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Noncardiothoracic nonobstetric surgery in mild-to-moderate pulmonary hypertension

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ABSTRACT: The anaesthetic management and follow-up of well-characterised patients with pulmonary arterial hypertension presenting for noncardiothoracic nonobstetric surgery has rarely been described.

The details of consecutive patients and perioperative complications during the period January 2000 to December 2007 were reviewed. Repeat procedures in duplicate patients were excluded. Longer term outcomes included New York Heart Association (NYHA) functional class, 6-min walking distance and invasive haemodynamics.

A total of 28 patients were identified as having undergone major (57%) or minor surgery under general (50%) and regional anaesthesia. At the time of surgery, 75% of patients were in NYHA functional class I–II. Perioperative deaths occurred in 7%. Perioperative complications, all related to pulmonary hypertension, occurred in 29% of all patients and in 17% of those with no deaths during scheduled procedures. Most (n=11, 92%) of the complications occurred in the first 48 h following surgery. In emergencies (n=4), perioperative complication and death rates were higher (100 and 50%, respectively; $p<0.005$). Risk factors for complications were greater for emergency surgery ($p<0.001$), major surgery ($p=0.008$) and a long operative time (193 *versus* 112 min; $p=0.003$). No significant clinical or haemodynamic deterioration was seen in survivors at 3–6 or 12 months of post-operative follow-up.

Despite optimal management in this mostly nonsevere pulmonary hypertension population, perioperative complications were common, although survivors remained stable. Emergency procedures, major surgery and long operations were associated with increased risk.

KEYWORDS: Anaesthesia, perioperative complications, perioperative mortality, pulmonary hypertension, pulmonary hypertensive crisis, right ventricular failure

Pulmonary hypertension (PH) is defined by a mean resting pulmonary arterial pressure ($\bar{P}_{pa}$) of $\geqslant$25 mmHg with a pulmonary capillary wedge pressure (P_{pcw}) of $\leqslant$15 mmHg [1]. Pulmonary arterial hypertension (PAH) defines a subgroup characterised by vascular cell proliferation and remodelling of low-resistance pulmonary arteries that causes elevated pulmonary vascular resistance (PVR), ultimately leading to right heart failure and death [1–3]. PAH is classified into idiopathic PAH, heritable PAH and PAH associated with conditions such as connective tissue diseases, portal hypertension and HIV infection, amongst others [4]. Survival remains poor, with a 15% mortality rate at 1 yr despite modern treatment [5]; however, increasingly, more types of therapy are available. Although PAH remains a rare disease, the most recent prevalence is increased, compared to previous eras, at 15 per million population in France [6].

Reflecting this increasing global health burden, patients are likely to present not only to PH referral units but also to nonspecialist centres for emergency and non-emergency surgery. Patients with PH represent one of the highest-risk groups of patients undergoing both cardiac [7] and noncardiac surgery [8–11], despite advances in perioperative monitoring and treatment. Potentially fatal complications relate to the consequences of right-sided circulatory failure, which may be precipitated by reduced right ventricular contractility, excessive volume loading or causes of further right ventricular pressure overload. A common mode of death appears to be minor stimulation resulting in tachycardia or increased PVR, followed by refractory hypotension, hypoxia and ultimately

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cardiovascular collapse [12, 13] due to a downwards spiral of worsening right ventricular function [14]. Perioperative increases in PVR may be precipitated by hypoxia [15], hypercapnia [16], high airway plateau pressure due to the effects of positive-pressure mechanical ventilation [17] and atelectasis or may follow acute pulmonary embolism [18]. Such PH complications, including death, may occur up to 1 week post-operatively [19, 20], or even later, reported following delivery by Caesarean section [21, 22]. Perioperative measures may be utilised to prevent rapid haemodynamic deterioration in the setting of right ventricular failure (RVF). These include the use of pulmonary vasodilator therapies to minimise right ventricular afterload [19, 23, 24], the avoidance of excessive fluid administration that may overload the right ventricle, maintaining appropriate systemic perfusion pressure for adequate coronary perfusion and enhancing myocardial contractility [25].

There have been very few studies of well-characterised patients with PH undergoing noncardiothoracic nonobstetric surgery. Perioperative mortality and complication rates have been described in one previous study as 7 and 42%, respectively [9], and 14 and 18% in a further smaller study [11]. Whereas perioperative care is likely to vary between institutions, further to the nature of the surgical procedure itself, it is not clear whether other aspects of anaesthetic or perioperative care may influence short-term outcomes in these patients. Furthermore, it is unclear whether operative procedures have implications on longer term PH end-points. It was, therefore, sought to describe the cohort of PH patients undergoing surgery at the French Reference Centre for Pulmonary Hypertension (University of Paris-South 11, Antoine Béclère Hospital, Clamart, France), details of their perioperative management and longer term PH outcomes.

