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      Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.
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Acknowledgements

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Original Article

Predictors of prolonged use of mechanical ventilation in patients with acute respiratory failure and acute heart failure in the CVCU RSUD Dr. Saiful Anwar Malang

Puspa Lestari[1], Setyasih Anjarwani[1], Novi Kurnianingsih[1], Indra Prasetya[1], Heny Martini[1]

Abstract

Background: Acute respiratory failure (ARF) is a critical condition that often complicates hospitalization and commonly arises from cardiopulmonary dysfunctions such as acute heart failure. Prolonged mechanical ventilation (PMV) in these patients is associated with increased morbidity, mortality of about 30%, and greater healthcare resource utilization. Identifying predictors of PMV is essential to improve outcomes and optimize management strategies.

Methods: A retrospective cohort study was conducted on all patients who underwent endotracheal intubation in the Cardiovascular Care Unit (CVCU) of RSUD Dr. Saiful Anwar Malang from 2015 to 2021. Patients with incomplete medical records or who died within 14 days of mechanical ventilation were excluded. Univariate and multivariate logistic regression analyses identified independent predictors of PMV. Receiver operating characteristic (ROC) curves were generated to assess model discrimination using the area under the curve (AUC), with corresponding sensitivity and specificity. Data were analyzed using SPSS 22.0.

Results: Five independent predictors of PMV were identified: tachycardia ($p = 0.013$), metabolic acidosis ($p = 0.002$), impaired renal function ($p = 0.009$), shock ($p = 0.006$), and major bleeding ($p = 0.002$). Multivariate analysis showed the following odds ratios (OR, 95% CI): tachycardia 2.06 (1.09–5.99), metabolic acidosis 2.03 (1.09–6.33), impaired renal function 2.87 (1.28–6.46), shock 2.83 (1.13–7.06), and major bleeding 1.36 (1.18–2.15). The model demonstrated good discrimination with an AUC of 0.83 (95% CI 0.77–0.88), sensitivity 0.87, and specificity 0.73.

Conclusions: In patients with respiratory failure due to acute heart failure, tachycardia, metabolic acidosis, impaired renal function, shock, and major bleeding were independent predictors of prolonged mechanical ventilation. The predictive model showed high sensitivity and acceptable specificity, supporting its clinical usefulness for early identification of high-risk patients and targeted intervention.

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Keywords: Predictor, Prolong Mechanical Ventilation, Acute Respiratory Failure, Acute Heart Failure

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Introduction

Acute Respiratory Failure (ARF) can occur as a complication in hospitalized patients and is brought on by a variety of cardiopulmonary dysfunctions, such as Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), pneumonia, and Acute Respiratory Distress Syndrome (ARDS). A patient's medical history and a clinical examination can be used to determine whether they have ARF, which is indicated by an arterial oxygen pressure of less than 60 mmHg. Intensive Care Unit (ICU) treatment is frequently prompted by ARF. Patients who need invasive mechanical ventilation have mortality rates in hospitals ranging from 33% to 37%. More than 365,000 patients in the Intensive Care Unit (ICU) in the United States are admitted with congestive heart failure and cardiogenic shock each year; 80,000 of these patients need mechanical breathing.[1]

For critically ill patients, intubation and mechanical ventilation are necessary to maintain an open airway and guarantee appropriate gas exchange.[2] In order to prevent adverse effects, management should be informed about the benefits and drawbacks of invasive mechanical breathing.[1] The use of mechanical ventilation necessitates an understanding of the fundamental physiology of the respiratory system, work standards, main ventilation settings, and knowledge of potential problems. In cases of cardiopulmonary malfunction, the ventilation strategy should be tailored to particular situations, such as decompensated congestive heart failure, chronic obstructive pulmonary disease, right heart failure, and protective ventilation in patients with healthy lungs.[1, 3]

From a cardiac and respiratory standpoint, ventilator management for critically ill patients should be customized to meet the specific requirements of each patient in order to maximize benefits while minimizing risks. Depending on the clinical situation's pathophysiology and planned aims, there are different requirements for starting mechanical breathing. The cardiovascular system can be impacted positively or negatively by Positive-Pressure Ventilation (PPV), although no overall effect has been observed because of the body's capacity to adjust to variations in intrathoracic pressure. Cardiovascular performance can be significantly changed by variations in intrathoracic pressure that are conveyed to the heart and lungs. The physiological reaction of the right and left ventricles to variations in intrathoracic pressure differs significantly. A proficient cardiologist must be familiar with the evidence-based uses of Invasive Mechanical Positive Pressure Ventilation (IM-PPV) and its interactions with the heart and lungs, as well as be able to modify ventilation techniques to the underlying cardiovascular status of each patient. All cardiologists who care for patients in the CVCU should be educated about these interventions as well.[4-6]

Nearly 80% of all cardiogenic shock patients in everyday practice have Acute Myocardial Infarction (AMI), which is linked to significant mortality and morbidity. The usage of mechanical ventilation and respiratory failure have increased, according to prior research, in cardiogenic shock. Long-term use of mechanical ventilation in critically ill patients is linked to a mortality rate of about 30% and much higher resource demand.[6] Identification of those who require long-term mechanical ventilation might change breathing techniques or possibly shorten the course of therapy and reduce associated problems. Therefore, it indicates that the length of time a patient uses mechanical ventilation is a substantial predictor of health issues. For medical objectives, with a focus on the most important factors, and to aid in clinical decisions about critical care patients, predictors of prolonged mechanical ventilation requirements among patients admitted to the CVCU are required.[4]

Methods

Study Design

This cohort retrospective study included patients intubated in CVCU room RSUD Dr. Saiful Anwar Malang from 2015 until 2021. There were 397 patients intubated in CVCU, 117 patients were excluded for the following reasons: incomplete medical record data and died before 14 days of mechanical ventilation. Data obtained from medical records include age, gender, vital signs (blood pressure, heart rate, respiratory rate), oxygen saturation, shock conditions, blood gas analysis (pH, PaO_2, $PaCO_2$, HCO_3, Base Excess), hemoglobin levels, leukocyte count, hematocrit level, platelet count, serum electrolytes (Sodium, Potassium, Chloride), random blood sugar, kidney function test (Urea, creatinine, estimated Glomerular Filtration Rate (eGFR)), pneumonia, emphysema lung, sepsis, major bleeding, Liver Function Test (AST/ALT), and Glasgow Coma Scale.

End Points and Operational Definitions

The primary endpoint of this study was the occurrence of Prolonged Mechanical Ventilation (PMV), defined as the requirement for invasive

mechanical ventilation for ≥14 consecutive days in patients with respiratory failure due to acute heart failure. Secondary endpoints included the identification of clinical and laboratory predictors associated with PMV, such as tachycardia, metabolic acidosis, impaired renal function, shock, and major bleeding, as well as the evaluation of the predictive performance of these variables. Predictive accuracy was assessed through sensitivity, specificity, Odds Ratios (ORs) with 95% confidence intervals, and the discriminative ability of the model, measured by the Area Under the Receiver Operating Characteristic (ROC) Curve (AUC).

For the purposes of this study, operational definitions were applied as follows: tachycardia was defined as a resting heart rate >100 beats per minute measured on admission or during CVCU stay; metabolic acidosis as arterial pH <7.25 on blood gas analysis; impaired renal function as an eGFR <30 mL/min/1.73m² using the CKD-EPI equation; shock as systolic blood pressure <90 mmHg or the requirement for vasopressor support to maintain adequate mean arterial pressure; and major bleeding as clinically overt bleeding resulting in a hemoglobin drop > 2 g/dL or requiring blood transfusion, hemodynamic support, or surgical intervention. Additional demographic, clinical, and laboratory variables—including age, sex, Glasgow Coma Scale, vital signs, oxygenation indices, complete blood count, serum electrolytes, renal and liver function tests, and comorbidities (e.g., pneumonia, sepsis) were also collected and analyzed.

Statistical Analysis

The mean and standard deviation for all data were displayed. The chi-square (x^2) was used to compare categorical variables. Two-sample t-tests were used to analyze mean differences for continuous variables. To find potential PMV predictors, we conducted both univariate and multivariate analyses. A multivariate analysis was performed on all variables that had a p-value of 0.05 or above in the univariate analysis. Logistic regression was used for the multivariate analysis. For these variables, ROC curves were built. The area under the curve was used to compare receiver operating characteristic curves (AUC). the sensitivity and specificity calculated for each positive variable count. Using SPSS 22.0, the data were examined.

Results

In this study, there were 33 patients (13.36%) with prolonged use of mechanical ventilation (>14 days) and 247 patients (86.64%) patients with mechanical ventilation <14 days.

There was no significant difference in the number of acute heart failure patient with a wet-warm subset as well as a wet-cold subset between the PMV and non-PMV group.

Table 1. Characteristics of a group patient respiratory failure with acute failure using mechanical ventilation.

Variable	Non PMV (n=247)	PMV (n = 33)	p-value
Age (years), (mean ± SD)	59.7 ± 11.7	62.8 ± 10.9	0.142
Gender			
Women (n, %)	103 (41.7%)	14 (42.4%)	0.93
Men (n, %)	144 (58.3%)	19 (57.6%)	
Glasgow Coma Scale (GCS)	11	11	0.762
Systolic Blood Pressure (mmHg)	115 ± 27	116 ± 29	0.843
Diastolic Blood Pressure (mmHg)	69 ± 18	74 ± 22	0.150
Heart Rate (beats per minute)	96 ± 24	99 ± 30	0.465
Temperature (°C)	36.5 ± 0.2	36.6 ± 0.2	0.403
Respiratory Rate (times per minute)	21 ± 6	21 ± 3	0.881
Oxygen saturation (%)	97.52 ± 4.26	96.06 ± 11.7	0.483
FiO_2 (%)	82 ± 23.2	79 ± 23.2	0.473
PaO_2/FiO_2	157 ±102	186 ± 128	0.139
Hemoglobin (g/dL)	12.3 ± 3.0	12.3 ± 2.92	0.273
Hematocrit (%)	37.81 ± 8.4	37.64 ± 8.7	0.257
WBC (cells/μL)	15257 ± 2174	24170 ± 5601	0.186

Platelet count ($\times 10^3/\mu L$)	211 ± 22	221 ± 90	0.696
Serum Creatinine (mg/dL)	1.48 ± 3.3	2.27 ± 5.0	0.067
Ureum (mg/dL)	81.49 ± 65.9	83.02 ± 49.5	0.898
eGFR (mL/min/1.73m^2)	50.1 ± 32.4	46.9 ± 27.2	0.593
Aspartate Aminotransferase (AST, IU/L)	45.3 ± 55.0	38.82± 21.8	0.567
Alanine Aminotransferase (ALT, IU/L)	55.53 ± 77.0	46.61± 56.78	0.980
Random Blood Glucose (mg/dL)	182 ± 122	163 ± 101	0.986
Sodium (Na^+, mEq/L)	134.2 ± 5.16	134.2 ± 4.6	0.517
Potassium (K^+, mEq/L)	4.18 ± 0.96	4.2 ± 1.22	0.793
Chloride (Cl^-, mEq/L)	105 ± 14.7	105 ± 6.2	0.852
Arterial pH	7.24 ± 0.14	7.28 ± 0.12	0.241
Bicarbonate (HCO_3^-, mEq/L)	18.5 ± 7.5	18.7 ± 5.9	0.859
Partial Pressure of Oxygen (PaO_2, mmHg)	117.42 ± 59.84	137.5 ± 82.3	0.09
Partial Pressure of Carbon Dioxide ($PaCO_2$, mmHg)	41.74 ± 23.87	40.19 ± 13.96	0.719
Arterial Oxygen Saturation (SaO_2, %)	93.92 ± 8.9	93.15 ± 12.2	0.662
Tachycardia (HR > 100 beats per minute)	110 (44.9%)	23 (69.7%)	0.013
Metabolic acidosis (PH < 7.25)	115 (47.1%)	25 (75.8%)	0.002
Impaired renal function (eGFR < 30 mL/min/1.73m^2)	80 (32.7%)	19 (57.6%)	0.009
Shock Condition	127 (51.6%)	26 (78.8%)	0.006
Major Bleeding (n, %)	9 (3.6%)	6 (18.2%)	0.002
Lung Emphysema (n, %)	9 (3.6%)	0 (0%)	0.605
Acute Coronary Syndrome			
Anterior MI	20 (8.09%)	3 (9.09%)	0.989
Anterior Extensive MI	15 (6.07%)	2 (6.06%)	
Anteroseptal MI	6 (2.43%)	1 (3.03%)	
Inferior MI	16 (6.47%)	1 (3.03%)	
Inferoposterior MI	11 (4.45%)	4 (12.12%)	
Inferoposterior MI + RV Infarct	18 (7.28%)	4 (12.12%)	
Non ST Elevation	29 (11.74%)	1 (3.03%)	
Unstable Angina Pectoris	9 (3.64%)	7 (21.21%)	
Killip			
I	28 (11.33%)	7 (21.21%)	0.277
II	5 (2.02%)	0	
III	16 (6.47%)	0	
IV	74 (29.95%)	10 (30.30%)	
Pneumonia	165 (66,8%)	21 (63.6%)	0.86
Sepsis	57 (23.3%)	5 (15.2%)	0.414
Hypoxemia	34 (13.8%)	7 (21.2%)	0.38
Hypercapnia	60 (24.3%)	7 (21.2%)	0.86
Forrester			
Dry Warm (n, %)	0	0	0.86
Dry Cold (n, %)	0	0	
Wet Warm (n, %)	114 (46.2%)	16 (48.4%)	
Wet Cold (n, %)	133 (53.8%)	17 (51.6%)	

The PMV group had a significantly greater number of patients with tachycardia, acidosis, grade III chronic kidney disease, shock, and major bleeding compared to the non PMV group. Hence, from univariate analysis, these five variables were identified as the independent predictor of PMV among the acute heart failure patients. Furthermore, multivariate analysis with logistic regression was performed on these variables.

Based on multivariate analysis, among the predictors, shock and impaired renal function had the highest odds of PMV. Furthermore, tachycardia

Table 2. Multivariate analysis with logistic regression.

