Journal of the American Heart Association

ORIGINAL RESEARCH

Clinical Characteristics of Patients Undergoing Right Heart Catheterizations in Community Hospitals

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BACKGROUND: Recognition of precapillary pulmonary hypertension (PH) has significant implications for patient management. However, the low a priori chance to find this rare condition in community hospitals may create a barrier against performing a right heart catheterization (RHC). This could result in misclassification of PH and delayed diagnosis/treatment of precapillary PH. Therefore, we investigated patient characteristics and echocardiographic parameters associated with the decision whether to perform an RHC in patients with incident PH in 12 Dutch community hospitals.

METHODS AND RESULTS: In total, 275 patients were included from the OPTICS (Optimizing PH Diagnostic Network in Community Hospitals) registry, a prospective cohort study with patients with incident PH; 157 patients were diagnosed with RHC (34 chronic thromboembolic PH, 38 pulmonary arterial hypertension, 81 postcapillary PH, 4 miscellaneous PH), while 118 patients were labeled as probable postcapillary PH without hemodynamic confirmation. Multivariable analysis showed that older age (>60 years), left ventricular diastolic dysfunction grade 2–3, left atrial dilatation were independently associated with the decision to not perform an RHC, while presence of prior venous thromboembolic events or pulmonary arterial hypertension-associated conditions, right atrial dilatation, and tricuspid regurgitation velocity ≥3.7 m/s favor an RHC performance.

CONCLUSIONS: Older age and echocardiographic parameters of left heart disease were independently associated with the decision to not perform an RHC, while presence of prior venous thromboembolic events or pulmonary arterial hypertension-associated conditions, right atrial dilation, and severe PH on echocardiography favored an RHC performance. As such, especially elderly patients may be at an increased risk of diagnostic delays and missed diagnoses of treatable precapillary PH, which could lead to a worse prognosis.

Key Words: diagnosis ■ elderly ■ pulmonary hypertension

See Editorial by Ryan et al.

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Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025143

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Older age is associated with the decision to abstain from performing a right heart catheterization, independently from known risk factors for precapillary pulmonary hypertension.

What Are the Clinical Implications?

- Not performing a right heart catheterization in older patients may contribute to diagnostic delays and missed diagnoses of treatable precapillary pulmonary hypertension, possibly leading to a worse prognosis.
- By knowing the key factors associated with the performance of a right heart catheterization in community hospitals, we can raise awareness of the possibility of precapillary pulmonary hypertension in older patients.

Nonstandard Abbreviations and Acronyms

CTEPH	chronic thromboembolic pulmonary hypertension
LA	left atrial
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
RA	right atrial
RHC	right heart catheterization
TRV	tricuspid regurgitation velocity

Pulmonary hypertension (PH) is relatively common in prevalent disorders such as chronic lung disease and left heart failure. At the same time, PH can point to the presence of a much rarer but treatable condition, such as pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH).[1,2] While routine radiology, pulmonary function testing, and echocardiography reveal most cases of chronic lung disease and left heart disease with systolic or valvular dysfunction as a cause of PH, it is much more challenging to differentiate between PAH, CTEPH, and PH attributable to heart failure with preserved ejection fraction.[3] The ultimate distinction often requires the performance of an invasive right heart catheterization (RHC) with measurement of the pulmonary arterial wedge pressure. PAH and CTEPH are forms of precapillary PH, diagnosed when the pulmonary arterial wedge pressure is ≤15 mm Hg.[1] In patients with suspected postcapillary PH, routine RHC is not recommended[3] and usually reserved for those listed for (transplant) surgery. While the identification of PAH and CTEPH has significant implications for patient management, the low a priori chance to find these rare conditions against the backdrop of a high prevalence of postcapillary PH, may create a barrier against performing an invasive RHC. This diagnostic dilemma is particularly felt in community hospitals, where the access to RHC may be limited and treatable precapillary PH is rarely seen. However, not performing an RHC in some patients could lead to a delay in diagnosis, misclassification of PH and withholding treatment for precapillary PH. Deaño et al already showed that one third of patients referred to PH centers for a diagnosis, initially received a misdiagnosis and were often referred late (World Health Organization functional class III and IV disease).[4]

It is currently unknown how clinicians in community hospitals deal with this diagnostic challenge and what factors determine their clinical decision whether or not to perform an RHC. Over the past 20 years, the time from onset of symptoms up to receiving the correct diagnosis of PH has not significantly decreased.[2] Therefore, it is essential to understand clinical decision making in community hospitals to improve the current diagnostic work-up for patients with PAH and CTEPH. We aimed to determine the patient characteristics and echocardiographic parameters associated with the performance of an RHC in the diagnostic work-up of patients with incident PH seen in community hospitals.

METHODS

Patients and Study Design

The authors declare that all supporting data are available within the article [and its online supplementary files]. Clinical characteristics of patients with incident PH prospectively enrolled in the Dutch OPTICS (Optimizing PH Diagnostic Network in Community Hospitals) registry between January 2015 and January 2019 were analyzed. The OPTICS network is a network of 12 community hospitals located in different regions in the Netherlands (see Figure S1), originally set up for external validation of the OPTICS risk score[5] and to optimize referral patterns for patients with (suspected) PH. The network of community hospitals is set up around 1 PH referral center at the Amsterdam University Medical Centre. Each community hospital in the network assigns a local multidisciplinary PH team consisting of at least 1 cardiologist and 1 pulmonologist. Members of the network attend annual meetings at the Amsterdam University Medical Centre to be updated on the diagnosis and treatment of PH. Because the OPTICS risk score predicting the presence of postcapillary PH was externally validated and communicated in the network in January 2019,[5] later patient entries were not included in the current analysis. The registry has been approved by the local

ethics committees of the participating hospitals and the analysis described in this paper was not considered to fall within the scope of the Medical Research Involving Human Subjects (WMO) (approval number 2014326). All requirements of the hospital research and ethical review board were met and no informed consent statement was required for entry into the registry.

Entry criteria for inclusion in the registry are (1) suspected PH on echocardiography (tricuspid regurgitation velocity [TRV] ≥2.8 m/s and/or other echocardiographic signs of PH), (2) uncertainty about the cause of PH (ie, possible precapillary PH, warranting multi-disciplinary consultation), and (3) incident cases, defined by either absence of signs of PH on previous echocardiography or RHC, or no previous investigations for PH performed. Patients with a likely diagnosis of PH attributable to systolic left heart failure (left ventricular ejection fraction <50%) or significant valvular heart disease (more than mild at PH diagnosis) according to current guidelines[6,7] are excluded from the registry. However, patients with mild to moderate left valvular heart disease were included in case of uncertainty about the cause of PH.

