Evaluation of pulmonary hypertension by right heart catheterisation: does timing matter?

To the Editor:

Haemodynamic measurements from right heart catheterisation (RHC) are used for diagnosis and risk stratification in pulmonary hypertension (PH) [1]. The risk stratification scheme implemented in the guidelines for pulmonary arterial hypertension (PAH) has been validated in real-life cohorts [1–5]. However, the timing of measurements during RHC is not specified. We aimed to investigate the influence of the timing of measurements on RHC parameters and the consequences for risk stratification and diagnosis.

We retrospectively investigated patients in the Giessen PH Registry [6]. Incident patients referred for diagnostic RHC between February 2010 and August 2017 were included, with most of the relevant RHC measurements (listed below) available at two consecutive time points: immediately after placing the sheath correctly (baseline-1) and after the patient had rested for a short period (baseline-2). Some patients had further RHC measurements after a second resting period (baseline-3). To exclude methodological issues, zero levelling was re-evaluated for all baselines and, if necessary, corrected [7–9]. However, in most cases the position of the pressure transducer was not changed. RHC was performed by experts who were not blinded to the clinical data or previous measurements. Almost all procedures were performed using the right jugular vein with ultrasound and local anaesthesia. All patients were diagnosed according to the current guidelines [1] using RHC measurements obtained at baseline-2. All diagnoses of PH were assessed by a multidisciplinary board. Patients were followed until December 2018 for survival analysis. The investigation conforms with the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Medicine at the University of Giessen. All participating patients gave written informed consent to be enrolled in the Giessen PH Registry.

RHC measurements included right atrial pressure (RAP), cardiac output (CO, direct Fick method or thermodilution if direct Fick was not available), cardiac index (CO/body surface area), mean pulmonary arterial pressure (mPAP), pulmonary artery wedge pressure (PAWP), pulmonary vascular resistance (PVR) and mixed venous oxygen saturation (S_{vO_2}). All vascular pressures were measured at end-expiratory breath hold for 5–7 s. Risk stratification was based on cardiac index, S_{vO_2} and RAP, to calculate a cumulative risk score [2, 3]. Statistical analyses were performed using R (The R Foundation, Vienna, Austria) and SPSS (Version 26, IBM, Armonk, USA).

In total, 1093 patients were included (median age 72.5 years, interquartile range 60.8–84.2 years; pulmonary venous hypertension (PVH), n=341; PH due to lung diseases (LD-PH), n=253; chronic thromboembolic PH (CTEPH), n=132; PAH, n=114; miscellaneous PH, n=44; PH excluded by RHC, n=209). The mean±SD duration between baseline-1 and the start of baseline-2 measurements was 21±9 min. 66 patients had baseline-3 values (mean duration between the start of baseline-2 and baseline-3 measurements: 25±17 min).

The difference in mPAP between baseline-1 and baseline-2 was 1.17±3.40 mmHg, while the difference in PAWP was 0.47±2.85 mmHg (both $p<0.001$). Diagnosis or exclusion of PH changed between baseline-1 and baseline-2 in 61 patients (5.6%). Of 773 patients with mPAP ⩾25 mmHg at baseline-1, 51 (6.6%) had mPAP <25 mmHg at baseline-2. Of 320 patients with mPAP <25 mmHg at baseline-1, 10 (3.1%) had mPAP ⩾25 mmHg at baseline-2 (PVH, n=3; LD-PH, n=5; CTEPH, n=1; miscellaneous PH, n=1).

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In patients undergoing right heart catheterisation, the timing of haemodynamic measurement after sheath insertion (immediately or after a short resting period) influences the diagnosis, classification and risk stratification of pulmonary hypertension https://bit.ly/2yHN9xq