METHODS

Subjects

Retrospective data were reviewed from patients referred to the French Reference Centre for Pulmonary Hypertension who had undergone general (GA) and regional anaesthesia (RA) for noncardiothoracic nonobstetric surgery between January 1, 2000 and December 31, 2007. Patients were included if a diagnosis of precapillary PH was confirmed before surgery by right heart catheterisation. Patients with chronic thromboembolic pulmonary hypertension (CTEPH) not amenable to endarterectomy were also included. Exclusion criteria included patients aged <18 yrs, those with PH due to left heart disease and those undergoing surgery for cardiothoracic or obstetric procedures. All clinical characteristics at diagnosis and follow-up were stored in the Registry of the French Network of Pulmonary Hypertension. This registry was set up in agreement with French bioethics laws (French Data Protection Authority, Paris, France), and all patients gave their informed consent [6].

Clinical and functional assessment

Patient demographics, aetiology of PH, clinical features and major comorbid conditions were recorded at the latest time-point prior to surgery, and at the 3–6 and 6–12 month evaluation following surgery. Clinical status was assessed using modified New York Heart Association (NYHA) functional class [4, 26] and the non-encouraged 6-min walking test, performed according to American Thoracic Society recommendations [27].

Haemodynamic measurements

Details of preoperative haemodynamic evaluation by right heart catheterisation were recorded for all subjects according to a previously described protocol [28]. Precapillary PH was defined as a $\bar{P}_{pa}$ of $\geqslant$25 mmHg with a normal P_{pcw} of $\leqslant$15 mmHg. $\bar{P}_{pa}$, P_{pcw}, right atrial pressure and mixed venous oxygen saturation (S_{v,O_2}) were recorded. Cardiac index (CI) was measured using the standard thermodilution technique. The indexed pulmonary vascular resistance (PVRI) was calculated as $(\bar{P}_{pa} - P_{pcw})/CI$.

Intra-operative factors

Anaesthetic and surgical charts were examined to determine the nature of the operative procedure, the occurrence of emergency surgery and operative time (from induction of anaesthesia until extubation or end of surgery). Major surgery was defined to include major laparotomy, hysterectomy, mastectomy and major orthopaedic surgery, and minor surgery to include hernia repair, appendicectomy and extremity orthopaedic surgery. RA was defined as neuraxial blockade or other regional blockade. Details of venous access, intra-operative haemodynamic monitoring and, for procedures under GA, ventilator settings, mean intra-operative fractional inspired oxygen concentration (F_{I,O_2}), peak end-expiratory carbon dioxide level, peak airway pressure (in centimetres of water) and the use of nitrous oxide as a supplementary anaesthetic agent were recorded.

Perioperative complications

Perioperative complications were defined as those occurring during surgery or in the 28-day post-operative period. Perioperative complications related to PH were recorded from operative charts and medical notes. Non-PH complications were also noted. PH complications with increased right ventricular afterload leading to RVF, cardiogenic shock and ventilation/perfusion mismatch were of varying severity, and were defined as follows. Major PH complications were defined by the occurrence of death or severe acute right heart failure (clinical signs of low cardiac output (CO) and RVF) requiring vasopressors, inotropes, inhaled nitric oxide and/or additional pulmonary vasodilator therapy (intravenous epoprostenol or nebulised iloprost). Minor PH complications were defined as hypoxia requiring an escalation of the mode of ventilation, isolated hypotension or RVF not requiring the use of continuous infusions of vasopressors or inotropes.

Statistical analysis

Statistical analysis was performed using StatView version 5.0 (Abacus Concepts, Inc., Berkeley, CA, USA). Data are presented as mean$\pm$SD and median (range) for parametric and nonparametric data, respectively. Statistical analysis was performed using parametric tests (Fisher's exact test and paired t-test) or nonparametric tests (Mann–Whitney U-test for unpaired data and Wilcoxon matched-pair test for paired data), as appropriate. The distribution of qualitative data was assessed using Pearson's Chi-squared test with Yates's correction for continuity or Fisher's exact test as appropriate.

Multivariate analysis was not performed because of the small number of procedures as compared to the number of risk factors identified on univariate analysis. A p-value of <0.05 was considered significant.

RESULTS

Preoperative patient characteristics

A total of 28 procedures were identified in 28 individual consecutive patients with idiopathic PAH (n=10; 36%), associated PAH (n=10; 36%; comprising five portopulmonary, three connective tissue disease-associated and two HIV-associated PAH) and CTEPH (n=8; 28%). The mean age of the patients was 53±16 yrs, with a female predominance (57%). At the time of surgery, patients were in NYHA functional class I–II (n=21; 75%) and class III (n=7; 25%), with no patients in class IV, and the 6-min walking distance (6MWD) was 388±114 m. Preoperative haemodynamics showed a $\bar{P}_{pa}$ of 43±12 mmHg, normal CI of 3.25±0.68 $L \cdot min^{-1} \cdot m^{-2}$ and low S_{v,O_2} (66±6%). Of the patients, 57% were on specific PAH therapy (table 1).

