Non-cardiothoracic non-obstetric surgery in mild-moderate pulmonary hypertension

Journal:	*European Respiratory Journal*
Manuscript ID:	ERJ-01130-2009.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	
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Key Words:	anaesthesia, Pulmonary hypertension, complications, mortality, perioperative

Non-cardiothoracic non-obstetric surgery in mild-moderate pulmonary hypertension:

Perioperative management of 28 consecutive individual cases

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Short-title: Surgery in mild-moderate pulmonary hypertension

Word count: 3844

References: 51

Figures: 1

Tables: 5

Key words: (MESH database): Anesthesia, perioperative mortality, perioperative complications, pulmonary hypertension, pulmonary hypertensive crisis, right ventricular failure.

ABBREVIATION LIST

CI: Cardiac index

CO: Cardiac output

NO: Nitric oxide

NYHA: New York Heart Association

PAH: Pulmonary arterial hypertension

mPAP: Mean pulmonary arterial pressure

PCWP: Pulmonary capillary wedge pressure

PVRi: Indexed pulmonary vascular resistance

RAP: Right atrial pressure

PaO_2: Partial pressure of arterial oxygen

SI: Systolic index

SpO_2: Pulse arterial oxygen saturation

SvO_2: Mixed venous oxygen saturation

TPRi: Indexed total pulmonary resistance

6MWD: 6-minute walk distance

ABSTRACT

Rationale Anesthetic management and follow-up of well-characterized patients with pulmonary arterial hypertension (PAH) presenting for non-cardiothoracic non-obstetric surgery has rarely been described.

Methods We reviewed details of consecutive patients and perioperative complications from January 2000 to December 2007. Repeat procedures in duplicate patients were excluded. Longer-term outcomes included New York Heart Association (NYHA) functional class; 6-minute walk distance (6MWD) and invasive hemodynamics.

Main results Twenty-eight patients were identified having major (57%) or minor surgery under general (GA) (50%) and regional anesthesia (RA). At the time of surgery, 75% patients were in NYHA functional class I-II. Perioperative deaths occurred in 7%. Perioperative complications, all related to pulmonary hypertension (PH), occurred in 29% of all patients and in 17% with no deaths in scheduled procedures. In emergencies (n=4), perioperative complication and death rates were higher (100% and 50% respectively, $p<0.005$). Risk factors for complications were higher emergency surgery ($p<0.001$), major surgery ($p=0.008$), and long operative time (193 vs. 112 minutes, $p=0.003$). No significant clinical or hemodynamic deterioration was seen in survivors at 3-6 or 12 month post-operative follow-up.

Conclusions Despite optimal management in this mostly non-severe PH population, perioperative complications were common, although survivors remained stable at 6 months. Emergency procedures, major surgery and long operations were associated with increased risk.

INTRODUCTION

Pulmonary hypertension (PH) is defined by mean resting pulmonary artery pressure (mPAP) greater than 25 mmHg with pulmonary capillary wedge pressure (PCWP) less than 15 mmHg (1). Pulmonary arterial hypertension (PAH) defines a subgroup characterized by vascular cell proliferation and remodeling of small resistance pulmonary arteries that causes elevated pulmonary vascular resistance, ultimately leading to right heart failure and death (1-3). PAH is classified into idiopathic, heritable PAH and those 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 one year despite modern treatment (5), however there are increasing therapies available. Although PAH remains a rare disease, the most recent prevalence has increased compared to previous eras, at 15 per million in France (6).

Reflecting this increasing global health burden, patients are likely to present not only to PH referral units but also to non-specialist centers for emergency and non-emergency surgery. Patients with PH present one of the highest risk groups of patients undergoing both cardiac (7) and non-cardiac 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 pulmonary vascular resistance (PVR), followed by refractory hypotension, hypoxia and ultimately 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), atelectasis or may follow acute pulmonary embolism (18). Such PH complications including death may occur up to a week post-operatively (19, 20), or even later namely following delivery for Caesarean section (21, 22). Perioperative measures may be undertaken to prevent rapid hemodynamic deterioration in the setting of right ventricular failure. These include the use of pulmonary vasodilator therapies to minimize right ventricular afterload (19, 23, 24), avoiding excessive fluid administration, maintaining appropriate systemic perfusion pressure for adequate coronary perfusion and enhancing contractility (25).