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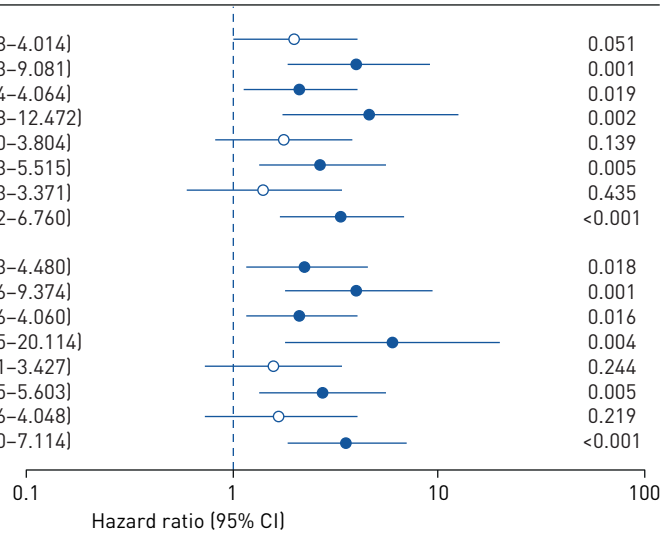
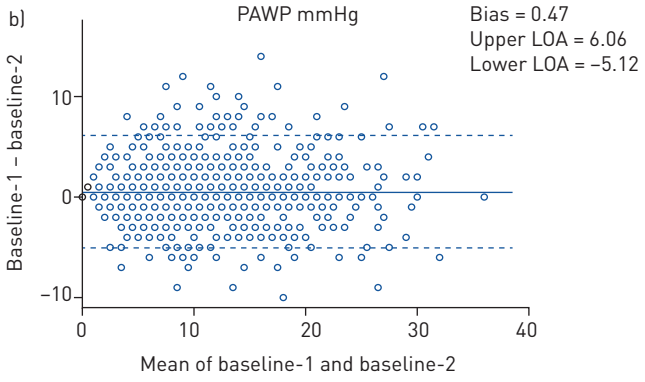
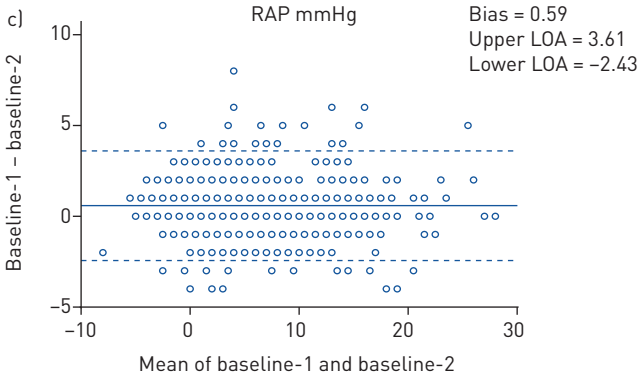
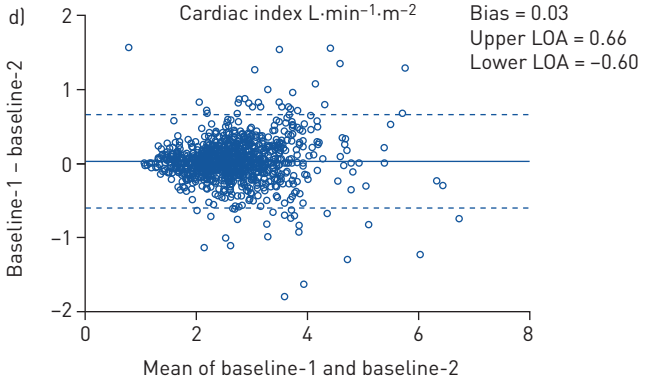
a)

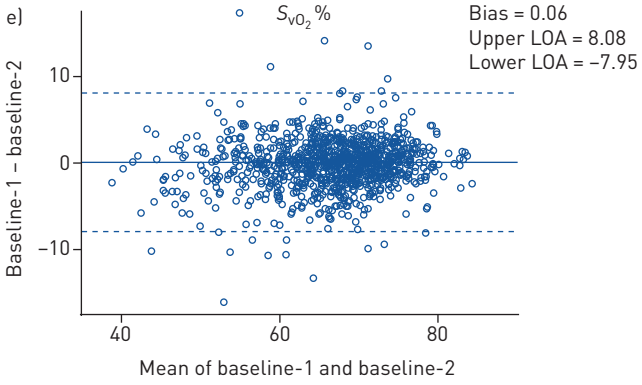
Parameter	Risk class	Hazard ratio (95% CI)	p-value
Univariate Cox regression at baseline-1			
Cumulative risk score	Intermediate	2.001 (0.998–4.014)	0.051
	High	4.068 (1.823–9.081)	0.001
RAP	Intermediate	2.146 (1.134–4.064)	0.019
	High	4.669 (1.748–12.472)	0.002
Cardiac index	Intermediate	1.777 (0.830–3.804)	0.139
	High	2.721 (1.343–5.515)	0.005
S_{vO_2}	Intermediate	1.414 (0.593–3.371)	0.435
	High	3.402 (1.712–6.760)	<0.001
Univariate Cox regression at baseline-2			
Cumulative risk score	Intermediate	2.273 (1.153–4.480)	0.018
	High	4.092 (1.786–9.374)	0.001
RAP	Intermediate	2.166 (1.156–4.060)	0.016
	High	6.009 (1.795–20.114)	0.004
Cardiac index	Intermediate	1.583 (0.731–3.427)	0.244
	High	2.756 (1.355–5.603)	0.005
S_{vO_2}	Intermediate	1.714 (0.726–4.048)	0.219
	High	3.628 (1.850–7.114)	<0.001