Variable	Sig.	OR	95% CI	
			Lower	Upper
Tachycardia (HR > 100 beats per minute)	0.31	2.058	1.091	5.996
Metabolic acidosis (PH <7.25)	0.31	2.027	1.090	6.330
Impaired renal function (eGFR < 30 mL/min/1.73 m^2)	0.11	2.873	1.278	6.460
Shock Condition	0.26	2.828	1.133	7.062
Major Bleeding	0.28	1.359	1.177	2.150

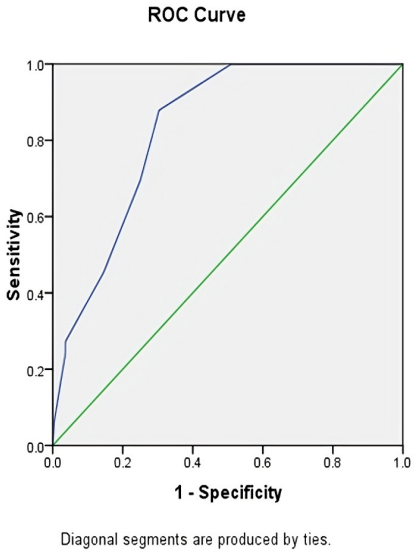

Figure 1. ROC curve of the predictor model for prolonged mechanical ventilation showing good discrimination (AUC = 0.83).

and metabolic acidosis had two times likelihood of PMV while major bleeding only had minor likelihood of PMV.

The predictor factors showed good discrimination with an area under the receiver operating curve (AUC) of 0.83 (95% CI 0.77–0.88) with a sensitivity of 0.87 (95% CI 0.82–0.94) and a specificity of 0.73 (95% CI 0.72–0.84).

Discussion

This study showed that tachycardia, metabolic acidosis, impaired renal function, shock, and major bleeding were important predictors of prolonged mechanical ventilation in patients with acute heart failure and respiratory failure. These findings highlight the clinical relevance of hemodynamic instability, acid base imbalance, renal dysfunction, and bleeding complications as barriers to successful weaning. Recognizing these predictors early may enable clinicians to anticipate difficulties and adjust management strategies accordingly. Compared with the study by Clark et al., the average duration of mechanical ventilation in our cohort was shorter. This difference may partly be explained by our exclusion of patients who died before day 14 of ventilation, which was done to avoid misclassification of early death as successful weaning. However, this methodological choice may also have contributed to a shorter overall duration of ventilator use compared with other studies. Differences in patient characteristics, disease severity, and supportive care practices may also explain the observed variation.[7]

In this study, patients were intubated primarily to secure the airway and provide prolonged ventilatory support due to underlying cardiac complica-

tions, particularly acute heart failure. The classification of acute heart failure in the study was divided based on Forrester's criteria, including: Warm and dry (normal); Warm and wet (congestion); Cold and dry (hypoperfusion); and Cold and wet (Congestion and hypoperfusion). Patients with acute heart failure were predominantly classified into wet-warm and wet-cold subsets, with similar proportions observed between those who required prolonged ventilation and those who did not. Previous literature notes that acute respiratory failure in this setting is often related to cardiogenic pulmonary edema. Supportive management with oxygen therapy remains the mainstay to correct hypoxemia, while the presence of hypercapnia may necessitate escalation to mechanical ventilation.[8] Mechanical ventilation provides cardiovascular system benefits in patients with left heart failure. In contrast, cardiovascular conditions are responsible for mechanical ventilation weaning failure in conditions of myocardial ischemia and cardiogenic pulmonary edema.[9-10]

Tachycardia conditions induce excessive catecholamine release in patients who have difficulty weaning mechanical ventilation and can shorten coronary perfusion time.[11-12] This condition causes (1) increased oxygen demand due to increased respiratory effort, (2) decreased myocardial oxygen delivery. Because at the time of weaning on mechanical ventilation there is hypoxemia, the decrease in arterial diastolic pressure associated with a decrease in intrathoracic pressure during inspiration is a sign of significant respiratory effort. This mechanism can lead to prolongation of mechanical ventilation.[12-15] Studies conducted by Hammash et al. in patients using mechanical ventilation who experience cardiac dysrhythmias, it is stated that tachycardia conditions contribute to the weaning process of mechanical ventilation, which can lead to prolonged use of mechanical ventilation. The negative effect of this tachycardia condition affects cardiac contractility and increases tissue oxygen demand, so that systematic heart rate evaluation in mechanically ventilated patients can help shorten weaning time and use mechanical ventilation.[16]

Metabolic acidosis also emerged as a relevant predictor of prolonged mechanical ventilation. Patients with lower pH values were more likely to remain ventilator-dependent compared to those with more stable acid–base balance. This finding emphasizes the importance of acid–base status in the weaning process, as persistent acidosis signals ongoing physiological stress that can delay recovery. In contrast, patients with adequate compensation or closer to normal pH were more likely to tolerate weaning, since sufficient correction of acidosis is one of the key criteria for safe liberation from mechanical support.[17]

The effect of mechanical ventilation on renal function remains incompletely understood, although beyond changes in carbon dioxide levels, it is known to influence fluid and electrolyte balance through mechanisms involving vasopressin and the renin–angiotensin–aldosterone system. These alterations may contribute to fluid overload and disturbances in acid–base status, thereby complicating recovery. In this study, patients with impaired renal function were more likely to experience prolonged ventilator dependence compared to those with preserved kidney function. This suggests that renal dysfunction, by worsening systemic imbalance and delaying clearance of metabolic byproducts, plays a critical role in extending the duration of mechanical ventilation.[18-19]

Previous research by Kimura et al. demonstrated that shock was an important predictor of prolonged mechanical ventilation, and our findings are consistent with this observation. Patients who developed shock in our cohort were more likely to remain ventilator-dependent compared with those who maintained stable hemodynamics. This association highlights how inadequate tissue perfusion and the need for vasopressor support create conditions that delay recovery and complicate the weaning process.[20]

Major bleeding was also associated with prolonged mechanical ventilation in this study. Patients who experienced significant bleeding were more likely to remain ventilator-dependent compared with those without bleeding complications. This can be explained by several mechanisms such as massive hemorrhage may precipitate hypovolemic shock and tissue hypoperfusion, transfusion can increase the risk of acute lung injury, and resuscitation efforts may lead to fluid overload that contributes to pulmonary edema. These combined effects create unfavorable respiratory conditions that make weaning from mechanical ventilation more difficult.[21]

Strengths and Limitations

The study benefited from a homogenous patient population and robust analytical methods, including multivariate logistic regression and ROC analysis, which strengthen confidence in the identified predictors. However, exclusion of patients who died before day 14 may have introduced survival bias, and outcome data after extubation were not available. As a single-center retrospective study, residual confounding cannot be excluded, and the relatively

small number of patients with prolonged ventilation may limit generalizability. Future prospective, multicenter studies with longer follow-up are warranted to validate these predictors and to assess whether targeted interventions can improve outcomes and reduce resource utilization.

Conclusion

Tachycardia, metabolic acidosis, impaired renal function, shock condition, and major bleeding were identified as the principal predictors of prolonged mechanical ventilation in patients with respiratory failure due to acute heart failure treated in the CVCU at RSUD Dr. Saiful Anwar Malang. These predictors demonstrated good discriminatory ability, with acceptable sensitivity and specificity for identifying patients at risk of prolonged mechanical ventilation. Their recognition may assist clinicians in anticipating high-risk cases, guiding preventive strategies, and promoting more cost-effective management of acute respiratory failure.

List of Abbreviations

AMI	Acute Myocardial Infarction
ARF	Acute Respiratory Failure
AUC	Area Under the Curve
CVCU	Cardiovascular Care Unit
COPD	Chronic Obstructive Pulmonary Disease
CHF	Congestive Heart Failure
eGFR	Estimated Glomerular Filtration Rate
ICU	Intensive Care Unit
IM-PPV	Invasive Mechanical Positive Pressure Ventilation
PPV	Positive Pressure Ventilation
PMV	Prolonged Mechanical Ventilation

Ethical Clearance

This study was reviewed and approved by the Ethics Commission of General Hospital Dr. Saiful Anwar, Malang, Indonesia (Approval No. 400/018/K.3/302/2022). All procedures were conducted in accordance with the ethical standards of the institutional and national research committee. The study adhered to the principles of the Declaration of Helsinki.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

Idea/concept: PL. Design: PL, SA. Control/supervision: SA. Data collection/processing: PL Analysis/interpretation: PL, SA, NK, IP, HM. Literature review: PL, SA, NK. Writing the article: PL. Critical review: All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Availability of Data and Materials

De-identified data and analytic code are available from the corresponding author upon reasonable request and subject to institutional policies

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The authors used PaperPal to assist in improving English language clarity and grammar during manuscript preparation. No AI tools were used to generate, analyze, or interpret data, figures, or scientific content. All text was reviewed, verified, and edited by the authors, who take full responsibility for the content.

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Original Article

The effect of a physical exercise program on functional capacity in patients with pulmonary arterial hypertension at Dr. M. Djamil Padang Hospital

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Abstract

Background: Pulmonary arterial hypertension (PAH) has been known to cause a decreases functional capacity. The underlying mechanisms include right ventricular dysfunction, chronotropic incompetence, ventilation abnormalities, and skeletal muscle dysfunction. Although exercise training programs are recommended, there is currently no standardized exercise training program that is easy to implement in patients with PAH. We aimed to investigate the effect of exercise training program on functional capacity in patients with PAH.

Methods: This study was a non-randomized clinical trial in adult patients with PAH who were divided into intervention and control groups. Cardiopulmonary exercise test (CPET) results were assessed before and after a four-week supervised program (5 sessions/week). The program followed the FITT principle: frequency 5 times/week, intensity 60–85% of six-minute walk test (6MWT) distance, time 25–30 minutes/session including warm-up and cool-down, type supervised indoor walking. Shapiro-Wilk normality test was performed before analyzing the numerical data, followed by the independent t-test or Mann-Whitney U test to determine differences between groups.

Results: This study included 26 patients with PAH, 14 in the intervention group, and 12 in the control group, consisting of 17 women (65%) and 9 men (35%) aged 18-54 years. Statistical analysis showed no significant differences in the baseline characteristics between the two groups ($p > 0.05$). Characteristics of the CPET examination results before and after the exercise program. At baseline, there was no difference in VO2 peak in the intervention group and the control group (888.29 ± 435.99 (95% CI: 314-1823) vs 641.92 ± 231.98 (95% CI: 408 – 1111), p-value >0.05). After the physical exercise program, the intervention group showed a significant increase in VO_2 peak (1047.71 ± 456.05 (95% CI: 413-2175) vs 656.5 ± 223.85 (95%CI: 401–1105), p-value < 0.05). Therefore, ΔVO_2 peak in the intervention group was significantly higher (159.42 ± 209.32 (95%CI: -92 – 707) vs 14.5 ± 60.4 (95%CI: -77 – 148), p-value < 0.05).

Conclusions: A four-week structured walking exercise program significantly improved functional capacity in PAH patients.

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Keywords: pulmonary arterial hypertension, exercise training, VO_2

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease with a prevalence of 15–50 cases per million population, and it is more common in women. In Indonesia, atrial septal defect (ASD) represents the most frequent congenital cause. This condition is known to significantly reduce patients' functional capacity. Exercise programs have been shown to improve functional outcomes; however, a standardized regimen that is simple and allows patients to adapt quickly is still lacking. To the best of our knowledge, there are only limited studies investigating the effectiveness of physical exercise programs for PAH patients in Indonesia. Therefore, further research is required to evaluate the effects of structured exercise training on cardiopulmonary stress test capacity in this population.[1-3]

Methods

Study Design

This study is a non-randomized clinical trial conducted at the Integrated Heart Center of RSUP Dr. M. Djamil Padang from November 2022 to September 2023. The subjects in this study were all patients with PAH who visited the cardiology clinic of RSUP, Dr. M. Djamil Padang.

The inclusion criteria were as follows: age between 18-54 years old and not pregnant, while the exclusion criteria were acute coronary syndrome within the last month; WHO FC III-IV; resting heart rate > 120 beats/min; systolic blood pressure <85 mmHg or >180 mmHg; diastolic blood pressure> 100 mmHg; peripheral oxygen saturation at rest <85%; history of syncope <1 week prior; and musculoskeletal abnormalities or disorders. Diagnosis was based on right heart catheterization: mean pulmonary artery pressure ≥20 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 Wood units, consistent with ESC/ERS guidelines.

Consecutive sampling was conducted in this study. All subjects who presented consecutively and met the eligibility criteria were enrolled in the study until the required sample size was reached. Subjects were then allocated into the intervention group or the control group. The intervention group consisted of subjects who underwent treatment and were given a physical exercise program. In contrast, the control group consisted of subjects who underwent medical treatment and were not given a physical exercise program. Before undergoing a physical exercise program, patients were first examined using a six-minute walk test (6MWT) and cardiopulmonary exercise test (CPET) at the initial meeting.

The exercise program in this study was walking exercise, the dosage of which was given in accordance with the Cardiovascular Rehabilitation Guidelines by PERKI in 2019. At each walking session, the dosage administered to the patient was increased by 100-200 meters per session. Exercise intervention followed the FITT principle: Frequency: 5 sessions/week for 4 weeks; Intensity: 60–85% of 6MWT-derived walking distance; Time: 25–30 minutes/session, including 5-min warm-up and 5-min cool-down. Walking doses could be split into 2–3 intervals within one session depending on tolerance; Type: supervised indoor walking in the hospital's cardiac rehabilitation room, naturally ventilated (non-air conditioned). During se ssions, HR (bpm), BP (mmHg), and SpO_2 (%) were monitored. Supplemental oxygen (2 L/min, titrated) was provided when SpO_2 <90%.[4-5] At the end of the exercise program, the subjects underwent a CPET re-examina-

Table 1. Dose of physical exercise based on 6-minute walk test.

6MWD	Walking dose		
	60%	70%	85%
120 m	360 m	420 m	510 m
150 m	450 m	525 m	640 m
180 m	540 m	630 m	770 m
210 m	630 m	735 m	900 m
240 m	720 m	840 m	1030 m
270 m	810 m	945 m	1160 m
300 m	900 m	1050 m	1290 m
350 m	1050 m	1225 m	1490 m
400 m	1200 m	1400 m	1700 m

Description: The walking dose can be divided into 2x sessions or 3x sessions according to the patient's physical ability.

tion. The VO_2 peak values before and after the intervention in the intervention group were compared with those in the control group.