There have been very few studies of well-characterized patients with PH undergoing non-cardiothoracic, non-obstetric 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 anesthetic or perioperative care may influence short-term outcomes in these patients. Furthermore, it is unclear if operative procedures have implications on longer-term PH endpoints. We therefore sought to describe the cohort of PH patients undergoing surgery at our institution, 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 (Université Paris-Sud 11, Hôpital Antoine Béclère, Clamart, France) undergoing general and regional anesthesia for non-cardiothoracic, non-obstetric surgery between 1st January 2000 and 31st December 2007. Patients were included if diagnosis of pre-capillary PH was confirmed before surgery by right-heart catheterization. Patients with chronic thromboembolic pulmonary hypertension (CTEPH) not amendable to endarterectomy surgery were also included. Exclusion criteria included patients <18 years, those with PH due to left heart disease and those having 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 Commission Nationale de l'Informatique et des Libertés) and all patients gave their informed consent (6).

Clinical and functional assessment

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

Hemodynamic measurements

Details of preoperative hemodynamic evaluation by right heart catheterization were recorded in all subjects according to our previously described protocol (28). Precapillary pulmonary hypertension was defined as mPAP ≥25 mmHg with a normal pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. The mPAP, PCWP, right atrial pressure (RAP) and mixed venous oxygen saturation (SvO2) were recorded. Cardiac index (CI) was measured by the standard thermodilution technique. The indexed pulmonary vascular resistance (PVRi) were calculated as (mPAP-PCWP)/CI.

Intra-operative factors

Anesthetic and surgical charts were examined to determine the nature of the operative procedure, the presence of emergency surgery and operative time (from induction of anesthesia 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. Regional anesthesia (RA) was defined as neuraxial blockade or other regional blockade. Details of venous access, intra-operative hemodynamic monitoring and, for procedures under GA, details of ventilator settings, average intra-operative fractional inspired oxygen concentration (FiO_2), peak end-expiratory CO_2, peak airway pressure (cmH_2O) and the use of nitrous oxide (N_2O) as a supplementary anesthetic agent were recorded.

Perioperative complications

Perioperative complications were defined as those occurring during surgery or in the 28-day postoperative 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 (RV) afterload leading to RV failure, cardiogenic shock and VQ 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 and right ventricular failure) requiring vasopressors and/or inotropes and/or inhaled nitric oxide (NO) and/or additional pulmonary vasodilator therapy (intravenous epoprostenol or nebulized iloprost). Minor PH complications were defined as major hypoxia requiring an escalation in the mode of ventilation or isolated hypotension or right ventricular failure not requiring the use of continuous infusions of vasopressors or inotropes.

Statistical analysis

Statistical analysis was performed using Stat view version 5.0 (Abacus Concepts Inc., Berkley, CA, USA). Data are presented as mean ± standard deviation (SD) or median (range) for parametric and non-parametric data respectively. Statistical analysis was performed using parametric tests (Fisher exact test, paired t-test) or non-parametric tests (Mann–Whitney *U*-test for unpaired data, Wilcoxon matched pair test for paired data) as appropriate. Distribution of qualitative data was assessed by Pearson's Chi-squared test with Yates' correction for continuity or Fisher-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 in univariate analysis. A *P* value <0.05 was considered significant.

RESULTS

Preoperative patient characteristics

Twenty-eight procedures were identified in 28 individual patients with idiopathic PAH (n=10, 36%), associated PAH (n=10, 36%, comprising 5 portopulmonary, 3 connective tissue disease-associated and 2 HIV PAH) and CTEPH (n=8, 28%). Mean age patient was 53±16 years 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 6MWD was 388±114 m. Preoperative hemodynamics showed mPAP of 43±12 mmHg, normal cardiac index of 3.25x±0.68 L/min/m² and low SvO2 (66±6%). 57% of all patients were on specific PAH therapy (**Table I).**

Operative characteristics

Of 28 procedures performed, 16 were abdominal surgery (9 inguinal hernias, 1 umbilical hernia, 2 laparoscopic cholecystectomies, 1 splenectomy, 1 open appendicectomy, 2 major bowel resections), 8 orthopedic procedures (of which 4 were major hip surgery, 2 were major knee surgery), 2 mastectomies and 2 hysterectomies. According to our definitions, 16 (57%) were major and 12 (43%) were minor surgical procedures. Fourteen procedures were performed under general anesthesia (GA) and 14 under regional anesthesia (RA). Four were emergency procedures, all performed under GA (hip hemiarthoplasty, bowel resection, laparotomy and appendicectomy).