All patients discussed by the local PH team were anonymously entered in an online registry (part of PAHtool, Inovoltus, Portugal). The majority of variables entered in this registry were dichotomously stored (graded present/absent, except age, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity (E/e'), ratio of early diastolic mitral inflow velocity to late diastolic mitral peak A velocity (E/A), NT-proBNP [N-terminal pro-B-type natriuretic peptide], and TRV). This set-up of the registry was chosen to cater to the busy schedule of the local physicians who preferred a quick enrollment in the study. By dichotomization, the true judgement/interpretation of the local physician was captured. In the current study, patients with a likely diagnosis of group 3 PH were also excluded, because a lack of benefit from PAH specific treatment usually renders RHC unnecessary in these patients. Diagnosis of PH and PH classification in all patients followed current guidelines.[1] The classical definition of PH (mean pulmonary artery pressure ≥25 mm Hg) was still in use at the time of data entry and can be considered as more relevant to the decision to perform an RHC, because the revised definition (mean pulmonary artery pressure >20 mm Hg) currently has no therapeutic consequences. All patients with a high suspicion of PAH/CTEPH were referred to an expert center for additional screening and treatment.

Role of Patient Characteristics and Echocardiographic Parameters in the Diagnostic Work-Up

To identify patient characteristics and echocardiographic parameters which are associated with the decision to perform an RHC, a comparison was made between patients who did or did not undergo a diagnostic RHC. If a patient was referred to another expert center for RHC instead of the Amsterdam University Medical Centre, these results were also captured in the registry. All available patient demographics, presence of comorbidities and parameters derived from transthoracic echocardiography were compared between groups. Conditions associated with PAH (graded as present/absent) included connective tissue disease, HIV infection, drug abuse, liver cirrhosis, congenital heart disease, and schistosomiasis. Transthoracic echocardiography was performed according to current guidelines.[8] The majority of measurements were dichotomously (ie, present or absent) entered in our registry by the local cardiologist. The presence of grade 1–3 diastolic dysfunction was measured during PH work-up by the local cardiologist according to current guidelines, using early diastolic mitral inflow velocity (E), late diastolic mitral peak A velocity (A), early diastolic mitral annular tissue velocity (e'), E/A and the E/e' ratio.[9] When atrial fibrillation was present, diastolic dysfunction was measured using Septal ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity (≥11).[9]

The effect of patient characteristics and echocardiographic parameters on the decision to perform an RHC was investigated with univariable- and multivariable logistic analysis. To ensure a fair comparison in these analysis, categorical and continuous variables were dichotomized. Diastolic dysfunction was classified dichotomously as overt diastolic dysfunction (grade 2–3) or absence/grade 1 diastolic dysfunction. This distinction was made because patients with precapillary PH frequently have risk factors for left ventricular diastolic dysfunction and may experience (mild) left ventricular diastolic dysfunction.[10,11] In addition, the cut-off TRV ≥3.7 m/s (equivalent of mean pulmonary artery pressure ≥40 mm Hg) was reported as a measure of moderate to severe PH.[12] The cut-off NTproBNP >300 ng/L was used as a measure of intermediate risk used in current PH guidelines.[1] The cut-off age >60 years was chosen because this cut-off is an independent predictor of heart failure with preserved ejection fraction (cause of postcapillary PH) and used in the H2FPEF score.[13]

Arguments for Not Performing a Right Heart Catheterization

To explore whether other factors than the collected patient characteristics and echocardiographic parameters affected the diagnostic work-up of patients with PH, arguments to abstain from performing an RHC were collected by means of an email to the local health care providers. Only the arguments for not performing an RHC were collected, because in these instances diagnoses

of treatable precapillary PH were potentially missed. For all 118 patients who did not receive an RHC, the following open question was asked to the local health care providers via email: "Which factors have guided you in the decision not to perform an RHC in this patient?". All members of the local PH team were asked this question, they were aware that their answers were part of the study. For all the 118 answers via email a thematic analysis was conducted.[14] Initial coding analysis of each answer was performed independently by Samara M.A. Jansen and Anna E. Huis in 't Veld. First, interesting features of the arguments were coded. Secondly, potential themes were made out of the collected codes. The codes and potential themes of each argument were discussed by the 2 researchers and modified until they reached agreement. After agreement, the main themes were derived. The emails were repeatedly read to check whether the derived themes were consistent with the data.

Statistical Analysis

Continuous variables are presented as mean±SD or median (interquartile range) and categorical variables as absolute numbers (%). Between-group differences were tested using 2-sided *t*-tests or Chi-square tests, after visually checking for normal distributions. Univariable logistic regression was performed to test the association between various patient characteristics and RHC performance as dependent variable. For this analysis all measurements were dichotomously (present or absent) entered, as mentioned in sections 2.1 and 2.2. The influence of potential confounders in the relationship between patient characteristics and RHC performance was explored by conducting multivariable logistic analysis selecting all univariable predictors (P <0.1). Once the full multivariable model was created, stepwise backward elimination was performed. The multivariable analysis was reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[15] In all analyses, a P value of <0.05 was considered statistically significant. Missing data were handled in the univariable/multivariable logistic analysis by using case-wise deletion.