Operative characteristics

Of 28 procedures performed, 16 were abdominal surgery (nine inguinal hernias, one umbilical hernia, two laparoscopic cholecystectomies, one splenectomy, one open appendicectomy and two major bowel resections), eight orthopaedic procedures (of which four were major hip surgery and two major knee surgery), two mastectomies and two hysterectomies. According to the present definitions, 16 (57%) were major and 12 (43%) minor surgical procedures. A total of 14 procedures were performed under GA and 14 under RA. Four were emergency procedures, all performed under GA (hip hemiarthoplasty, bowel resection, laparotomy and appendicectomy).

Anaesthesia characteristics

For the 14 patients that had procedures under GA, all patients received opioids and propofol for induction of anaesthesia, and anaesthesia was maintained with sevoflurane (10 out of 14), isoflurane (two out of 14) or desflurane (two out of 14). Nitrous oxide was used as a supplemental anaesthetic agent in four patients, and the intra-operative F_{I,O_2} was 0.60±0.17 (table 2).

RA consisted of neuraxial blockade in 11 out of 28 patients (spinal anaesthesia in two and combined spinal–epidural anaesthesia in nine), and three other regional blocks (supraclavicular block, femoral block and lumbar plexus block) were combined with sedation in all three cases. For patients undergoing neuraxial blockade (n=11), the spinal needles were 27G in size, and the spinal doses used were 4.8 (3.0–7.5) μg sufentanil (data available for n=9) combined with 0.5% heavy bupivacaine, and epidural top-ups used 2% lidocaine in all patients. No patients required conversion to GA. All of those previously on warfarin (n=5) were switched to low-molecular-weight (LMW) heparin (prophylactic dose) preoperatively, and there were no reported bleeding complications relating to the site of regional blockade, including in the patients receiving continuous intravenous epoprostenol.

There was no significant age or sex difference, or 6MWD or NYHA functional class difference, between those undergoing GA and RA (table 1). As compared to RA, patients that had procedures under GA showed less severe haemodynamic impairment, with a significantly lower $\bar{P}_{pa}$ (36±10 *versus* 48±11 mmHg; p=0.003) and PVRI (7.2±2.9 *versus* 13.9±5.5 WU (Wood units)·m^{-2}; p=0.0003) and a higher CI (3.6±0.6 *versus* 2.94±0.6; p=0.009). Patients undergoing RA were more likely to be on specific PAH therapy than those under GA (86 *versus* 29%; p=0.002).

Perioperative complications

Perioperative complications relating to PH occurred in eight (29%) out of 28 procedures (table 3). There were no reported non-PH complications. Two (7%) deaths occurred in the 28 procedures performed, due to refractory right heart failure in

TABLE 1 Preoperative patient factors in patients receiving general (GA) and/or regional anaesthesia (RA)

	All patients	GA±RA	RA alone	p-value
Surgical cases	28	14	14	
Age at surgery yrs	53±16	53±15	53±17	0.89
Female sex	16 (57)	8 (57)	8 (57)	1
PH type				
Idiopathic PAH	10 (36)	2 (14)	8 (57)	0.03
Associated PAH[#]	10 (36)	8 (57)	2 (14)	
CTEPH	8 (28)	4 (29)	4 (29)	
Specific therapy				
No	12 (43)	10 (71)	2 (14)	0.002
Yes	16 (57)	4 (29)	12 (86)	
Bosentan[¶]	10	8	2	
Sildenafil[¶]	2	1	1	
Epoprostenol[¶]	5	1	4	
Other prostanoids[+]	2	1	1	
CCBs	1	0	1	
NYHA class				
I–II	21 (75)	11 (79)	10 (71)	0.66
III	7 (25)	3 (21)	4 (29)	
6MWD m	388±114	394±94	383±133	0.81
Haemodynamics				
$\bar{P}_{pa}$ mmHg	43±12	36±11	49±9.5	0.003
P_{ra} mmHg	6±4	5±3	7±4	0.08
P_{pcw} mmHg	8.8±3	8.5±3	8.9±3	0.77
CI $L \cdot min^{-1} \cdot m^{-2}$	3.25±0.68	3.60±0.62	2.93±0.58	0.009
SVI $mL \cdot m^{-2}$	42±10	44±9	39±11	0.33
PVRI $WU \cdot m^{-2}$	11.1±5.7	7.1±3.2	14.5±5.0	<0.001
S_{v,O_2} %	66±6	70±2	64±7	0.04

Data are presented as n, mean±SD or n (%), unless otherwise stated. Means were compared using unpaired t-tests. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CCB: calcium channel blocker; NYHA: New York Heart Association; 6MWD: 6-min walking distance; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{ra}: right atrial pressure; P_{pcw}: pulmonary capillary wedge pressure; CI: cardiac index; SVI: stroke volume index; PVRI: indexed pulmonary vascular resistance; WU: Wood unit; S_{v,O_2}: mixed venous oxygen saturation. [#]: comprising five portopulmonary hypertension, three connective tissue disease-associated PAH and two HIV-associated PAH patients; [¶]: includes patients on combination therapy; [+]: including beraprost and iloprost.