Statistical Analysis

Univariate analysis was performed to obtain an overview of the baseline characteristics of the study subjects, which are displayed in the form of a frequency distribution table. Bivariate analysis was performed to examine the relationship between the independent and dependent variables. Before bivariate analysis, data normality testing was performed using the Shapiro-Wilk test. An independent t-test was performed to compare the difference in VO_2 peak between the two groups if the VO_2 peak data were normally distributed, and the Wilcoxon test if the data VO_2 peak were not normally distributed. If the p-value was < 0.05, the null hypothesis (H0) was rejected, and there was a significant difference between the VO peak values before and after the rehabilitation program. Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Mac version 27.

Results

This study included 30 subjects, 16 in the intervention group and 14 in the control group. The subjects included 20 women (66%) and 10 men (44%). Of the 30 subjects, four dropped out, leaving 26 subjects who completed the study. The 26 subjects included 17 (65%) females and 9 (35%) males. Two patients dropped out of the intervention group, and two dropped out of the control group. The dropouts in the intervention group were due to one patient's death and another patient's relocation, preventing him from completing the exercise program. Dropouts in the control group were due to patients not attending the post-test CPET examination.

At baseline characteristic data, there were no significant sample differences between the intervention group and the control group, except for the PVR data; also, it can be seen that the subjects who most often experienced PAH were female and had a low body weight. ASD was the most common cause of PAH with 7 (50%) patients in the intervention group and 5 (41.7%) patients in the control group. In addition, phosphodiesterase-5 inhibitors (PDE5I) were the most commonly used drugs, with 7 (39.28%) in the intervention group and 10 (83%) in the control group.

The characteristics of the CPET examination showed a statistically significant difference in the variables of exercise tolerance time and peak heart rate achievement (Table 3).

Table 2. Baseline Characteristics.

Variable	Intervention group	Control group	p-value
Sex			
Male, n(%)	5 (55.6)	4 (44.4)	1.0
Female, n(%)	9 (44.4)	8 (47.1)	
Age (years)	24 (18-54)	27 (18-51)	0.13[b]
Height (cm)	159.4 ± 7.5	160.9 ±8.1	0.63[b]
Weight (kg)	44 (37-75)	49 (35-65)	0.37[b]
Body mass index (BMI) (kg/m^2)	17.1 (14.5-27.9)	18.4 (13.8-24.2)	0.8[a]
Etiology			
Ventricular septal defecr, n(%)	5 (35.7)	4 (33.3)	0.15
Atrial septal defect, n(%)	7 (50)	5 (41.7)	
Primary pulmonary hypertension, n(%)	0	3 (25)	
Patent ductus arteriosus, n(%)	2 (14.3)	0	
Right Heart Catheterization			
Mean Pulmonary Artery Pressure (mmHg)	45 (22-76)	48.5 (22-94)	0.54[a]
Pulmonary vascular resistance (WU)	2.57 (2.12-18)	10.45 (2.22-23.69)	0.01[a]
Echocardiography			
LVEF (%)	67.93±10.18	65.3±6.9	0.57[b]
TAPSE (mm)	2.15 (1.4-3.6)	1.9 (1-2.2)	0.07[a]
Drugs			
PDE5i, n(%)	7 (50)	10 (83.3)	0.11
Prostacyclin analogue, n(%)	3 (20)	5 (41.7)	0.40

CCB, n(%)	1 (7.1)	0	1
Diuretik, n(%)	1 (7.1)	2 (41.7)	0.58
MRA, n(%)	3 (21.4)	1 (8.3)	0.59
BB, n(%)	5 (35.7)	6 (50)	0.69
ACEi/ARB, n(%)	9 (64.3)	8 (66.7)	1

[a]Wilcoxon test (Mann-Whitney)
[b]Independent T-test
p-values for categorical variables (e.g., drugs) were calculated using chi-square or Fisher's exact test

Table 3. Cardiopulmonary exercise test characteristics.

No	Variable	Intervention group	Control group	p-value
1.	Resting systolic blood pressure (mmHg)			
	Pre-test	110.43 ± 23.86	112.67 ± 12.78	0.97[b]
	Post-test	112.43 ± 18.10	114.5 ±11.91	
	Δ pre-post test	2.0 ± 16.49	1.8 ± 2.4	
2.	Peak systolic blood pressure (mmHg)			
	Pre-test	146.5 ±23.9	138.83 ±10.75	0.89[b]
	Post-test	149.42 ±23.67	140.67 ±11.75	
	Δ pre-post test	2.92 ±25.75	1.83 ±9.40	
3.	Resting diastolic blood pressure (mmHg)			
	Pre-test	66.79 ±17.09	73.08 ±10.63	0.34[b]
	Post-test	72.14 ±12.71	73 ±8.53	
	Δ pre-post test	5.36 ±18.05	-0.08 ±7.26	
4.	Peak diastolic blood pressure (mmHg)			
	Pre-test	82.07 ± 11.24	85.42 ± 8.11	0.14[a]
	Post-test	83.00 ±7.07	81.67 ±7.89	
	Δ pre-post test	4.5 (-36–15)	0 (-20–2)	
5.	Resting heart rate (bpm)			
	Pre-test	94.86 ±11.98	85 ±3.86	0.85[a]
	Post-test	93.43 ±12.69	82.92 ±9.87	
	Δ pre-post test	-1.43 ±8.38	-2.08 ±9.05	
6.	Peak heart rate (bpm)			
	Pre-test	148.07 ± 17.93	136.58 ±29.45	0.008[a]
	Post-test	154.50 ±21.08	122.08 ±26.85	
	Δ pre-post test	6.5 (-49–36)	-7.5 (-98–13)	
7.	Resting SpO_2 (%)			
	Pre-test	97.43 ±2.31	95.00 ±4.16	0.40[a]
	Post-test	97.14 ±2.25	93.42 ±5.55	
	Δ pre-post test	0 (-3.0 –1.0)	-5.0 (-8 –3)	
8.	Peak SpO_2(%)			
	Pre-test	95.14 ±3.92	92.50 ±7.05	0.43[a]
	Post-test	94.93 ±5.97	90.58 ±8.84	
	Δ pre-post test	0 (-16.0 – 13.0)	-0.5 (28 – 18)	
9.	Exercise tolerance time (minutes)			
	Pre-test	8.3 ±2.51	7.21 ±2.83	0.002[a]
	Post-test	10.14 ±3.23	7.12 ±2.64	
	Δ pre-post test	2.3 (-1 – 5.5)	0 (-1 – 1)	
10.	Anaerobic Threshold (AT) (ml/min)			

	Pre-test	565.29 ±256.75	462.5 ±159.23	0.41[a]
	Post-test	678.43 ±227.27	480.92 ±147.93	
	Δ pre-post test	64 (-222.0 – 569.0)	8 (-154.0 – 175.0)	
11.	VE/VCO_2			
	Pre-test	46.53 ±7.44	60.69 ±15.00	0.83[b]
	Post-test	44.04 ±7.52	58.40 ±14.18	
	Δ pre-post test	-2.49 ±8.6	-2.28 ±6.67	

[a]Wilcoxon test (Mann-Whitney)
[b]Independent T-test

The results of the normality test of the VO_2 peak at the initial measurement showed that the data were not normally distributed; therefore, the non-parametric Wilcoxon (Mann-Whitney) test was performed to compare the VO_2 peak values at the initial measurement, the measurement after four weeks of research, and the ΔVO_2 peak (Table 3).

Table 4. Bivariate analysis of VO_2.

	Group	N	Mean ± SD	Median (min-max)	p-value*
VO_2 peak pre-test (ml/min)	Intervention	14	888.29 ± 435.99	839 (314 – 1823)	0.136
	Control	12	641.92 ± 231.98	578.5 (408 – 1111)	
VO_2 peak post-test (ml/min)	Intervention	14	1047.71 ± 456.05	999 (413 – 2175)	0.013
	Control	12	656.5 ± 223.85	537.5 (401 – 1105)	
ΔVO_2 peak pre-post test(ml)	Intervention	14	159.42 ± 209.32	120 (-92 – 707)	0.018
	Control	12	14.5 ± 60.4	-1.5 (-77 – 148)	

*Wilcoxon test (Mann-Whitney)

Based on the bivariate analysis, there was no significant difference in VO_2 peak between the intervention group and the control group before the physical exercise program was conducted (888.29 ± 435.99 (314-1823) vs 641.92 ± 231.98 (408-1111), p = 0.136). After the four-week physical exercise program, a significant difference was found in VO2 peak between the intervention and control groups (1047.71 ± 456.05 (413-2175) vs 656.5 ± 223.85 (401-1105), p = 0.013). In addition, a significant difference was found in the comparison of ΔVO_2 between the intervention group and the control group (159.42 ± 209.32 (-92 – 707) vs 14.5 ± 60.4 (-77 – 148), p-value = 0.018). The results of this analysis indicate that the intervention group who underwent a four-week physical exercise program experienced a more significant increase in VO_2 peak than the control group who did not undergo a physical exercise program (Table 3).

Discussion

Several variables did not show a statistically significant difference between the intervention and control groups, except for the PVR data, likely due to the consecutive sampling method, which could lead to the potential for uneven sample division of the intervention and control groups. Nevertheless, there was no statistically significant difference in VO_2 peak values between the intervention and control groups before the exercise program (Table 3). This study showed that most PAH patients are young adult women who have a low body weight and a significant age difference ranging from 18 to 54 years. The data from this study are in line with previous studies that show that PAH is more common in women aged 30-60 years. However, the life expectancy of women with PAH is better than that of men, which is thought to be related to the influence of estrogen. The phenomenon known as the "estrogen paradox" in women suggests that this hormone can interact with other factors to increase chronic effects and damage pulmonary vessels. Conversely, it can have a protective effect in patients with PAH. However, the exact cause of this paradox remains unknown.[6-7]

Previous studies have shown that low body weight is more common in patients with PAH, and patients with low body weight were 2.9 times more likely to be found in the PAH population than in the general population. Low body weight is also known to be associated with a worse prognosis, especially in younger patients.[8] This study found that ASD was the most common cause of PAH in the study subjects, in line with the COHARD-PH registry, which

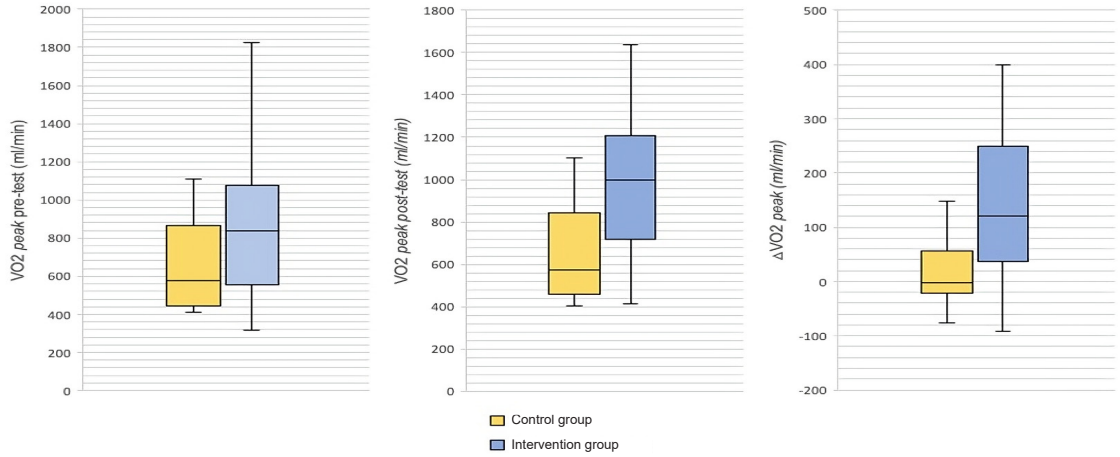

Figure 1. VO_2 peak difference between the intervention and control groups.

reported that ASD is the most common congenital heart disease that causes PAH in Indonesia, at 73.4%.[9]

This study also found that PDE5Is were the most common specific PAH treatment administered to the study subjects. PDE5Is, especially sildenafil, have been shown to be safe and effective in improving exercise capacity, hemodynamics, and outcomes in patients with PAH. In a study by Oudiz et al., sildenafil improved the functional capacity and ventilatory efficiency in patients with PAH. This is due to the improvement of pulmonary blood flow, which causes an improvement in ventilation efficiency.[10] However, PDE5Is are also effective in treating PAH, but they also have side effects, such as headache, redness, and muscle pain. In addition, there are some contraindications to the use of PDE5Is, such as ischemic heart disease, congestive heart failure, and hypertension. Therefore, not all study subjects used PDE5Is.[11-12]

Based on the results of this study, it was found that there were no statistically significant differences in some characteristics of the CPET between the two groups after the four-week research period except for the HR peak and time to exercise intolerance data. The intervention group showed better exercise endurance than did the control group after the physical exercise program. Several studies have shown that exercise programs can increase exercise tolerance time.[13-14]

De Man et al. showed improved exercise endurance in the exercise program group, supported by evidence of increased capillaryization in the quadriceps muscle and oxidative enzyme capacity, especially in type 1 muscle fibres (slow twitch), which indicates an increase in muscle work that predominantly uses aerobic metabolism.[14] However, this difference may be due to the limited number of samples and the short duration of the exercise, which may have caused an increase in one of the hemodynamic parameters to occur by chance. A study by Grunig et al. also found a significant increase in maximum blood pressure, peak heart rate, and maximum peripheral saturation in the intervention group, which is likely due to a chance.[15]

A previous study found that the blood pressure of PAH patients is often low but still tolerable owing to the use of vasodilators. HR at rest is associated with the prognosis of PAH patients. In a study by Hildenbrand et al., resting HR below 82 beats per minute was associated with better long-term prognosis in patients with PAH.[16] In another study, it is mentioned that high resting HR at the initial measurement without other known causes can indicate right ventricular failure.[17-18]

Exercise programs are expected to lower PVR and increase cardiac output, thereby lowering resting HR in patients with PAH. In addition, it is also expected to increase pulmonary blood flow and reduce right-to-left shunts, thereby improving peripheral oxygen saturation in patients with PAH. In this study, there were no significant differences in resting HR or resting/exercise oxygen saturation between the intervention and control groups. This may be due to the relatively short duration of the exercise program, which may have needed to be longer to produce significant differences in some hemodynamic parameters. In a study by Elkhen et al., the exercise program did not show a significant improvement in resting systolic blood pressure, resting

HR, resting diastolic blood pressure, or maximum diastolic blood pressure in patients with PAH who underwent 15 weeks of exercise training compared to the control group.[4,15,19-20]

