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Research

Pulmonary to Systemic Flow Ratio in Precapillary Pulmonary Hypertension Without Left-to-Right Shunts: A Prognostic Implication of the Fick Method

Soldan Sağa Şantı Olmayan Prekapiller Pulmoner Hipertansiyonda Pulmoner/Sistemik Akım Oranı: Fick Yönteminin Prognostik Bir Sonucu

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ABSTRACT

Objective: We routinely calculate the pulmonary to systemic (Qp/Qs) ratio to avoid missing any left-to-right shunts in patients with precapillary pulmonary hypertension (PH). However, the pulmonary artery oxygen saturation ($SpaO_2$) was lower than the mixed venous oxygen saturation ($SmvO_2$) calculated using the formula; hence, the Qp/Qs ratio was calculated as less than "1" in some patients despite the absence of any detectable shunt. We hypothesized that this observation might have prognostic significance; however, to the best of our knowledge, it has not been investigated yet. Therefore, we aimed to examine the prognostic value of the Qp/Qs ratio in precapillary PH without left-to-right shunts.

Methods: In this retrospective cohort study of 173 consecutive patients, hospital files were scanned for clinical, echocardiographic, and hemodynamic data including the Qp/Qs ratio calculated using the Fick method.

Results: During a median follow-up of 25 months, 74 patients died. Nonsurvivors had lower Qp/Qs ratio than survivors (0.76±0.19 vs. 1.02±0.07 p<0.001). The multivariate logistic regression analysis showed that a decreased Qp/Qs ratio and poor functional capacity (World Health Organization class III-IV) were independent predictors of mortality. The receiver operating characteristic curve analysis revealed that the optimal cutoff value of the Qp/Qs ratio for predicting mortality was 0.90 with a sensitivity of 76% and specificity of 98%.

Conclusion: The Qp/Qs ratio calculated using the Fick method was an independent predictor of mortality. This prognostic implication was based on the difference between $SpaO_2$ and $SmvO_2$ calculated using the formula. Nevertheless, this result might be a reflection of a potential intrinsic methodological flaw of the Fick method.

Keywords: Pulmonary hypertension, prognosis, fick method, oxygen, mortality

ÖZ

Amaç: Prekapiller pulmoner hipertansiyonlu (PH) hastalarda soldan sağa şantları kaçırmamak için pulmoner/sistemik oranı (Qp/Qs) rutin olarak hesaplamaktayız. Şaşırtıcı bir şekilde pulmoner arter oksijen satürasyonunun ($SpaO_2$) formülle hesaplanan mikst venöz oksijen satürasyonundan ($SmvO_2$) daha düşük olduğunu gözlemledik. Bu nedenle, saptanabilir herhangi bir şant olmamasına rağmen bazı hastalarda Qp/Qs değeri "1"den küçük olarak hesaplandı. Bu gözlemin prognostik öneme sahip olabileceğini varsaydık ve bildiğimiz kadarıyla bu henüz çalışılmadı. Bu nedenle soldan sağa şantı olmayan prekapiller PH'de Qp/Qs'in prognostik değerini araştırmayı amaçladık.

Gereç ve Yöntem: Ardışık 173 hastayı içeren bu retrospektif kohort çalışmada, hastane dosyaları, Fick yöntemiyle hesaplanan Qp/Qs'i de içeren klinik, ekokardiyografik ve hemodinamik veriler için tarandı.

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Bulgular: Ortanca 25 ay takipte 74 hasta öldü. Ölenler, hayatta kalanlardan daha düşük Qp/Qs'e sahiplerdi (0,76±0,19'a karşılık 1,02±0,07; p<0,001). Çok değişkenli lojistik regresyon analizi, düşük Qp/Qs ve kötü fonksiyonel kapasitesinin (Dünya Sağlık Örgütü sınıf III-IV) mortalitenin bağımsız öngörücüleri olduğunu gösterdi. ROC eğrisi analizi, mortaliteyi tahmin etmek için Qp/Qs'in optimal kestirim değerinin %76 duyarlılık ve %98 özgüllük ile 0,90 olduğunu ortaya koydu.