f)

Parameter	Bias	Upper LOA	Lower LOA
PAWP mmHg	–0.45	3.09	–3.98
RAP mmHg	0.17	3.40	–3.07
Cardiac index L·min^{-1}·m^{-2}	–0.04	0.48	–0.57
S_{vO_2} %	–0.97	4.77	–6.07

FIGURE 1 a) Univariate Cox regression of the cumulative risk score (using only haemodynamic parameters from the European Society of Cardiology/European Respiratory Society risk stratification scheme), right atrial pressure (RAP), cardiac index and mixed venous oxygen saturation (S_{vO_2}) in patients with pulmonary arterial hypertension. The cumulative risk score was a significantly better predictor of survival when applied to baseline-2 values instead of baseline-1 values (likelihood ratio test: p<0.001). b–e) Bland–Altman plots of haemodynamic parameters at baseline-1 and baseline-2. Horizontal axes show the average of baseline-1 and baseline-2 values; vertical axes show the difference between the two baseline values. f) Biases and limits of agreement (LOA) of pulmonary artery wedge pressure (PAWP), RAP, cardiac index and S_{vO_2} at baseline-2 and baseline-3.

Moreover, the categorisation of PH as pre- or post-capillary was influenced by the waiting period. Of 223 patients classified as having post-capillary PH (PAWP >15 mmHg [1, 10]) at baseline-1, 45 patients (20.2%) were classified with pre-capillary PH at baseline-2. Conversely, 21 of 596 patients (3.5%) with pre-capillary PH according to baseline-1 values were classified with post-capillary PH at baseline-2. Between baseline-2 and baseline-3, no patient changed between pre- and post-capillary PH.

The cumulative risk score changed between baseline-1 and baseline-2 in 154 patients (14.1%; PVH, n=54; LD-PH, n=28; CTEPH, n=25; PAH, n=20; miscellaneous PH, n=10; PH excluded by RHC, n=17). Using baseline-2 instead of baseline-1 data resulted in the reclassification of 6.1% of low-risk patients (n=636) as intermediate-risk, 3.8% and 12.6% of intermediate-risk patients (n=365) as high-risk and low-risk, respectively, and 20.7% of high-risk patients (n=92) as intermediate-risk. Overall, 9.4%, 15.6% and 16.1% of the patients changed their risk class based on RAP, cardiac index and S_{vO_2}, respectively. Regarding RAP, 23.3% of high-risk patients (n=73) and 21.7% of intermediate-risk patients (n=295) improved their risk class, whereas 2.2% and 1.4% of low- (n=723) and intermediate-risk patients, respectively, worsened. Regarding cardiac index, 13.7% and 16.3% of high- (n=182) and intermediate-risk patients (n=300) improved whereas 11.0% and 8.0% of low- (n=608) and intermediate-risk patients worsened. Regarding S_{vO_2}, 20.7% and 12.6% of high- (n=202) and intermediate-risk patients (n=192) improved, whereas 6.1% and 3.8% of low- (n=695) and intermediate-risk patients worsened. In patients with PAH, the cumulative risk class showed higher prognostic power at baseline-2 than at baseline-1; only the cumulative risk class at baseline-2 significantly predicted mortality in intermediate-risk patients (figure 1a). In patients who changed their risk class, baseline-2 values predicted 5-year survival more accurately than baseline-1 values (area under the receiver operating characteristic curve 0.722 (95% CI 0.514–0.930) *versus* 0.624 (95% CI 0.374–0.873)). The predictive values of RAP, cardiac index and S_{vO_2} are shown in figure 1a.