Anesthesia characteristics

For the 14 patients that had procedures under GA, all patients received opioids and propofol for induction of anesthesia, and anesthesia was maintained with sevoflurane

(10/14), isoflurane (2/14) or desflurane (2/14). Nitrous oxide was used as a supplemental anesthetic agent in 4 patients and the intra-operative FiO2 was 0.60±0.17 (**Table II).**

RA consisted of neuraxial blockade in 11/28 (spinal anesthesia in 2, combined spinal-epidural anesthesia in 9 patients) and 3 other regional blocks (supraclavicular block, femoral block, lumbar plexus block) were combined with sedation in all three cases. For patients undergoing neuraxial blockade (n=11), spinal needles were 27G in size, spinal doses used were sufentanil 4.8 μg (3-7.5, data available for n=9) combined with 0.5% heavy bupivicaine, and epidural top-ups used 2% lidocaine in all patients. No patients required conversion to GA. All those previously on warfarin (n=5) were switched to low molecular weight (LMW) heparin (prophylactic dose) pre-operatively, and there were no reported bleeding complications relating to the site of regional blockade, including in the patients on continuous intravenous epoprostenol.

There was no significant age or sex difference, or 6MWD or NYHA functional class difference, between those having GA or RA (**Table I**). As compared to RA, patients that had procedures under GA had less severe hemodynamic impairment with a significantly lower mPAP (36±10 mmHg vs. 48±11mmHg, p=0.003), PVRi (7.2±2.9 vs. 13.9±5.5 UW/m², p=0.0003) and a higher CI (3.6±0.6 vs. 2.94±0.6, p=0.009). Patients having RA were more likely to be on specific PAH therapy than those having GA (86% vs. 29%, p=0.002).

Perioperative complications

Perioperative complications relating to PH occurred in 8/28 (29%) of procedures (**Table III**). There were no reported non-PH complications. Two deaths occurred in

28 procedures performed (7%), due to refractory right heart failure in both cases: one intraoperatively and the other at day 11. In the 4 emergency procedures, perioperative complications relating to PH (n=4, 100%) including death (n=2, 50%) were higher compared to the non-emergency procedures (with 4/24 (17%) complications and no deaths - altogether p<0.001, **Table II**). More patients that had PH perioperative complications had undergone major surgery compared to minor surgery (8/16 (50%) and 0/12 (0%) respectively, p=0.008, **Table II**). Mortality related to major surgery was 2/16 (13%) compared to no deaths in patients having minor surgery.

Most of the complications occurred during or in the first 48h following the procedure (7/8, 88%). Complications included 3 severe acute right heart failure (following which 2 patients died), 3 cases of isolated hypotension and 2 of severe hypoxemia. One death occurred at the time of surgery due to a refractory right heart failure (patient 5), and the other (patient 8) was due to ongoing PH and right ventricular failure at day 11 postoperatively (see **Table IV**).

Prognostic factors

There was no significant difference in age or PH etiology between patients who had or did not have perioperative complications. There was a suggestion that patients in NYHA I-II were less likely to have perioperative complications than those in NYHA III-IV preoperatively (n=17, 80% vs. n=3, 20%, respectively; p=0.14), and that patients with a higher preoperative 6MWD had fewer complications (411+/-99 vs. 311+/-140m, p=0.058). However, there was no significant difference in resting pre-operative hemodynamics 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 III**).

There was a suggestion that more perioperative complications occurred in procedures performed under GA compared to RA (6, 75% vs. 2, 25% with GA and RA, respectively, p=0.12). Procedures with associated perioperative complications were longer than uncomplicated procedures (193 (120-420) vs. 112 (45-465 minutes, p=0.003). More patients with CVP or intra-arterial monitoring (3, 38%) and in whom cardiac output monitoring (using PAC or esophageal Doppler) (3, 38%) was used had complications than those without (0 and 5%, respectively) (**Table II**).

In patients undergoing GA, there was no significant difference in FiO2 between patients with (0.60±0.12) or without perioperative complications (0.59±0.20), and 3 (38%) of patients with complications were given the supplemental anesthetic agent nitrous oxide compared to 1 (5%) of those without complications. High peak end-tidal (ET) CO_2 and peak airway pressure were not significantly associated with perioperative complications (p=0.17 and p=0.51, respectively; **Table II**).

