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Outcomes of noncardiac, nonobstetric surgery in patients with PAH: an international prospective survey

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ABSTRACT: We conducted an international, prospective, 3-year questionnaire-based survey among 11 pulmonary hypertension centres to assemble data from patients with pulmonary arterial hypertension (PAH) undergoing noncardiac and nonobstetric surgery.

Data were collected between July 2007 and June 2010 from 114 patients with PAH (70% female, mean age 57 years) who underwent major surgery. At the time of surgery, 43% were in functional class III/IV. 82% of the interventions were performed under general anaesthesia and 18% under spinal anaesthesia. Major complications occurred in seven (6.1%) of the patients, of whom four died, resulting in an overall perioperative mortality rate of 3.5%. The mortality rate was 15% (two out of 13) in emergency procedures, compared with 2% (two out of 101) in nonemergency procedures (p=0.01). Risk factors for major complications were an elevated right atrial pressure (OR 1.1, 95% CI 1.0–1.3; p=0.01), a 6-min walking distance <399 m at the last preoperative assessment (OR 2.2, 95% CI 1.1–3.7; p=0.04), the perioperative use of vasopressors (OR 1.5, 95% CI 1.2–2.7; p=0.03) and the need for emergency surgery (OR 2.4, 95% CI 1.4–3.6; p=0.01).

Major surgery in patients with PAH continues to be a high-risk procedure, particularly when emergency interventions are needed.

KEYWORDS: Anaesthesia, hypertension, pulmonary, surgery, survival

Patients with pulmonary hypertension (PH), in particular those with pulmonary arterial hypertension (PAH) [1], are at high risk when undergoing anaesthesia and major surgery [2–6]. The perioperative management of these patients can be challenging as it is frequently complicated by a systemic inflammatory response, profound hypoxaemia, worsening of PH and right heart failure (sometimes presenting as so-called pulmonary hypertensive crisis) [7]. In addition, pre-treatment with anticoagulants and prostacyclin analogues increases the risk of bleeding complications.

In a study by RAMAKRISHNA *et al*. [8], which included 145 surgical patients with various forms of PH, the perioperative mortality rate was 7%. MINAI *et al*. [9] reported a mortality rate of 18% among 21 patients with well-defined PAH undergoing noncardiac surgery. Both studies were retrospective in design and included patients treated up to 2003, *i.e*. before modern therapies for PAH became widely available [6]. More recently, PRICE *et al*. [10] reported on another retrospective series of 28 patients (20 PAH and eight chronic thromboembolic PH) undergoing noncardiothoracic nonobstetric surgery between 2000 and 2007, with a mortality rate of 7%. It is possible that with contemporary PAH treatment [6, 11], modern anaesthesia [4, 7, 12, 13] and modern intensive care management [14, 15], surgery may be associated with better outcomes in this patient population [16].

We conducted a 3-year, prospective international survey to provide a more comprehensive overview of current practices and outcomes of noncardiac and nonobstetric surgery in patients with PAH under follow-up at specialised PH centres.

METHODS

This was a prospective, multicentre, international, noninterventional survey of surgery or

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pregnancy in patients with PAH (the results from the pregnancy part of the study have already been published elsewhere [17]). The project was investigator-initiated. Data were collected between July 1, 2007 and June 30, 2010. All participating centres were university hospitals with expertise in PAH. Data from patients diagnosed with PAH who underwent noncardiac surgical interventions during the study period were collected, regardless of whether the procedures were performed in the centre or at another hospital.

Inclusion criteria were an established diagnosis of PAH according to current criteria (including ascertainment of diagnosis by right heart catheterisation showing a mean pulmonary artery pressure $\geqslant$25 mmHg at rest and a pulmonary capillary wedge pressure $\leqslant$15 mmHg) in male and female patients aged $\geqslant$18 years, undergoing planned or unplanned noncardiac surgical intervention requiring general or spinal anaesthesia. Patients were excluded if they suffered from other forms of PH or when they underwent minor surgery not requiring general or spinal anaesthesia. Patients undergoing obstetric surgery, cardiac surgery or lung transplantation were also excluded. The investigators completed structured questionnaires for every patient fulfilling the inclusion and exclusion criteria. The questionnaire can be found in the online supplementary material. The data set included age at surgery, sex, type of PAH, New York Heart Association (NYHA) functional class, 6-min walking distance (6MWD) and haemodynamics at last assessment before surgery, background medication including anticoagulation, and details on the surgical procedure including setting (PH centre *versus* other hospital), urgency (elective, intermediate or emergency), perioperative complications, type of anaesthesia, medications and outcome.