Sonuç: Fick yöntemiyle hesaplanan Qp/Qs'in mortalitenin bağımsız bir öngördürücüsü olduğu gösterildi. Bu prognostik çıkarım, $SpaO_2$ ile formül aracılığıyla hesaplanan $SmvO_2$ arasındaki farka dayanmaktadır. Bununla birlikte, bu sonuç, Fick yönteminin potansiyel bir içsel metodolojik kusurunun bir yansıması olabilir.

Anahtar Kelimeler: Pulmoner hipertansiyon, prognoz, fick yöntemi, oksijen, mortalite

INTRODUCTION

Pulmonary hypertension (PH) is characterized by elevated mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest during right-sided cardiac catheterization (RSCC) (1). PH is a life-threatening condition that ultimately causes right ventricular failure and death. Since the prognostic evaluation is critical for PH, several risk assessment tools were developed to predict its prognosis and optimize treatment (2-7).

RSCC is accepted as the gold standard diagnostic tool for the definitive diagnosis of PH and used for prognostic purposes (1). The pulmonary to systemic flow (Qp/Qs) ratio is a calculation for estimating the direction and severity of shunting, especially in congenital heart diseases. This ratio is typically calculated using the Fick method (8), and it is essential in the differential diagnosis and management of PH in patients with left-to-right shunts (9). We routinely calculate the Qp/Qs ratio to avoid missing any left-to-right shunts in patients with precapillary PH. However, the pulmonary artery oxygen saturation ($SpaO_2$) was lower than the mixed venous oxygen saturation ($SmvO_2$) calculated using the formula; hence, the Qp/Qs ratio was calculated as less than "1" in some patients despite the absence of any detectable shunt. We hypothesized that this observation might have prognostic significance; however, to the best of our knowledge, it has not been investigated yet. Therefore, we aimed to investigate the prognostic value of the Qp/Qs ratio in patients with precapillary PH without any left-to-right shunt.

METHODS

Study Population

This retrospective cohort study was conducted in the Department of Cardiology of Dokuz Eylül University Hospital. This study was approved by the Local Ethics Committee. Informed consent was obtained for the RSCC procedure from all patients.

The medical records of 225 consecutive patients who underwent RSCC combined with oximetric study through the Fick method (8) for differential diagnosis of PH were screened from the hospital database. All patients were diagnosed with precapillary PH by an algorithm recommended in the guideline (1). After excluding 52 patients with confirmed left-to-right shunt not only through the oximetric analysis but also with other diagnostic modalities, the remaining 173 patients with precapillary PH were considered for the final analysis. Precapillary PH was defined as mPAP ≥25 mmHg along with pulmonary artery wedge pressure (PAWP) ≤15 mmHg (1).

Transthoracic Doppler Echocardiography

Thorough transthoracic echocardiography that specifically focused on investigating the function and pressure within the right side of the heart was performed by using a Philips HD11 XE Ultrasound system with 3.2 MHz transducer (Philips Healthcare, Best, Netherlands).

Data Collection and Patient Follow-up

All patients were routinely evaluated every 3 months in the PH outpatient clinic. The functional capacity (FC) of the patients was recorded according to the World Health Organization (WHO) functional classification (10). Results of the 6-min walking distance (6MWD) test, echocardiographic values, and laboratory parameters were obtained. All-cause mortality was noted during follow-up, and patients were compared as survivors versus nonsurvivors for analysis.

