

Complications of Right Heart Catheterization Procedures in Patients With Pulmonary Hypertension in Experienced Centers

Marius M. Hoeper, MD,* Stephen H. Lee, MD,† Robert Voswinckel, MD,‡ Massimiliano Palazzini, MD,§ Xavier Jais, MD,|| Alessandro Marinelli, MD,§ Robyn J. Barst, MD,¶ Hossein A. Ghofrani, MD,‡ Zhi-Cheng Jing, MD,|| Christian Opitz, MD,# Hans-Juergen Seyfarth, MD,** Michael Halank, MD,†† Vallerie McLaughlin, MD,‡‡ Ronald J. Oudiz, MD,§§ Ralf Ewert, MD,||| Heinrike Wilkens, MD,¶¶ Stefan Kluge, MD,## Hinrich-Cordt Bremer, MD,*** Eva Baroke,* Lewis J. Rubin, MD†

Hannover, Giessen, Berlin, Leipzig, Dresden, Greifswald, Homburg, Hamburg, and Freiburg, Germany; La Jolla and Torrance, California; Bologna, Italy; Clamart, France; New York, New York; and Ann Arbor, Michigan

OBJECTIVES	This study sought to assess the risks associated with right heart catheter procedures in patients with pulmonary hypertension.
BACKGROUND	Right heart catheterization, pulmonary vasoreactivity testing, and pulmonary angiography are established diagnostic tools in patients with pulmonary hypertension, but the risks associated with these procedures have not been systematically evaluated in a multicenter study.
METHODS	We performed a multicenter 5-year retrospective and 6-month prospective evaluation of serious adverse events related to right heart catheter procedures in patients with pulmonary hypertension, as defined by a mean pulmonary artery pressure >25 mm Hg at rest, undergoing right heart catheterization with or without pulmonary vasoreactivity testing or pulmonary angiography.
RESULTS	During the retrospective period, 5,727 right heart catheter procedures were reported, and 1,491 were reported from the prospective period, for a total of 7,218 right heart catheter procedures performed. The results from the retrospective and the prospective analyses were almost identical. The overall number of serious adverse events was 76 (1.1%, 95% confidence interval 0.8% to 1.3%). The most frequent complications were related to venous access (e.g., hematoma, pneumothorax), followed by arrhythmias and hypotensive episodes related to vagal reactions or pulmonary vasoreactivity testing. The vast majority of these complications were mild to moderate in intensity and resolved either spontaneously or after appropriate intervention. Four fatal events were recorded in association with any of the catheter procedures, resulting in an overall procedure-related mortality of 0.055% (95% confidence interval 0.01% to 0.099%).
CONCLUSIONS	When performed in experienced centers, right heart catheter procedures in patients with pulmonary hypertension are associated with low morbidity and mortality rates. (J Am Coll Cardiol 2006;48:2546–52) © 2006 by the American College of Cardiology Foundation

Invasive diagnostic tests, including right heart catheterization, pulmonary vasoreactivity testing, and pulmonary angiography, remain essential tools in the diagnosis and subsequent management of patients with pulmonary hypertension (1,2). Right heart catheterization is the only method that can definitively establish a hemodynamic diagnosis of pulmonary hypertension because it directly measures pulmonary artery pressure and cardiac function. For this reason, major clinical trials in pulmonary hypertension often require right heart catheterization to establish a definitive

diagnosis before study entry. In addition, repeat right heart catheterizations are often used to assess hemodynamic efficacy of novel treatments (3–10). However, the safety of right heart catheterization has never been formally assessed in an extensive multicenter evaluation, which is surprising because patients with severe pulmonary hypertension are hemodynamically fragile. Complications related to right heart catheterization in patients with pulmonary hypertension were reported in the literature soon after right heart catheterization was introduced into clinical medicine