Perioperative complications were defined as those occurring during anaesthesia, surgery, the same hospital stay, or during the first 28 post-operative days. Major complications were prespecified as any of the following: major bleeding with estimated blood loss >1 L; systemic inflammatory response or septicaemia requiring catecholamine therapy; right heart failure requiring inotropic support; or any death during the hospital stay.

Institutional review board approval and informed consent

Institutional review board approval was obtained from all participating centres before start of the survey. Informed consent was obtained where required by local regulations. In some countries, informed consent was waived due to the noninterventional design of the survey and full data protection. Where required, informed consent was obtained prior to surgery from all patients undergoing planned surgery. *Post hoc* informed consent was obtained, when possible, after unplanned surgery. Informed consent was waived if patients died during or after unplanned surgery, in order to avoid bias.

Statistical analysis

Categorical data are displayed as number of patients and respective relative frequency as percentage. For continuous data, normally distributed data are displayed as mean$\pm$SD; otherwise, median (interquartile range) are shown. For comparison of continuous data, group differences for normally distributed data were tested with a two-sided t-test; otherwise, a two-sided Mann–Whitney U-test was used. Frequency distributions between the groups were compared using the Chi-squared test or Fisher's test. Univariate regression analyses were used to identify risk factors of major complications. A p-value <0.05 was considered significant.

RESULTS

Of the 19 PH centres originally invited, 13 agreed to participate and 11 submitted their data (table S1). These 11 centres confirmed complete enrolment of all patients fulfilling the inclusion criteria. Thus, this survey enrolled 114 consecutive patients undergoing noncardiac, nonobstetric surgery from 11 PAH centres. Details of these patients are shown in table 1. At the time of surgery, all patients received targeted medical therapy for PAH and suffered from moderate-to-severe functional impairment, with 54% of them presenting in NYHA functional class I or II. The median 6MWD (assessed within 6 months before surgery) was 399 m. The last haemodynamic assessments prior to surgery (median interval between right heart catheterisation and surgery: 9 months, range 4–26 months) showed an average right atrial pressure of 7 mmHg, mean pulmonary artery pressure of 45 mmHg, pulmonary vascular resistance of 579 dyn·s·cm^{-5} and cardiac index of 2.9 L·min^{-1}·m^{-2}, indicating relatively well preserved right ventricular function in most patients.

The majority (82%; n=93) of the operations were performed under general anaesthesia, while the remaining 18% (n=21) were performed under spinal anaesthesia. 70 (61%) of the surgical interventions were elective, 31 (27%) were of intermediate urgency and 13 (11%) were classified as emergency interventions. 75% of all surgical procedures and 57% of the emergency interventions were performed in PH centres. There were no differences in baseline variables between patients undergoing emergency and nonemergency surgery (table S2). The majority of surgical interventions were abdominal, followed by trauma/orthopaedic surgery, gynaecological/urological surgery and others (table 1 and table S3).

The PAH medications were continued throughout the perioperative period in almost all cases. 20 (18%) of the patients had one or more PAH medications added during the perioperative period (inhaled nitric oxide n=4; inhaled iloprost n=12; *i.v.* prostacyclin analogues n=2; phosphodiesterase type 5 inhibitors n=3; and endothelin receptor antagonists n=1). Oral anticoagulants were always discontinued prior to surgery. Some centres routinely used pre-operative heparin when the international normalised ratio was <2.0 while other centres restarted anticoagulation only after surgery. Almost all patients were scheduled for intensive care unit treatment after the procedures. A Swan–Ganz catheter was used for perioperative haemodynamic monitoring in 15 (13%) patients.