Longer-term outcomes

When perioperative deaths had been excluded, the remaining survivors (n=26) showed no evidence of significant clinical or hemodynamic deterioration at 3-6 months follow-up. At preoperative baseline, 19/26 (73%) of survivors were in NYHA functional class I-II compared with 22/26 (85%) at 3-6 months' follow-up (p=0.31). Accordingly, 7/26 (27%) patients were in NYHA functional class III-IV before surgery and 4 (15%) at follow up (including one patient in NYHA class IV) (p=0.77) (**Table V**). Only 2 patients (8%) had an increase in PAH therapy over this period.

There was no significant worsening in 6MWD (n=17) or hemodynamics (n=11) for those where follow-up data were available at 3-6 months. Even for the 6 patients who suffered perioperative complications and survived, NYHA functional class, 6MWD and hemodynamic 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 perioperative complications had occurred or not (**Figure I**).

DISCUSSION

In this single-centre study, we described the anesthetic management, perioperative complications and PH outcomes in this high-risk population undergoing non-cardiothoracic, non-obstetric surgery. In this cohort of well-characterized 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 non-severe patients in an experienced PH center.

Data on complications and mortality after non-cardiothoracic, non-obstetric surgery in this population are rare with only two previous single-centre studies available. One study of 145 patients showed that 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-characterized patients with regard to PH classification: some patients had PH secondary to lung disease, and some were diagnosed using echocardiography without hemodynamic confirmation (9). The second is a smaller study of well-characterized patients with more severe PAH compared to this study (mPAP 53±14 mmHg, 62% NYHA III-IV) undergoing 28 surgical procedures. Of these, 12 were abdominal, 6 thoracic (including lung biopsies and resections but not endarterectomy surgery), 4 gynecological and 4 orthopedic procedures, and 79% were performed under GA. Most complications reported related to the surgical procedure itself, with only 14% of cases complicated by reversible right ventricular failure, although deaths occurred in 18% patients (11). The lower overall mortality in our study probably reflects the fact that patients had less severe disease, no thoracic procedures were performed, and only 50% had GA compared to this last study.

However, mortality/complication rates of patients in our 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 fourfold increase in maternal mortality (univariate analysis, OR 4.37, 95% CI 1.28–16.5, p=0.02). (22). This has also been suggested in patients with Eisenmenger's syndrome where of 103 non-cardiac anesthetics, perioperative mortality of those receiving GA was 18% compared to 5% of those undergoing RA, although this may well have been an indirect indicator of the increased mortality seen in major vs. minor surgery (24% vs. 5%, p<0.01) as more patients having GA also had more major surgery (29). Patients with PAH that tolerate pregnancy have a particularly high perioperative risk, with 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 in this study for this reason. However, useful experience with obstetric RA is extrapolated to the non-obstetric 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 hemodynamic compromise following sympathetic blockade, however using a low intrathecal dose minimizes 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 anesthetic 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 anti-platelet aggregation effects of prostacyclins.

Both deaths reported in this study followed refractory acute right heart failure, with one death intraoperatively and one at day 11. Most non-fatal complications occurred intraoperatively, and related in varying degrees to isolated right ventricular failure not requiring vasopressors and/or inotropes. Previous studies have showed that similar causes of perioperative deaths in patients undergoing non-cardiac, non-obstetric surgery may occur suddenly (11, 20) or up to 48 hours following surgery (32). Obstetric PAH deaths have been reported even up to one month after delivery (22), and guidelines suggest that obstetric patients should be monitored for at least up to 72 hours post-operatively (33). In this study, we recorded perioperative complications related to PH and death in a 28-day post-operative period, with most (11/12, 92%) of the complications occurring in the first 48h.

In this 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, shorter 6MWD. Preoperative resting invasive hemodynamics 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 pre-operative cardiopulmonary exercise testing in the general surgical population. In a prospective study of patients (including those <60y with cardiac disease) undergoing major abdominal surgery, pre-operative

anaerobic threshold (AT) predicted outcome, whereby no patients died when AT exceeded 11ml/min/kg, but 4.6% died when AT<11ml/min/kg (34). AT was used as it is independent of patient effort and occurs well below VO2max, the more usually recorded value in PH, where VO2max <10.4ml/min/kg has been shown to predict poor survival (35). It would be useful to know from future studies if AT above a certain threshold was also predictive of better surgical outcomes in this specific patient population.