From the *Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany; †Division of Pulmonary and Critical Care Medicine, University of California, San Diego Medical Center, La Jolla, California; ‡University of Giessen Lung Center, Department of Internal Medicine, Giessen, Germany; §Institute of Cardiology, University of Bologna, Bologna, Italy; ||Service de Pneumologie, Antoine Bécélère Hospital, South-Paris University, Clamart, France; ¶Columbia University College of Physicians and Surgeons, New York, New York; #Medizinische Klinik II–Kardiologie, DRK Kliniken Berlin Westend, Berlin, Germany; **Department of Pulmonary Medicine, University Leipzig, Leipzig, Germany; ††Internal Medicine I, University Hospital Carl Gustav Carus of Technical University Dresden, Dresden, Germany; ‡‡Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan

Health System, Ann Arbor, Michigan; §§Liu Center for Pulmonary Hypertension, Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, California; |||Department of Respiratory Medicine, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany; ¶¶Department of Respiratory Medicine, University of the Saarland, Homburg, Germany; ##Department of Intensive Care, University Hospital Eppendorf, Hamburg, Germany; and the ***Department of Respiratory Medicine, University Hospital Freiburg, Freiburg, Germany. Part of this work comprised the doctoral thesis of Daniel Brestowsky, University of Giessen Lung Center. Teresa DeMarco, MD, acted as Guest Editor for this article.

Manuscript received May 15, 2006; revised manuscript received July 20, 2006, accepted July 24, 2006.

Abbreviations and Acronyms

CI	= confidence interval
NO	= nitric oxide
PAH	= pulmonary arterial hypertension

(11,12). In 1984, Fuster et al. (13) reported 5 fatal complications associated with 120 right heart catheterizations performed in patients with severe pulmonary hypertension. Ten serious adverse events but no deaths were noted among 187 procedures documented in the National Institutes of Health registry on pulmonary hypertension (14). More recent data on the safety of right heart catheterization in patients with pulmonary hypertension are unavailable.

Pulmonary vasoreactivity testing with inhaled nitric oxide (NO), intravenous epoprostenol, or intravenous adenosine is recommended as part of the diagnostic workup of patients with pulmonary arterial hypertension (1,2,15) because patients who are acutely vasoreactive may benefit from high-dose, long-term calcium channel blocker therapy (16). Again, the safety of these procedures has not been assessed in multicenter studies.

Pulmonary angiography is often performed when the possibility of chronic thromboembolic pulmonary hypertension is raised and, if present, to assess operability for pulmonary endarterectomy (17,18). Pulmonary angiography has been associated with fatal complications (12,19–22), although some small case series document a low incidence of serious complications, especially when nonionic contrast agents are selectively injected into the pulmonary arteries (23,24). A series of 402 patients with pulmonary hypertension reported no procedure-related mortality (25). In contrast, a more recent survey of 202 pulmonary angiographies performed in patients with pulmonary hypertension reported three procedure-related fatal complications (26).

Overall, the current state of knowledge on the safety of right heart catheter procedures in patients with pulmonary hypertension is based predominantly on single-center, retrospective analyses with relatively small sample sizes. Therefore, we launched a multicenter evaluation to obtain a reliable estimate of the risks associated with these procedures.

PATIENTS AND METHODS

Fifteen centers with an established record of treating patients with pulmonary hypertension participated in this study. The period of data collection was divided into 2 parts: a retrospective arm from January 1, 2000, through December 31, 2004, and a prospective arm from January 1, 2005, through June 30, 2005. The participating centers agreed to contribute data from all right heart catheter procedures that were performed within the indicated time frames in patients with pulmonary hypertension as defined by a mean pulmonary artery pressure >25 mm Hg at rest (1).

For the retrospective arm, each center reported aggregate data based on chart log review on the number and types of right heart catheter procedures performed, associated serious adverse events, and patient diagnosis. The definition of a serious adverse event was in accordance with the International Conference on Harmonization guidelines and included any event that was causally related to the intervention or occurred within 24 h after the procedure, and: 1) was medically significant, 2) required intervention to prevent an adverse outcome, 3) resulted in hospital admission or prolongation of hospitalization, 4) was life-threatening, or 5) resulted in disability or death. For every serious adverse event recorded, details of the procedure, adverse event, intervention undertaken, and outcome were obtained.

For the prospective arm, a standardized data form was used to collect information about diagnosis, hemodynamic variables, and details of each procedure performed, regardless of whether or not a serious adverse event occurred.

The study protocol was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all patients whose data were used for the prospective analysis.