Major complications occurred in seven (6.1%) of the surgical interventions (table 2). Three patients required catecholamine therapy for post-operative right heart failure and recovered. Four (3.5%) patients died. Three of the fatalities occurred after abdominal surgery and one was associated with hip replacement after traumatic fracture. Three of these interventions were performed under general anaesthesia and one under spinal anaesthesia. Causes of death were sepsis and/or right heart failure in all cases.

TABLE 1 Baseline characteristics (last measurements prior to surgery) of the entire patient population and of patients with or without major perioperative complications (POCs)

	All patients	POC	No POC
Subjects n	114	7	107
Age years	57 (48–67)	54 (46–67)	57 (48–67)
Female	80 (70)	5 (71)	75 (70)
Type of PAH			
Idiopathic PAH	57 (50)	2 (28.6)	51 (48)
Familial PAH	2 (1.8)	1 (14)	1 (1)
Associated PAH	55 (48)	4 (57)	55 (51)
NYHA class[#]			
NYHA I/II	61 (54)	1 (14)	60 (56)
NYHA III/IV	49 (43)	6 (86)	43 (41)
6MWD[¶]			
6MWD <399 m	46 (40)	6 (86)	40 (37)
6MWD ⩾399 m	49(43)	1 (14)	48 (45)
Haemodynamics			
mRAP[+] mmHg	7 (3–10)	7 (4–10)	7 (3–10)
mPAP[§] mmHg	45 (38–55)	49 (38–58)	45 (38–55)
mPCWP[ƒ] mmHg	9 (6–12)	9 (7–12)	9 (6–12)
Cardiac output[##] $L \cdot min^{-1}$	5.0 (4.2–5.9)	5.1 (4.3–6.0)	5 (4.2–5.9)
Cardiac index[¶¶] $L \cdot min^{-1} \cdot m^{-2}$	2.9 (2.5–3.5)	2.9 (2.4–3.3)	2.9 (2.5–3.5)
PVR[+] $dyn \cdot s \cdot cm^{-5}$	579 (368–804)	616 (368–952)	579 (368–804)
S_{vO_2}[++] %	66 (63–70)	66 (62–69)	66 (63–70)
Interval between last RHC and surgery months	9 (4–26)	6 (3–14)	9 (4–26)
Type of surgery			
Abdominal	45 (39)	4 (57)	41 (38)
Gynaecology/urology	22 (19)	1 (14)	21 (20)
Trauma/orthopaedic	21 (18)	1 (14)	20 (19)
Other	26 (22)	1 (14)	27 (25)
Location of surgery			
PH centre	86 (75)	4 (57)	82 (77)
Other	28 (25)	3 (43)	25 (23)
Urgency			
Elective/intermediate	101 (89)	3 (43)	98 (92)
Emergency	13 (11)	4 (57)	9 (8)
Monotherapy			
PDE5I	17 (15)	1(14)	16 (15)
ETRA	23 (20)	2 (28)	21 (20)
Prostanoid (nebulised)	1 (1)	0 (0)	1 (1)
Prostanoid (parenteral)	11 (10)	1 (14)	10 (10)
Combination therapy			
ETRA + PDE5I	22 (19)	0 (0)	22 (21)
ETRA + PDE5I + prostanoid (nebulised)	2 (2)	1 (14)	1 (1)
ETRA + PDE5I + prostanoid (parenteral)	6 (5)	0 (0)	6 (6)
Prostanoid (nebulised) + PDE5I	1 (1)	0 (0)	1 (1)
Prostanoid (parenteral) + PDE5I	9 (8)	0 (0)	9 (8)
ETRA + prostanoid (nebulised)	2 (2)	0 (0)	2 (2)
ETRA + prostanoid (parenteral)	1 (1)	0 (0)	1 (1)

Data are presented as median (interquartile range) or n (%), unless otherwise stated. PAH: pulmonary arterial hypertension; NYHA: New York Heart Association; 6MWD: 6-min walking distance; mRAP: mean right artery pressure; mPAP: mean pulmonary artery pressure; mPCWP: mean pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; RHC: right heart catheterisation; PH: pulmonary hypertension; PDE5I: phosphodiesterase-5-inhibitor; ETRA: endothelin receptor antagonist. [#]: missing, n=4; [¶]: missing, n=9; [+]: n=111; [§]: n=114; [ƒ]: n=106; [##]: n=113; [¶¶]: n=100; [++]: n=87.

