

## The Relationship of Systolic Pulmonary Artery Pressure with Perioperative Mortality and Morbidity in Patients Undergoing Non-Cardiac Surgery: A Single-Center Experience

### Kalp Dışı Cerrahiye Giden Hastalarda Sistolik Pulmoner Arter Basıncının Perioperatif Mortalite ve Morbidite ile İlişkisi: Tek Merkez Deneyimi

#### ABSTRACT

**Objective:** Pulmonary hypertension (PH) is associated with adverse perioperative events in patients undergoing non-cardiac surgery. In this study, we aimed to investigate the relationship between systolic pulmonary artery pressure (sPAP), evaluated by transthoracic echocardiography (TTE) before surgery, and perioperative mortality and morbidity in patients who underwent non-cardiac surgery in our center.

**Methods:** Of the 3425 retrospectively screened patients who underwent non-cardiac surgery, 3049 patients whose estimated sPAP values were previously determined by TTE were included in the study. Patients were classified into 3 groups according to their estimated sPAP levels. sPAP <35 mmHg formed group 1, 35–39 mmHg group 2, and ≥ 40 mmHg group 3. All demographic and perioperative data obtained from the database of our institute were compared in three groups.

**Results:** Of the 3049 patients enrolled in the study, 2406 (78.9%) were in group 1, 259 (8.5%) in group 2, and 384 (12.6%) in group 3. Thirty-day all-cause mortality was observed in 82 (2.7%) patients, cardiac mortality occurred in 9 patients (0.3%). In the group with sPAP ≥40 mmHg, cardiac mortality was 0.5% and all-cause mortality was 7.3%. Thirty-day all-cause mortality, acute pulmonary edema, and acute renal failure were significantly higher in group 3 than in the other groups. Cardiac mortality did not differ significantly between the groups. Age, sPAP value, and chronic obstructive pulmonary disease history were revealed as independent predictors of all-cause mortality in multivariate logistic regression analysis.

**Conclusion:** In conclusion, increased sPAP is associated with adverse postoperative outcomes. The evaluation of sPAP with TTE before non-cardiac surgery in patients whose clinical features and examination findings suggest PH may contribute to preoperative risk assessment.

**Keywords:** Non-cardiac surgery, preoperative cardiac evaluation, pulmonary hypertension

#### ÖZET

**Amaç:** Pulmoner hipertansiyon (PH) kalp dışı cerrahiye giden hastalarda olumsuz perioperatif olaylarla ilişkili bir durumdur. Çalışmamızda, merkezimizde kalp-dışı cerrahiye giden hastalarda cerrahi öncesinde transtorasik ekokardiyografi (TTE) ile değerlendirilen sistolik pulmoner arter basıncının (sPAB) perioperatif mortalite ve morbidite ile ilişkisinin araştırılması amaçlanmıştır.

**Yöntemler:** Kalp dışı cerrahi uygulanan 3425 hasta geriye dönük olarak tarandı ve öncesinde tahmini sPAB değerleri TTE ile belirlenmiş olan 3049 hasta çalışmaya dahil edildi. Hastalar tahmini sPAB seviyelerine göre 3 gruba ayrıldı. sPAB <35 mmHg, grup 1, 35–39 mmHg grup 2 ve ≥ 40 mmHg grup 3'ü oluşturdu. Merkezimizin veri tabanından elde edilen tüm demografik ve perioperatif veriler üç grupta karşılaştırıldı.

**Bulgular:** Çalışmaya alınan 3049 hastanın 2406'sı (%78.9) grup 1'de, 259'u (%8.5) grup 2'de, 384'ü (%12.6) grup 3'te idi. Otuz günlük tüm nedenlere bağlı mortalite 82 hastada, (%2.7) kardiyak mortalite ise 9 hastada (%0.3) görüldü. sPAP ≥ 40 mmHg olan grupta kardiyak mortalite %0,5 ve tüm nedenlere bağlı mortalite %7.3 idi. Otuz günlük tüm nedenlere bağlı mortalite, akut pulmoner ödem ve akut böbrek yetmezliği grup 3'te diğer gruplara göre anlamlı olarak daha yüksekti. Kardiyak mortalite gruplar arasında anlamlı farklılık göstermedi. Yaş, sPAP değeri ve KOAH öyküsü, çok değişkenli lojistik regresyon analizinde tüm nedenlere bağlı mortalitenin bağımsız belirteçleri olarak ortaya konuldu.