In this study, there was no significant difference in ventilation efficiency between the intervention and control groups after four weeks of exercise. However, both groups showed a simultaneous improvement in ventilation efficiency after four weeks, as evidenced by an increase in VO_2 at AT and a decrease in VE/VCO_2. Pulmonary vascular remodelling in patients with PAH leads to perfusion deficits in the pulmonary arteries, which can increase the ventilation-perfusion ratio (V/Q) and alveolar dead space fraction (Vd/Vt), and cause ventilatory inefficiency that contributes to decreased functional capacity. The improvement in efficiency observed in the control group may be due to the use of medications, such as sildenafil. A study by Oudiz et al. showed that sildenafil significantly increased AT and decreased VE/CO_2 compared with the control group. This is related to the increase in pulmonary blood flow, which improves ventilatory efficiency.[10]

Previous studies have shown that physical exercise significantly increases the VO_2 peak. However, there was no significant difference in ventilation efficiency parameters, which suggests that an acute exercise program does not improve ventilation-perfusion. Still, the increase in functional capacity is due to improvements in skeletal muscle strength and endurance. However, no studies have confirmed this finding.[21-22]

In this study, there was a significantly more significant increase in VO_2 peak in patients with PAH who underwent an exercise program than in those who did not undergo an exercise program. Physical exercise is beneficial for the management of PAH. Although different exercise protocols have been used in various studies, physical exercise can improve functional capacity in patients with PAH[2-3,20,23]

Several mechanisms can influence the improvement in functional capacity in subjects who undergo an exercise program, such as improvement in right ventricular function, increased adaptation and strength of the respiratory muscles, and increased strength and endurance of the skeletal muscles. At the molecular level, physical exercise can reduce inflammatory mediators such as Th17 lymphocytes, Tumor Necrosis Factor α (TNF-α), IL-1, and IL-6, which play a role in inducing inflammation in patients with pulmonary hypertension.[24-25]

Some studies have shown that physical exercise can improve right ventricular function, as assessed by a decrease in systolic pulmonary arterial pressure and an increase in pulmonary perfusion flow.[4,15,19] This suggests that physical exercise also plays a role in lowering PVR. However, it is still unknown whether reverse remodelling of pulmonary vessels occurs.[25] Gonzalez et al. also found that physical exercise can increase respiratory muscle strength, as evidenced by a significant increase in Pimax after an eight-week exercise program. In addition, exercise programs increase the strength and endurance of skeletal muscles.[14,26] Other studies have shown that physical exercise is not effective in improving the functional capacity and quality of life in patients with pulmonary hypertension. This may be due to several factors, such as small study sample size, inconsistent patient selection criteria, low intensity and frequency of exercise, variability of exercise programs, different study durations, and heterogeneity of the patient population.[27]

Further research with a larger sample size, more consistent patient selection criteria, higher intensity and frequency of exercise, and longer study duration is needed to determine whether physical exercise is effective for patients with pulmonary hypertension. Based on the above discussion, this study shows that an exercise program can improve the functional capacity of patients with PAH; in this case, an increase in VO_2 peak. To the best of our' knowledge, this study is the one that uses the most easily adaptable exercise program, but can significantly improve functional capacity in patients with PAH. The results of this study support the importance of physical exercise as a non-pharmacological approach in the management of PAH.

Limitation

This study demonstrated the benefits of exercise in PAH patients as measured by VO_2 peak, yet several limitations should be acknowledged. First, the study did not assess other variables that may contribute to improvements in VO_2 peak, such as right ventricular function, PVR, respiratory muscle strength, skeletal muscle strength, pulmonary blood flow, or molecular changes following exercise. Second, the baseline data revealed a significant difference in PVR between the intervention and control groups, which could have introduced bias, since the intervention group had a lower baseline PVR. Nevertheless, the baseline VO_2 peak values were not significantly different between the two groups prior to the exercise program. Finally, because consecutive sampling was used—a non-probability technique—there is a possibility of selection bias, which may limit the generalizability of the findings.

Conclusion

This study showed that PAH is more common in young adult women with low body weight, the most common diagnosis being atrial septal defect, and the most common treatment is PDE5I. The study showed a significant increase in the peak HR and exercise intolerance time in the intervention group. However, there were no significant differences in other hemodynamic characteristics such as blood pressure and peripheral oxygen saturation. In addition, the ventilation efficiency variables in both groups after the four-week study period, such as anaerobic threshold and VE/VCO_2 ratio before and after the physical exercise program, also did not show a significant difference. The study showed a significant increase in VO_2 peak in PAH patients who underwent a physical exercise program compared to PAH patients who did not undergo the program. This study can be continued with a multivariate analysis by measuring other variables that can affect VO_2 peak measurement results. Physical exercise can be performed as a routine rehabilitation therapy for PAH patients as safe, easy, and effective management to improve patient quality of life.

List of Abbreviations

6MWT Six-Minute Walk Test
6MWD Six-Minute Walk Distance
CPET Cardiopulmonary Exercise Test
DBP Diastolic Blood Pressure
HR Heart Rate
LVEF Left Ventricular Ejection Fraction
mPAP Mean Pulmonary Artery Pressure
PAH Pulmonary Arterial Hypertension
PAWP Pulmonary Artery Wedge Pressure
PVR Pulmonary Vascular Resistance
SBP Systolic Blood Pressure
TAPSE Tricuspid Annular Plane Systolic Excursion

Ethical Clearance

Ethical approval was obtained from the Ethics Committee of RSUP Dr. M. Djamil Padang (No. LB.02.02/5.7/329/2023). All patients provided written informed consent.

Publication Approval

Institutional approval for publication has been obtained.

Authors Contributions

F. H. S.: Conceptualization, study design, patient recruitment, data collection, data analysis, statistical analysis, manuscript drafting and editing; C. K. K.: Conceptualization, study design, exercise session supervision, and critical revision for important content; R. H.: Conceptualization, study design, exercise session supervision, and critical revision for important content.

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Conflict of Interest

The authors declare no conflict of interest.

Availability of Data and Materials

Data are available from the corresponding author upon reasonable request.

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Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that no generative AI or AI-assisted technologies were used in the writing this manuscript. All content was produced entirely by the authors.

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Review Article

Phrenic nerve stimulation as a novel therapeutic approach for heart failure with central sleep apnea: a systematic review

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Abstract
Heart failure (HF) is a chronic condition associated with significant morbidity and mortality. Phrenic nerve stimulation (PNS) is an innovative therapeutic approach targeting HF patients with central sleep apnea (CSA), a condition linked to worsened cardiac outcomes. This systematic review evaluated the efficacy and safety of PNS, focusing on its impact on clinical outcomes such as the apnea-hypopnea index (AHI), central apnea index (CAI), left ventricular ejection fraction (LVEF), and sleep quality. A comprehensive literature search of studies published between 2014 and 2023 identified five relevant studies, following PRISMA guidelines and utilizing the Newcastle-Ottawa Scale for quality assessment. Results from current studies consistently demonstrated that PNS significantly reduces CSA severity, improves cardiac function, and enhances sleep quality, with minimal adverse events and high patient satisfaction. While these findings highlight PNS as a promising additional treatment for HF patients with CSA especially for patients who do not improve despite optimal guideline-directed medical therapy (GDMT), further large-scale randomized trials are needed to confirm its long-term efficacy and safety.

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Keywords: Heart Failure, Phrenic Nerve Stimulation, Central Sleep Apnea, Device-based Therapy

Introduction

Heart failure (HF) is a complex medical condition caused by any structural or functional issue that impairs the heart's ability to fill with or pump blood.[1] HF remains a significant clinical challenge, affecting millions worldwide and leading to significant morbidity, frequent hospitalizations, and elevated mortality rates. Central sleep apnea (CSA) is a sleep disorder characterized by the brain's failure to send appropriate signals to the muscles controlling breathing, leading to pauses or reductions in respiratory effort during sleep. Unlike obstructive sleep apnea (OSA), which results from physical airway blockages, CSA is associated with various medical conditions, particularly heart failure.[2]

The prevalence of CSA in HF ranges from 25% to 40% and is linked to increased mortality and poor prognosis.[3] Recurrent apneic events in CSA lead to disrupted sleep, chronic fatigue, and decreased daytime functioning, contributing to a diminished quality of life for these individuals.[4] Furthermore, the occurrence of CSA in heart failure patients is linked to increased hospitalizations, elevated healthcare costs, and higher mortality rates.[5]

The recurrent episodes of apnea and hypopnea in CSA lead to intermittent hypoxia and hypercapnia, triggering a cascade of pathophysiological responses. These responses include sympathetic nervous system activation, inflammation, and oxidative stress, which can further impair cardiac function and exacerbate heart failure.[6] Various treatment modalities exist for CSA in HF, such as phrenic nerve stimulation, which has shown promise in improving CSA.[4] Adaptive servo-ventilation has been studied for its effects on CSA in HF patients, showing potential benefits in improving sleep structure.[7] This method involves the electrical stimulation of the phrenic nerve to activate the diaphragm, promoting regular diaphragmatic contractions and mitigating apneic events during sleep.[8]

The remedē System, approved by the FDA, uses transvenous phrenic nerve stimulation (PNS) to treat moderate to severe CSA in adults.[9] PNS stabilizes respiratory patterns, reducing the frequency and severity of CSA episodes, which improves oxygenation and decreases nocturnal hypoxia—crucial for heart failure patients.[10] Additionally, PNS improves cardiac function by controlling breathing patterns and reducing sympathetic activation and oxidative stress, thus alleviating cardiac burdens associated with HF.[11] Finally, PNS enhances quality of life by improving sleep quality and reducing daytime symptoms, leading to a better overall quality of life for heart failure patients with CSA.[12]

This systematic review aims to comprehensively evaluate the efficacy and safety of phrenic nerve stimulation in heart failure patients, particularly those suffering from CSA, by analyzing data from clinical studies and providing insights into its potential role as a therapeutic modality.

Methods

A comprehensive search was conducted across multiple databases to find related studies about Phrenic Nerve Stimulation as a novel therapy in heart failure patients. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines to report our findings.[13] The research protocol was registered at PROSPERO (ID: CRD42024604614).

Searching Strategy

A literature search was conducted on 4 online databases (Pubmed, Web of Science, Science Direct, and ProQuest) on June 22, 2024 using the keywords "(phrenic nerve stimulation) AND (heart failure)". All retrieved articles were imported into Rayyan for duplicate removal. The titles and abstracts of the remaining articles were screened independently by the authors to exclude irrelevant studies. Discrepancies were resolved through discussion. Full texts of potentially relevant articles were then reviewed based on pre-established eligibility criteria.

Eligibility Criteria

Specific inclusion and exclusion criteria were established to ensure a comprehensive and relevant analysis. The inclusion criteria encompassed studies involving adult patients (aged 18 years and above) diagnosed with heart failure who also experienced central sleep apnea. Only studies that utilized phrenic nerve stimulation as an intervention and reported its efficacy and safety in treating heart failure were considered. Eligible studies included randomized controlled trials, non-randomized trials, and observational studies. Furthermore, only articles published in English were included to maintain consistency in data interpretation. Conversely, the exclusion criteria aimed to filter out irrelevant or non-applicable studies. This included studies that did not involve heart failure patients or used interventions other than phrenic nerve stimulation. Non-human studies were excluded to focus on clinically relevant human data. Additionally, reviews, case reports, opinion pieces, and articles not published in English were excluded to maintain a high standard of evidence and ensure clarity in data analysis.

Data Extraction

Data were extracted independently by three authors using a standardized extraction form. The extracted data included authors, publication year, study location, study design, sample size, patient characteristics, intervention details, primary and secondary outcomes, and adverse events. The data were compiled into an online spreadsheet and cross-verified by other authors to ensure accuracy. Disagreements were resolved through consensus.

Quality Assessment

The risk of bias in the included studies was assessed using the Newcastle-Ottawa Scale (NOS). The assessment was independently performed by three authors, with disagreements resolved by discussion. The risk of bias was categorized as high, medium, or low based on the number of stars attributed to each study.

Table 1. Quality assessment of selected studies based on the Newcastle-Ottawa scale (NOS).

Author, Year	Selection	Comparability	Exposure	Overall Grade
Costanzo, *et. al.*, 2018	****	**	***	9
Scwarts, *et. al.*, 2021	***	*	**	6
Hill, *et. al.*, 2023	****	*	**	7
Prtratz, *et. al.*, 2021	**	**	***	7
Zhang, *et. al.*, 2015	**	*	***	6

Literature Selection

A total of 1227 articles were identified after initial literature search performed on 4 databases [104 articles from PubMed/MEDLINE, 181 from Science Direct, 316 from Web of Science, and 625 from ProQuest (Figure 1)]. 303 duplicates were removed before screening. A total of 924 articles were identified through screening of titles and abstracts from initial results. Full-text review of all the articles was then completed. All articles were published in 2014 - 2023. Of the 5 articles included, a total of 203 patients underwent device implantation.

Results

The following baseline and study characteristics were collected for each selected article: first author, publication year, nation, and study patient characteristics (Table 2). Efficacy outcome measures included the apnea-hypopnea index (AHI), central apnea index (CAI), percent of sleep with O_2 saturation <90% (T90), sleep efficiency, and Epworth Sleepiness Scale (ESS) (Table 3).

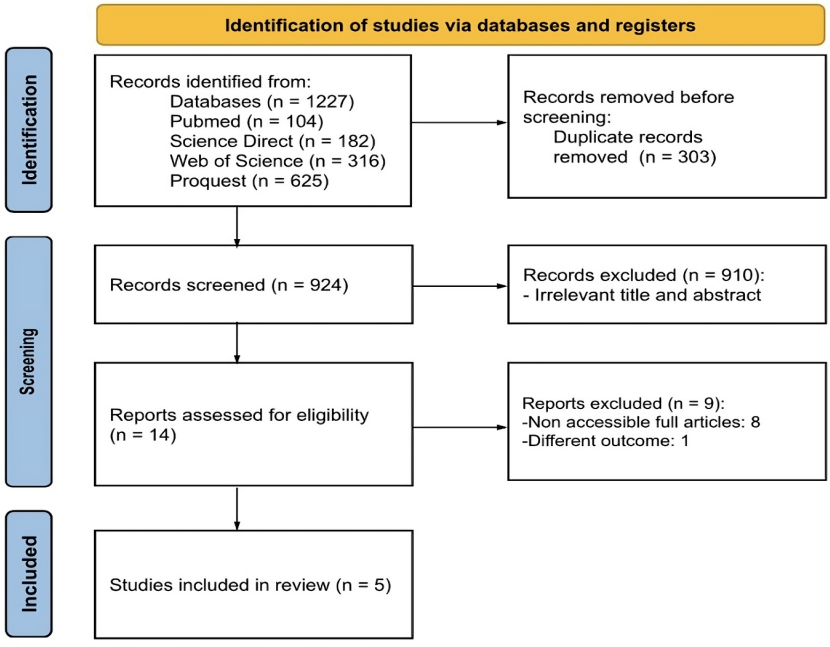

Figure 1. PRISMA flowchart of literature search.