Right-Sided Cardiac Catheterization

All patients underwent RSCC at rest that was performed by experienced cardiologists. Neither sedation nor supplemental oxygen was administered during the study. Pressure records and the oximetric study were performed with multipurpose angled catheters (end hole only). The right atrial pressure and PAP, along with the PAWP, were recorded. Blood samples from the pulmonary artery, right atrium, right ventricle, superior vena cava (SVC), inferior vena cava (IVC), and systemic artery were obtained routinely, and the Qp/Qs ratio was calculated using the following formula: systemic artery oxygen saturation - $SmvO_2$/pulmonary artery wedge oxygen saturation - $SpaO_2$ (8). To calculate $SmvO_2$, this formula was used: [(3×SVC oxygen saturation ($SsvcO_2$) + IVC oxygen saturation ($SIvcO_2$))/4] (11). In cases with no record of the pulmonary artery wedge saturation,

it was assumed to be similar to the systemic artery oxygen saturation. The cardiac index was calculated by dividing Qs values by the measure of the total surface area of the body. Transpulmonary gradient determined by subtracting PAWP from mPAP was divided by Qp to calculate the pulmonary vascular resistance (PVR).

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 (institutionally registered software). Normality was assessed with the Kolmogorov-Smirnov test. Data were reported as percentages for categorical variables and mean ± standard deviation or median (interquartile range) for continuous variables. Student's t-test or Mann-Whitney U test was used to compare continuous variables, and the appropriate chi-squared test was performed to compare categorical variables. To predict mortality, the optimal cutoff threshold for the Qp/Qs ratio was obtained by analyzing the receiver operating characteristics (ROC) curve. The Kaplan-Meier analysis with a cutoff value of 0.90 for the Qp/Qs ratio was used to designate the survival curves. Logistic regression analyses were performed to define predictors of mortality. Variables with p-value <0.1 in the univariate regression analysis were included in the multivariate logistic regression analysis. For all statistical analyses, p-value of ≤0.05 was accepted as significant.

RESULTS

This study included 45 men and 128 women, with a mean age of 60.2±15.5 years. The follow-up duration ranged from 25 months to 128 months. A total of 74 (42.7%) deaths were noted during the follow-up. Baseline demographics and clinical and echocardiographic comparisons of survivors versus nonsurvivors are presented in Table 1. According to functional class, 91.8% of the nonsurvivors and 54.5% of the survivors had WHO FC III-IV. Nonsurvivors had significantly lower 6MWD, tricuspid annular plane systolic excursion, and right ventricular outflow tract maximum systolic velocity values. Pericardial effusion more frequently occurred in nonsurvivors, and they had significantly higher brain natriuretic peptide and lactate dehydrogenase levels (Table 1).

Baseline hemodynamic data obtained from RSCC are shown in Table 2. Nonsurvivors had significantly lower Qp and Qp/Qs ratio (3.52±1.48 vs. 4.53±1.43, p<0.001; 0.76±0.19 vs. 1.02±0.07, p<0.001) than survivors, respectively. The mPAP and PVR levels were significantly higher in nonsurvivors.

The multivariate logistic regression analysis showed that the Qp/Qs ratio and poor FC (WHO FC III-IV) (p=0.002,

Table 1. Baseline clinical and echocardiographic characteristics of the study population

Variables	Survivors (n=99)	Non-survivors (n=74)	p
Female n (%)	72 (72.7)	56 (75.7)	0.662
Age (year)	58.97±15.3	61.0±16.3	0.384
WHO/FC III-IV n (%)	48 (54.5)	67 (91.8)	**<0.001**
6-min walking distance (m)	330 (221-380)	264 (120-320)	**0.043**
BNP (pg/mL)	206 (100-442)	614 (253-1186)	**<0.001**
Hemoglobin (mg/dL)	12.43±2.23	12.29±2.32	0.714
Uric acid (mg/dL)	6.89±2.44	7.02±2.38	0.751
Serum LDH (mg/dL)	223 (183-263)	265 (188-344)	**0.027**
sPAP (mmHg)	79.38±20.19	82.76±16.92	0.255
TAPSE (mm)	18.1±5.3	16.1±4.8	**0.020**
RVOT maximum systolic velocity (m/sec)	0.87±0.20	0.75±0.18	**0.002**
Pericardial effusion, n (%)	14 (15.7)	27 (43.5)	**<0.001**