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**Sonuç:** Artmış sistolik pulmoner arter basıncı, postoperatif olumsuz sonuçlarla ilişkilidir. Klinik özellikleri ve muayene bulguları PH düşündüren hastalarda, kalp dışı cerrahi öncesi sPAB değerinin TTE ile belirlenmesi, operasyon öncesi risk değerlendirmesine katkı sağlayabilir.

**Anahtar Kelimeler:** Kalp dışı cerrahi, ameliyat öncesi kardiyak değerlendirme, pulmoner hipertansiyon

**P**ulmonary hypertension (PH) represents a disorder characterized by an increase in pulmonary artery pressure as a result of a heterogeneous group of diseases.<sup>1</sup> The presence of PH is associated with increased morbidity and mortality in patients undergoing non-cardiac surgery as well as in the general population, regardless of the etiology.<sup>2,3</sup>

Perioperative adverse events in individuals with PH are mostly related to the effect of mechanical ventilation, positive end-expiratory pressure, and increased sympathetic activation on pulmonary hemodynamics. As a result, acute decompensation of right heart functions, systemic hemodynamic disorder, myocardial ischemia, deterioration of left heart functions, cardiac arrhythmias, and eventually cardiac arrest may develop.<sup>4</sup> The severity of complications is related to the factors such as the risk of the operation, other comorbidities, and the functional status of the patients.

The incidence of PH is increasing in the general population, especially due to the increasing cardiovascular and respiratory diseases.<sup>5</sup> This indicates that PH may be found more frequently in patients who will undergo non-cardiac surgery. Nevertheless, preoperative cardiac assessment guidelines and risk scoring systems are insufficient in the detection, approach, and management of these patients.<sup>6-9</sup>

This study aimed to investigate the association of estimated pulmonary systolic artery pressure by transthoracic echocardiography (TTE) and perioperative adverse events in patients who were evaluated preoperatively in the cardiology department of our center.

## Materials and Methods

In this retrospectively designed study, 3425 patients who were planned for non-cardiac major surgery under general anesthesia in our center in 2018-2019 and referred for preoperative cardiology evaluation were screened. Among these patients, 3049 patients who underwent TTE and whose estimated systolic pulmonary artery pressure (sPAP) could be determined were included in the study. Patients were classified into 3 groups according to their estimated sPAP levels. sPAP <35 mmHg formed group 1, 35-39 mmHg group 2, and ≥40 mmHg group 3. Demographic data, clinical characteristics, cardiovascular risk factors, type of surgery to be performed, echocardiographic evaluation, and post-operative follow-up results of the

patients were obtained from the database of our institute. All demographic and perioperative data were compared in three groups. Hypertension is defined as repeated office systolic blood pressure values ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.<sup>10</sup> Patients with a history of treatment for HT were also considered hypertensive patients. Diabetes mellitus (DM) is defined as a fasting plasma glucose level ≥126 mg/dL or a casual plasma glucose level ≥200 mg/dL or a 2-h post-load glucose level ≥200 mg/dL.<sup>11</sup> Patients receiving treatment for DM were also accepted as diabetic, irrespective of their blood glucose and HbA1c levels. Chronic kidney disease is defined as an estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>, persisting for 3 months or more, regardless of the etiology.<sup>12</sup> Perioperative events were determined as cardiovascular and all-cause death, acute pulmonary edema, myocardial infarction, atrial fibrillation (AF), acute renal failure, and stroke during the operation and within 30 days. Surgical risk classification which predicts the risk of 30-day CV death, MI, and stroke was made by considering the type of surgery or intervention to be performed according to current cardiovascular assessment and management of patients undergoing non-cardiac surgery guideline.<sup>13,14</sup> The operation risk was classified as low risk if the estimated 30-day risk of CV death, MI, and stroke was <1%, moderate if 1-5%, and high-risk if >5%. This classification defines the risk of surgical procedures according to the severity of postoperative adverse events, independent of the patient's comorbidities.<sup>15</sup>

This study was performed in compliance with the Declaration of Helsinki and the ethical approval of the study protocol was obtained by Ethics Committee of Koç University (Approval No: 2019.265.IRB2.087, Date: 26.08.2019).