There was a suggestion that patients monitored with CO monitoring (either PAC or esophageal Doppler) had more complications, although these are likely to indicate the more complex patients. Intra-operative invasive hemodynamic monitoring is not without risk, with both arrhythmias and pulmonary artery thrombosis and rupture reported (36), although using a PAC is useful with a falling cardiac output and mPAP and a rising CVP as markers of acute right ventricular decompensation (25). The perioperative use of PAC in patients with PH is debated. With the background that many complications are potentially avoidable, and that good team-work improves outcomes, a recent study in non-cardiac surgery has shown that use of a standardized safety checklist reduced complications (37).

This study has suggested that the use of GA as compared to RA was associated with worse outcomes. Most patients having GA were undergoing emergency or major surgery, known to be associated with worse outcomes (38, 39) and these are likely to be major confounding factors. However, there were more severe patients having RA, indicated by both hemodynamics and that significantly more patients on specific PAH therapy had RA than GA. The use of GA may increase PVR through several mechanisms including increased sympathetic stimulation during airway instrumentation at laryngoscopy (40), effects of volatile agents (41), high

airway plateau pressure due to the effects of positive-pressure mechanical ventilation (12, 13]), hypoxia (15) and hypercapnia (16). Our data suggested more complications occurred in those with higher $ETCO_2$ and peak airway pressure, although many confounding factors may affect these values. Anesthetic volatile agents may also adversely affect right ventricular preload and contractility (25), as well as afterload (41), although isoflurane has been used in human PAH (42). Desflurane appears to exert worse pulmonary vascular effects than isoflurane probably through sympathetic activation (43, 44). Some studies suggest that nitrous oxide as a supplemental anesthetic agent may increase PVR, especially in those with elevated pre-existing PVR (45), and it may also adversely influence endothelial function (46). An increase in adverse cardiovascular events following major surgery has been observed (47), possibly also through adverse pulmonary vascular effects of increased sympathomimetic stimulation (48, 49) or hypoxia (50), and a study addressing these questions is ongoing (51).

Despite the fact that patients having complications had worse functional capacity, longer-term PH outcomes (including 6MWD, NYHA and hemodynamics) at 3-6 months were not adversely influenced by having had surgery. For those where 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. 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 evolution of the disease after the perioperative period, suggesting that essential surgical procedures may not always be contraindicated in patients with stable PH.

In addition to the confounding influence by the surgical disease severity and the type of surgery performed, limitations to this study include its retrospective nature. However, selection bias was minimized 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 the surgical type, on PH complications would require much larger patient numbers. This retrospective study does, however, emphasize several issues, which will be addressed further in an ongoing prospective multicenter international registry.

In conclusion**,** this study has shown that the incidence of complications associated with non-cardiothoracic, non-obstetric surgery remain high even in patients with mild to moderate PAH, especially in those having longer operations, emergency and major procedures, and those performed under GA, with most occurring within the first 48 hours 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. Regional anesthesia 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 center in the pre, peri and post-operative periods.

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Table I: Pre-operative patient factors in patients having general and/or regional anesthesia

	All patients	GA (or GA+RA)	RA alone	p value
Surgical cases	28	14 (50%)	14	
Age at time of surgery (yrs)	53 +/- 16	53.3 +/- 15	52.5 +/- 17	0.89
Sex (% female)	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	
Calcium channel blockers	1	0	1	
** includes patients on combination Rx*				
NYHA (%)				
Class I+II	21 (75%)	11 (79%)	10 (71%)	0.66
Class III	7 (25%)	3 (21%)	4 (29%)	
6MWD (m)	388 +/- 114	394 +/- 94	383 +/- 133	0.81
Hemodynamics:				
mPAP, mmHg	43±12	36±11	49±9.5	0.003
RAP, mmHg	6±4	5±3	7±4	0.08
PCWP, mmHg	8.8±3	8.5±3	8.9±3	0.77

CI, L/min/m²	3.25±0.68	3.60±0.62	2.93±0.58	0.009
SVI, ml/m²	42±10	44±9	39±11	0.33
PVRi, UW/m²	11.1±5.7	7.1±3.2	14.5±5.0	<0.001
SvO2, %	66±6	70±2	64±7	0.04