TABLE 2 Major perioperative pulmonary hypertension-related complications during general anaesthesia (GA): operative factors

	All patients	POCs	No POCs	p-value
Patients	28	8	20	
Emergency surgery	4 (14)	4 (50)	0	<0.001
Major surgery	16 (57)	8 (100)	8 (40)	0.008
Minor surgery	12 (43)	0	12 (60)	
GA	14 (50)	6 (75)	8 (40)	0.12
RA	14 (50)	2 (25)	12 (60)	
Operative time min	133 (45–465)	193 (120–420)	112 (45–465)	0.003
Additional monitoring				
CVP/arterial line[#]	3	3	0	
CO[¶]	4	3	1	
GA patient characteristics				
F_{I,O_2}	0.60±0.17	0.60±0.12	0.59±0.20	0.90
Use of nitrous oxide	4	3	1	
Peak P_{ET,CO_2} mmHg	36.1±5.4	38.6±6.7	34.1±3.5	0.17
Peak P_{aw} cmH_2O	20.8±6.8	22.4±8.8	19.6±5.0	0.51

Data are presented as n, n (%), median (range) or mean± SD. Major perioperative complications (POCs) were defined by the occurrence of death or severe acute right ventricular failure with clinical signs of low cardiac output (CO) requiring vasopressors, inotropes, inhaled nitric oxide and/or additional pulmonary vasodilator therapy (intravenous epoprostenol or nebulised iloprost). All of the patients underwent standard monitoring, including ECG, noninvasive blood pressure measurement and oximetry; additional forms of monitoring were used in some cases. Major surgery included laparotomy, hysterectomy, mastectomy and major orthopaedic surgery. Minor surgery included hernia repair and extremity orthopaedic surgery. Comparisons were performed using an unpaired t-test or Mann–Whitney test for parametric/nonparametric data, respectively. RA: regional anaesthesia; CVP: central venous pressure; F_{I,O_2}: inspiratory oxygen fraction; P_{ET,CO_2}: end-tidal carbon dioxide tension; P_{aw}: airway pressure. [#]: for invasive arterial blood pressure monitoring (if used, most patients also underwent CVP monitoring); [¶]: includes monitoring with pulmonary artery catheterisation or the use of oesophageal Doppler.

both cases: one intra-operatively, and the other at day 11. In the four emergency procedures, perioperative complications relating to PH (n=4; 100%), including death (n=2; 50%), occurred more frequently than in the non-emergency procedures (with four (17%) out of 24 complications and no deaths; p<0.001) (table 2). More patients that had PH-related perioperative complications had undergone major surgery compared to minor surgery (eight (50%) out of 16 and none out of 12, respectively; p=0.008) (table 2). Mortality related to major surgery was two (13%) out of 16 compared to no deaths in patients undergoing minor surgery.

Most of the complications occurred during the procedure or during the following 48 h (seven (88%) out of eight). Complications included three patients with severe acute right heart failure (following which two died), three cases of isolated hypotension and two of severe hypoxaemia. One death occurred at the time of surgery due to refractory right heart failure (patient No. 5), and the other (patient No. 8) was due to ongoing PH and RVF at day 11 post-operatively (table 4).

TABLE 3 Perioperative[#] pulmonary hypertension (PH)-related complications: patient factors

	All patients	POCs	No POCs	p-value
Patients	28 (100)	8 (29)	20 (71)	
Age yrs	53±16	52±18	54±15	0.76
PH type				
Idiopathic PAH	10 (36)	3 (37)	7 (35)	
Associated PAH[¶]	10 (36)	4 (50)	6 (30)	0.44
CTEPH	8 (28)	1 (13)	7 (35)	
Specific therapy				
No	12 (43)	4 (50)	8 (40)	0.69
Yes	16 (57)	4 (50)	12 (60)	
Oral therapy alone	9	0	9	
Bosentan[+]	10	0	10	
Sildenafil[+]	2	1	1	
Epoprostenol[+]	5	3	2	
Other prostanoids[§]	2	1	1	
CCBs	1	0	1	
NYHA class				
I–II	21 (75)	4 (50)	17 (80)	0.14
III	7 (25)	4 (50)	3 (20)	
6MWD m	388±114	311±140	411±99	0.058
Haemodynamics				
$\bar{P}_{pa}$ mmHg	43±12	44±13	43±12	0.77
P_{ra} mmHg	6.3±4.0	6.2±4.1	6.3±3.9	0.93
P_{pcw} mmHg	9.0±3.0	9.3±3.9	8.6±2.7	0.59
CI L·min^{-1}·m^{-2}	3.25±0.68	3.28±0.52	3.24±0.75	0.89
SVI mL·m^{-2}	42±10	38±8	43±10	0.25
PVRI WU·m^{-2}	11.1±5.7	10.0±4.6	11.5±6.1	0.60
S_{v,O_2} %[f]	66±6	71±6	64±6	0.05