RESULTS

Study Population

Clinical data from 275 patients in the OPTICS registry was used (Figure 1). RHC was used to come to a final diagnosis in 157 patients; this included 81 cases of postcapillary PH and 76 cases of potentially treatable precapillary PH (27% of the original population and 48% of those undergoing RHC). Thirty-eight precapillary cases were ultimately classified as PAH, 34 as CTEPH, and 4 as PH attributable to miscellaneous conditions. One hundred eighteen patients did not undergo RHC and all were labeled by the local teams, on the basis of clinical determination, as most likely postcapillary PH (Figure 1). Mean age of the total cohort was 71±12 years. Patient characteristics are presented in Table 1. Patients in whom no RHC was performed were on average 9 years older (76±9 versus 67±12 years, P<0.001), were predominantly

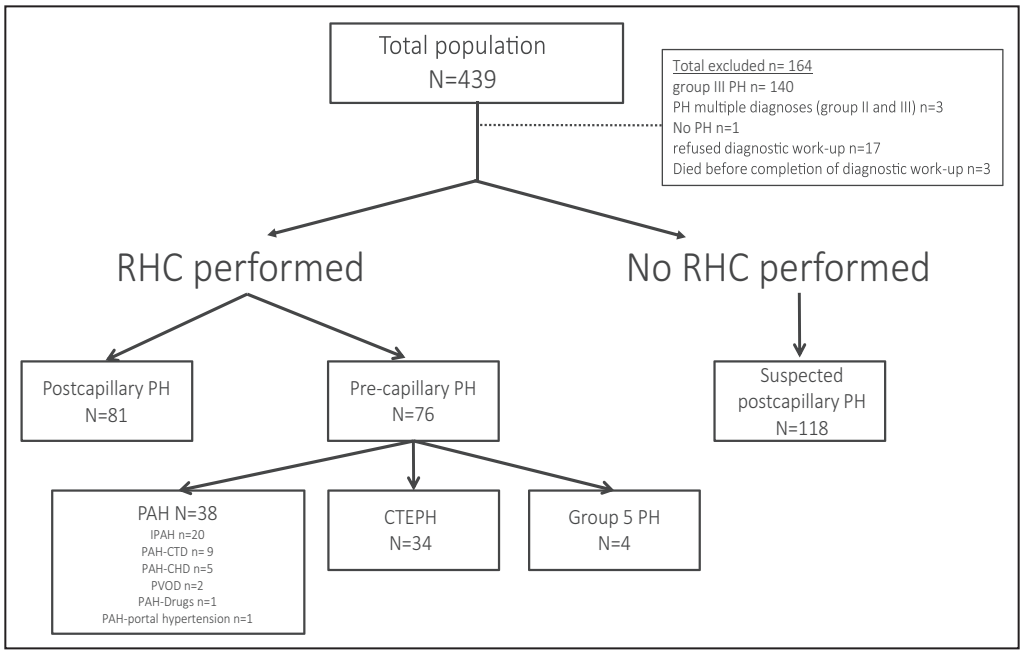

Figure 1. Flowchart representing patients' numbers and study methods.
CTEPH indicates chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and RHC, right heart catheterization.

Table 1. Characteristics of Patients in Whom RHC is Performed Versus No RHC

	RHC not performed	RHC performed	*P* value
Patients, n	118	157	
Sex (Women), n (%)	83 (70%)	82 (52%)	0.004
Age, y	76±9	67±12	<0.001
BMI, kg/m^2	28.6±5.6	29.7±6.8	0.218
Comorbidities			
Hypertension, n (%)	99 (84%)	114 (73%)	0.038
Hypercholesterolemia, n (%)	49 (42%)	60 (38%)	0.667
Diabetes, n (%)	34 (29%)	40 (25%)	0.631
Coronary artery disease, n (%)	33 (28%)	44 (28%)	1.000
Obesity, n (%)	38 (32%)	57 (36%)	0.562
AF, n (%)	58 (49%)	44 (28%)	0.001
COPD, n (%)	14 (12%)	23 (15%)	0.623
Prior VTE, n (%)	8 (7%)	41 (26%)	<0.001
PAH-associated conditions, n (%)	4 (3%)	32 (21%)	<0.001
No. of comorbidities*	3 [2–4]	3 [2–4]	0.760
Echocardiography			
LV hypertrophy, n (%)	39 (33%)	39 (25%)	0.715
LA dilatation, n (%)	89 (75%)	76 (48%)	<0.001
TRV ≥3.7 m/s, n (%)	10 (8%)	50 (32%)	<0.001
TRV (m/s)	3.2±0.3	3.5±0.6	<0.001
RV dilatation, n (%)	34 (29%)	83 (53%)	<0.001
RA dilatation, n (%)	57 (48%)	91 (58%)	0.032
Overt diastolic dysfunction grade 2–3, n (%)	38 (32%)	25 (16%)	<0.001
E/e'	11.7 [9.6–15.1]	9.9 [6.5–12.8]	0.002
E/A	1.1 [0.8–1.5]	0.8 [0.6–1.1]	<0.001
NT-proBNP >300 ng/L, n (%)	51 (43%)	81 (52%)	0.906
NT-proBNP (ng/L)	1150 [444–2635]	1281 [509–3049]	0.703

Data are given as mean (SD), median (interquartile range) or percentages (%). AF indicates atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; E/e', ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity; E/A, ratio of early diastolic mitral inflow velocity to late diastolic mitral peak A velocity; LA, left atrial; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RA, right atrial; RHC, right heart catheterization; RV, right ventricular; TRV, tricuspid regurgitation velocity; and VTE, venous thromboembolic event.

*Total number of comorbidities (min 0-max 9). PAH associated causes included: (connective tissue disease, congenital heart disease, liver cirrhosis, HIV, drug abuse).

women, and had more comorbidities such as atrial fibrillation (all *P* values <0.05). As shown in Table 1, left atrial (LA) dilatation and overt diastolic dysfunction grade 2–3 were more often present in patients who did not undergo RHC, while right ventricular dilatation and right atrial (RA) dilatation were more pronounced in patients in whom RHC was performed (all *P* values <0.05). Additionally, RHC was more commonly performed in patients with moderate to severe PH on echocardiography (TRV ≥3.7 m/s) and with a history of venous thromboembolic events (VTE) or PAH-associated conditions. Comparing the characteristics of patients who had confirmed postcapillary PH via RHC to patients with presumed postcapillary PH without RHC, patients with confirmed postcapillary PH were younger (69 versus 76, *P* ≤0.001) and had higher pressures (TRV ≥3.7 m/s, 21% versus 8%, *P*=0.034), Table S1.

