# Indonesian Journal of Cardiology

An Official Publication of the Indonesian Heart Association

Volume 45, Issue IV, 2024

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## AUTHOR GUIDELINES

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    - Running title (16 characters)
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- Cite references in numerical order according to the first mention in the text. Prior to submitting the manuscript, ensure the accuracy of spelling and details of publication.
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  - ***Article in a journal supplement***
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    Healthwise Knowledgebase. US Pharmacopeia,

Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

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### Conflict of interest

Every conflict of interest-financially or non-financial-should be stated explicitly. Please state "None" if no conflict exists.

### Sources of funding

All sources of support for the research should be listed under this heading.

Original Article

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# Risk Factor for Postoperative Pneumonia after Coronary Artery Bypass Grafting

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**Abstract**

**Background:** Postoperative pneumonia (POP) is a common infectious complication of coronary artery bypass grafting (CABG), leading to significant morbidity, mortality, and increased healthcare costs. This study found that the prevalence of POP was nearly double that reported in previous studies, underscoring the urgent need to identify specific risk factors. These findings emphasize the importance of local data in refining preventive strategies and improving clinical outcomes in CABG patients.

**Material and Methods:** This is a retrospective cohort study. The subjects comprised patients who underwent CABG procedures at a single institution between June 2020 and June 2024. A logistic regression analysis model for evaluating the risk of POP was established.

**Results:** This study observed a POP rate of 41.7%, significantly exceeding the 2–24% range reported in previous studies. Key risk factors included elevated creatinine levels, eGFR <60 ml/min/1.73 $m^2$, and low early postoperative albumin. POP strongly correlated with prolonged hospitalization, with an odds ratio of 13.043 (95% CI: 6.130–27.751, p<0.001), underscoring its substantial impact on patient outcomes.

**Conclusions:** The present study delineates renal impairment and hypoalbuminemia postoperative as pivotal risk factors for POP following CABG. It emphasizes the importance of tailored interventions, structured institutional practices, and continuous research to enhance preventive strategies and patient outcomes.

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**Keywords:** *Coronary artery bypass grafting; postoperative pneumonia; risk factor*.

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## Introduction

Coronary revascularization may be conducted through two principal approaches: surgical coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). CABG is generally considered a higher-risk procedure in comparison to PCI and is frequently linked to a more extended recovery period. Nevertheless, in the long term, CABG is correlated with a reduced recurrence rate of coronary artery disease.[1,2] Despite advancements in CABG, significant risks persist due to complications during and after the procedure, raising morbidity and mortality rates. To reduce these risks, comprehensive strategies for preventing, monitoring, evaluating, and promptly managing complications are essential. Understanding patient risk factors, healthcare performance, and postoperative conditions is crucial to effectively prevent and manage post-CABG complications. Addressing these factors is key to improving patient outcomes and reducing complication rates procedures.[3]

Postoperative infections are common complications, occurring in up to 16% of cases. They can delay healing, prolong hospital stays, and increase mortality. Various strategies exist to reduce these infections, starting with preoperative screening and extending to postoperative care ICU.[4] Postoperative pneumonia constitutes a significant infectious complication subsequent to cardiac surgery, resulting in substantial increases in morbidity, mortality, and healthcare expenditures. Postoperative pneumonia incidence varies between 2.1% and 21.6%. The demographic profile of cardiac surgery patients has evolved significantly. Despite advancements in surgical techniques and anesthesia, the aging population with multiple comorbidities and rising antibiotic-resistant pathogens increases the number of high-risk patients for complications POP.[6]

The majority of investigations concerning risk factors associated with POP have taken place in developed regions, including the United States and Europe, while data from Southeast Asia remain limited. Variations in patient demographics and medical histories have the potential to affect these risk factors, thereby underscoring the necessity for region-specific research. This study endeavors to fill this gap by identifying crucial risk factors for POP following CABG and aims to offer valuable insights that could enhance clinical outcomes in Southeast Asian populations.

## Materials and Methods

This study utilized an analytical observational approach with a retrospective cohort design. The target population was CAD patients after CABG-only surgery. The accessible population in this study were CAD patients after CABG-only surgery registered in the "Cardiac Surgery Registry" at Dr. Hasan Sadikin General Hospital, Bandung, with the ethical number DP.04.03/D.XIV.6.5/324/2024.

The research focused on patients with heart disease who underwent CABG procedures at Dr. Hasan Sadikin General Hospital in Bandung. The study included all CABG patients from June 2020 to June 2024. Patients with the following conditions were excluded from this study: acquired pneumonia within two weeks before surgery, death or discharge within 48 hours after surgery, and combination surgery with another procedure besides CABG. Patients who had the CABG procedure more than once were also excluded.

Clinical data were collected from the hospital's records system. Preoperative variables included demographics (sex, age, height, weight, BMI, smoking history), comorbidities (hypertension, diabetes, Chronic Obstructive Pulmonary Disease COPD, peripheral arterial disease, renal disease), left ventricular ejection fraction, and laboratory values. Intraoperative variables included CPB time. Postoperative variables covered mechanical ventilation duration, early albumin levels, hospital stay length, and mortality.