Statistical analysis. Results are reported as mean values \pm standard deviation, with 95% confidence intervals (CI) where appropriate.

RESULTS

Table 1 depicts the number of right heart catheter procedures performed and patient classification by pulmonary hypertension type. A total number of 7,218 right heart catheter procedures were reported from 15 centers in the U.S. and Europe. There were 5,727 procedures in the retrospective arm and 1,491 procedures in the prospective arm. Of the 7,218 procedures, 5,267 (73.0%) included pulmonary vasoreactivity testing, and 1,214 (16.8%) included pulmonary angiography.

The most common underlying diseases were pulmonary arterial hypertension (PAH) (51.5%), followed by chronic thromboembolic pulmonary hypertension (28.1%), pulmonary hypertension associated with left heart disease (9.2%), and pulmonary hypertension associated with lung disease (7.1%).

Table 2 shows the hemodynamic values of patients in the prospective analysis. Table 3 provides an overview of the total number of vasoreactivity testing procedures performed and the agents used for vasoreactivity testing. Overall, inhaled NO (44.8%) and inhaled iloprost (29.6%) were the most commonly used agents for acute vasoreactivity testing. Table 4 lists the venous access sites used during the prospective period. The internal jugular vein was the preferred access site (72.7% of all procedures) and was associated with a very low rate of access-related complications (0.3%). Most operators used ultrasound guiding only when they experienced difficulties accessing the jugular vein.

Table 1. Number of Procedures and Baseline Characteristics of Patients

	Retrospective Analysis 2000-2004	Prospective Analysis January-June 2005	Total 2000-2005
Total number of procedures	5,727 (100)	1,491 (100)	7,218 (100)
Vasoreactivity testing	4,043 (70.6)	1,224 (82.1)	5,267 (73.0)
Pulmonary angiographies	1,050 (18.3)	164 (11.0)	1,214 (16.8)
Total number of patients*	4,990 (100)	1,491 (100)	6,481 (100)
PAH	2,499 (50.0)	837 (56.1)	3,336 (51.5)
Idiopathic PAH	1,540 (30.9)	444 (29.8)	1,984 (30.6)
Familial PAH	0	25 (1.7)	25 (0.4)
PAH, connective tissue disease	371 (7.4)	145 (9.7)	516 (8.0)
PAH, congenital heart disease	312 (6.3)	65 (4.4)	377 (5.8)
PAH, portal hypertension	182 (3.7)	81 (5.4)	263 (4.1)
PAH, HIV	94 (1.9)	51 (3.4)	145 (2.2)
PAH, appetite suppressants	0 (0)	26 (1.7)	26 (0.4)
PH, left heart disease	480 (9.6)	114 (7.6)	594 (9.2)
PH, lung disease	323 (6.5)	137 (9.2)	460 (7.1)
PH, COPD	133 (2.7)	48 (3.2)	181 (2.8)
PH, interstitial lung disease	190 (3.8)	89 (6.0)	279 (4.3)
CTEPH	1,493 (29.9)	327 (21.9)	1,820 (28.1)
Miscellaneous†	195 (3.9)	76 (5.1)	271 (4.2)

Values expressed as n (%). *The number of patients is not identical to the number of procedures because several patients underwent repeated right heart catheterization. †Miscellaneous includes pulmonary vasculitis, pulmonary capillary hemangiomatosis, pulmonary hypertension related to the usage of amphetamine or metamphetamine, obesity hypoventilation syndrome, obstructive sleep apnea, sickle cell disease, thalassemia, fibrosing mediastinitis, and pulmonary vascular stenoses.

COPD = chronic obstructive pulmonary disease; CTEPH = chronic thromboembolic pulmonary hypertension; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

The catheter procedures were performed by pulmonologists (57%) or cardiologists (43%). Pulmonary angiographies were performed either by radiologists or by cardiologists. Except for the pulmonary angiographies, the vast majority (>90%) of the catheter procedures were done with balloon-tipped catheters. Whether the catheter studies were performed in an outpatient or an inpatient setting depended mostly on local arrangements and varied substantially between U.S. centers and European centers. Overall, more than 90% of the catheterization procedures performed in the U.S. were done in the outpatient setting, whereas more than 80% of the procedures performed in Europe were done in the inpatient setting. There was no difference in the rate of serious adverse events between U.S. centers and European centers.