Clinical Factors Associated With a Diagnostic Work-Up Using RHC

Univariable and multivariable logistic analyses were done to investigate patient characteristics and echocardiographic parameters associated with the decision to perform RHC. Some variables used in the univariable/multivariable analysis had missing data. For example, on a total of 275 patients the gradation of diastolic dysfunction was not available in 69 patients and LA dilatation was missing in 34 cases. These values were missing because they were not measured on echocardiography or the image quality was poor and therefore no conclusion could be made. Univariable logistic analysis demonstrated that older age (>60 years), sex (women), left ventricular diastolic dysfunction, LA dilatation, atrial fibrillation, and hypertension were associated with the decision to forgo RHC. In contrast, the presence of RA

dilatation, right ventricular dilatation, and TRV ≥3.7 m/s on echocardiography, prior VTE, and PAH-associated conditions were associated with performing RHC (Table 2 and Figure 2). Subsequently, backward multivariable logistic regression analysis was performed, including the parameters with a predictive *P* value <0.1. In multivariable analyses, only age >60 years, diastolic dysfunction grade 2–3, LA dilatation, TRV <3.7 m/s, absence of prior VTE or PAH-associated conditions, and absence of RA dilatation remained significantly associated with the decision not to perform RHC (Table 2). No independent predictive value of sex (women) was observed. Figure 3 shows the distribution of RHC performance according to these 6 independent predictors. RHC was performed in only 17 (27%) patients >80 years. Nine of these patients (53%) were diagnosed with precapillary PH after RHC (5 CTEPH, 3 PAH attributable to connective tissue disease, and 1 idiopathic PAH). In contrast, 86% of patients aged <60 years (32 patients) underwent RHC and precapillary PH was diagnosed in 18 cases (56%) after RHC (8 CTEPH, 5 IPAH, 1 pulmonary veno occlusive disease, 2 PAH with congenital heart disease, 1 PAH attributable to drug intoxication and 1 PAH attributable to connective tissue disease). In addition, prior VTE was an independent predictor of RHC performance. In the group of patients with an RHC performance patients with precapillary PH had more often a history of VTE compared with patients with postcapillary PH (37% versus 16%, *P*=0.006).

Argument Not to Perform RHC According to the Health Care Providers

To explore whether other arguments than the collected patient characteristics and echocardiographic parameters affected the diagnostic work-up of patients with PH, local health care providers were asked to indicate the factors that had played a role in their decision not to perform RHC. In total, 118 patients did not receive an RHC and of those patients arguments for not performing RHC were collected. All 24 physicians responded with arguments for these patients, there were no missing cases. As shown in Figure 4, evident diastolic dysfunction was the dominant argument against RHC in the majority of cases (39%). In 23% of patients, older age was one of the main reasons not to perform an

Table 2. Univariable and Multivariable Analysis of Predictors for the RHC Performance

	Univariable analysis			Multivariable analysis			
	Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value	Chi-square value
Age >60 y	0.17	0.07–0.43	<0.001	0.19	0.06–0.66	0.008	<0.001
Overt diastolic dysfunction grade 2–3	0.31	0.16–0.58	<0.001	0.43	0.50–0.92	0.029	0.007
LA dilatation	0.33	0.19–0.57	<0.001	0.41	0.19–0.90	0.026	0.007
Atrial fibrillation	0.40	0.24–0.67	<0.001				
Sex (Women)	0.46	0.28–0.76	0.003				
Systemic hypertension	0.51	0.28–0.93	0.028				
NT-proBNP >300 ng/L	0.85	0.34–2.14	0.726				
Diabetes	0.85	0.49–1.44	0.537				
Hypercholesterolemia	0.87	0.54–1.42	0.579				
LV hypertrophy	0.88	0.50–1.51	0.613				
Coronary artery disease	1.00	0.59–1.71	0.991				
No. of comorbidities	1.04	0.89–1.23	0.577				
Obesity	1.25	0.75–2.07	0.392				
COPD	1.28	0.63–2.60	0.504				
RA dilatation	1.78	1.08–2.94	0.024	3.04	1.37–6.73	0.006	0.006
RV dilatation	2.98	1.76–5.05	<0.001				
Prior VTE	4.90	2.20–10.92	<0.001	3.57	1.23–10.38	0.019	0.014
TRV ≥3.7 m/s	6.52	3.12–13.64	<0.001	3.52	1.41–8.82	0.007	<0.001
PAH-associated conditions	7.34	2.52–21.44	<0.001	4.03	1.01–16.16	0.049	0.033

Variables entered in the backward stepwise model in the multivariable analysis: Age above 60 years, overt diastolic dysfunction grade 2–3, left atrial dilatation, atrial fibrillation, women, systemic hypertension, right atrial dilatation, right ventricular dilatation, tricuspid regurgitation velocity ≥3.7 m/s, prior venous thromboembolic event, pulmonary arterial hypertension-associated conditions. COPD indicates chronic obstructive pulmonary disease; LA, left atrial; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PAH, pulmonary arterial hypertension; RA, right atrial; RHC, right heart catheterization; RV, right ventricle; TRV, tricuspid regurgitation velocity; and VTE, venous thromboembolic event.