Postoperative pneumonia was defined by new or progressive pulmonary infiltrates on chest radiographs and at least one of the following: fever over 38 °C without known cause, leukocytosis $>12\times10^9$/L, leukopenia $<4\times10^9$/L, and purulent secretions. Semiquantitative cultures were employed to ascertain the microbiological etiology of pneumonia from sputum through initial microscopic examination alongside quantitative bacterial cultures. Hypertension is defined as a blood pressure of 140/90 mmHg or higher, a prior diagnosis, or the use of antihypertensive medication. Diabetes mellitus is characterized by fasting glucose of 126 mg/dl or more, random glucose of 200 mg/dl or higher, a past diagnosis, or the use of diabetes medication. A history of smoking includes both current and past daily

**Table 1.** Baseline Characteristics of Patients.

| Variable | N=206 |
|---|---|
| Age | |
| Mean±Std | 57.76±8.485 |
| Age Category | |
| >=60 y.o | 92(44.7%) |
| <60 y.o | 114(55.3%) |
| Sex | |
| Male | 171(83.0%) |
| Female | 35(17.0%) |
| BMI | |
| Median | 24.70 |
| IQR (Q1-Q3) | 4.34(22.86-27.20) |
| BMI Category | |
| >22.9 | 151(73.3%) |
| <22.9 | 55(26.7%) |
| Risk Factors | |
| DM | 56(27.2%) |
| Hypertension | 123(59.7%) |
| Dyslipidemia | 75(36.4%) |
| Smoking | 147(71.4%) |
| COPD (n=97) | 8(8.2%) |
| PAD | 89(43.2%) |
| LVEF | |
| Median | 50.00 |
| Range (min-max) | 22.00(38.00-60.00) |
| LVEF Category | |
| <=40% | 63(30.6%) |
| >40% | 143(69.4%) |
| Hemoglobin | |
| Mean±Std | 13.80±1.799 |
| WBC | |
| Median | 7925.00 |
| IQR (Q1-Q3) | 2227.50(6932.50-9160.00) |
| Platelet | |
| Median | 260000.00 |
| IQR (Q1-Q3) | 83500.00(220500.00-304000.00) |
| Creatinin | |
| Median | 1.10 |
| IQR (Q1-Q3) | 0.40(0.93-1.33) |
| eGFR | |
| Mean±Std | 73.51±23.103 |
| eGFR Category | |
| <60 | 50(24.3%) |
| >60 | 156(75.7%) |
| Early Postoperative Albumin | |
| Mean±Std | 2.93±0.568 |
| Early Postoperative Albumin | |
| <=2.93 g/dL | 119(57.8%) |
| >2.93 g/dL | 87(42.2%) |
| NLR | |
| Median | 2.15 |
| IQR (Q1-Q3) | 1.52(1.67-3.18) |
| RDW-CV | |
| Median | 13.15 |
| IQR (Q1-Q3) | 1.20(12.70-13.90) |
| RDW-SD | |
| Median | 41.50 |
| IQR (Q1-Q3) | 3.93(39.88-43.80) |
| Clinical presentation preoperative | |
| ACS | 40(19.4%) |
| CCS | 166(80.6%) |
| Pump CABG | |
| On pump | 77(37.4%) |
| Off pump | 129(62.6%) |
| CPB Time | |
| Median | 0.00 |
| IQR (Q1-Q3) | 81.25(0.00-81.25) |
| CPB Time Category | |
| >92 minutes | 36(17.5%) |
| <92 minutes | 170(82.5%) |
| Mechanical Ventilaton Duration | |
| Median | 0.00 |
| IQR (Q1-Q3) | 1.00(0.00-1.00) |
| Hospital LOS | |
| Median | 7.00 |
| IQR (Q1-Q3) | 4.00(5.00-9.00) |
| Complication | |
| Dengan POP | 86(41.7%) |
| Tanpa POP | 120(58.3%) |
| Mortality | |
| Yes | 10(4.9%) |
| No | 196(95.1%) |

Descriptions: SD: Standard Deviation; BMI: Body-Mass Index; CABG: Coronary Artery Bypass Grafting; COPD: Chronic Obstructive Pulmonary Disease; eGFR: estimated Glomerular Filtration Rate; LOS: Length of Stay; LVEF: Left Ventricle Ejection Fraction; PAD: Peripheral Artery Disease; POP: Postoperative Pneumonia; WBC: White Blood Cell.