Procedure-related mortality. In the retrospective analysis, there were 3 fatal events related to any of the 5,727 catheter procedures (0.052%, 95% CI 0% to 0.111%). A single fatal event was reported among the 1,491 procedures in the prospective analysis (0.067%, 95% CI 0% to 0.197%),

Table 2. Baseline Hemodynamics of Patients Undergoing Right Heart Catheterization in 2005

	Prospective Analysis January-June 2005
Number of procedures	1,491
Mean right atrial pressure (mm Hg)	8 ± 6 (-2-48)
PAPmean (mm Hg)	47 ± 15 (26-153)
Cardiac index (l/min/m ²)	2.7 ± 1.9 (0.7-10.4)
PVR (dynes·s·cm ⁻⁵)	749 ± 510 (32-8,560)
SvO ₂ (%)	62 ± 9 (27-91)

Values expressed as n or mean ± SD (range).

PAPmean = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SvO₂ = mixed venous oxygen saturation.

resulting in an overall number of 4 fatal events among 7,218 procedures (0.055%, 95% CI 0.01% to 0.099%). All of these events occurred in patients who underwent either elective inpatient (n = 3) or outpatient (n = 1) catheter studies and who were hemodynamically stable before the procedures.

Of the 4 fatal events, only 2 were directly related to right heart catheterization: a 67-year-old woman with PAH associated with connective tissue disease died of massive hemoptysis and asphyxiation after rupture of the pulmonary artery during an elective procedure with a balloon-tipped catheter. Another patient with presumed chronic thromboembolic pulmonary hypertension had an arrest 15 min after pulmonary angiography. An autopsy showed diffuse intrapulmonary hemorrhage, plexogenic pulmonary arteriopathy, intact major pulmonary arteries, and right heart failure. The pathogenesis of this catastrophic event remained unexplained. The other 2 fatal events did not seem to be directly related to any right heart catheter procedure. One patient with idiopathic PAH died suddenly while being prepared for catheterization. An autopsy showed a massive pulmonary embolism. Warfarin treatment had been discontinued 5 days before the event without the use of heparin. The physicians in charge linked this event directly to discontinuation of warfarin. The last patient was found dead in his room the morning after an apparently uneventful right heart catheterization for pulmonary hypertension associated with dilated cardiomyopathy. An autopsy was denied. The caregivers thought that the death was related to his underlying diagnosis and not causally related to the procedure.

Serious adverse events. A total of 57 serious adverse events, including the 3 fatalities mentioned above, occurred in association with the 5,727 retrospectively analyzed pro-

Table 3. Agents Used for Pulmonary Vasoreactivity Testing

	Retrospective Analysis 2000–2004	Prospective Analysis January–June 2005	Total 2000–2005
Number of procedures*	4,043 (100)	1,224 (100)	5,267 (100)
Inhaled nitric oxide	1,729 (42.8)	628 (51.3)	2,357 (44.8)
Inhaled iloprost†	1,240 (30.7)	236 (19.3)	1,476 (28)
Intravenous epoprostenol	97 (2.4)	2 (0.2)	99 (1.9)
Intravenous iloprost	49 (1.2)	1 (0.1)	50 (1.0)
Intravenous adenosine	0 (0)	0 (0)	0 (0)
Calcium channel blockers	79 (2.0)	0 (0)	79 (1.5)
Sildenafil	0 (0)	270 (22.1)	270 (5.1)
Others‡	764 (18.9)	87 (7.1)	851 (16.2)

Values expressed as n (%). *Some patients were exposed to more than 1 agent during the procedure. †Inhaled iloprost for pulmonary vasoreactivity testing was used predominantly in German centers. ‡Others include nitrates, oxygen, and inhaled treprostinil.

cedures (1.0%, 95% CI 0.7% to 1.3%). Nineteen serious adverse events including 1 fatality were reported among the 1,491 prospectively analyzed procedures (1.3%, 95% CI 0.7% to 1.9%). Thus, the total number of serious adverse events was 76 among 7,218 procedures (1.1%, 95% CI 0.9% to 1.3%).