Data are presented as n (%), mean±SD or n, unless otherwise stated. POC: perioperative complication; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CCB: calcium channel blocker; NYHA: New York Heart Association; 6MWD: 6-min walking distance; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{ra}: right atrial pressure; P_{pcw}: pulmonary capillary wedge pressure; CI: cardiac index; SVI: stroke volume index; PVRI: indexed pulmonary vascular resistance; WU: Wood unit; S_{v,O_2}: mixed venous oxygen saturation. [#]: up to day 28; [¶]: comprising five portopulmonary hypertension, three connective tissue disease-associated PAH and two HIV-associated PAH patients; [+]: includes patients on combination therapy; [§]: including beraprost and iloprost; [f]: n=18.

Prognostic factors

There was no significant difference in age or PH aetiology between patients who had and did not have perioperative complications. There was a suggestion that patients in NYHA class I–II preoperatively were less likely to exhibit perioperative complications than those in NYHA class III–IV (n=17 (80%) *versus* n=3 (20%), respectively; p=0.14), and that patients with a higher preoperative 6MWD (411±99 *versus* 311±140 m; p=0.058) showed fewer complications. However, there was no significant difference in resting preoperative haemodynamics between these patient groups. There was no influence of the use of all PH-specific therapy on complications, although no complications occurred in patients receiving oral therapy alone (n=9) (table 3).

TABLE 4 Pulmonary hypertension (PH)-related perioperative complications

Patient No.	Age yrs	PH type	NYHA class	Therapy	Surgery				Complication	
					Type	Emergency	Anaesthesia	Time min	Details	Timing
1	83	Associated#	III	None	Hemiarthoplasty	Yes	GA+RA	120	Hypotension	Intra-operative
2	44	Associated#	II	None	THR	No	GA+CSE	210	Hypoxia	Intra-operative
3	44	Idiopathic	II	Flolan	Knee arthrodesis	No	RA (CSE)	180	Tachycardia, hypotension	Day 1 post-operatively
4	63	Idiopathic	III	Flolan+sildenafil	Humerus ORIF	No	RA (supraclavicular block)	120	Hypoxia	Intra-operative
5	43	Associated#	II	Flolan	Bowel resection	Yes	GA	180	Refractory RVF; died at time of surgery	Intra-operative
6	61	Associated#	II	Beraprost	Laparotomy	Yes	GA	150	Hypotension, arrhythmias	Following intubation
7	55	CTEPH	III	None	Pancreatectomy	No	GA	420	Acute RVF	Following intubation
8	20	Idiopathic	IV	None; later flolan+ bosentan	Appendix	Yes	GA	NA	Refractory RVF; died on day 11	Intra- and post-operative

Major perioperative complications were defined by the occurrence of death or severe acute right ventricular failure (RVF), with clinical signs of low cardiac output requiring vasopressors, inotropes, inhaled nitric oxide and/or additional pulmonary vasodilator therapy (intravenous epoprostenol or nebulised iloprost). Minor PH complications were defined as major hypoxia requiring an escalation of the mode of ventilation, isolated hypotension or RVF not requiring the use of continuous infusions of vasopressors or inotropes. NYHA: New York Heart Association; CTEPH: chronic thromboembolic pulmonary hypertension; THR: total hip replacement; ORIF: open reduction with internal fixation; GA: general anaesthesia; RA: regional anaesthesia; CSE: combined spinal–epidural; NA: not available. #: PAH associated with conditions such as connective tissue diseases, portal hypertension and HIV infection.

There was a suggestion that more perioperative complications occurred in procedures performed under GA compared to RA (n=6 (75%) *versus* n=2 (25%), respectively; p=0.12). Procedures with associated perioperative complications were longer than uncomplicated procedures (193 (120–420) *versus* 112 (45–465) min; p=0.003). More patients undergoing central venous pressure or intra-arterial monitoring (n=3; 38%) and in whom CO monitoring (using pulmonary artery catheterisation (PAC) or oesophageal Doppler) was used (n=3; 38%) had complications than those without (0 and 5%, respectively) (table 2).