## Echocardiographic Assessment

Echocardiographic evaluation of the patients was performed with Epiq 7C ultrasound system (Philips, Andover, MA, USA) using a 2.3-3.5 MHz transducer probe accompanied by simultaneous ECG recording. Conventional measurements were made on the images obtained from standard parasternal and apical windows in accordance with the recommendations of the American Society of Echocardiography.<sup>16</sup> The left ventricular ejection fraction (LVEF) was calculated by the modified two-dimensional biplane Simpson's method.<sup>17</sup> Pulmonary artery systolic pressure was measured by adding the estimated right atrial pressure to the gradient calculated by Bernoulli's equation over the peak velocity of tricuspid valve regurgitation flow.<sup>18</sup>

## Statistical Analysis

Data analyses were performed using Statistical Package for the Social Sciences 26.0 (SPSS, Chicago, IL, USA) program. The normality of data was assessed with Kolmogorov-Smirnov test. Results are described as number and percentages for categorical variables and mean ± standard deviation for continuous variables. The means of

## ABBREVIATIONS

AF	Atrial fibrillation
DM	Diabetes mellitus
LVEF	Left ventricular ejection fraction
PH	Pulmonary hypertension
PH	Transthoracic echocardiography
sPAP	Systolic pulmonary artery pressure

continuous variables were compared with the one-way ANOVA test. The chi-square test was used to compare categorical variables. The  $P < 0.05$  was considered statistically significant. Pearson analysis was used for continuous variables in the correlation analyses, and the correlation coefficient ( $r$ ) was calculated. Multivariable logistic regression analysis was performed to evaluate the determinants of 30-day all-cause and cardiac mortality.

**Results**

Of the 3049 patients enrolled in the study, 2406 (78.9%) were in group 1, 259 (8.5%) in group 2, and 384 (12.6%) in group 3. While age, CV risk factors, CAD, congestive heart failure and chronic obstructive pulmonary disease (COPD) were significantly higher in group 3, no significant difference was found between the groups in terms of age, body mass index, smoking history (Table 1). LVEF was significantly lower in group 3. There were 64 patients (2.1%) with LV EF  $<40\%$ , and the rate of patients with LVEF  $<40\%$  was significantly higher in group 3 than in groups 1 and 2 (9.1%/n = 35, 0.9%/n = 22, 1.9%/n = 5,  $P < 0.001$ , respectively). In addition, the operative risk ratios were not significantly different between the groups (Table 2). In the correlation analysis, sPAP showed a significant positive

correlation with age ( $r = 0.312$ ,  $P < 0.001$  and a significant negative correlation with EF ( $r = -0.298$ ,  $P < 0.001$ ).

Thirty-day all-cause mortality was observed in 82 (2.7%) patients, cardiac mortality occurred in 9 patients (0.3%). In the group with sPAP  $\geq 40$  mmHg, cardiac mortality was 0.5%, and all-cause mortality was 7.3%. A comparison of postoperative event rates between the groups demonstrated that all-cause mortality, acute pulmonary edema, and acute renal failure were significantly higher in group 3 than in the other groups. There was no difference between groups 1 and 2 in terms of these parameters. Cardiac mortality did not differ significantly between the groups. Postoperative AF rate was significantly higher in groups 2 and 3 compared to group 1. No significant difference was observed between group 2 and 3 in terms of AF development rate. Cerebrovascular event rate was significantly higher in group 3 than group 1 (Table 3).

Multivariable logistic regression analysis revealed age, sPAP value, and presence of COPD as independent predictors of all-cause mortality (Table 4). No independent relationship was found between demographic and clinical characteristics and cardiac death (Table 5).

**Table 1. Baseline Demographic, Clinical, and Echocardiographic Characteristics of the Study Groups**

Parameter	Group 1 (sPAP < 35 mmHg) (n = 2406)	Group 2 (sPAP = 35-39 mmHg) (n = 259)	Group 3 (sPAP $\geq 40$ mmHg) (n = 384)	P
Age	59.66 $\pm$ 17.01	69.53 $\pm$ 15.65	72.92 $\pm$ 13.39	<b>&lt;0.001</b>
Male, % (n)	50.5 (1214)	49.2 (128)	50.3 (193)	0.929
BMI (kg/m <sup>2</sup> )	27.65 $\pm$ 5.87	27.52 $\pm$ 5.56	26.70 $\pm$ 5.65	0.934
HT, % (n)	57.9 (1393)	77.7 (202)	75.8 (291)	<b>&lt;0.001</b>
DM % (n)	24.5 (590)	32.3 (84)	28.1 (108)	<b>0.012</b>
Smoking, % (n)	30.6 (736)	27.7 (72)	27.6 (106)	0.346
CAD, % (n)	19.2 (461)	20.4 (53)	28.4 (109)	<b>&lt;0.001</b>
MI history, % (n)	8.1 (195)	8.8 (23)	19.3 (74)	<b>&lt;0.001</b>
CABG history, % (n)	6.9 (166)	6.9 (18)	10.7 (41)	<b>0.03</b>
CHF, % (n)	2.5 (59)	6.5 (17)	18.2 (70)	<b>&lt;0.001</b>
AF, % (n)	5.1 (123)	16.2 (42)	36.7 (141)	<b>&lt;0.001</b>
COPD, % (n)	5 (121)	8.1 (21)	13.3 (51)	<b>&lt;0.001</b>
CKD, % (n)	14.1 (339)	21.9 (57)	23.7 (91)	<b>&lt;0.001</b>
LV EF (%)	59.34 $\pm$ 4.90	57.47 $\pm$ 5.66	55.02 $\pm$ 9.34	<b>&lt;0.001</b>
sPAP (mmHg)	25.85 $\pm$ 4.27	36.32 $\pm$ 1.61	48.36 $\pm$ 9.06	<b>&lt;0.001</b>