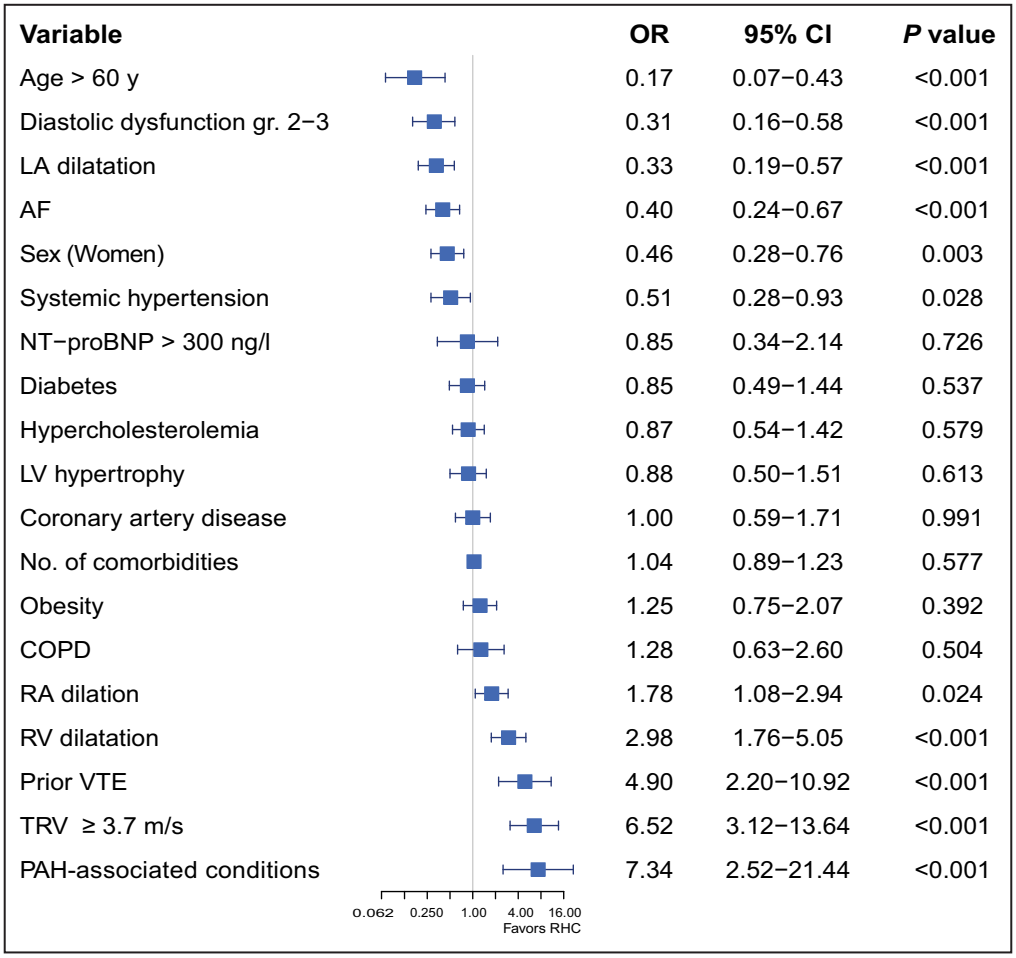

Figure 2. Univariable predictors for right heart catheterization performance.
AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; LA, left atrial; LV, left ventricular; OR, odds ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RA, right atrial; RV, right ventricular; and TRV, tricuspid regurgitation velocity.

RHC. Factors such a frailty and mild symptoms led to a decision to forgo an RHC in older patients only (9% and 16%, respectively). These patients had some signs of diastolic dysfunction, but this was not the main reason to forgo an RHC. In only 6% of cases, patient preferences determined the decision to abstain from performing an RHC. An overview of quotes and themes on the open question on what factors played a role in the decision not to perform a right heart catheterization is shown in Table S2. One patient was referred for RHC after re-evaluating her case, but the RHC confirmed the prior tentative diagnosis of postcapillary PH.

DISCUSSION

We analyzed patient characteristics and echocardiographic parameters associated with the diagnostic work-up of patients with PH without overt chronic left heart disease or chronic lung disease in community hospitals to improve the current diagnostic work-up for patients with PAH and CTEPH. As expected, prior VTE, PAH-associated conditions and an echocardiographic suggestion of moderate to severe PH (TRV ≥3.7 m/s and RA dilatation) were independently associated with the decision to perform an RHC. The presence of overt diastolic dysfunction (grade 2–3) and LA dilatation did not favor RHC performance. Remarkably, older age (>60 years) was independently associated with the decision to abstain from RHC. In response to the open question for arguments against performing an RHC, older age was one of the main reasons reported by local clinicians. Therefore, especially elderly patients may be at an increased risk of diagnostic delays and missed diagnoses of treatable precapillary PH.

Risk factors for pre- and postcapillary PH are well-known.[1,3,6] However, it is much less clear how these risk factors guide local clinicians in their decision to perform an RHC and/or refer patients to an expert center. In the present study, we assessed patient