Tables 5 and 6 provide the classification of serious adverse events encountered, the procedures to which they were related, and detailed descriptions of all nonfatal serious adverse events. With the exception of the 4 fatalities, most of the remaining 72 serious adverse events were mild to moderate in severity and resolved quickly, either without specific measures or with appropriate medical intervention. Only a single patient had permanent disability resulting from persistent radiating pain in his leg after developing a groin hematoma. Twenty-one nonfatal serious adverse events (28%) resulted in hospital admission or prolongation of hospital stay. The majority of the nonfatal serious adverse events were related to obtaining venous access (n = 29; 38%), right heart catheterization itself (n = 22; 29%), or pulmonary vasoreactivity testing (n = 15; 20%). The most frequent complications were hematoma at puncture sites, pneumothoraces, arrhythmias, vasovagal episodes, and hypotensive episodes. Only 6 nonfatal serious adverse events were considered to be related to pulmonary angiography.

DISCUSSION

In the present retrospective and prospective surveys of complications associated with right heart catheterization, vasoreactiv-

ity testing, and pulmonary angiography in patients with pulmonary hypertension, the overall rate of serious adverse events was 1.1% and the number of fatal complications was <0.1%. These numbers were lower than expected because patients with pulmonary hypertension are a high-risk population, and fatal complications of invasive procedures have been repeatedly reported in these patients (11–13,21,26,27). Earlier series from the 1980s and 1990s reported much higher complication rates. In the 1984 article by Fuster et al (13), catheterization-related mortality was 4.2%. In the series of the National Institutes of Health registry obtained between 1981 and 1985, no fatal events were reported from 187 procedures, but the rate of major procedure-related complications was 5.3% (14). It seems that a learning curve in pulmonary hypertension centers has contributed to reducing the risks of catheter-related complications. In fact, the complication rates from the present survey are very similar to current procedure-related serious adverse event and mortality rates (1.7% and 0.11%, respectively) of left heart catheterization and coronary angiography (28).

The serious adverse events observed in this study can be categorized into 4 groups according to their association with venous access, right heart catheterization, pulmonary vasoreactivity testing, or pulmonary angiography. As anticipated, hematoma, vagal reactions, and pneumothoraces were the most frequent complications associated with venous access. These complications, taken together, occurred in <1% of all procedures, a number that is consistent with a recent report of the use of pulmonary artery catheters in the intensive care unit (29).

Overall, complications directly related to right heart catheterization such as arrhythmias or hypotensive episodes were uncommon, occurring in 22 of 7,218 right heart catheterization procedures. Although the vast majority of these adverse events resolved with minimal or no intervention, the potential for serious complications exists. Certain adverse events may require aggressive intervention to stabilize the patient.

Pulmonary vasoreactivity testing was occasionally complicated by serious systemic hypotension. This occurred not only with the use of nonselective vasodilators such as calcium channel blockers and nitrates, but also in association

Table 4. Venous Access Sites

	Prospective Analysis January–June 2005	Serious Adverse Events Related to Venous Access January–June 2005
Number of procedures	1,491 (100)	7 (0.5)
Internal jugular vein	1,084 (72.7)	3 (0.3)
Subclavian vein	5 (0.3)	0 (0)
Femoral vein	184 (12.3)	2 (1.1)
Brachial vein	203 (13.6)	2 (1.0)
Unknown	15 (1)	0 (0)

Values expressed as n (%).