WHO/FC: World Health Organization/functional capacity, BNP: Brain natriuretic peptide, LDH: Lactate dehydrogenase, sPAP: Systolic pulmonary arterial pressure, TAPSE: Tricuspid annular plane systolic excursion, RVOT: Right ventricular outflow tract

Table 2. Baseline hemodynamic data obtained from right-sided cardiac catheterization

Variables	Survivors (n=99)	Non-survivors (n=74)	p
Qp (L/min)	4.53±1.43	3.52±1.48	**<0.001**
Qs (L/min)	4.5±1.5	4.7±1.7	0.431
Qp/Qs ratio	1.02±0.07	0.76±0.19	**<0.001**
Systolic PAP at catheterization (mmHg)	73.4±23.3	77.7±18.0	0.207
Mean PAP at catheterization (mmHg)	43.0±12.5	47.1±12.1	**0.038**
Diastolic PAP at catheterization (mmHg)	25.57±10.10	28.23±9.42	0.093
Pulmonary vascular resistance (wood unit)	6.5 (4.1-9.5)	8.6 (5.0-12.8)	**0.006**
Right atrial pressure (mmHg)	10.7±5.3	10.2±6.0	0.598
Cardiac index (L/min/m^2)	2.5±0.8	2.7±0.9	0.147

Qp: Pulmonary blood flow, Qs: Systemic blood flow, Qp/Qs: pulmonary to systemic blood flow ratio, PAP: Pulmonary arterial pressure

p<0.001 respectively) were independent predictors of mortality (Table 3). The optimal Qp/Qs cutoff for predicting mortality was 0.90 with 76% sensitivity and 98% specificity (area under the curve=0.845, 95% CI: 0.778-0.913, p<0.001) based on the ROC curve analysis (Figure 1). The Kaplan-Meier analysis of Qp/Qs >0.90 and Qp/Qs ≤0.90 yielded diverging survival curves (p<0.001) (Figure 2). Qp/Qs ≤0.90 was noted in 34.7% of the patients, and Qp/Qs ratio ≤0.90 was significantly more common in nonsurvivors than in survivors (75.7% vs. 4%; p<0.001).

DISCUSSION

Hemodynamic parameters obtained from RSCC are valuable for predicting the prognosis of PH (1). The Fick method relies on measuring oxygen concentrations in blood samples obtained by a catheter positioned at several points and serves as a reference procedure for the evaluation of blood flow (Qp/Qs) (8) and shunts (9). Qp, Qs, and Qp/Qs ratio are routinely calculated in patients

Table 3. Multivariate logistic regression analysis to predict mortality

Variables	Univariate OR, 95% CI	p	Multivariate OR, 95% CI	p
WHO/FC III-IV	6.306 (3.654-8.696)	**<0.001**	7.297 (2.410-9.257)	**<0.001**
6MWD	0.997 (0.995-1.0)	**0.046**	0.993 (0.984-1.002)	0.149
BNP	1.001 (1.000-1.001)	**0.001**	0.999 (0.998-1.001)	0.561
Serum LDH	1.005 (1.001-1.008)	**0.010**	1.009 (0.996-1.022)	0.164
TAPSE	0.925 (0.865-0.989)	**0.023**	1.124 (0.851-1.486)	0.410
RVOT maximum systolic velocity	0.162 (0.023-1.165)	**0.071**	0.205 (0.027-0.826)	0.504
Pericardial effusion,	0.443 (0.267-0.737)	**<0.001**	0.729 (0.371-1.432)	0.246
Qp/Qs	0.599 (0.467-0.770)	**<0.001**	0.117 (0.030-0.450)	**0.002**
Mean PAP at catheterization	1.027 (1.027-1.054)	**0.040**	0.995 (0.893-1.108)	0.206