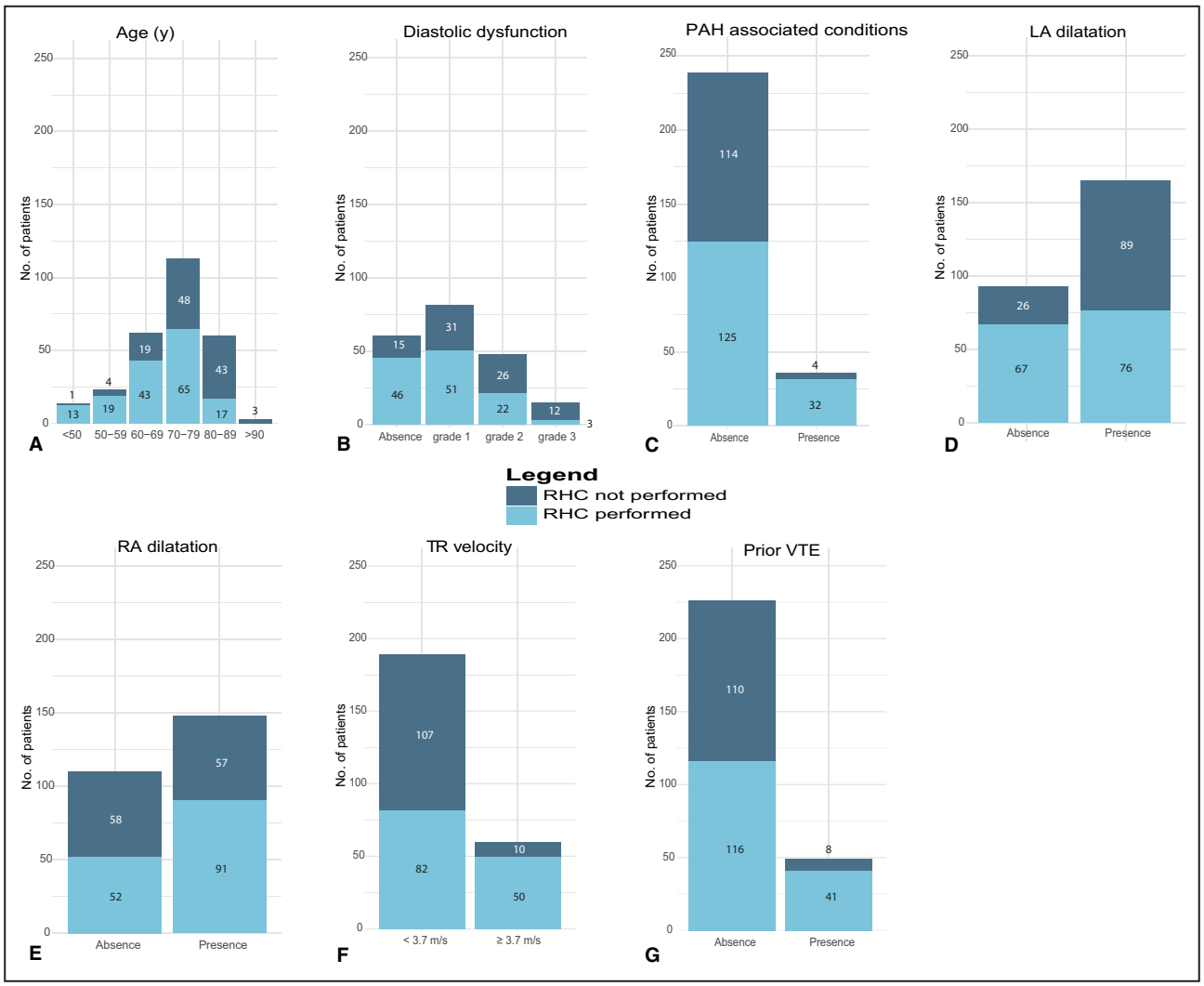

Figure 3. Independent predictors for the performance of right heart catheterization (RHC) in patients suspected of pulmonary hypertension.
A, Shows the number of patients with or without RHC according to the distribution of age. **B**, Shows the different stadia of diastolic dysfunction and within this group the number of RHC performance. **C**, The distribution of pulmonary arterial hypertension-associated conditions (present or absent) as an independent predictor for RHC performance. **D**, Shows the number of patients with or without RHC performance according to the presence or absence of RA dilatation on echocardiography. **E**, Shows that patients suspected of pulmonary hypertension with a tricuspid regurgitation velocity ≥3.7 m/s have more RHC performed. **F**, Highlights that patients with a prior venous thromboembolic event received more RHCs. **G,** focusses on the distribution of prior VTE in patient with of without a RHC. PAH indicates pulmonary arterial hypertension; RA, right atrial; TR, tricuspid regurgitation; and VTE, venous thromboembolic events.

characteristics and echocardiography parameters that affect the decision to perform an RHC. This knowledge could ultimately improve the current diagnostic work-up for patients with PAH and CTEPH. Of note, systolic or valvular left heart disease and chronic lung disease were excluded in all patients in the study. We confirmed several echocardiographic parameters as independent factors associated with the decision to perform an RHC.[1] RA dilatation and TRV ≥3.7 m/s are well established risk factors for PAH; for instance higher hemodynamic pressures (mean pulmonary artery pressure, ie, higher TRV) are found in PAH compared with postcapillary PH.[16–18] The fact that an RHC is less likely to be performed in patients with overt diastolic dysfunction grade 2–3 and/or LA dilatation is also in line with the current guidelines, in which presence of diastolic dysfunction/ LA dilatation is considered as a sign of left heart disease and thus increases the possibility of post-capillary PH.[1,6]

In the present study, we only included echocardiographic parameters which pointed towards precapillary and/or postcapillary PH. Another way to improve the diagnostic work-up of precapillary PH and to detect this condition in an earlier phase, is using a more sensitive screening modality. Cardiac magnetic resonance imaging could be the screening modality of choice to

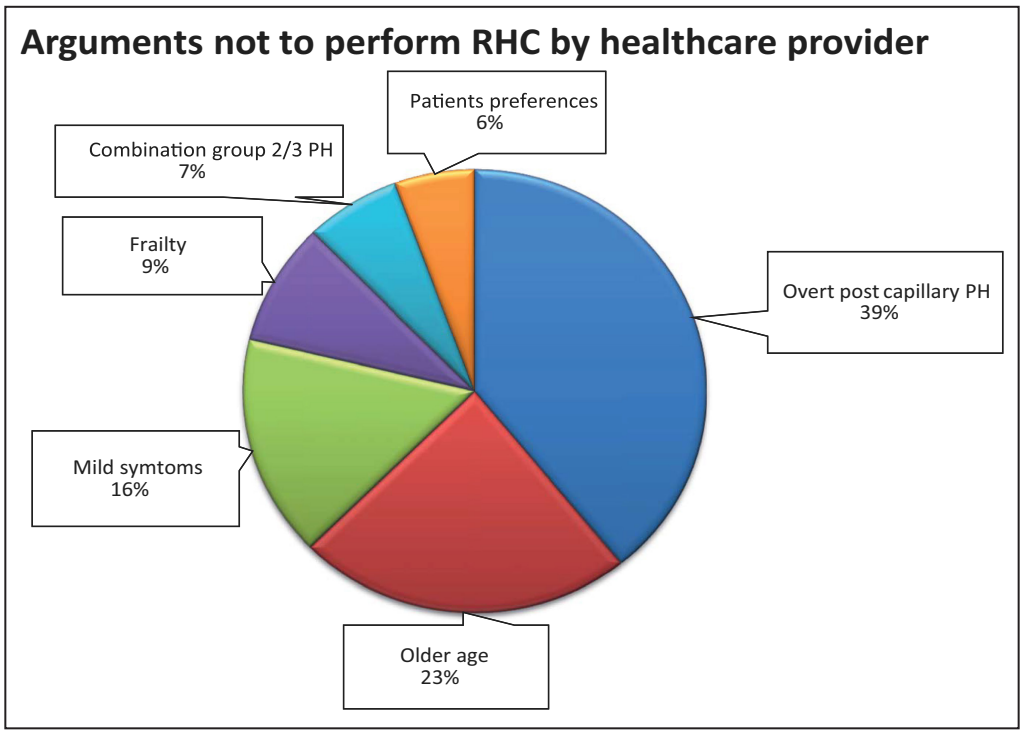

Figure 4. Arguments not to perform a right heart catheterization (RHC) by the health care provider.
PH indicates pulmonary hypertension.

detect early cardiac changes in PH. It provides not only information on global heart function (ventricular ejection fraction, ventricular volumes), but also regional heart function (wall motion).[19] Recent extensive improvements/developments in cardiac magnetic resonance imaging sequences and post-processing techniques enable better diagnostic accuracy in the onset stage of cardiovascular diseases.[20] However, for measuring diastolic dysfunction echocardiography is still the golden standard.[6] Furthermore, echocardiography is more affordable and more accessible. Not all centers, especially the community centers, have an MRI with cardiac modality available. Therefore, echocardiography would always be the screenings modality of choice in the work-up of patients with incident PH seen in community hospitals.