Table 5. Serious Adverse Events Related to Right Heart Catheter Procedures in Patients With Pulmonary Hypertension

	Retrospective Analysis 2000-2004	Prospective Analysis January-June 2005	Total 2000-2005
Number of procedures	5,727	1,491	7,218
Total number of serious adverse events	57 (1) [0.7-1.3]	19 (1.3) [0.7-1.9]	76 (1.1) [0.9-1.3]
Hospitalization required*	16 (0.3) [0.2-0.4]	5 (0.3) [0-0.6]	21 (0.3) [0.2-0.4]
Disabilities	1 (0.02) [0-0.05]	0 [0-0]	1 (0.01) [0-0.03]
Fatalities	3 (0.052) [0-0.111]	1 (0.067) [0-0.197]	4 (0.055) [0.01-0.099]

Values expressed as n (%) [95% confidence interval]. *Includes new or prolonged hospitalization.

with agents that are usually considered pulmonary selective, such as inhaled iloprost (30). Iloprost-induced systemic hypotension is dose related and the acute combination with other vasodilators such as phosphodiesterase-5 inhibitors increases the risk of systemic side effects during vasoreactivity testing. Inhaled iloprost is used for pulmonary vaso-

reactivity testing mainly in Germany (31), which explains why it was used in approximately 30% of this multinational survey, where German centers are overrepresented. The international guidelines (1,2,15) do not advise using inhaled iloprost to test for acute pulmonary vasoreactivity because of the absence of published data on its utility as a predictor of

Table 6. Description of Nonfatal Serious Adverse Events Related to Right Heart Catheter Procedures in Patients With Pulmonary Hypertension Performed in the Years 2000 to 2005

Description of SAE	n	Interventions and Outcomes
Total number of nonfatal SAEs	72	
Related to venous access	29	
Hematoma at puncture site	10	Transfusion and surgery required in 2 cases, persistent groin pain in 1 patient
Vagal reaction with bradycardia and hypotension	8	All successfully managed with fluids and/or atropine
Pneumothorax	5	No intervention required in 3 cases, 2 patients received chest tubes for 3 and 5 days, respectively
Arteriovenous fistula	3	1 case resolved spontaneously, 1 patient required percutaneous intervention, and 1 required surgery
Puncture of carotid artery	2	No sequela with manual compression
Hypertensive crisis during puncture	1	Resolved with treatment
Related to right heart catheterization	22	
Supraventricular tachycardia	7	1 resolved spontaneously, 1 required vagal maneuvers, 1 resolved after adenosine and diltiazem, 2 required overdrive pacing, and 2 required electrical cardioversion
Vagal reaction with bradycardia and hypotension	3	All successfully managed with fluids and/or atropine
Ventricular tachycardia	3	2 resolved after catheter removal and 1 required antitachycardic pacing
Systemic hypotension	2	1 required fluids, the other required fluids and catecholamines
Transient ischemic attack	2	Both resolved completely without specific intervention; PFO in 1 patient ascertained, unclear in the other patient
Hypertensive crisis	2	1 with pulmonary edema, both resolved with appropriate treatment
Chest pain and hemothysis after balloon inflation	1	Resolved without intervention
Hypotension after balloon rupture	1	Resolved without intervention
New right bundle branch block	1	Asymptomatic
Related to vasoreactivity testing	15	
Systemic hypotension	11	Linked to intravenous epoprostenol (n = 1), inhaled iloprost (n = 4), inhaled iloprost plus sildenafil (n = 2), sildenafil (n = 1), nitrates (n = 2), calcium channel blockers (n = 1); all recovered, but transient catecholamine therapy required in 6 patients
Bronchospasm during prostanoid inhalation	4	Linked to inhaled iloprost (n = 1) or inhaled treprostinil (original formulation, no longer in use; n = 3)
Related to pulmonary angiography	6	
Hypertensive crisis and pulmonary edema after dye injection	3	Resolved with treatment in all patients
Second-degree AV block after dye injection	1	Required temporary pacemaker treatment
Chest pain after dye injection	1	Resolved spontaneously but prolonged hospital stay
Vomiting after dye injection	1	Resolved with corticosteroids but prolonged hospital stay

AV = atrioventricular; PFO = patent foramen ovale; SAE = serious adverse event.

calcium channel blocker response. In highly experienced centers comfortable with its use, however, it has been used in this fashion. Although the present data do not address its utility as a predictor, they do support its safety. Similar considerations apply to the use of sildenafil for vasoreactivity testing because it is unknown whether this drug serves as a predictor of calcium channel blocker response.