In patients undergoing GA, there was no significant difference in F_{I,O_2} between patients with (0.60 ± 0.12) and without perioperative complications (0.59 ± 0.20), and three (38%) patients with complications were given the supplemental anaesthetic agent nitrous oxide compared to one (5%) of those without complications. High peak end-tidal carbon dioxide tension (P_{ET,CO_2}) and peak airway pressure were not significantly associated with perioperative complications (p=0.17 and p=0.51, respectively) (table 2).

Longer term outcomes

When perioperative deaths were excluded, the remaining survivors (n=26) showed no evidence of significant clinical or haemodynamic deterioration at 3–6 months of follow-up. At preoperative baseline, 19 (73%) out of 26 survivors were in NYHA functional class I–II compared with 22 (85%) out of 26 at 3–6 months of follow-up (p=0.31). Accordingly, seven (27%) out of 26 patients were in NYHA functional class III–IV before surgery and four (15%) at follow up (including one patient in NYHA functional class IV) (p=0.77) (table 5). Only two (8%) patients had their PAH therapy increased over this period. There was no significant worsening of 6MWD (n=17) or haemodynamics (n=11) for those in whom follow-up data were available at 3–6 months. Even for the six patients who suffered perioperative complications and survived, NYHA functional class, 6MWD and haemodynamic assessment were unchanged at 3–6 months (data not shown). Furthermore, there was no significant deterioration in clinical status in survivors assessed at 6–12 months, whether or not perioperative complications had occurred (fig. 1).

DISCUSSION

In the present single-centre study, anaesthetic management, perioperative complications and PH outcomes are described in a high-risk population undergoing noncardiothoracic nonobstetric surgery. In this cohort of well-characterised patients with mostly mild-to-moderate PAH and non-operable CTEPH, overall perioperative mortality was 7%, and the incidence of perioperative complications up to day 28 was 29%. These are relatively high adverse event rates despite operating on mostly nonsevere patients in an experienced PH centre.

Data on complications and mortality following noncardiothoracic nonobstetric surgery in this population are rare, with only two previous single-centre studies available. One study of 145 patients showed that the perioperative mortality and 30-day morbidity rates were 7 and 42%, respectively, for patients of similar NYHA functional class undergoing similar surgical procedures under GA, although this study did not include such well-characterised patients with regard to PH classification:

TABLE 5 Follow-up data[#]

	Baseline	3–6 months	p-value
Clinical status			
NYHA I–II	19 (73)	22 (85)	0.31
NYHA III–IV	7 (27)	4 (15)	
Increase in therapy		2 (8)	
6MWD m[¶]	382±112	387±124	0.77
Haemodynamics[+]			
P_{ra} mmHg	7±4	10±4	0.06
PVRI WU·m^{-2}	14.50±5.60	12.02±6.59	0.04
P_{pa} mmHg	49±11	46±12	0.49
CI L·min^{-1}·m^{-2}	2.94±0.57	3.54±1.18	0.05
P_{pcw} mmHg	8±3	9±3	0.31
S_{v,O_2} %[§]	63±9	59±11	0.33

Data are presented as n (%) or mean±SD. NYHA: New York Heart Association; 6MWD: 6-min walking distance; P_{ra}: right atrial pressure; PVRI: indexed pulmonary vascular resistance; WU: Wood unit; P_{pa}: mean pulmonary arterial pressure; CI: cardiac index; P_{pcw}: pulmonary capillary wedge pressure; S_{v,O_2}: mixed venous oxygen saturation. [#]: paired survivors (n=26) only; [¶]: n=17; [+]: n=11 for paired values; [§]: n=5.

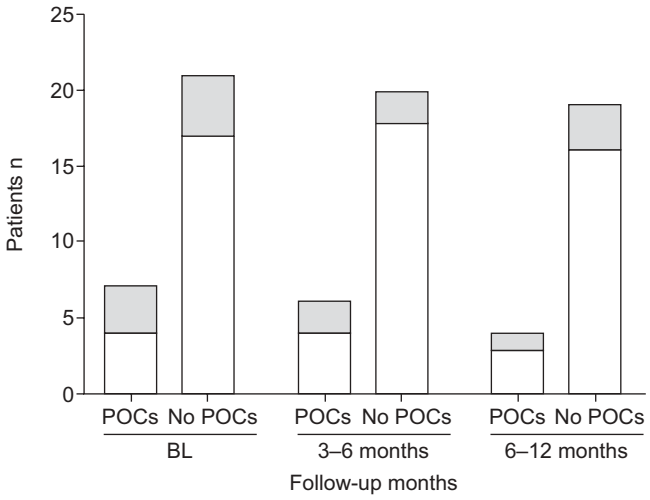

FIGURE 1. New York Heart Association (NYHA) functional class (□: class I–II; ■: class III–IV) of patients at baseline (BL) and after 3–6 and 6–12 months of follow-up, according to those suffering perioperative complications (POCs). At BL, 43% of patients with POCs were in NYHA class III–IV, compared to 19% of those without POCs. At 3–6 months of follow-up, there were similarly more patients with POCs in NYHA III–IV (33% with POCs compared to 10% without POCs). At 6–12 months of follow-up, 25% of those who had POCs were in NYHA class III–IV, and 16% of those without POCs. There was an increase in therapy in two patients at 3–6 months of follow-up, neither of whom had suffered a POC. At 12 months, three patients were receiving increased pulmonary arterial hypertension therapy, one of whom had suffered a POC.