Remarkably, older age was an independent factor associated with the decision to forgo an RHC in the diagnostic work-up of local health care providers. This finding raises the concern that RHC is underutilized in the elderly. In the current era, patients with precapillary PH are older at diagnosis and present with more comorbidities.[21–23] It is known that comorbidities can mask symptoms of PAH, leading to a delay in the correct diagnosis.[24,25] Humbert et al showed that 9% of the population in PH centers in France were >70 years at the time of diagnosis.[26] PAH attributable to connective tissue disease is also frequently seen in older patients, for example 57% of scleroderma patients >60 years developed PAH.[27] In addition, CTEPH is a disease of older age with a mean age ranging from 60 to 69 years.[28,29] Because left-sided heart disease is the main cause of PH in the elderly[17,30] and the pretest likelihood of precapillary PH in the elderly remains low, clinical scoring systems such as the OPTICS risk score may help to tailor the decision to perform an RHC.[5]

Not performing an RHC and misclassifying a patient with precapillary PH as having postcapillary PH has major consequences. Mclaughlin et al showed that in the work-up of patients with PAH an RHC was missing in 10% of cases (4% in academic centers and 16% in community centers).[31] The V/Q scan, which is recommended for excluding CTEPH, was not done in 43% of patients (36% in academic centers and 51% in community centers).[31] Both diagnostic test are essential in the work-up of patients with a possible diagnosis of patients with precapillary PH. Humbert et al showed that early diagnosis (ie, World Health Organization functional class I/II) is important for a better prognosis in patients with PAH.[32] This is also important for CTEPH, as it is the only curable subgroup of PH. Pulmonary endarterectomy may cure most patients with CTEPH with an estimated 3-years survival of 93%.[33] In patients who do not undergo treatment (ie, pulmonary endarterectomy, balloon pulmonary angioplasty or medication) for CTEPH, severe functional

limitations, poor quality of life, and a worse prognosis is at play.[33,34] Early diagnosis of CTEPH and referral to an expert center for treatment is therefore essential to improve prognosis or to cure the disease.

One important remaining question is whether identifying precapillary PH in the elderly leads to effective treatment. Previous research has shown that CTEPH can be treated effectively in the elderly.[35,36] Garcia-Alonso et al showed that response to and complications from treatment with balloon pulmonary angioplasty or pulmonary endarterectomy are comparable between older and younger patients.[37] It therefore remains of paramount importance to consider acute or chronic thromboembolism in all incident patients with PH and perform the appropriate imaging study, as indicated in the diagnostic algorithm from the sixth world symposium of PH.[2] Like CTEPH, PAH is treatable in elderly patients.[23–25] Hoeper et al reported that after 1 year of therapy 23% (87 patients) of patients with PAH >65 years were in functional class I/II compared with 4.5% (17 patients) at baseline.[23] Several studies have shown, however, that older patients diagnosed with idiopathic PAH usually do not receive upfront combination therapies or prostacyclins, whether or not related to side effects and drug discontinuations.[23,25,38] Despite the low pretest likelihood of precapillary PH in the elderly, older age should not be one of the main reasons not to perform RHC as treatment could still be effective when used carefully. Because many randomized clinical trials systematically excluded elderly patients with PH with comorbidities, more clinical studies are needed to address the benefit of PAH treatment in the geriatric population.

Limitations

Several limitations in this study need to be recognized. Although the OPTICS registry encompasses a high number of relevant clinical parameters, some missed variables may also have played a role in the decision to perform RHC. However, by including arguments from the local health care providers we limited the likelihood of missing clinically relevant variables. In addition, most of the variables were entered in our registry as dichotomous values, making the inclusion process fast and easy for local physicians. The interpretation of these variables could be slightly different among physicians working at different community hospitals. However, via these dichotomous variables the true judgement of the local physicians was captured. We used for our statistical analysis a stepwise backward elimination approach with variables with a P value ≤0.1 in the univariable logistic analysis. We are aware that this method has limitations.[39] Centers included in the OPTICS registry are not necessarily representative for other community hospitals in- or outside the Netherlands. The educational sessions and training provided to physicians in the OPTICS network may have influenced the quality of patient care and the availability of RHC. It may be expected that the relative underutilization of RHC in the elderly is more prevalent outside of the OPTICS network.

CONCLUSIONS

Older age (>60 years) and echocardiographic parameters of left heart disease (LA dilatation and diastolic dysfunction grade 2–3) were independently associated with absence of an RHC in the clinical work up, while presence of prior VTE- or PAH-associated conditions, RA dilation and severe PH on echocardiography were associated with an RHC performance in patients with incident PH without evident left heart or lung disease. As such, especially older age could contribute to diagnostic delays and missed diagnoses of treatable precapillary PH, possibly leading to a worse prognosis. The performance of an RHC in the elderly may be even lower outside a network of hospitals as used in this study.

ARTICLE INFORMATION

Received January 3, 2022; accepted April 19, 2022.

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Acknowledgments

Author contributions: The Conceptualization of this project was done by Prof. Dr. Anton Vonk Noordegraaf and Prof. Dr. Harm Jan Bogaard. The Methodology of this study was created by Dr. Frances S. de Man, Prof. Dr. Harm Jan Bogaard and Prof. Dr. Anton Vonk Noordegraaf. The Formal Analysis for this manuscript was done by Dr. Samara M.A. Jansen and Dr. Anna E. Huis in 't Veld. Investigations for this manuscript were done by Dr. Samara M.A. Jansen and Dr. Anna E. Huis in 't Veld. The data used in this manuscript were collected by Dr. Peter Hans C.G. Tolen, Dr. Wouter Jacobs, Dr. H.M. Willemsen, Dr. Hans P. Grotjohan, Dr. Marc Waskowsky, Dr. Jan van der Maten, Dr. Arno van der Weerdt, Dr. Romke Hoekstra, Dr. Ana J. Perez Matos, Dr. Maria J. Overbeek, Dr. Sjoerd A. Mollema, Dr. Lahssan H. Hassan El Bouazzaoui, Dr. Joris W.J. Vriend, Dr. J. Milena M. Roorda, Dr. Ramon de Nooijer, Dr. Ivo van der Lee, Dr. A.J. Voogel, Dr. Johannes C. Post, Dr. Thomas Macken, Dr. Jacqueline M. Aerts, Dr. Marjo J.T. van de Ven, Dr. Heidi Bergman, Dr. Mirjam Bakker-de Boo, and Dr. Roline C. de Boer. The manuscript was prepared and written by Dr. Samara M.A. Jansen and Dr. Anna E. Huis in 't Veld, thereafter it was reviewed and edited by all coauthors. Supervision was done by Dr. Frances S. de Man, Prof. Dr. Harm Jan Bogaard and Prof. Dr. Anton Vonk Noordegraaf. All authors have read and agreed to the published version of the manuscript.