In addition to the hypotensive episodes, there were 4 episodes of bronchospasm after pulmonary vasoreactivity challenge with inhaled prostanoids, mostly with the original treprostinil formulation; this formulation is no longer being used. Of note, no serious adverse events were reported in conjunction with either inhaled NO or intravenous epoprostenol, underlining the suitability of these compounds for acute pulmonary vasoreactivity testing (1,2). Intravenous adenosine was not used by any of the participating centers, preventing any statement on the safety of this agent when used for pulmonary vasoreactivity testing.

Pulmonary angiography was associated with few complications (7 serious adverse events among 1,214 procedures, 1 of them fatal), mostly hypertensive episodes with pulmonary edema, which responded well to conventional therapy. It is unclear why fatal alveolar hemorrhage developed in 1 patient after the procedure. There were no episodes of a severe allergic reaction to the contrast medium and also no contrast-associated renal failure. In addition, there were no episodes of right heart failure after pulmonary angiography, which may have been because all centers used selective injections of low-osmolar nonionic contrast into the right and left pulmonary arteries as recommended in recent guidelines (2). This technique avoids major hemodynamic alterations in patients with pulmonary hypertension (24,32–34).

Of the 4 fatal events, only 2 were considered directly related to a specific right heart catheter procedure. One of these events, rupture of the pulmonary artery, is a known complication of right heart catheterization that can occur with any type of catheter (35). The pathogenesis of the other event, electromechanical dissociation and diffuse intrapulmonary hemorrhage after pulmonary angiography in a patient with idiopathic PAH, remains unexplained. The 2 other fatal events were not thought to be directly related to the procedure. In the patient found dead the morning after a right heart catheterization for pulmonary hypertension associated with dilated cardiomyopathy, considered uneventful by the investigator, there was no apparent causal association with the procedure. The final case of a patient with idiopathic PAH who died of massive pulmonary embolism just before catheterization serves as a reminder that interruption of anticoagulation can result in thromboembolic complications, even in patients without previous thromboembolic disease, and that bridging with heparin should be considered. An alternative strategy could be to keep the patients on moderate-intensity oral anticoagulants throughout the procedure. Preliminary data suggest that maintaining a patient at a target international normalized ratio of 1.5 to 2.0 during the procedure may be safe with

regard to both thromboembolic and hemorrhagic complications (36), although further study is needed before this concept should be widely used.

It is important to note that right heart catheterization, acute pulmonary vasoreactivity testing, and pulmonary angiography can usually be completed within 1 to 2 h, and in many cases, in <30 min if only a right heart catheterization for hemodynamic measurements is made. These procedures are often performed on an outpatient basis but in the setting of a fully equipped cardiac catheterization laboratory. This is very different from using a pulmonary artery catheter in the inpatient intensive care unit setting as an aid to diagnose and manage a variety of critical conditions. It is this latter setting in which controversy persists with respect to the usefulness and safety of pulmonary artery catheters (29,37,38). Additionally, these patients are at significant risk for infectious and thromboembolic complications related to indwelling vascular catheters that usually remain in place for several days (39). These complications are extremely rare when right heart catheterization is performed in the pulmonary hypertension population as discussed in this study given the short procedural time.

The main limitation of the present survey is that it included only centers with broad expertise in caring for patients with pulmonary hypertension, which may be a main reason for the fact that the observed rate of serious complications was much lower than expected. Thus, the present results may not be extendable to less experienced centers. However, the complication rate of any invasive procedure is a function of the experience and skill of the operator, and the low rate of adverse events in this study was probably related to the fact that the procedures were done in high-volume centers by experienced operators, reinforcing the recommendation to perform these procedures only in specialized institutions.

In summary, the present data provide reassurance that right heart catheterization, pulmonary vasoreactivity testing, and pulmonary angiography in adult patients with pulmonary hypertension are associated with a low risk of serious complications, at least when performed in experienced centers.

Reprint requests and correspondence: Dr. Marius M. Hoeper, Department of Respiratory Medicine, Hannover Medical School, 30623 Hannover, Germany. E-mail: hoeper.marius@mh-hannover.de.

REFERENCES

1. Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43:40S–7S.
2. Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004;25:2243–78.
3. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;347:322–9.

4. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-23.
5. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148-57.
6. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005;46:529-35.
7. Galie N, Humbert M, Vachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496-502.
8. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004;169:441-7.
9. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:800-4.
10. Hoepfer MM, Oudiz RJ, Peacock A, et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol* 2004;43:48S-55S.
11. Calдини P, Gensini GG, Hoffman MS. Primary pulmonary hypertension with death during right heart catheterization. A case report and a survey of reported fatalities. *Am J Cardiol* 1959;4:519-27.
12. Snider GL. Primary pulmonary hypertension: a fatality during pulmonary angiography. Clinical conference from Boston University School of Medicine. *Chest* 1973;64:628-35.
13. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984;70:580-7.
14. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216-23.
15. McGoon M, Guterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:14S-34S.
16. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005;111:3105-11.
17. Fedullo PF, Auger WR, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2001;345:1465-72.
18. Klepetko W, Mayer E, Sandoval J, et al. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43:73S-80S.
19. Moser KM, Auger WR, Fedullo PF. Chronic major-vessel thromboembolic pulmonary hypertension. *Circulation* 1990;81:1735-43.
20. Watson H. Severe pulmonary hypertensive episodes following angiography with sodium metrizoate. *Lancet* 1964;171:732-3.
21. Mills SR, Jackson DC, Older RA, Heaston DK, Moore AV. The incidence, etiologies, and avoidance of complications of pulmonary angiography in a large series. *Radiology* 1980;136:295-9.
22. Perlmutter LM, Braun SD, Newman GE, Oke EJ, Dunnick NR. Pulmonary arteriography in the high-risk patient. *Radiology* 1987;162:187-9.
23. Nicod P, Peterson K, Levine M, et al. Pulmonary angiography in severe chronic pulmonary hypertension. *Ann Intern Med* 1987;107:565-8.
24. Pitton MB, Duber C, Mayer E, Thelen M. Hemodynamic effects of nonionic contrast bolus injection and oxygen inhalation during pulmonary angiography in patients with chronic major-vessel thromboembolic pulmonary hypertension. *Circulation* 1996;94:2485-91.
25. Hudson ER, Smith TP, McDermott VG, et al. Pulmonary angiography performed with iopamidol: complications in 1,434 patients. *Radiology* 1996;198:61-5.
26. Hofmann LV, Lee DS, Gupta A, et al. Safety and hemodynamic effects of pulmonary angiography in patients with pulmonary hypertension: 10-year single-center experience. *AJR Am J Roentgenol* 2004;183:779-86.
27. Hoepfer MM, Galie N, Murali S, et al. Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2002;165:341-4.
28. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 1999;33:1756-824.
29. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005;366:472-7.
30. Olschewski H, Walrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996;124:820-4.
31. Hoepfer MM, Olschewski H, Ghofrani HA, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH Study Group. *J Am Coll Cardiol* 2000;35:176-82.
32. Peck WW, Slutsky RA, Hackney DB, Mancini GB, Higgins CB. Effects of contrast media on pulmonary hemodynamics: comparison of ionic and non-ionic agents. *Radiology* 1983;149:371-4.
33. Smith TP, Lee VS, Hudson ER, et al. Prospective evaluation of pulmonary artery pressures during pulmonary angiography performed with low-osmolar nonionic contrast media. *J Vasc Interv Radiol* 1996;7:207-12.
34. Pitton MB, Kemmerich G, Herber S, Mayer E, Thelen M, Duber C. Hemodynamic effects of monomeric nonionic contrast media in pulmonary angiography in chronic thromboembolic pulmonary hypertension. *AJR Am J Roentgenol* 2006;187:128-34.
35. Kaiser CA, Hugli RW, Haegeli LM, Pfisterer ME. Selective embolization of a pulmonary artery rupture caused by a Courmand catheter. *Catheter Cardiovasc Interv* 2004;61:317-9.
36. Larson BJ, Zumberg MS, Kitchens CS. A feasibility study of continuing dose-reduced warfarin for invasive procedures in patients with high thromboembolic risk. *Chest* 2005;127:922-7.
37. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA* 2005;294:1664-70.
38. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 2005;294:1625-33.
39. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001;286:700-7.

APPENDIX

For details regarding the number of procedures performed by each center from this study, please see the online version of this article.