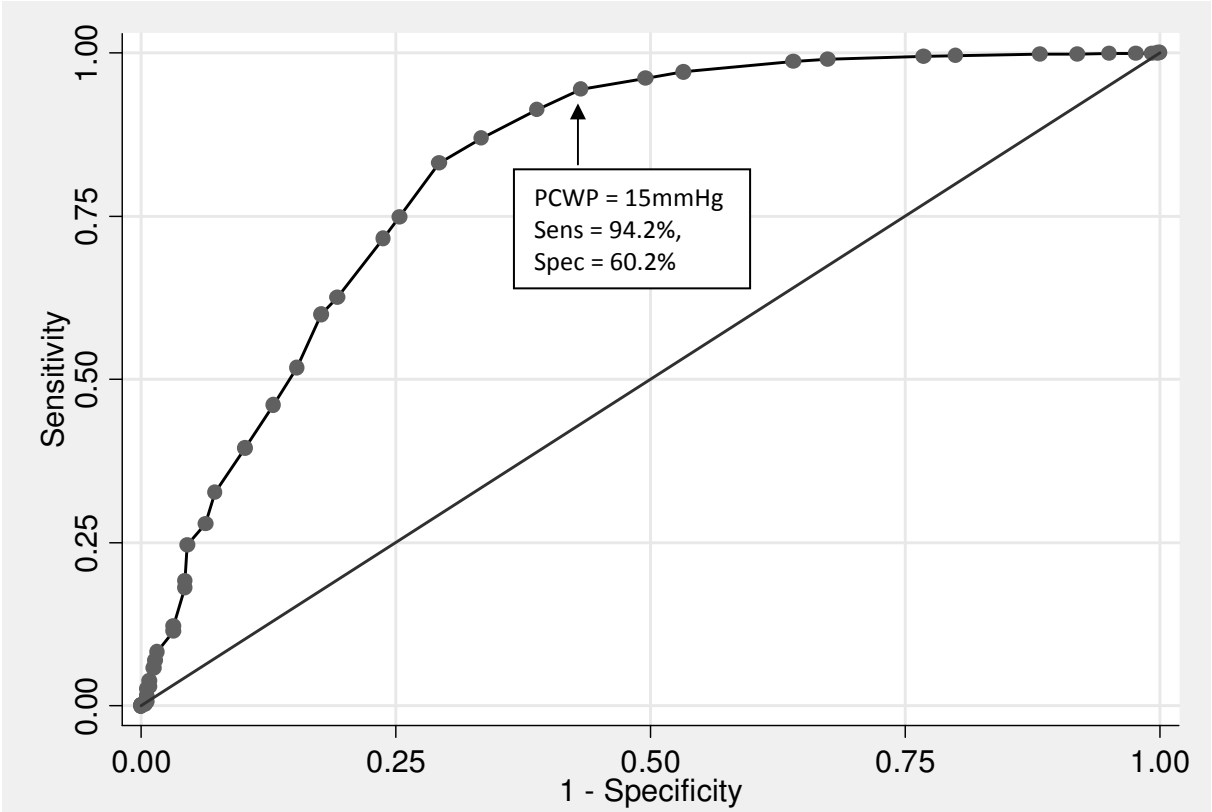

Figure 1: Flow diagram

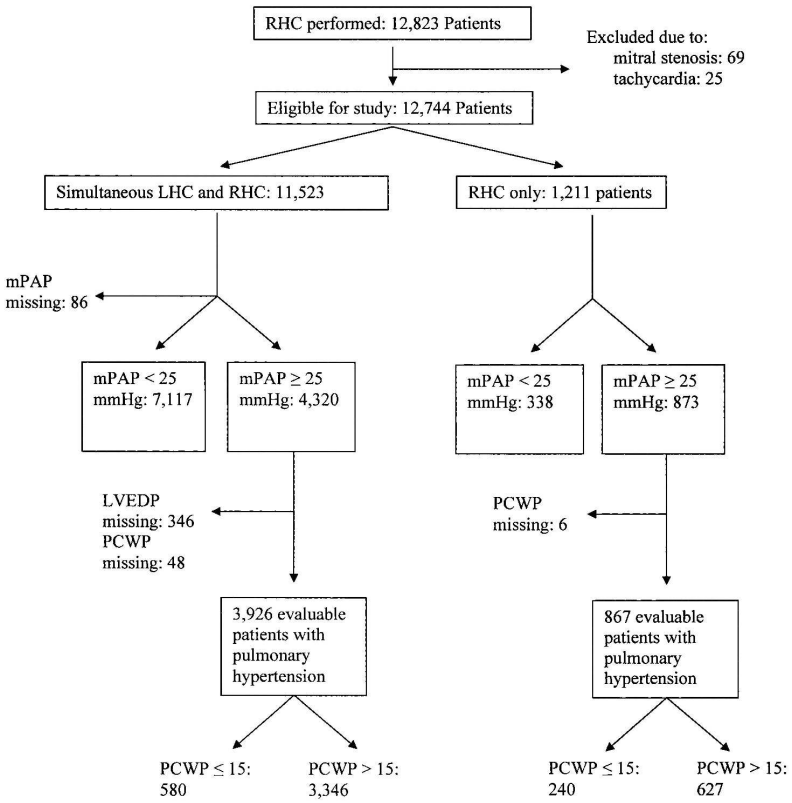

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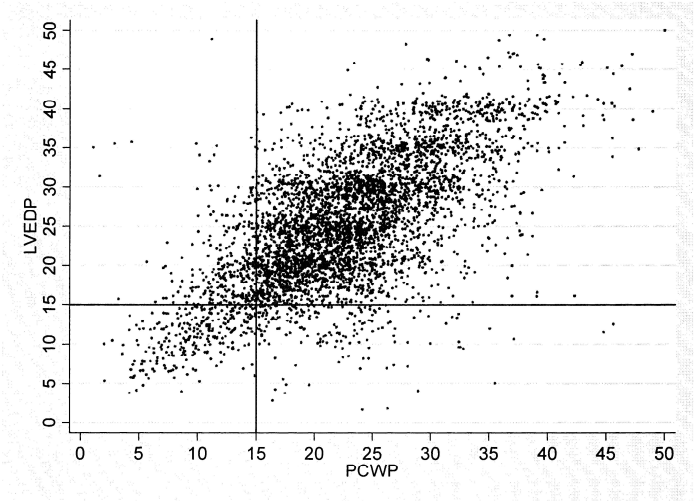
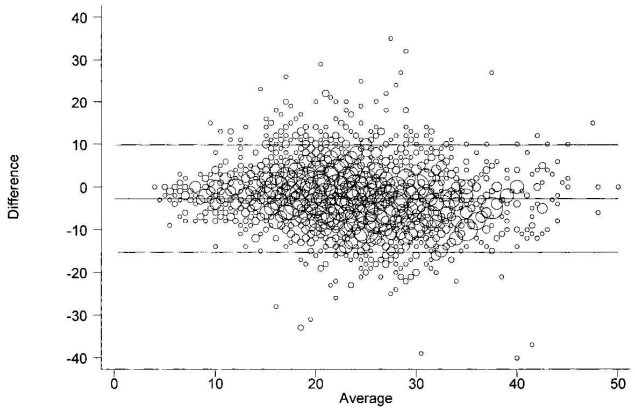
Figure 2: Scatter plot of PCWP and LVEDP among 3,926 patients with pulmonary hypertension



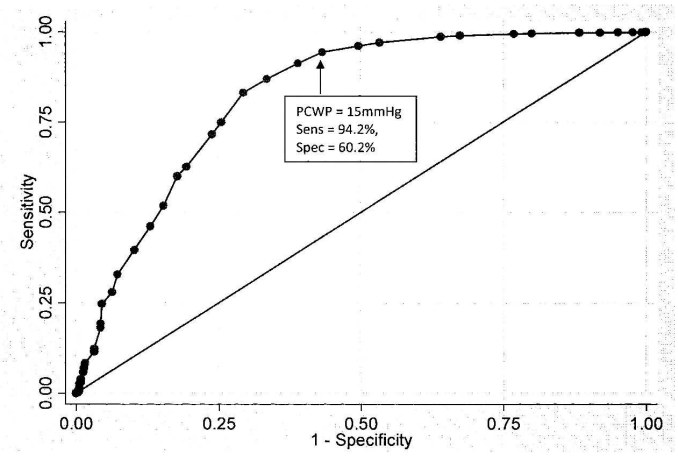
215x283mm (600 x 600 DPI)

Figure 3: Bland-Altman plot of PCWP and LVEDP among 3,926 patients with pulmonary hypertension



215x283mm (600 x 600 DPI)

Figure 4: Receiver operating-characteristic curve of PCWP against LVEDP among 3,926 patients with pulmonary hypertension



215x283mm (600 x 600 DPI)

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Chest; Prepublished online March 2, 2009;
DOI 10.1378/chest.08-2784