Sources of Funding

This work was supported by the Netherlands Cardiovascular Research Initiative: An initiative with the support of the Dutch Heart Foundation (CVON2018-29 PHAEDRA-IMPACT).

Disclosures

H.J.B. and A.V.N. received unrestricted research support for the OPTICS registry from Actelion, Merck Sharp & Dohme, Ferrer, and GlaxoSmithKline. A.V.N. was supported by NWO-VICI [Netherlands Organisation for Scientific Research] (2002406). The remaining authors have no disclosures to report.

Supplemental Material

Tables S1-S2
Figure S1

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Supplemental Material

Table S1. Comparison characteristics of patients who had a right heart catheterisation (RHC) and confirmed post-capillary pulmonary hypertension (PH) to patients with presumed post-capillary PH without RHC.

	Presumed post-capillary PH without RHC	Post-capillary PH with RHC performance	P-value
Patients n	118	81	
Sex (Female), n (%)	83 (70%)	48 (59%)	0.142
Age (years)	76 ± 9	69 ± 11	<0.001
BMI (kg/m^2)	28.6 ± 5.5	31.2 ± 7.3	0.004
NYHA functional class (I/II/III/IV) (n)	32/62/16/3	2/34/32/3	<0.001
Comorbidities			
Hypertension, n (%)	99 (84%)	71 (88%)	0.594
Hypercholesterolemia, n (%)	49 (42%)	42 (52%)	0.196
Diabetes, n (%)	34 (29%)	30 (37%)	0.287
Coronary artery disease, n (%)	33 (28%)	30 (37%)	0.232
Obesity, n (%)	38 (32%)	38 (47%)	0.051
AF, n (%)	58 (49%)	33 (41%)	0.305
COPD, n (%)	14 (12%)	16 (20%)	0.185
VTE, n(%)	8 (7%)	13 (16%)	0.059
PAH risk factors, n(%)	4 (3%)	9 (11%)	0.058
Number of comorbidities*	3 [2-4]	3 [2-5]	0.006
Echocardiography			
LV hypertrophy, n (%)	39 (33%)	21 (36%)	0.941
LA dilation, n (%)	89 (75%)	56 (70%)	0.319
TRV ≥ 3.7 m/s, n (%)	10 (8%)	14 (21%)	0.034
RV dilation, n (%)	34 (29%)	29 (40%)	0.371
RA dilation, n (%)	57 (48%)	42 (55%)	0.597
Overt diastolic dysfunction grade 2-3, n (%)	38 (32%)	20 (25%)	0.206
NT-proBNP >300 ng/l, n (%)	51 (43%)	41 (51%)	0.907

Data are given as mean (SD), median (IQR) or percentages (%). * total number of comorbidities (min 0-max 9). Bold values are statistically significant. AF: atrial fibrillation, BMI: body mass index, LVH: left ventricular hypertrophy, LA: left atrial, RA: right atrial, RV: right ventricular, TRV: tricuspid regurgitation velocity.

Table S2. Overview of quotes and themes regarding the open question what factors played a role in the decision not to perform a right heart catheterisation.

Theme	Number of mentions, (n)	Results/Quotes
Overt post-capillary PH	n=70	"Based on the presence of left atrial dilatation and diastolic dysfunction grade II is group 2 PH considered as final diagnosis and a RHC unnecessary." "Based on left branch bundle block on ECG, high E/e', older age and systemic hypertension in medical history is left-sided heart failure considered as cause of PH." "PH caused by left heart disease such as mild valvular heart disease, ischemic cardiomyopathy, LAVI 66 and decreased left ventricular systolic function during follow-up. No therapeutic consequences with/without a RHC partly due to older age."
Older age	n=42	"It was a very elderly woman. After recompensation therapy with diuretics by her cardiologist she was much better." "due to older age and already treated with anticoagulation a RHC would not have clinical consequences. " "Based on left atrial dilatation and older age post-capillary PH would be the obvious cause of PH."
Mild symptoms	n=29	"Normal pulmonary artery pressures with follow-up, mild symptoms and overt post-capillary PH." "Clinically only a few complaints in combination with older age, therefore a conservative approach was performed. " "No complaints and diastolic dysfunction/ HFpEF most obvious cause of PH."
Frailty	n=16	"Based on older age and overall fragile condition a RHC was not performed." "Based on impaired cognition and older age". "Wheelchair bound with extensive comorbidities, died in 2017 and did not prefer a RHC."
Combination group 2/ 3 PH	n=12	"Clearly post-capillary PH, but also combined with group 3 PH due to obstructive sleep apnoea syndrome." "Mildly elevated pulmonary artery pressures caused by obesity hypoventilation syndrome in combination with post-capillary PH." "Diastolic dysfunction in combination with COPD."
Patients preferences	n=10	"Other comorbidities, overall poor condition and patient did not preferred a RHC procedure". "No RHC performed at request of the patient. " "Patient did not want any further diagnostics, possible post-capillary PH based on atrial fibrillation for which a pacemaker and diastolic dysfunction."

Figure S1. Situation map of the Dutch OPTICS network.

The yellow point represents the Amsterdam UMC location Vrije Universiteit. Point 1 represents Spaarne Gasthuis at Hoofddorp, point 2 is Haaglanden medical centre at The Hague, point 3 represents Haga hospital at The Hague, point 4 is Jeroen Bosch hospital at ‘s Hertogensbosch, point 5 represents Catharina hospital at Eindhoven, point 6 is Rijnstate at Arnhem, point 7 represents Gelre hospital at Apeldoorn, point 8 is Ziekenhuisgroep Twente at Almelo, point 9 represents Isala at Zwolle, point 10 is Antonius hospital at Sneek, point 11 represents Medical centre Leeuwarden at Leeuwarden and point 12 is Martini hospital at Groningen. The small dots around the hospital signifies other annexes of the hospital.