some of the patients had PH secondary to lung disease, and some were diagnosed using echocardiography without haemodynamic confirmation [9]. The second was a smaller study of well-characterised patients with more severe PAH than in the larger study ($\bar{P}_{pa}$ 53±14 mmHg; 62% in NYHA class III–IV) undergoing 28 surgical procedures. These included 12 abdominal, six thoracic (including lung biopsy and resection but not endarterectomy), gynaecological and orthopaedic procedures, and 79% were performed under GA. Most complications reported related to the surgical procedure itself, with only 14% of cases complicated by reversible RVF, although deaths occurred in 18% of patients [11]. The lower overall mortality in the present study probably reflects the fact that patients had less severe disease, no thoracic procedures were performed and only 50% underwent GA compared to this last study. However, the mortality/complication rates of patients in the present study undergoing emergency or major procedures (100/50 and 13/50%, respectively) were very high, and previous studies have not divided surgical procedures in this way to enable true comparisons.

Previous studies have suggested that RA may be safer than GA in patients with PH, although this may, at least partly, be explained by reducing the risk imparted by GA. A recent series of 73 PAH obstetric deliveries suggested that GA was associated with a four-fold increase in maternal mortality (univariate analysis; odds ratio 4.37; 95% confidence interval 1.28–16.5; p=0.02) [22]. This has also been suggested in patients with Eisenmenger's syndrome, where, using 103 noncardiac anaesthetics, the perioperative mortality of those receiving GA was 18% compared to 5% in those undergoing RA, although this may well have been an indirect indicator of the increased mortality seen in major *versus* minor surgery (24 *versus* 5%; p<0.01) as more patients undergoing GA also underwent more major surgery [29]. Patients with PAH that tolerate pregnancy have a particularly high perioperative risk, with a historical mortality of 36–50% [21, 30], which, even in the modern treatment era, remains as high as 25% [22]. Obstetric operative deliveries were excluded from the present study for this reason. However, useful experience with obstetric RA can be extrapolated to the nonobstetric setting. Successful incremental regional blockade has been used in PAH obstetric deliveries [21], and is well tolerated by mothers with PH [31]. RA was previously thought harmful in patients with PH because of the haemodynamic compromise following sympathetic blockade; however, using a low intrathecal dose minimises this potential drop in afterload, and careful incremental epidural top-ups are well tolerated. RA techniques have also been useful in patients with PH in general surgery [9, 10]. RA may be an inappropriate anaesthetic technique, however, for many procedures, as well as in emergencies, when planned cessation of anticoagulation is not possible. In well-selected non-emergency patients undergoing suitable procedures, however, these data suggest relative safety of RA compared to GA in PH. The lack of reported bleeding at the site of neuraxial puncture, even in patients on epoprostenol, is notable, with the theoretical increased risk due to the antiplatelet aggregation effects of prostacyclins.

Both deaths reported in the present study followed refractory acute right heart failure, with one death intra-operatively and one at day 11. Most nonfatal complications occurred intra-operatively, and related in varying degrees to isolated RVF not requiring vasopressors and/or inotropes. Previous studies have shown that similar causes of perioperative death

in patients undergoing noncardiac nonobstetric surgery may occur suddenly [11, 20] or up to 48 h following surgery [32]. Obstetric PAH deaths have been reported even up to 1 month after delivery [22], and guidelines suggest that obstetric patients should be monitored for at least 72 h post-operatively [33]. In the present study, perioperative complications related to PH and death were recorded over a 28-day post-operative period, with most of the complications occurring in the first 48 h (11 (92%) out of 12).