BSA, body surface area; BMI, body mass index; HT, hypertension; DM; diabetes mellitus; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery by-pass graft; CHF, congestive heart failure; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; LV EF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure.

**Table 2. Comparison of Groups According to Operation Risk**

Operation risk	Group 1 (sPAP < 35 mmHg) (n = 2406)	Group 2 (sPAP = 35-39 mmHg) (n = 259)	Group 3 (sPAP $\geq 40$ mmHg) (n = 384)	P
Low, % (n)	30.3 (728)	30.4 (79)	26.6 (102)	
Intermediate, % (n)	52.3 (1257)	53.8 (140)	54.2 (208)	0.559
High, % (n)	17.5 (420)	15.8 (41)	19.3 (74)	

**Table 3. Comparisons of Postoperative Adverse Events Ratios in Study Groups**

Parameter	Group 1 (sPAP < 35 mmHg) (n = 2406)	Group 2 (sPAP = 35-39 mmHg) (n = 259)	Group 3 (sPAP ≥ 40 mmHg) (n = 384)	P
Cardiovascular mortality, % (n)	0.2 (6)	0.4 (1)	0.5 (2)	0.636
All cause mortality, % (n)	1.9 (46)	3.1 (8)	7.3 (28)	<0.001 <sup>a</sup>
Acute pulmonary edema, % (n)	0.2 (6)	0 (0)	3.9 (15)	<0.001 <sup>a</sup>
Atrial fibrillation, % (n)	2.5 (61)	6.2 (16)	6.3 (24)	<0.001 <sup>b</sup>
Myocardial infarction, % (n)	0.3 (8)	0.4 (1)	0.8 (3)	0.427
Acute renal failure, % (n)	0.7 (16)	1.2 (3)	2.3 (9)	0.005 <sup>a</sup>
Cerebrovascular event, % (n)	0.2 (4)	0.8 (2)	1.8 (7)	<0.001 <sup>c</sup>

sPAP, systolic pulmonary artery pressure. <sup>a</sup>A significant difference was observed between group 3 and other groups, but there was no significant difference between group 1 and 2. <sup>b</sup>Postoperative AF rate was significantly higher in Groups 3 and 2 compared to group 1. No significant difference was observed between group 2 and 3. <sup>c</sup>There was a significant difference between group 1 and 3.

**Table 4. Multivariable Regression Analysis for Postoperative Cardiovascular Mortality**

	Cardiovascular mortality		
	P	OR	95% Confidence interval
Age	0.684	1.010	0.961-1.062
sPAP	0.629	0.984	0.921-1.051
LV EF	0.071	0.915	0.830-1.008
HT	0.730	0.743	0.138-4.005
DM	0.665	1.402	0.304-6.467
CAD	0.934	0.928	0.161-5.353
CHF	0.268	0.267	0.026-2.756
AF	0.309	0.427	0.083-2.200
CKD	0.860	0.867	0.176-4.259

sPAP, systolic pulmonary artery pressure; LV EF, left ventricular ejection fraction; HT, hypertension; DM; diabetes mellitus; CAD, coronary artery disease; CHF, congestive heart failure; AF, atrial fibrillation; CKD, chronic kidney disease.

**Discussion**

PH is associated with poor perioperative outcomes in patients undergoing non-cardiac surgery and has become a more common problem in preoperative evaluation due to advanced age and improved survival of PH patients related to current diagnostic approaches and treatment modalities.

In our study, the relationship between sPAP, evaluated by TTE and the perioperative adverse events in patients undergoing non-cardiac surgery was examined, and it was found to be independently associated with 30-day all-cause mortality. In addition, acute pulmonary edema, acute renal failure and cerebrovascular events were significantly higher in group 3 and AF in groups 2 and 3. All-cause mortality was also independently associated with age and COPD in multivariate logistic regression analysis.