*GA general anesthesia, RA regional anesthesia. *Treatments included those on combination therapy. 'Other prostanoids' included beraprost and iloprost. Data expressed as mean ± SD. Means were compared using unpaired t-tests. **Comprising 5 Portopulmonary PH, 3 Connective tissue disease-PAH and 2 HIV-PAH patients*

Table II: Major perioperative complications during GA: Operative factors

	All patients	Patients with perioperative PH complications (8)	Patients without perioperative PH complications (20)	p value
Emergency surgery	4/28 (14%)	4 (100%)	0	<0.001
Major surgery **Minor surgery**	16 12	8 (100%) 0	8 (40%) 12 (60%)	0.008
GA **RA**	14 14	6 (75%) 2 (25%)	8 (40%) 12 (60%)	0.12
Operative time (min)	133 (45-465)	193 (120-420)	112 (45-465)	0.003
Monitoring	Standard monitoring with: +CVP/arterial line +CO (PAC or esophageal Doppler)	 3 3	 0 1	
General anesthesia (n=14)				
FiO2	0.60 +/- 0.17	0.60 +/- 0.12	0.59 +/- 0.20	0.90
Use of anaesthetic agent nitrous oxide (N_2O)/GA total	4	3	1	
Peak ETCO2 (mmHg)	36.1 +/- 5.4	38.6 +/- 6.7	34.1 +/- 3.5	0.17
Peak airway pressure (cmH_2O)	20.8 +/- 6.8	22.4 +/- 8.8	19.6 +/- 5.0	0.51

Major perioperative complications were defined by the occurrence of death or severe acute RVF (right ventricular failure) with clinical signs

of low cardiac output requiring vasopressors and/or inotropes and/or inhaled nitric oxide (NO) and/or additional pulmonary vasodilator therapy (intravenous epoprostenol or nebulized iloprost).
All patients had standard monitoring, which includes ECG, non-invasive BP and oximetry. CVP is central venous pressure and art line is invasive arterial blood pressure monitoring (if used, most patients had both). Cardiac output (CO) includes monitoring with pulmonary artery catheterization (PAC) or the use of esophageal Doppler.
Major surgery included laparotomy, hysterectomy, mastectomy and major orthopaedic surgery. Minor surgery included hernia repair and extremity orthopaedic surgery.
Data expressed as mean +/-SD for parametric or median (min-max) for non-parametric data. Comparisons were made using unpaired t-test or Mann Whitney tests for parametric/non-parametric data respectively.

Table III: Perioperative PH complications: Patient factors

	All patients	With perioperative PH complications up to D28	Without perioperative PH complications up to D28	p value
Patients	28	8 (29%)	20 (71%)	
Age (years)	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 Rx only	9	0	9	
*Bosentan**	*10*	0	10	
*Sildenafil**	*2*	1	1	
*Epoprostenol**	*5*	3	2	
Other prostanoids	*2*	1	1	
CCBs	*1*	0	1	
** includes combination Rx*				
NYHA				
Class I+II	21 (75%)	4 (50%)	17 (80%)	0.14
Class III	7 (25%)	4 (50%)	3 (20%)	
6MWD m	388 +/- 114	311 +/- 140	411 +/- 99	0.058

Hemodynamics				
mPAP, mmHg	43 +/- 12	44 +/- 13	43 +/- 12	0.77
RAP, mmHg	6.3 +/- 4	6.2 +/- 4	6.3 +/- 4	0.93
PCWP, mmHg	9 +/- 3	9.3 +- 4	8.6 +/- 3	0.59
CI, L/min/m²	3.25 +/- 0.68	3.28 +/- 0.52	3.24 +/- 0.75	0.89
SVI, ml/m²	42 +/- 10	38 +/- 8	43 +/- 10	0.25
PVRi, UW/m²	11.1 +/- 5.7	10.0 +/- 4.6	11.5 +/- 6.1	0.60
SvO2, % (n=18)	66 +/- 6	71 +/- 6	64 +/- 6	0.05

**The treatments included those on combination therapy. 'Other prostanoids' were beraprost and iloprost. **Associated PAH consisted of 5 Portopulmonary PH, 3 Connective tissue disease-PAH and 2 HIV-PAH patients*