In the present study, significant univariate predictive factors for perioperative complications, including death, were found to be emergency surgery, major surgery and long operative time. Increased risk was suggested by the use of GA rather than RA, more severe preoperative NYHA functional class and a shorter 6MWD. Preoperative resting invasive haemodynamics were not predictive of outcome, which may reflect the small sample size, or perhaps indicate that exercise end-points are more sensitive in this setting, which bears similarities to preoperative cardiopulmonary exercise testing in the general surgical population. In a prospective study of patients undergoing major abdominal surgery (including those aged <60 yrs with cardiac disease), the preoperative anaerobic threshold (AT) predicted outcome, such that no patients died when the AT was >11 $mL \cdot min^{-1} \cdot kg^{-1}$, but 4.6% died when the AT was <11 $mL \cdot min^{-1} \cdot kg^{-1}$ [34]. The AT was used as it is independent of patient effort and occurs well below maximal oxygen uptake, the more usually recorded value in PH, where a maximal oxygen uptake of <10. $mL \cdot min^{-1} \cdot kg^{-1}$ has been shown to predict poor survival [35]. It would be useful to know from future studies whether an AT above a certain threshold was also predictive of better surgical outcomes in this specific patient population.

There was a suggestion that patients monitored for CO (using either PAC or oesophageal Doppler) had more complications, although these are likely to indicate the more complex patients. Intra-operative invasive haemodynamic monitoring is not without risk, with both arrhythmias and pulmonary artery thrombosis and rupture reported [36], although using PAC is useful, with falling CO and $\bar{P}_{pa}$ and rising CVP being markers of acute right ventricular decompensation [25]. The perioperative use of PAC in patients with PH is therefore debated. With the background that many complications are potentially avoidable, and that good teamwork improves outcomes, a recent study in noncardiac surgery has shown that use of a standardised safety checklist reduced complications [37].

The present study has suggested that the use of GA, as compared to RA, was associated with worse outcomes. Most patients receiving GA were undergoing emergency or major surgery, known to be associated with worse outcomes [38], and these are likely to be major confounding factors. However, there were more severe patients undergoing RA, indicated by both haemodynamics and the fact that significantly more patients on specific PAH therapy received RA than GA. The use of GA may increase PVR through several mechanisms, including increased sympathetic stimulation during airway instrumentation on laryngoscopy [39], effects of volatile agents [40], high airway plateau pressure due to the effects of positive-pressure mechanical ventilation [12, 13], hypoxia [15] and hypercapnia [16]. The present data suggested that more complications occurred in those with higher P_{ET,CO_2} and peak airway pressure, although many confounding factors may affect these values. Volatile anaesthetic agents may also adversely affect right ventricular preload and contractility [25], as well as afterload [40], although isoflurane has been used safely in human PAH [41]. Desflurane appears to exert worse pulmonary vascular effects than isoflurane, probably through sympathetic activation [42, 43]. Some studies suggest that nitrous oxide as a supplemental anaesthetic agent may increase PVR, especially in those with pre-existing elevated PVR [44], and it may also adversely influence endothelial function [45]. An increase in adverse cardiovascular events following its use in major surgery has been observed [46], possibly also through adverse pulmonary vascular effects of increased sympathomimetic stimulation [47, 48] or hypoxia [49], and a study addressing these questions is ongoing [50].

Despite the fact that patients experiencing complications showed worse functional capacity, longer term PH outcomes (including 6MWD, NYHA class and haemodynamics) at 3–6 months were not adversely influenced by having undergone surgery. For those in whom data were available at 6–12 months, NYHA functional class was similarly unchanged. The occurrence of perioperative complications did not adversely influence these outcomes. This is likely to relate to appropriate patient selection and perioperative management of complications in those that survived. These data suggest that the risk of procedures was associated with perioperative complications, and the possibility of occurrence of complications related to PH may not influence the progression of the disease following the perioperative period, suggesting that essential surgical procedures may not always be contraindicated in patients with stable PH.

In addition to the confounding influence of surgical disease severity and type of surgery performed, limitations to the present study include its retrospective nature. However, selection bias was minimised by examining consecutive cases. A further limitation relates to the small sample size, preventing the use of multivariate analysis. The potential influence of GA, in addition to surgical type, on PH complications would require much larger patient numbers. This retrospective study does, however, emphasise several issues, which will be further addressed in an ongoing prospective international multicentric registry.

In conclusion, the present study has shown that the incidence of complications associated with noncardiothoracic nonobstetric surgery remains high, even in patients with mild-to-moderate PAH, especially in those undergoing longer operations, emergency and major procedures, and those performed under GA, with most occurring within the first 48 h following surgery. The suggestion that more patients with worse functional status had more complications indicates that assessment of exercise tolerance should form part of preoperative examination. RA may be a safe approach in appropriately selected patients. Perioperative deaths occurred, especially following emergency procedures, but the mortality rate remains lower than following obstetric operative deliveries in patients with PH [22, 30]. Long-term follow up after surgery suggested no disease deterioration in surviving patients. Non-emergency procedures may not necessarily be contraindicated in appropriately selected PH

patients if managed in an experienced PH centre during the pre-, peri- and post-operative periods.

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STATEMENT OF INTEREST

Statements of interest for D. Montani, X. Jaïs, G. Simonneau, O. Sitbon and M. Humbert can be found at www.erj.ersjournals.com/misc/statements.dtl

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