TABLE 2 Major perioperative complications and fatalities after noncardiac, nonobstetric surgery in patients with pulmonary arterial hypertension (PAH)

Patient	Age	Sex	PAH type	Type of surgery	Anaesthesia	Urgency	Complications	Outcome
1	49	F	POPH	Gynaecology (mastectomy for breast cancer)	General	Elective	Right heart failure requiring catecholamines	Recovered
2	61	F	POPH	Trauma surgery (total hip-arthoplasty)	Spinal	Intermediate	Refractory right heart failure	Died
3	73	M	PVOD	Vascular surgery (saphenectomy)	Spinal	Elective	Right ventricular failure requiring catecholamines	Recovered
4	73	M	IPAH	Abdominal (bowel obstruction)	General	Emergency	Sepsis	Died
5	38	F	CTD-PAH	Abdominal (open cholecystectomy)	General	Intermediate	Right ventricular failure requiring catecholamines	Recovered
6	40	F	FPAH	Abdominal (laparoscopic cholecystectomy)	General	Elective	Bacterial peritonitis and sepsis	Died
7	78	F	IPAH	Abdominal (exploratory laparotomy)	General	Emergency	Post-operative respiratory failure, sepsis	Died

F: female; M: male; POPH: portopulmonary hypertension; PVOD: pulmonary veno-occlusive disease; IPAH: idiopathic PAH; CTD: connective tissue disease; FPAH: familial PAH.

Risk factors for major complications after surgery were: a 6MWD <399 m and a right atrial pressure >7 mmHg on the last assessments prior to surgery; intra- or post-operative need for vasopressors; and the need for emergency surgery (table 3). The mortality rate associated with emergency surgery was two (15%) out of 13 compared to two (2%) out of 101 in nonemergency surgery (p=0.01 Fisher's test).

DISCUSSION

To the best of our knowledge, this is the first prospective, multicentre assessment of outcomes after noncardiac, non-obstetric surgery in patients with a catheter-based diagnosis of PAH. Our data showed an overall mortality rate of 3.5%. The highest mortality rate (15%) was seen in emergency procedures, while the mortality rate in nonemergency surgery was 2%. Besides the need for emergency surgery, other factors associated with perioperative complications were lower pre-operative 6MWD, higher right atrial pressure and the requirement for catecholamines during the perioperative period.

The mortality rates observed in this survey appear somewhat lower than those reported in previous series of patients with PH undergoing surgery [8, 9, 10]. Comparisons, however, are difficult. RAMAKRISHNA *et al*. [8] studied patients with various forms of PH and the diagnoses were mainly based on echocardiography (estimated right ventricular systolic pressure >35 mmHg) with confirmation by right heart catheterisation in only 68 (47%) out of 145 patients. Surgery-associated mortality was 7%, with the majority of deaths being attributed to respiratory or right heart failure, but it is unclear how many of these patients had an ascertained diagnosis of PAH. In contrast, MINAI *et al*. [9] evaluated 28 surgical procedures in 21 patients with well-defined PAH and reported a mortality rate of 18%, predominantly due to right heart failure. Both series

TABLE 3 Univariate analysis of risk factors for major complications after surgery in patients with pulmonary arterial hypertension

	OR (95% CI)	p-value
Age years	0.9 (0.9–1.0)	0.52
6MWD m	2.2 (1.1–3.7)	0.04
NYHA functional class	1.04 (0.5–2.0)	0.72
mRAP mmHg	1.1 (1.0–1.3)	0.01
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	1.6 (0.92–4.9)	0.36
mPAP mmHg	0.97 (0.8–1.1)	0.21
PVR $dyn \cdot s \cdot cm^{-5}$	0.91 (0.78–1.1)	0.22
S_{vO_2} **%**	1.2 (0.9–1.3)	0.07
Surgery performed in PH centre	0.2 (0.05–1.0)	0.06
General *versus* spinal anaesthesia	1.9 (0.3–2.7)	0.50
Use of vasopressors	1.5 (1.2–2.7)	0.03
Emergency procedure	2.4 (1.4–3.6)	0.01