Variables entered into the univariate logistic regression analysis: sex, age, WHO/FC III-IV, 6MWD, BNP, hemogram, uric acid, serum LDH, systolic pulmonary arterial pressure, TAPSE, RVOT maximum systolic velocity, pericardial effusion, Qp/Qs ratio, systolic PAP at catheterization (mmHg), mean PAP at catheterization (mmHg), pulmonary vascular resistance, right atrial pressure, cardiac index. WHO/FC: World Health Organization/functional capacity, 6MWD: 6-min walking distance, BNP: Brain natriuretic peptide, LDH: Lactate dehydrogenase, TAPSE: Tricuspid annular plane systolic excursion, RVOT: Right ventricular outflow tract, Qp/Qs: pulmonary to systemic blood flow ratio, PAP: Pulmonary arterial pressure

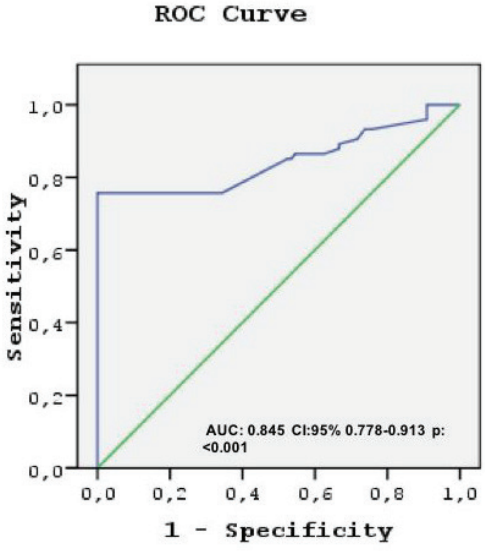

Figure 1. Receiver operating characteristic curves of the Qp/Qs ratio for predicting mortality
Qp/Qs: pulmonary to systemic blood flow ratio, ROC: Receiver operating characteristics, CI: Confidence interval, AUC: Area under curve

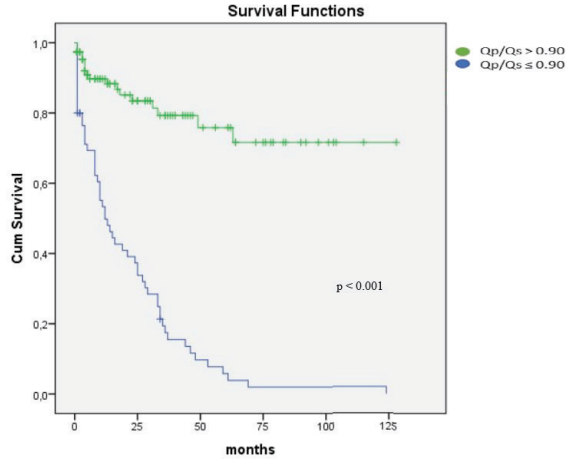

Figure 2. Kaplan-Meier survival estimates for mortality in all patients with precapillary pulmonary hypertension based on the Qp/Qs ratio of ≤0.90 vs. >0.90
Qp/Qs: pulmonary to systemic blood flow ratio

with PH, except in settings with technical obstacles in our clinic. In real-life practice, without any shunting, the Qp/Qs ratio should be equal to 1. However, during routine RSCC