Table 2. Characteristics of selected studies (n=5) and subjects.

Author, Year	Country	Study Design	Sample Size	Age (Year)	Male (%)	BMI (kg/m^2)	NYHA class (%)	LVEF (%)	Type of HF	AHI (events/ h)	CAI (events/ h)	Follow up (mo)
Costanzo, *et. al*., 2018	USA	Prospective, RCT, MC	96	67±12	87	30.7	I: 19 II: 43 III: 39	34.5	HFrFF	47.1	26.2	6
Schwarts, *et. al*, 2021	Not specified	RCT	151	67.1	89	30.6	NA	40.71	HFmrFF	44.7	26.2	6 & 12
Hill, *et. a*l, 2023	USA Germany and Poland	RCT	75	67±8	93	31	I: 20 II: 48 III: 32	34.6	HFrFF	45.6	24.3	12
Potratz, *et. al.,* 2021	Germany	Prospective	24	67.1± 11.2	92	34.6	II: 62 III: 38	42.4	HFmrFF	38.1	18	6
Zhang, *et. al*., 2015	China	Prospective, SC	8	51.5± 4	75	24.6	III: 62.5 IV: 37.5	37.3	HFrFF	31.2	29.4	6

Values are presented as number or mean; RCT: Randomized Controlled Trial; MC: Multicenter; SC: Single Center; BMI: Body Mass Index; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; AHI: Apnea Hypopnea Index; CAI: Central Apnoea Index.

Table 2 shows that CSA in heart failure patients often occurs in elderly men who are obese (BMI ≥ 30kg/m^2) and especially those who have several comorbidities such as cardiovascular disease and metabolic disease.[9-10,13-14] The majority of patients are heart failure patients with Left Ventricular Ejection Fraction (LVEF) ≤ 45.[9-10,14-16] 3 out of 5 studies had a majority of patients with EF ≤ 40, which is included in the HFrEF (heart failure with reduced ejection fraction) category[9,14-15,] while the other 2 studies used samples with a mean LVEF of 40.71 and 42.4, respectively.[10,16] Most of them are included in NYHA class II-III.[9-10,15-16]

Table 3. Results and conclusion of selected studies (n=5).

Author, Year	Medication status	Comorbidities	Intervention	Adverse Effect	Outcomes	Conclusion
Costanzo, et. al., 2018	Patients had to be medically stable for 30 days on GDMT prior to baseline assessments and have a qualifying polysomnogram. Medications used such as: ACEi or ARB, statins, beta-blocker, antiplatelet, MRA, loop diuretic, thiazide, digoxin and CCB.	history of AF, HT, CAD, DM, stroke, renal impairment	Unilateral TPNS vs no TPNS	33% patients reported non-serious therapy-related discomfort through 12 months	Reduces CSA severity, improvement LVEF and AHI, fewer arousals, less hypoxaemia, and improvement in REM sleep and QoL	TPNS reduces CSA severity in patients with HF
Schwarts, et. al, 2021	Patients included are medically stable for 30 days prior to all baseline testing including not using any PAP therapy. Medications not specified.	AF, CAD, history of jaw/ neck surgery	TPNS; active and deferred 6-mo therapy	One-third patients complaint discomfort	Reduces AHI to <20/h and CAI to ≤2/h, reductions in daytime sleepiness and fatigue	TPNS improved AHI, CAI, QoL of the patients with CSA

Hill, et. al, 2023	Patients who were medically stable on GDMT for >30 days. Medications not specified.	DM, AF, concomitant cardiac device, HT, CAD	TPNS; active and deferred 6-mo therapy	Not reported	Reductions in daytime sleepiness and fatigue, resolution of insomnia/fragmented sleep and snoring	TPNS improved QOL, sleep quality, and reduced daytime sleepiness
Potratz, et. al., 2021	Patients included already received treatment with optimal guideline-based HF medication and cardiac devices for at least 6 months. Medications not specified.	Not reported.	TPNS	No serious adverse events	Significant decrease in AHI and CAI, significant improvement in 6MWD and hypoxemic burden	TPNS can reduce hypoxemic burden and improve physical capacity
Zhang,et. al., 2015	All the patients were on standard therapy for HF based on their ejection fraction and medically stable prior to the procedure. Medications used such as: digoxin, diuretics, beta-blocker, nitroglycerin and ACEi.	Cardiomyopathy, AF	TPNS	1 out of 8 patients have dislodgement	Significant decrease in AHI and CAI, improvement in 6MWD, and statistical elevation of LVEF	TPNS is safe and feasible for HF patients with CSA

TPNS: Transvenous Phrenic Nerve Stimulation; AF: Atrial Fibrillation; HT: Hypertension; CAD: Coronary Artery Disease; DM: Diabetes Mellitus; CSA: Central Sleep Apnoea; GDMT: Guideline-Directed Medical Therapy; ACEi: ACE Inhibitors; ARB: Angiotensin Receptor Blocker; MRA: Mineralocorticoid Receptor Antagonist; CCB: Calcium Channel Blocker; AHI: Apnea Hypopnea Index; CAI: Central Apnoea Index; LVEF: Left Ventricular Ejection Fraction; 6MWD: Six-Minute Walk Distance; REM: Rapid Eye Movement; QoL: Quality of Life; HF: Heart Failure.

As presented in Table 3, patients included in these studies were already on GDMT for HF and medically stable prior to TPNS intervention.[9,10,14,16] All the studies maintained a standard approach where PNS was implemented as an adjunctive therapy rather than a replacement for GDMT. The study on PNS for treating CSA in HF patients demonstrates that PNS significantly reduces the AHI and CAI.[9-10,14,16] PNS also improves sleep quality and oxygenation, thereby improving the global well-being of patients.[9,14-15] There is also improvement in physical performance that is measured using 6MWD.[10,16] During the 6 and 12 months follow-up, some studies report one-third of patients complaining of discomfort after PNS implantation.[9,15] In other studies, there is no serious adverse effect or mortality has been mentioned, but one of them had dislodgement and the lead was subsequently repositioned after follow-up.[10,15-16]

Discussion

Despite advancements in HF treatments, many patients remain symptomatic and experience compromised quality of life, leading to high readmission rates.[17] Sleep-disordered breathing, particularly CSA, significantly contributes to the high morbidity and mortality in HF patients.[9] CSA in these patients is driven by hyperventilation, circulatory delay, and cerebrovascular reactivity. Hyperventilation is triggered by increased chemosensitivity and stimulation of lung receptors due to pulmonary interstitial congestion.[18] Fluid movement during sleep exacerbates this congestion, causing chronic hyperventilation and reduced $PaCO_2$ levels, which leads to periodic breathing cessation or known as central apnea.[19] Additionally, underlying cardiac disease activates peripheral chemoreceptors, triggering an exaggerated response to the decreased CO_2 levels, resulting in apnea. This apnea increases CO_2 levels, leading to hyperventilation and creating a cyclical pattern known as Cheyne-Stokes respiration. CSA in HF often manifests as Cheyne-Stokes Respiration (CSR), a cyclical pattern of waxing and waning breathing. This is driven by the delayed circulation time between the lungs and the brain, leading to a lag in the

feedback mechanism that regulates breathing. When CO_2 levels drop too low, it dampens the brain's drive to breathe, causing apnea. The subsequent rise in CO_2 from apnea stimulates hyperventilation, perpetuating the cycle.[18] Recognizing CSA in HF patients is crucial for providing intensive therapy to improve prognosis and quality of life.

Treating CSA in HF patients involves various strategies aimed at enhancing both cardiac function and respiratory stability. The primary approach typically involves optimizing HF medications. Additionally, device-based therapies such as cardiac resynchronization therapy (CRT) have been shown to improve CSA by boosting cardiac efficiency and reducing episodes of sleep-disordered breathing.[9] Beyond these methods, Continuous Positive Airway Pressure (CPAP) and PNS are two other treatment options, each with its unique benefits and considerations.[20-21]

CPAP is a widely used therapy for CSA, primarily effective in patients with both obstructive and central sleep apnea. It works by providing a constant stream of air through a mask, keeping the airways open and preventing apnea episodes. Studies have shown that CPAP can improve sleep quality, reduce daytime sleepiness, and enhance overall cardiovascular outcomes in HF patients. However, adherence to CPAP therapy can be a challenge due to discomfort and the cumbersome nature of the equipment.[18,20]

PNS involves implanting a device that stimulates the phrenic nerve, which controls the diaphragm, thereby helping to regulate breathing patterns during sleep. The study on PNS for treating CSA in HF patients shows that PNS significantly reduces the AHI, enhances sleep quality, and improves oxygenation, making it a promising alternative therapy, especially for those who struggle with CPAP adherence. Unlike CPAP, PNS has shown higher tolerance and compliance rates among patients. PNS also have minimal serious adverse events over a 12-month follow-up. The therapy also improves cardiac structure and systolic function, reduces the hypoxemic burden (SaO_2 < 90%), and enhances physical performance, as measured by the 6MWD.[10,16] Significant reductions in central respiratory events, including decreases in AHI and the CAI, were observed, though obstructive apnea index (OAI) and LVEF did not differ significantly. However, the left atrial diameter showed notable improvements. These findings support PNS as an effective and safe option as an additional therapeutic option on top of established GDMT for HF patients with CSA specifically for patients who do not improve with standard treatment or who experience side effects from primary treatments such as CPAP. Further randomized, controlled trials are needed to evaluate its long-term efficacy and safety, especially in relation to other implanted cardiac devices and its broader applicability, including for those with coexisting obstructive apnea.[20-21]

Conclusion

Despite optimal GDMT, CSA remains prevalent across all stages of HF. Phrenic nerve stimulation presents a promising alternative for improving both cardiac and sleep outcomes, particularly in patients who cannot tolerate CPAP. This review highlights that PNS significantly reduces apnea events, enhances sleep quality, improves oxygenation and cardiac structure, and increases physical performance. PNS is well tolerated, with a high success rate and minimal serious side effects. However, further large-scale, randomized controlled trials are needed to establish its long-term efficacy and safety in this population.

List of Abbreviations

6MWD	Six-Minute Walk Distance
AHI	Apnea–Hypopnea Index
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
CAI	Central Apnea Index
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CPAP	Continuous Positive Airway Pressure
CRT	Cardiac Resynchronization Therapy
CSA	Central Sleep Apnea
DM	Diabetes Mellitus
EF	Ejection Fraction
ESS	Epworth Sleepiness Scale
GDMT	Guideline-Directed Medical Therapy
HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
LVEF	Left Ventricular Ejection Fraction
NOS	Newcastle–Ottawa Scale
NYHA	New York Heart Association
OSA	Obstructive Sleep Apnea
PNS	Phrenic Nerve Stimulation
PRISMA	Preferred Reporting Items for

	Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RCT	Randomized Controlled Trial
REM	Rapid Eye Movement
TPNS	Transvenous Phrenic Nerve Stimulation

Ethical Clearance
Not applicable.

Publication Approval
All authors have reviewed and approved the final version of the manuscript and consent to its publication in the Indonesian Journal of Cardiology.

Authors Contributions
C.A., R.A.F.K., and A.Z.F.R. contributed to the conception and design of the study, literature search, data extraction, analysis, and interpretation of data. All authors have reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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The authors affirm that artificial intelligence (AI) tools were employed exclusively for language refinement, grammar correction, and formatting. No AI tools were used to generate, analyze, or alter the scientific content, data interpretation, or conclusions of this manuscript.

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Case Reports

Inverted U wave & de Winter pattern: under-recognized sign of acute coronary occlusion

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Abstract

Background: Interpreting ECGs for evidence of ischemia in patients with noticeable changes, such as ST-segment elevation and ST-segment depression, can be easily identified. However, identifying & recognizing atypical ECG patterns of acute coronary syndrome is essential in preventing significant mortality and morbidity. In the following case report, we describe inverted U wave & de Winter pattern.

Case Illustration: A 58-year-old male presented to the emergency department with pressure-like chest pain. His initial evaluation revealed normal blood pressure and elevated blood glucose levels, and an initial ECG was incorrectly interpreted as normal. Eight hours later, he returned with worsened chest pain. The new ECG revealed the de Winter ECG pattern, which indicates acute occlusion of the left anterior descending artery. Additionally, previously overlooked inverted U waves in the initial ECG suggested myocardial ischemia. Eventually, the angiography revealed a complete occlusion of the proximal left anterior descending coronary artery. The patient underwent stent placement and have a good outcome.

Conclusions: Inverted U wave and the de Winter pattern described in this case indicates an acute LAD occlusion. It's a rare finding, but it is critical for emergency physicians to recognize it for urgent reperfusion therapy. Unfamiliarity with these high-risk ECG pattern may lead to delays in appropriate treatment, causing negative effects on morbidity and mortality.

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Keywords: inverted U wave, de Winter pattern, acute coronary syndrome, left anterior descending artery.

Introduction

Patients with suspected Acute Coronary Syndrome (ACS) present in a broad range of clinical scenarios and it is crucial to take a focused medical history and accurately characterize the presenting symptoms in order to manage the patient via the appropriate care pathway as soon as possible. The resting 12-lead Electrocardiogram (ECG) is the first-line diagnostic tool in the assessment of patients with suspected ACS. It is recommended that an ECG is obtained immediately upon first-medical contact and interpreted by a qualified emergency medical technician or physician within 10 minutes.[1-2]

In the appropriate clinical context, ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: New ST elevation at the J-point in at least two contiguous leads: (a) ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women regardless of age in leads V2–V3, (b) and/or ≥1 mm in the other leads (in the absence of left ventricular hypertrophy or left bundle branch block).[2] Interpreting ECG for evidence of ischemia in patient with obvious changes, such as ST-segment elevation, can easily identified with criteria mentioned before. However, identifying & recognizing atypical ECG patterns of acute coronary syndrome is essential in preventing significant mortality and morbidity.