Bland–Altman plots showed no meaningful biases but wide limits of agreement between baseline-1 and baseline-2 (figure 1b–e). The precision of PAWP, cardiac index and S_{vO_2} improved between baseline-2 and baseline-3 (figure 1f), with no directionality in risk class changes (three patients improved and three worsened).

Our results indicate that haemodynamic measurements taken following a short resting period differ from those taken immediately after sheath insertion, altering diagnosis/exclusion of PH and categorisation of PH as pre- or post-capillary in subsets of patients and influencing risk stratification in PAH. Although Bland–Altman analysis revealed imprecision at each timepoint, these changes could be clinically meaningful in individuals. Baseline-2 measurements showed higher prognostic and discriminatory power than baseline-1. Of note, only arbitrary changes were observed between baseline-2 and baseline-3.

Spontaneous variability of RHC measurements was described decades ago [11, 12]. Rich *et al.* [11] assessed 12 patients hourly for six consecutive hours and observed spontaneous haemodynamic variability, analogous to our results, concluding that particularly mPAP, PVR and CO are time-dependent. Furthermore, variability of PAWP is a well-known reason for misclassification of PH [1, 13]. Our results showed a predominant direction of change between baseline-1 and baseline-2 in addition to the previously described intrinsic variability. Time-dependent differences of variability may be one possible explanation for these changes. However, due to imprecision at each time point, the usefulness of multiple measurements (as suggested in the guidelines [1]) should be questioned.

Our results suggest that defining a waiting period after sheath placement with consideration of the clinical context may help to standardise diagnosis, risk stratification and treatment decisions. However, our study is limited by its retrospective design, small number of patients with baseline-3 data and lack of blinding. Prospective studies are needed to identify the optimum time point of measurement. Nevertheless, we believe that allowing a short resting period between sheath placement and haemodynamic assessment in defined environmental conditions leads to an enhanced stratification of haemodynamic function and risk in patients with PH. In practice, this could be implemented by remeasuring mPAP, RAP and PAWP after measuring CO. We conclude that the timing of haemodynamic measurements after RHC sheath placement is of major importance and should be clarified in future guidelines.

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References

1 Galie N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J* 2015; 46: 903–975.
2 Delcroix M, Staehler G, Gall H, *et al.* Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. *Eur Respir J* 2018; 52: 1800248.
3 Hoeper MM, Kramer T, Pan Z, *et al.* Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J* 2017; 50: 1700740.
4 Kylhammar D, Kjellstrom B, Hjalmarsson C, *et al.* A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2018; 39: 4175–4181.
5 Boucly A, Weatherald J, Savale L, *et al.* Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017; 50: 1700889.
6 Gall H, Felix JF, Schneck FK, *et al.* The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups. *J Heart Lung Transplant* 2017; 36: 957–967.
7 Kovacs G, Avian A, Pienn M, *et al.* Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. *Am J Respir Crit Care Med* 2014; 190: 252–257.
8 Rosenkranz S, Preston IR. Right heart catheterisation: best practice and pitfalls in pulmonary hypertension. *Eur Respir Rev* 2015; 24: 642–652.
9 Kovacs G, Avian A, Olschewski A, *et al.* Zero reference level for right heart catheterisation. *Eur Respir J* 2013; 42: 1586–1594.
10 Humbert M, Montani D, Evgenov OV, *et al.* Definition and classification of pulmonary hypertension. *Handb Exp Pharmacol* 2013; 218: 3–29.
11 Rich S, D'Alonzo GE, Dantzker DR, *et al.* Magnitude and implications of spontaneous hemodynamic variability in primary pulmonary hypertension. *Am J Cardiol* 1985; 55: 159–163.
12 Packer M, Medina N, Yushak M. Hemodynamic changes mimicking a vasodilator drug response in the absence of drug therapy after right heart catheterization in patients with chronic heart failure. *Circulation* 1985; 71: 761–766.
13 LeVarge BL, Pomerantsev E, Channick RN. Reliance on end-expiratory wedge pressure leads to misclassification of pulmonary hypertension. *Eur Respir J* 2014; 44: 425–434.