procedures in patients with high-risk status and precapillary PH, the Qp/Qs ratio calculated using the Fick method was <1. $SpaO_2$ was lower than $SmvO_2$ calculated using the formula; therefore, the Qp/Qs ratio was calculated as <1. In the absence of shunting, the downward deviation of the Qp/Qs value from the expected normal value of 1 might initially appear to be strange in a closed-loop system and might be ignored as test result variability. However, the Qp/Qs ratio calculated using the Fick method is based on oxygen consumption, and the main determinant of this ratio is a difference between $SpaO_2$ and $SmvO_2$. Moreover, $SmvO_2$ is measured directly from the pulmonary artery (12) or calculated using a formula (11). However, various potential flow sources such as the coronary sinus (CS) can be neglected by calculating $SmvO_2$ from $SsvcO_2$ and $SIvcO_2$. This may not matter in patients with normal cardiac function. However, this phenomenon becomes important in patients with heart failure (13). CS oxygen saturation ($ScsO_2$) was a strong predictor of the severity of heart failure due to deranged metabolic demands (14). Similarly, we thought that in the presence of right ventricular dysfunction caused by a chronic pressure overload in PH, the metabolic demand of the right ventricle increases, and it may result in reduced $ScsO_2$. This causes a difference between $SpaO_2$ and $SmvO_2$ calculated using the formula. A study that supported our hypothesis showed that the major reason for the calculation between average venous oxygen saturation and $SpaO_2$ was the deoxygenated blood of the CS in patients who underwent cardiac surgery (15). While the contribution of deoxygenated blood derived from the myocardium via the CS to venous SO_2 can be taken into account in the measurement of $SmvO_2$ from the pulmonary artery, the effect of the myocardium can be ignored in the measurement of SO_2 from the central veins. Therefore, direct measurement of $SmvO_2$ through pulmonary artery catheterization is more accurate in patients with critical illness (16), including patients undergoing cardiac surgery and/or patients with impaired cardiac function (17,18). The contribution of CS drainage to venous SO_2 could have significant effects in the late stages of PH that might also serve as a basis for the Qp/Qs deviation in the Fick method (19). In the present study, we think that the $SpaO_2$ value is lower than that of $SmvO_2$ because of right ventricular dysfunction in patients with precapillary PH. The low $SpaO_2$ indicates that the heart cannot meet the tissue oxygen demand. The Qp/Qs ratio was calculated as <1 because a low $SpaO_2$ and, not surprisingly, decreased Qp/Qs ratio was an independent predictor of mortality. Similarly, $SpaO_2$ was shown to be a more valuable prognostic factor than the cardiac index in patients with PH (20).

Study Limitations

This retrospective cohort analysis had several limitations. First, our study was conducted on a limited number of patients from a single center without any data about treatment-related issues, which can potentially influence outcomes. Second, blood samples from the CS were not obtained. Analyses of $ScsO_2$ that can reflect an intrinsic error in the calculation of $SmvO_2$ should be ideally incorporated in the final evaluation of patients with PH and right ventricular dysfunction. However, the potential value of this issue in calculating the Qp/Qs ratio through the Fick method remains to be established. Third, we could not compare $SmvO_2$ with $SpaO_2$ because of the absence of oxygen saturation values in our hospital records. Fourth, thermodilution, which is the preferred method for determining cardiac output in patients with PH (19), was not utilized in this cohort because it was not available during the study period. Therefore, we could not compare the cardiac output obtained by thermodilution with Qp and Qs calculated using the Fick method. Essentially, further prospective randomized controlled studies with larger sample sizes are strongly recommended for the validation of the results of this study.

CONCLUSION

In this study, decreased Qp/Qs ratio calculated using the Fick method was an independent predictor of mortality in patients with precapillary PH without left-to-right shunts. This prognostic implication was based on the difference between $SpaO_2$ and $SmvO_2$ calculated using the formula. Nevertheless, it remains to be elucidated whether this is a reflection of an intrinsic methodological flaw in the Fick method.

ETHICS

Ethics Committee Approval: This retrospective cohort study was conducted in the Department of Cardiology of Dokuz Eylül University Hospital. This study was approved by the Local Ethics Committee (no: 2018/07-32, date: 15.03.2018).

Informed Consent: Informed consent was obtained for the RSCC procedure from all patients.

Authorship Contributions

Surgical and Medical Practices: B.Ş., Concept: B.Ş., B.A., E.Ö., Design: B.Ş., B.A., M.B.Y., M.B., C.S., Data Collection or Processing: B.Ş., B.A., E.Ö., D.S., B.Ö.K., K.C.T., Analysis or Interpretation: B.Ş., B.A., M.B.Y., E.Ö., D.S., B.Ö.K., B.Ac., M.B., C.S., Literature Search: B.Ş., Writing: B.Ş., B.A., M.B.Y., E.Ö., D.S., B.Ö.K., B.Ac., K.C.T., M.B., C.S.

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