In the following case report, we describe inverted U wave as an early sign of acute coronary occlusion, later developed into de Winter ECG pattern. These patterns are sign of acute coronary occlusion in the Left Anterior Descending coronary artery (LAD).

Case Illustration

A 58-year-old male presented to the emergency department with pressure-like chest pain on the right and left sides of the chest, radiating to the back, accompanied by sweating, which occurred especially during exercise and improved with rest. No radiation to the neck or left hand. The pain comes and goes in the last 4 days. No prior history of hypertension, diabetes, or family history of heart disease. The patient was an active smoker for the last 20 years. Blood pressure at 110/70 mmHg, heart rate at 74 BPM, no significant abnormality on physical examination, and no sign of congestion in both lungs. ECG was recorded and labelled as a normal sinus rhythm (Figure 1). Patient then treated for muscle-related chest pain with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), an antispasmodic drug, and discharged.

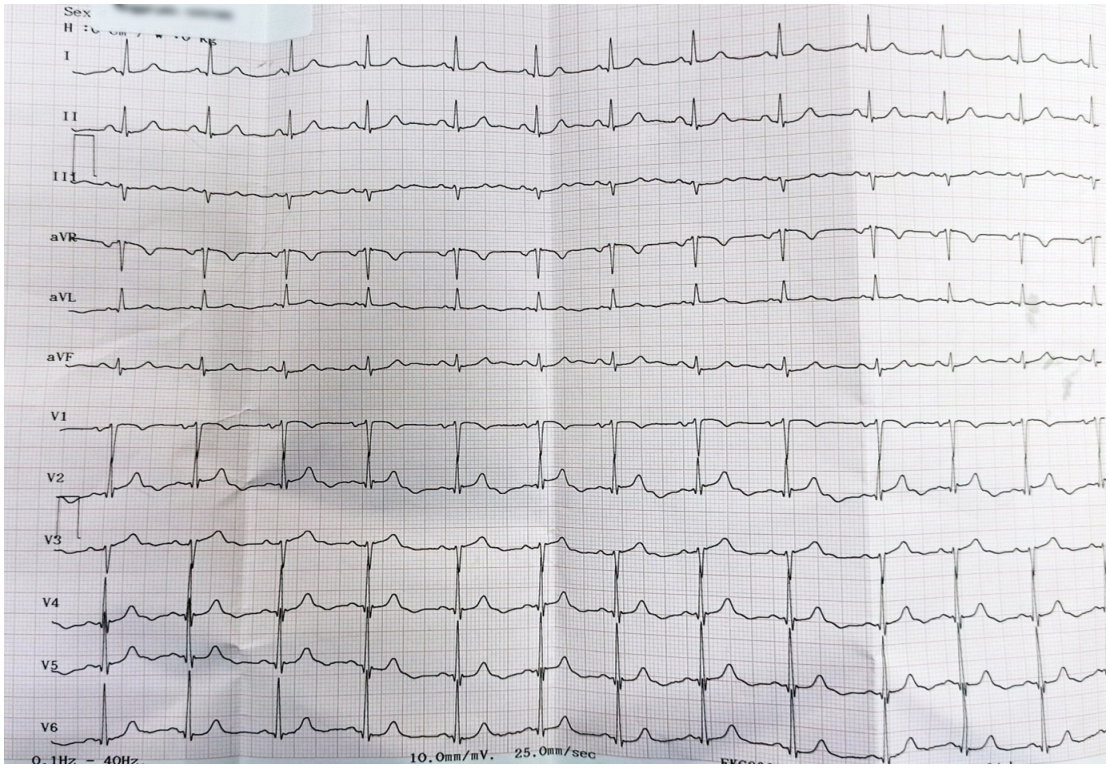

Figure 1. Electrocardiogram at the first emergency department visit.

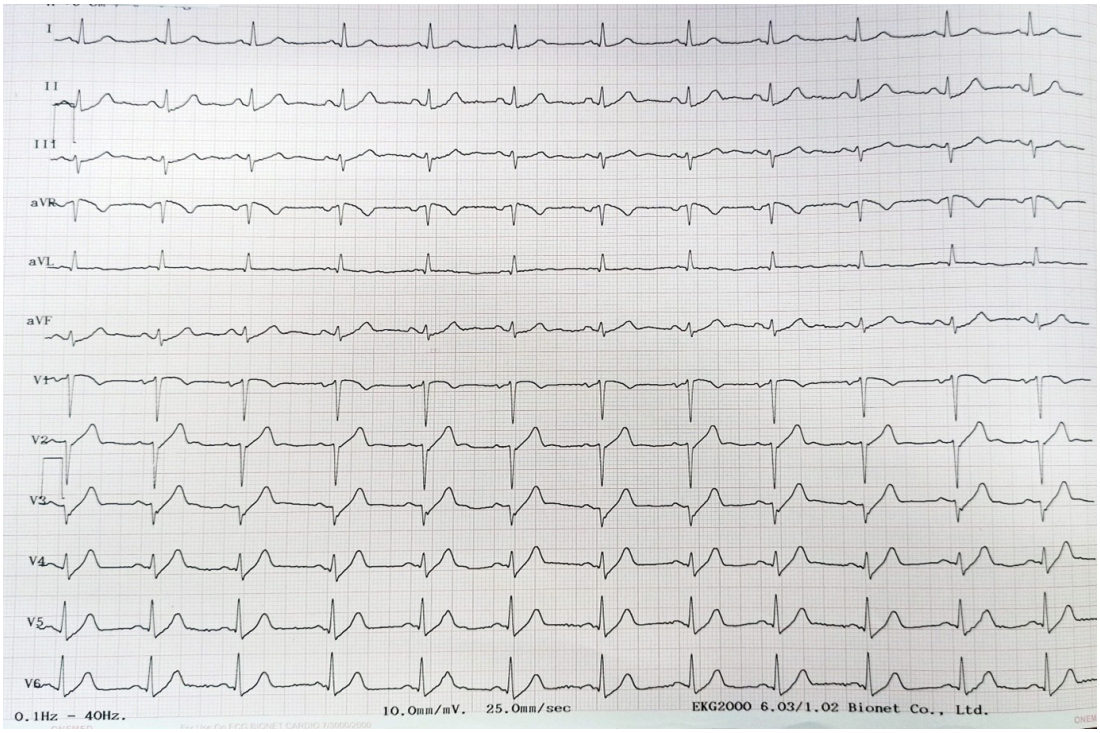

Figure 2. Electrocardiogram at the second emergency department visit, 8-hours after first visit.

Eight hours later, in the next shift, the patient came back with worsened chest pain accompanied by diaphoresis and shortness of breath. Blood pressure at 110/70 mmHg, heart rate at 76 BPM, oxygen saturation at 98% in room air. In the physical examination, we found fine crackles on both sides of the lungs, indicating pulmonary congestion. Recent ECG shows upsloping ST depression and peaked T waves in the precordial leads (V2-V5), which we recognized as the de Winter pattern, an anterior ST-Segment Elevation Myocardial Infarction (STEMI) equivalent (Figure 2). We performed a bedside echocardiography, which showed decreased contractility of the left ventricle, particularly in the basal-mid anteroseptal region, possibly due to myocardial stunning. The patient now receives proper therapy for ACS, including aspirin, clopidogrel, and nitrates. We also give furosemide to relieve the congestion. Laboratory results show random glucose at 232 mg/dl (hyperglycaemia suggesting diabetes) and elevated cardiac troponin-I at 8.12 ng/mL. Patient was immediately transferred to a higher-care hospital with a Percutaneous Coronary Intervention (PCI) capability.

During PCI, we found a total occlusion in the proximal LAD, a 70% stenosis in the proximal Left Circumflex coronary artery (LCX), and a 30% distal stenosis in the Right Coronary Artery (RCA). A stent was inserted into the LAD after successful balloon dilatation. Follow-up angiography demonstrates TIMI grade III flow. The Patient then transferred to the Intensive Cardiovascular Care Unit for further observation. After 2 days of observation, echocardiography was performed and shows normal valvular and chamber with normokinetic left ventricle (LVEF 82%), with diastolic dysfunction (E/A: 0.8). Patient then discharged in an excellent condition and gets oral therapy including Ticagrelor 2x90mg, Acetylsalicylate Acid 1x80mg, Atorvastatin 1x20mg, Bisoprolol 1x2,5mg, Isosorbide Dinitrate 3x5mg, Candesartan 8mg 1x1, and Metformin 3x500mg.

Discussion

Despite the obvious clinical presentation of acute coronary syndrome, the first emergency physician discharged the patient because there are no typical ECG findings and the ECG didn't meet the STEMI criteria. Currently, there are still many emergency physicians who are only focused on the clinical presentation of acute coronary syndrome with ST elevation or depression ECG changes, so that early changes in the ECG that represent other acute coronary syndromes may be missed. The ECG at the first encounter only showed negative or inverted U waves in the precordial leads (Figure 3) and had been missed as an early sign of acute coronary occlusion. Failure to recognize this ECG

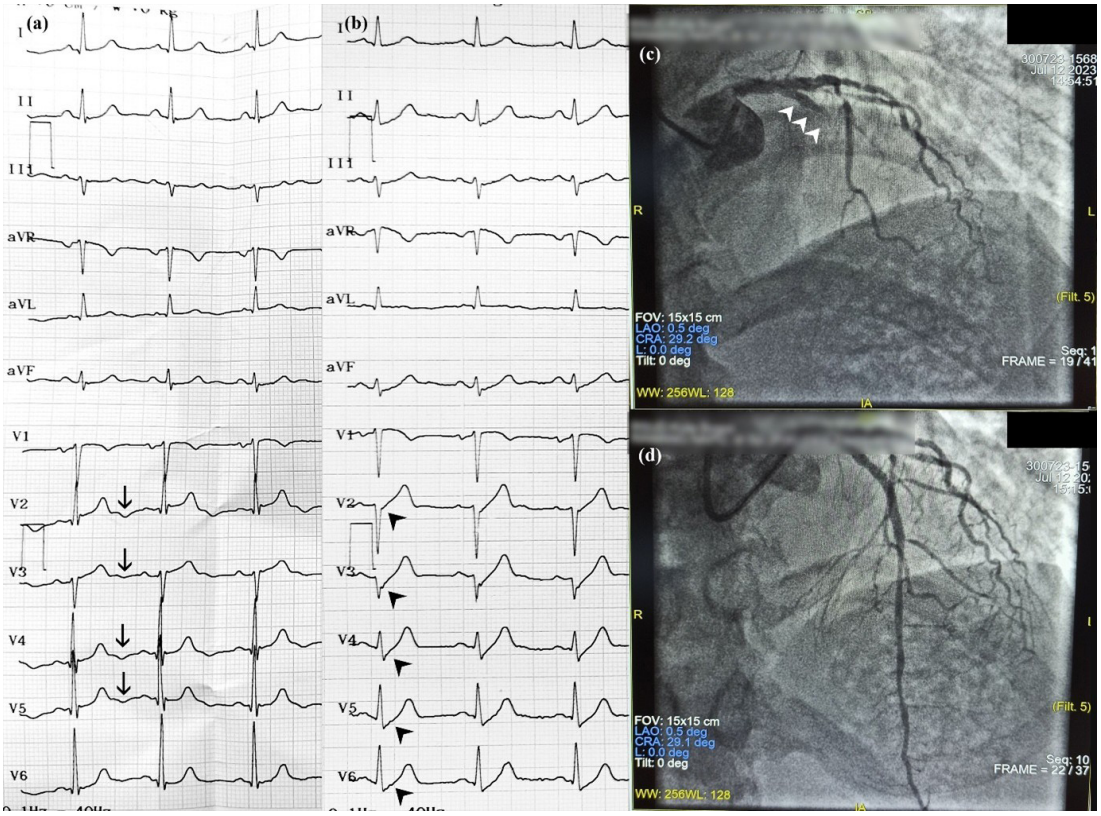

Figure 3. Comparison between initial ECG and serial ECG 8-hours later. (a) Inverted U waves in precordial lead marked by black arrow. (b) Upsloping ST depression in precordial lead marked by black arrowhead. (c) Total occlusion of proximal LAD marked by white arrowhead. (d) After PCI in LAD, TIMI grade III flow.

pattern led to the patient's discharge without a diagnosis of acute coronary syndrome, resulting in a lack of aggressive treatment from the outset. Inversion of the U-wave with an upright T-wave has pathological significance. An inverted U wave appears in various pathological conditions, including myocardial ischemia, coronary vasospasm, valvular disease, hypertension and cardiomyopathy.[3-4] In a patient with acute chest pain, a negative U-wave in the precordial leads represents a significant LAD lesion until proven otherwise.[5]

Interestingly, patients with an anterior wall myocardial infarction and negative U waves in the precordial leads have smaller infarcts, less ST-elevation, better collateral circulation, and a larger amount of stunned but viable myocardium.[5] The stunned myocardial we've seen in first bed-side echocardiography represent this statement. Decrease left ventricular contractility because of stunned myocardium responsible for the pulmonary congestion we found in second encounter with the patient. After reperfusion therapy, echocardiography shows improvement in contractility with no regional wall motion abnormality and preserved ejection fraction.

The de Winter ECG pattern first described in 2008 as new typical ECG pattern in patients with ischemic chest pain and a large acute transmural anterior myocardial infarction.[6-7] It has been linked with significant occlusion of the proximal LAD and in some cases total occlusion, as in our case.[8–12] Instead of the signature ST-segment elevation, the ST segment showed a 1- to 3-mm upsloping ST-segment depression at the J point in leads V1 to V6 that continued into tall, positive symmetrical T waves. The QRS complexes were usually not widened or were only slightly widened, and in some there was a loss of precordial R-wave progression. In most patients there was a 1- to 2-mm ST-elevation in lead aVR.[6-7] This pattern seen in 2% of acute LAD occlusions. Additionally, de Winter pattern is often considered to be an 'STEMI equivalent'.[13] Therefore, these patients qualify for immediate reperfusion therapy.[6-7] It

is of great importance that all physicians and paramedics involved in triage of patients with chest pain do recognize this ECG pattern, and immediately refer these patients for immediate reperfusion therapy.[6]

The presentation of these two rare and often under-recognized ECG patterns in a single patient is truly unique. The presence of the inverted U wave, alongside the de Winter ECG pattern, serves as a significant indicator of an acute proximal occlusion of the LAD artery. These findings align with established medical literature, as angiography revealed a total occlusion in the proximal segment of the LAD artery in this patient.