Table IV: PH-related perioperative complications

Patient	PH type, age, NYHA, therapy	Surgery	Emergency	Anesthesia	Operative time (minutes)	Complication details (including death)	Timing of onset of complication
1	Associated, 83y NYHA III, No therapy	Hemiarthoplasty	Y	GA+RA	120	Hypotension	Intra-operative
2	Associated, 44y NYHA II No therapy	Total hip replacement (THR)	N	GA+CSE	210	Hypoxia	Intra-operative
3	Idiopathic, 44y NYHA II, Flolan	Knee arthrodesis	N	RA (CSE)	180	Tachycardia and hypotension	D1 post-operatively
4	Idiopathic, 63y NYHA III Flolan+ sildenafil	ORIF humerus	N	RA (supraclavicular block)	120	Hypoxia	Intra-operative
5	Associated, 43y NYHA II Flolan	Bowel resection	Y	GA	180	Refractory RVF; died at time of surgery	Intra-operative
6	Associated, 61y NYHA II,	Laparotomy	Y	GA	150	Hypotension, arrhythmias	Following intubation

	Beraprost						
7	CTEPH, 55y NYHA III, No therapy	Pancreatectomy	N	GA	420	Acute RVF	Following intubation
8	Idiopathic, 20y NYHA IV None; flolan + bosentan later	Appendix	Y	GA	n/a	Refractory RVF, death D11	Intra-operative and post-operative

Major perioperative complications were defined by the occurrence of death or severe acute RVF (right ventricular failure) with clinical signs of low cardiac output requiring vasopressors and/or inotropes and/or inhaled nitric oxide (NO) and/or additional pulmonary vasodilator therapy (intravenous epoprostenol or nebulized iloprost). Minor PH complications were defined as major hypoxia requiring an escalation in the mode of ventilation or isolated hypotension or right ventricular failure not requiring the use of continuous infusions of vasopressors or inotropes.

Table V: Follow-up data (for paired survivors only, n=26)

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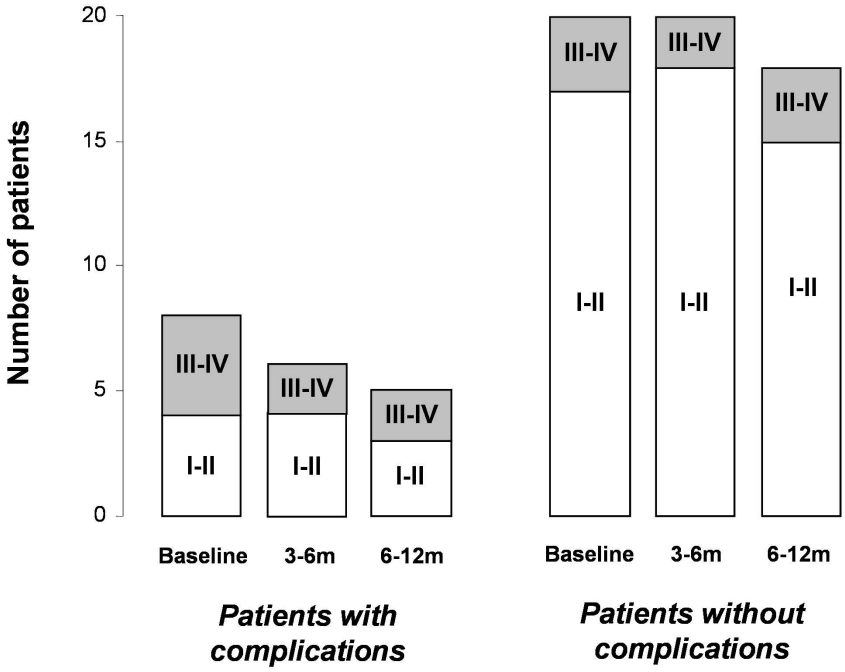
	All survivors (n=26)		
	Baseline	**3-6 months**	**P**
Clinical status **NYHA I-II** **NYHA III+IV**	19 (73%) 7 (27%)	22 (85%) 4 (15%)	0.31
Increase in therapy		2 (8%)	
6MWD (m) (n=17)	382 +/- 112	387 +/- 124	0.77
Hemodynamics (n=11 for paired values)			
RAP, mmHg	7 +/- 4	10 +/- 4	0.06
PVRi, UW/m²	14.5 +/- 5.60	12.02 +/- 6.59	0.04
mPAP, mmHg	49 +/- 11	46 +/- 12	0.49
CI, L/min/m²	2.94 +/-0.57	3.54+/-1.18	0.05

PCWP, mmHg	8 +/- 3	9 +/- 3	0.31
SvO2, % (n=5)	63 +/- 9	59 +/- 11	0.33



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