The rate of patients with an sPAP value of 40 mmHg and above was found to be 12.6%. In a large-scale study covering 10 years in the USA, the prevalence of PH in patients who underwent non-cardiac surgery was found to be 0.8%, and this rate was observed

**Table 5. Multivariable Regression Analysis for Postoperative All-Cause Mortality**

	All-cause mortality		
	P	OR	95% Confidence interval
Age	0.005	1.025	1.007-1.042
sPAP	0.001	1.037	1016-1.058
LV EF	0.528	0.986	0.945-1.029
HT	0.443	1.244	0.712-2.172
DM	0.544	0.853	0.511-1.424
CAD	0.118	1.534	0.897-2.623
CHF	0.579	0.741	0.257-2.137
AF	0.676	0.869	0.450-1.678
COPD	0.005	2.390	1.303-4.386
CKD	0.116	1.551	0.897-2.680

sPAP, systolic pulmonary artery pressure; LV EF, left ventricular ejection fraction; HT, hypertension; DM; diabetes mellitus; CAD, coronary artery disease; CHF, congestive heart failure; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

as 1.2% over the age of 45 years.<sup>3</sup> This significant difference in the incidence of PH was considered to be related to the diagnostic method and patient population. While sPAP estimated by TTE was calculated in all patients in our study, patients diagnosed with PH by scanning the ICD code were evaluated in this US-based study, and it was emphasized that this could lead to an underestimation in the diagnosis of PH. In addition, the fact that our study included kidney, liver transplant, oncologic surgery patients may contribute to explain this difference.

Various studies have demonstrated the association between PH and increased perioperative risk of mortality and morbidity in patients undergoing non-cardiac surgery.<sup>19,20</sup> In the large cohort of Smilowitz et al.<sup>3</sup>, cardiovascular mortality rate was approximately 4 times higher than in those without PH (4.4% vs. 1.1%). In our study, 30-day cardiac mortality rate was found to be 0.5%, and sPAP was not found to be an independent determinant of this. It was assumed to be related to the low number of patients with cardiac death. Similar to our results,

Ramakrishna et al.<sup>21</sup> found a 30-day mortality rate of 7% in 145 patients with PH who underwent non-cardiac surgery.<sup>21</sup> Unlike our study, PH associated with left heart disease was excluded in this study. Studies conducted in different etiologies of PH patients and different types of operations have shown that regardless of its etiology, PH increases the perioperative risk in surgical procedures.<sup>22-25</sup> Although our study patients were heterogeneous in terms of operation type and clinical features, the operative risk did not differ significantly between groups classified according to pulmonary artery pressures. However, despite a similar operative risk, increased PAP was independently associated with higher postoperative mortality.

High pulmonary artery pressure causes intolerance to hemodynamic changes in the perioperative period. Since PAP is a dynamic parameter, i.e., affected by the patient's volume load, hemodynamic and metabolic status, it may be more beneficial to evaluate it close to the operation. Previous studies investigating the effect of PH on perioperative adverse events included patients who were either scanned with the ICD code or were diagnosed with right heart catheterization earlier. In our study, estimated sPAP was determined by TTE shortly before the operation. Determining the pulmonary artery pressure and hemodynamic status of the patients before the operation will help to regulate the treatment and reduce the associated risks. Studies have shown that PH originating from the left heart (group 2) is the most common cause of pulmonary HT.<sup>26-28</sup> These patients may have a rapid hemodynamic response to medical treatment.

The main limitations of the study are that it was a retrospective study and the sPAP measures were not evaluated by right heart catheterization, which is the gold standard method. In addition, the WHO classification of PH was not available because the study was retrospective, and PH was detected in some patients during preoperative evaluation. Another limitation is that the study was performed in a heterogeneous patient group in terms of clinical features and operation type. In addition, the low rate of cardiac mortality may have affected the determination of its statistically significant predictors. The strengths of the study are that it had a large sample size and had a detailed cardiac evaluation of all patients. It is also important that all patients had echocardiography before the operation. In addition, results of the study support the importance of pulmonary arterial pressure assessment in selected patients, which is not included in preoperative risk scoring systems.

## Conclusion

Increased sPAP values is associated with postoperative adverse events. TTE is an easily applicable method for examining sPAP values of patients preoperatively. It is also valuable for evaluating cardiac functions and the etiology of PH. The evaluation of sPAP with TTE before non-cardiac surgery in patients whose clinical features and examination findings suggest PH may contribute to preoperative risk assessment.

**Ethics Committee Approval:** Ethics committee approval was obtained from Ethics Committee of Koç University (Approval No: 2019.265. IRB2.087, Date: 26.08.2019).

**Informed Consent:** Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

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