Unfortunately, in the first encounter patient has been prematurely discharged and not getting the proper treatment. In suspected ACS, acquire and interpret ECG within 10 minutes to guide management. If the initial ECG is nondiagnostic, perform serial 12-lead ECGs, especially if suspicion remains high or symptoms persist. Current guidelines recommend serial troponin testing using the 0 h/1 h (preferred) or 0 h/2 h algorithms. Measure high-sensitivity cardiac troponin (hs-cTn) at 0 h and 1 h/2 h; a very low initial hs-cTn or no increase indicates rule-out pathway, while high levels or an increase suggest rule-in pathway. If hs-cTn is unavailable, repeat conventional cardiac troponin (cTn) assays after 3 to 6 hours. Patients who don't fit these criteria should be observed, with a third measurement at 3 h. Echocardiography and CT angiography can help identify patients with non-obstructive coronary arteries.[2,14-15] However, many hospitals in Indonesia face financial limitations that restrict their ability to implement these strategies. The most practical approach available is to conduct a serial ECG at 30 to 90-minute intervals or, if available, to use a conventional serial cTn assay.

In the end, our findings on this case adds new evidence to the literature showing that in the clinical context of chest pain, if we found negative U wave in the precordial leads, it represents a significant LAD lesion until proven otherwise. This later can develop into more atypical pattern of acute coronary occlusion such as de Winter ECG pattern. These two kinds of ECG didn't meet the typical STEMI criteria but still a sign of acute coronary occlusion and should not be missed.

Conclusion

In summary, an inverted U wave and the de Winter pattern described in this case indicates an acute LAD occlusion. It's a rare and atypical finding, but it is critical for emergency physicians to recognize it for urgent reperfusion therapy. Unfamiliarity with these high-risk ECG pattern may lead to delays in appropriate treatment, causing negative effects on morbidity and mortality.

List of Abbreviations

ACS	Acute Coronary Syndrome
cTn	Cardiac Troponin
ECG	Electrocardiogram
hs-cTn	High-Sensitivity Cardiac Troponin
LAD	Left Anterior Descending Artery
LCX	Left Circumflex Coronary Artery
LVEF	Left Ventricular Ejection Fraction
NSAID	Non-Steroidal Anti-Inflammatory
PCI	Percutaneous Coronary Intervention
RCA	Right Coronary Artery
STEMI	ST-Segment Elevation Myocardial Infraction
TIMI	Thrombolysis In Myocardial Infarction

Ethical Clearance

Formal ethical approval from Ethics Comittee RSUD Kota Bogor.

Publication Approval

The corresponding author confirms that all listed authors have read and approved the final manuscript for submission and affirm that the work is original and has not been simultaneously submitted or previously published elsewhere.

Authors Contributions

Z.F.M. was primarily responsible for collecting the patient data, performing the literature review, and drafting the initial manuscript. R.M. was provided the clinical care for the patient, contributed to the conception and design of the case presentation and critically revised the manuscript. All authors

meet the ICMJE criteria for authorship and take responsibility for the integrity of the content.

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Conflict of Interest

All authors declare no competing interests (financial, personal, or professional) relevant to the subject matter or materials discussed in this case report.

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Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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Case Reports

Acute ST-Elevation Myocardial Infarction in a 25-Year-Old Female with Polycystic Ovary Syndrome: A Cardiometabolic Risk in Women of Reproductive Age

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Abstract

Background: Acute myocardial infarction is relatively rare in young patients. The age of onset gradually decreases due to multiple risk factors. The causes of Myocardial Infarction (MI) among patients aged less than 45 can be divided into four groups: atheromatous coronary artery disease, non-atheromatous coronary artery disease, hypercoagulable states, and MI related to substance misuse.

Case Illustration: A 25-year-old female came to the emergency department with chest discomfort for the past 40 minutes, has a history of diabetes for the past 3 years, and a Polycystic Ovary Syndrome (PCOS) history. Her vital signs show elevated Blood Pressure (BP) 150/100 mmHg. ECG showed sinus rhythm with ST elevation in the anterior leads. Random Blood Glucose (RBG) was 477 mg/dL, High Sensitivity (HS)-troponin 403 ng/L, and blood ketone 3.1 mmol/L. She was initially treated with: ticagrelor 180 mg, Acetosal 320 mg, insulin 4 u/hour. She was diagnosed with ST-Segment Elevation Myocardial Infarction (STEMI) and Diabetic Ketoacidosis (DKA). Coronary angiography revealed 95% stenosis in proximal Left Anterior Descending (LAD) and was treated as the culprit lesion, while 85% stenosis in mid Right Coronary Artery (RCA) was considered as the residual stenosis. Primary Percutaneous Coronary Intervention (PCI) was initiated at the proximal LAD, and post-PCI angiography showed a good result with TIMI 3 flow to the distal LAD.

Conclusions: PCOS increases cardiovascular risk primarily by promoting insulin resistance and metabolic dysfunction. Young individuals suspected of elevated cardiovascular risk should undergo a comprehensive cardiometabolic evaluation. PCI remains the cornerstone treatment for STEMI across all ages due to its well-established mortality benefit.

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Keywords: CAD, PCOS, LAD, DM

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Introduction

Acute Myocardial Infarction (AMI) is relatively rare in younger individuals, with reported incidence rates ranging from 2% to 10%.[1-2] Although younger patients generally have a more favorable prognosis and the condition occurs less frequently in individuals under the age of 45, AMI can still be life-threatening and lead to lasting disability.[3]

In young adults, AMI can result from a variety of causes, broadly categorized into four main groups: atheromatous and non-atheromatous Coronary Heart Disease (CHD), hypercoagulable states, and substance abuse. In young individuals, the development of atheromatous CHD is linked to the same common risk factors seen in adults. Smoking is highly prevalent, affecting up to 92% of young patients, especially those under 40 years old. Non-atheromatous causes include congenital coronary artery abnormalities, though rare, which can cause myocardial infarction in young adults. One such condition, myocardial bridging, can lead to significant ischemia and MI. Hypercoagulable states such as antiphospholipid syndrome, which often affects young adults in their 30s, are associated with recurrent arterial and venous thrombosis. It can occur as a primary condition or secondary to autoimmune diseases like systemic lupus erythematosus. Patients with this syndrome frequently show increased platelet adhesiveness and early signs of atherosclerosis. Substance abuse, particularly cocaine use, significantly increases the risk by inducing coronary vasospasm, with other substances like amphetamines and cannabis. Excessive alcohol intake has been connected to MI in young people, although its exact role is unclear.[4]

Case Illustration

A 25-year-old woman presented to the emergency department with acute chest discomfort lasting for 40 minutes. Her past medical history was notable for type 2 diabetes mellitus, diagnosed three years earlier, and polycystic ovary syndrome (PCOS). A comprehensive clinical assessment was performed to evaluate her condition. On examination, her vital signs were as follows: heart rate 100 beats per minute, respiratory rate 20 breaths per minute, blood pressure 150/100 mmHg, and body temperature 36.0°C. Physical examination revealed no significant abnormalities.

An Electrocardiogram (ECG) was performed, revealing a sinus rhythm with significant ST-segment elevation in the anterior leads. (Figure 1).

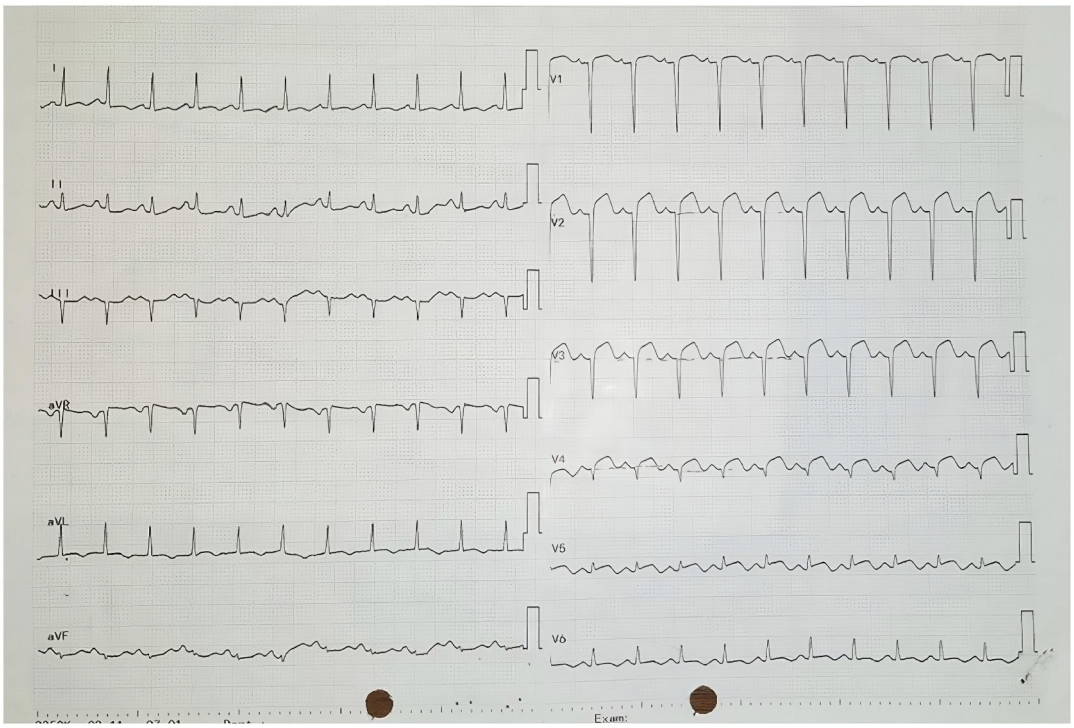

Figure 1. Electrocardiogram showing sinus tachycardia and anterior STEMI (ST-Elevation Mycocardial Infarction).

Immediate treatment was initiated. She received a loading dose of ticagrelor 180 mg along with acetylsalicylic acid 320 mg, atorvastatin 80 mg, and morphine 1 mg due to pain. Her RBG was 477 mg/dL, therefore, insulin administration was deferred until serum potassium levels were determined. The patient was admitted to the cathlab for primary Percutaneous Coronary Intervention (PCI).

Laboratory findings revealed elevated High Sensitivity (HS)-troponin 403 ng/L, blood ketone 3.1 mmol/L, confirming a diagnosis of Diabetic Ketoacidosis (DKA). The urea level was 25 mg/dL, Natrium 132 mmol/L, Kalium 4.2 mmol/L, and Chloride 95 mmol/L. An insulin infusion was commenced at a rate of 4 units per hour to manage hyperglycemia and facilitate correction of ketoacidosis.

Coronary angiography revealed significant multi-vessel coronary artery disease. A critical 95% stenosis was localized to the proximal LAD, which was identified as the culprit lesion responsible for the patient's acute myocardial ischemia. Furthermore, a significant residual stenosis of 85% was noted in the mid RCA. This secondary lesion was designated for future, staged percutaneous coronary intervention (Figure 2).

Following PCI, post-procedural angiography demonstrated successful revascularization with TIMI grade 3 flow to the distal LAD (Figure 3).

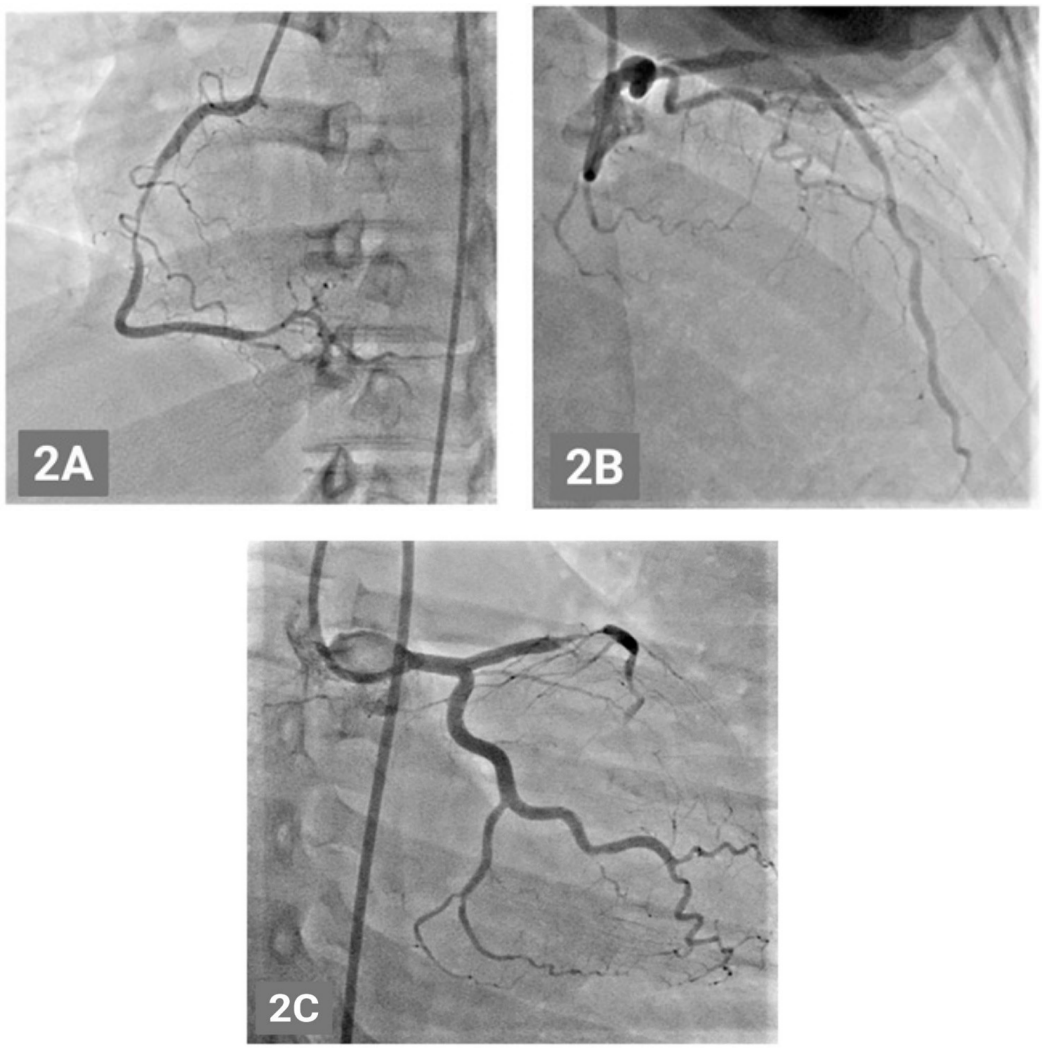

Figure 2. Coronary angiography views revealing multi-vessel stenosis. (A) Right coronary artery, RAO CRA view. (B) Left anterior descending, RAO CRA view. (C) Left anterior descending, RAO CAU view.