6MWD: 6-min walking distance; NYHA: New York Heart Association; mRAP: mean right artery pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; PH: pulmonary hypertension.

enrolled most of their patients before 2002; *i.e.* before most of the modern treatments for PAH became widely available. A more recent study from France reported two deaths (7%) among 28 patients with PAH or chronic thromboembolic PH enrolled between 2000 and 2007 [10]. Of note, the two fatal outcomes seen in that study occurred during emergency procedures.

The present series provides the largest data set of patients with a well-established diagnosis of PAH undergoing surgery and it indicates that the associated mortality, although still considerable, is not as high as previously reported, especially in nonemergency procedures. It is important to note that all of our patients received targeted therapy for PAH and their diseases appeared relatively well controlled, as indicated by a median 6MWD of 399 m at the last assessment (within 6 months before surgery) and the fact that 54% of the patients were in NYHA functional class I/II at the time of surgery. This may, in part, explain the low mortality rate of 2% among patients who had nonemergency surgical interventions. Specifically, only one of these patients died from right heart failure, while the other died from sepsis after cholecystectomy. The vast majority of patients who had elective surgical interventions survived, most of them without experiencing major complications. Elective procedures were preferentially performed in the PH centres, which might have contributed to the relatively good outcome. The sample size of the present study was too small to assess the effect of centre volume and experience on the post-operative outcome. We were unable to collect detailed data on the perioperative management of all patients, but it appears that modern anaesthesiology is capable of preventing haemodynamic deterioration in most cases. Although there is consensus amongst anaesthesiologists that regional anaesthesia is preferred over general anaesthesia in patients with PH [18, 19], there is no indication from our study that general anaesthesia is associated with more frequent or more serious complications than regional anaesthesia. However, our study was not sufficiently powered to compare the risks and complication of these approaches. Two recent papers on pregnancy in patients with PAH from two centres using disparate approaches to anaesthesia (one utilising almost exclusively epidural/spinal anaesthesia and one using exclusively general anaesthesia) reported similar outcomes, suggesting that both approaches are appropriate [20, 21].

In addition, the present study was not designed to assess the usefulness of intra-operative haemodynamic monitoring using a Swan–Ganz catheter. Since the majority (87%) of the surgical interventions did not use a Swan–Ganz catheter, it appears that they are not necessary in patients with stable disease. However, it is unclear whether the use of Swan–Ganz catheters or other devices to measure pulmonary vascular pressures and cardiac output may help to improve the outcome of selected patients presenting in an unstable haemodynamic situation.

There are several limitations to this study. Although being one of the largest surveys of its kind, the sample size is still small and the number of events is limited, prohibiting detailed analyses of risk factors for major complications and death. As this was a multicentre, multinational survey many centres used anaesthetic strategies; details of which we did not collect. Missing data cannot be fully excluded although all centres did follow their patients on a regular basis, making it unlikely that surgeries would have been missed, especially when associated with serious complications or even death. Our study included mainly patients with relatively well-controlled PAH, indicating that surgery is avoided in patients with advanced disease. Our results may therefore not be applicable to patients with severe PAH and/or manifest right heart failure. Importantly, there are no standard guidelines for management of these patients in the perioperative or post-operative periods. Our physicians may have applied simple measures such as meticulous use of anticoagulants, fluid balance, oxygen requirements, blood pressure or heart rate goals that allowed for better outcomes. Future studies are needed to determine this in detail.

In summary, noncardiac, nonobstetric surgery in patients with PAH is still associated with a considerable risk, but morbidity and mortality are lower than previously reported, at least in patients with well-controlled disease undergoing elective surgery. However, emergency procedures in patients with PAH continue to be associated with a high mortality.

SUPPORT STATEMENT

The project was investigator-initiated and there was no reimbursement and no third-party funding.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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