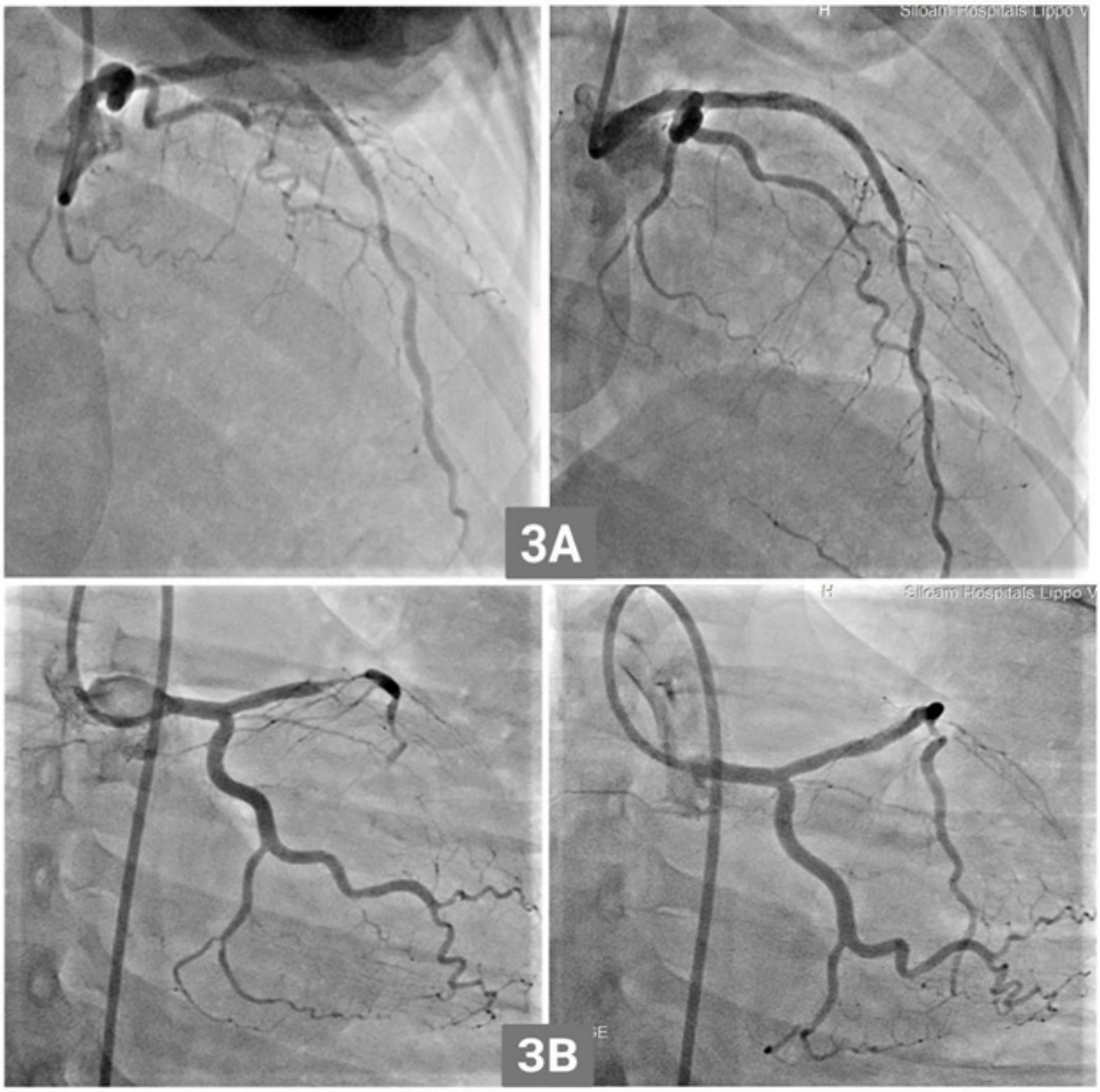

Figure 3. Post-percutaneous coronary intervention (PCI) results in the Left Anterior Descending Artery (LAD). (A) Left anterior descending, RAO CRA view & post-PCI. (B) Left anterior descending, RAO CAU view & post-PCI.

Femoral access was preferred due to the spasm of the radial artery. The lesion was predilated with a balloon (®Pantera pro-2.5x20 mm) inflated to 18 atm. Drug Eluting Stent (DES ®Supraflex Cruz 3.5x20 mm) was inserted at proximal LAD, inflated 16 atm. Door-to-balloon time was 90 minutes, and the duration from the onset of symptoms to coronary artery recanalization was 130 minutes. The patient was stable after PCI. Post-revascularization ECG was done, showing anterior Q waves with V2-V6 T inversion. (Figure 4).

Discussion

AMI in young adults is predominantly caused by premature atherosclerosis, with plaque rupture or erosion accounting for nearly 90% of cases with comorbidities including diabetes mellitus, metabolic syndrome, hypertension, chronic kidney disease, and smoking. The remaining 10% arise from non-atheromatous etiologies.[5] New studies emphasize the rising importance of non-traditional risk factors, such as chronic inflammation, autoimmune disorders, hypercoagulability, and substance abuse, in causing acute MI among younger populations.[6]

Historically, AMI in young women was considered uncommon, primarily due to the presumed protective effects of estrogen.[7] However, this perspective is challenged by the presence of PCOS, a common endocrinological disorder affecting 6–13% of women of reproductive age worldwide.[8] This endocrinological disorder is increasingly acknowledged as a contributor to heightened cardiovascular risk factors. A meta-

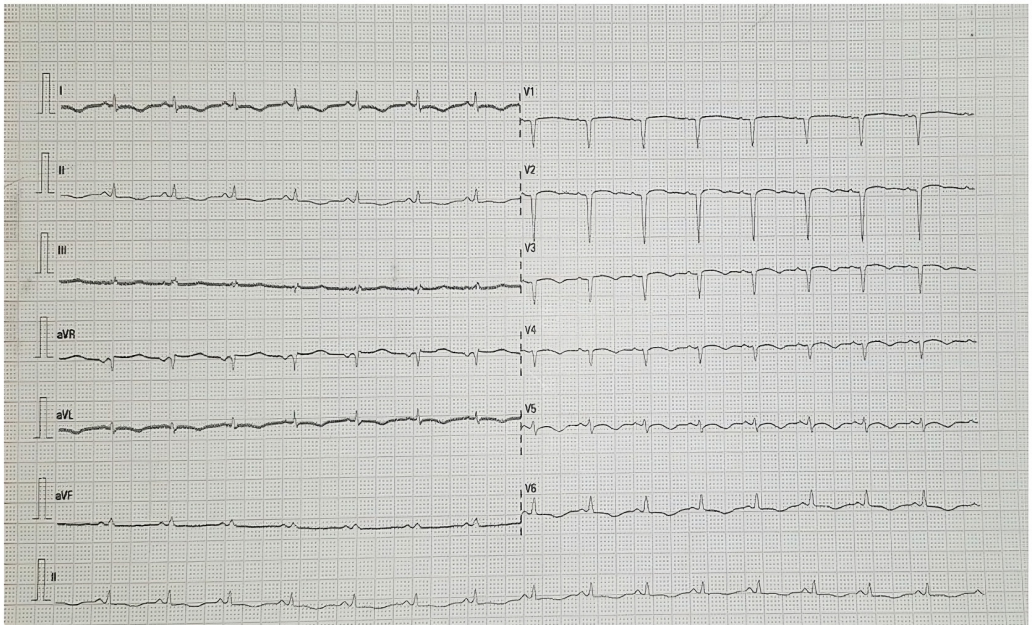

Figure 4. Electrocardiography post Percutaneous Coronary Intervention (PCI).

analysis of 104,392 subjects demonstrated that PCOS is independently associated with increased Cardiovascular Disease (CVD) risk, particularly coronary heart disease (odds ratio [OR] 1.44; 95% confidence interval [CI]: 1.13–1.84).[9-10.]

PCOS is characterized by hyperandrogenism, insulin resistance, and metabolic disturbances such as dyslipidemia, hypertension, and obesity—all established traditional cardiovascular risk factors.[11] Elevated free testosterone levels have been correlated with higher systolic blood pressure and adverse lipid profiles, further aggravating endothelial dysfunction. Importantly, women with PCOS frequently develop type 2 Diabetes Mellitus (DM).[12] DM is a complex metabolic disorder characterized by chronic hyperglycemia due to defects in insulin secretion, insulin action, or both.[13] In this case, insulin resistance is most likely driven by the presence of PCOS. Hyperandrogenism, often resulting from PCOS, impairs insulin signaling both directly and indirectly by altering fat distribution and promoting a proinflammatory state. Furthermore, a feedback loop exists in which hyperinsulinemia stimulates additional androgen production. This complex interplay contributes to the metabolic and reproductive abnormalities characteristic of PCOS.[14]

The link between DM and CVD is multifaceted and involves both macrovascular and microvascular dysfunction. Chronic hyperglycemia contributes to endothelial dysfunction by impairing nitric oxide bioavailability, promoting oxidative stress, and triggering inflammatory pathways. These effects lead to inflammation and injury of blood vessels, accelerating atherosclerosis development—a key factor in coronary artery disease, stroke, and peripheral vascular disease.[15]

In the current case, the patient's history of PCOS combined with poorly controlled diabetes mellitus presents a unique intersection of metabolic and cardiovascular risks. While substance abuse was ruled out based on clinical presentation and history, the prothrombotic milieu associated with PCOS likely contributed to the acute event.[16] Furthermore, hyperandrogenism in PCOS exacerbates insulin resistance and systemic inflammation, leading to endothelial injury and the promotion of atherosclerosis. This chronic inflammatory state impairs endothelial function, which is a key precursor to plaque development and instability.[17] PCOS often coexists with obesity, which at the cellular level induces a chronic inflammatory state that damages vascular walls and impairs endothelial function. This sustained inflammation promotes venous wall fibrosis and dysfunction, leading to impaired blood flow and subsequent venous stasis.[18] Collectively, these pathological changes contribute to the components of Virchow's triad—endothelial injury, hypercoagulability, and blood flow abnormalities — thereby increasing the risk of thrombosis in this case.[19]

The coexistence of DKA and STEMI poses an added complexity. DKA is known to provoke systemic inflammation and a prothrombotic state with increased Von Willebrand factor and decreased free protein S and protein C activity, ultimately

impairing myocardial perfusion and increasing the risk of adverse cardiovascular outcomes.[20]

In this case, femoral access was preferred due to the spasm of the radial artery. Door-to-balloon time was 90 minutes, and the duration from the onset of symptoms to coronary artery recanalization was 130 minutes. The patient was stable after PCI and started a routine medications consisting of 80 mg of acetosal, 90 mg of ticagrelor, 40 mg of atorvastatin, 2.5 mg of bisoprolol after PCI.

STEMI should be managed according to standard protocols, regardless of patient age. Urgent reperfusion via primary PCI remains the cornerstone of treatment across all age groups due to its proven mortality benefit. Compared to other cases, this case follows the same management approach, with the only additional consideration being the implementation of the DKA protocol.

It is important to note that women and diabetic patients are more likely to present with atypical symptoms, leading to potential diagnostic delays.[21] A comprehensive cardiometabolic evaluation should be performed even in young individuals who are suspected of being at increased cardiovascular risk. Timely identification reduces the risk of associated complications.

Conclusion

This case emphasizes the importance of comprehensive cardiovascular risk assessment even in young females. PCOS increases cardiovascular risk primarily by promoting metabolic disturbances. DKA triggers systemic inflammation and a prothrombotic state, together with endothelial dysfunction due to hyperglycemia, leading to impaired blood flow and venous stasis—key elements of Virchow's triad. The diagnosis might be challenging in some cases due to the presence of atypical symptoms, which are more commonly observed in female and diabetic patients, potentially leading to delayed recognition. STEMI should be treated according to established standard protocols regardless of the patient's age, with primary PCI as the urgent and vital treatment due to its proven impact on reducing mortality across all age groups. Future investigations, including advanced vascular imaging, may provide deeper insights into the structural and functional vascular changes in such patients, guiding personalized therapeutic strategies.

List of Abbreviations

AMI Acute Myocardial Infarction
CAD Coronary Artery Disease
CAU Caudal
CRA Cranial
CVD Cardiovascular Disease
DES Drug-Eluting Stent
DKA Diabetic Ketoacidosis
DM Diabetes Mellitus
ECG Electrocardiogram
IVUS Intravascular Ultrasound
LAD Left Anterior Descending artery
LCX Left Circumflex artery
MI Myocardial Infarction
PCI Percutaneous Coronary Intervention
PCOS Polycystic Ovary Syndrome
RAO Right Anterior Oblique
RBG Random Blood Glucose
RCA Right Coronary Artery
SCAD Spontaneous Coronary Artery Dissection
STEMI ST-Elevation Myocardial Infarction

Ethical Clearance

Not applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

E.A.K. collected the clinical, laboratory, and imaging data. Contributed to the literature review, case analysis, discussion, and assisted with manuscript formatting and editing. N. N. W. supervised the clinical aspects of the case, contributed to the literature review, and provided expert review of the manuscript drafts. W. W. S. participated in case analysis and assisted with manuscript formatting and editing. G. L. T. contributed to case analysis and supported manuscript formatting and editing. All authors have read and approved the final manuscript.

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Conflict of Interest

The author declared no conflict of interest.

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Generative AI and AI-Assisted Technologies in the Writing Process
Generative AI tools were utilized to support the preparation of this manuscript. Perplexity AI was used to assist in searching for up-to-date and relevant case reports and literature. ChatGPT (OpenAI) was used to help refine wording, improve clarity, and correct grammar and spelling. All content was critically reviewed and edited by the authors to ensure accuracy, originality, and adherence to ethical standards.

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