**Table 2.** Univariate analysis of risk factors for POP.

| Predictors | Complication | | OR (95% CI) | p-value |
|---|---|---|---|---|
| | With POP N=86 | Without POP N=120 | | |
| Age | | | | 0.446 |
| Mean±Std | 58.29±7.633 | 57.38±9.059 | | |
| Age Category | | | 1.049 | 0.866 |
| >=60 y.o | 39(45.3%) | 53(44.2%) | (0.601-1.831) | |
| <60 y.o | 47(54.7%) | 67(55.8%) | | |
| Sex | | | 1.705 | 0.174 |
| Male | 75(87.2%) | 96(80.0%) | (0.785-3.700) | |
| Female | 11(12.8%) | 24(20.0%) | | |
| BMI | | | | 0.630 |
| Median | 25.37 | 24.38 | | |
| IQR (Q1-Q3) | 4.60(22.74-27.34) | 4.09(22.89-26.99) | | |
| BMI Category | | | 0.996 | 0.990 |
| >22.9 | 63(73.3%) | 88(73.3%) | (0.533-1.862) | |
| <22.9 | 23(26.7%) | 32(26.7%) | | |
| Risk factors | | | | |
| DM | 21(24.4%) | 35(29.2%) | 0.785 | |
| (0.418-1.473) | 0.450 | | | |
| Hypetension | 52(60.5%) | 71(59.2%) | 1.056 | |
| (0.600-1.857) | 0.851 | | | |
| Dyslipidemia | 35(40.7%) | 40(33.3%) | 1.373 | |
| (0.773-2.436) | 0.279 | | | |
| Smoking | 65(75.6%) | 82(68.3%) | 1.434 | |
| (0.768-2.678) | 0.256 | | | |
| COPD (n=97) | 6(13.3%) | 2(3.8%) | 3.846 | |
| (0.736-20.111) | 0.139 | | | |
| Peripheral Artery Disease | 37(43.0%) | 52(43.3%) | 0.987 | |
| (0.565-1.727) | 0.965 | | | |
| LVEF | | | | 0.699 |
| Median | 49.00 | 53.00 | | |
| Range (min-max) | 21.25(38.00-59.25) | 22.00(38.00-60.00) | | |
| LVEF Category | | | 0.972 | |
| (0.533-1.774) | 0.926 | | | |
| <=40% | 26(30.2%) | 37(30.8%) | | |
| >40% | 60(69.8%) | 83(69.2%) | | |
| Hemoglobin | | | | 0.662 |
| Mean±Std | 13.74±1.810 | 13.85±1.798 | | |
| WBC | | | | 0.831 |
| Median | 7950.00 | 7805.00 | | |
| IQR (Q1-Q3) | 2317.50(6812.50-9130.00) | 2242.50(6945.00-9187.50) | | |
| Platelet | | | | 0.578 |
| Median | 263000.00 | 256500.00 | | |
| IQR (Q1-Q3) | 76500.00(220500.00-297000.00) | 97750.00(219000.00-316750.00) | | |
| Creatinin | | | | 0.186 |
| Median | 1.15 | 1.10 | | |
| IQR (Q1-Q3) | 0.52(0.95-1.47) | 00.34(0.92-1.26) | | |
| eGFR | | | | 0.281 |
| Mean±Std | 71.45±22.681 | 74.98±23.383 | | |
| eGFR Category | | | 2.150 | |
| (1.127-4.103) | 0.019 | | | |
| <60 | 28(32.6%) | 22(18.3%) | | |
| >60 | 58(67.4%) | 98(81.7%) | | |
| Early Postoperative Albumin | | | | <0.001 |
| Mean±Std | 2.73±0.488 | 3.07±0.580 | | |
| Early Postoperative Albumin | | | 3.438 | |
| (1.881-6.283) | <0.001 | | | |
| <=2.93 g/dL | 64(74.4%) | 55(45.8%) | | |

| | | | | |
|---|---|---|---|---|
| >2.93 g/dL | 22(25.6%) | 65(54.2%) | | |
| NLR | | | | 0.126 |
| Median | 2.02 | 2.42 | | |
| IQR (Q1-Q3) | 1.46(1.62-3.08) | 1.48(1.71-3.19) | | |
| RDW-CV | | | | 0.244 |
| Median | 13.20 | 13.10 | | |
| IQR (Q1-Q3) | 1.30(12.70-14.00) | 0.88(12.70-13.58) | | |
| RDW-SD | | | | 0.569 |
| Median | 41.55 | 41.50 | | |
| IQR (Q1-Q3) | 4.95(39.05-44.00) | 3.60(40.00-43.60) | | |
| Clinical Presentation preoperative | | | 2.869 | |
| (1.405-5.857) | 0.003 | | | |
| ACS | 25(29.1%) | 15(12.5%) | | |
| CCS | 61(70.9%) | 105(87.5%) | | |
| Pump CABG | | | 1.387 | 0.260 |
| On pump | 36(41.9%) | 41(34.2%) | (0.784-2.455) | |
| Off pump | 50(58.1%) | 79(65.8%) | | |
| CPB Time | | | | 0.077 |
| Mean±Std | 42.79±53.303 | 29.37±42.961 | | |
| Median | 0.00 | 0.00 | | |
| IQR (Q1-Q3) | 94.75(0.00-94.75) | 77.75(0.00-77.75) | | |
| CPB Time category | | | 3.005 | 0.003* |
| >92 minutes | 23(26.7%) | 13(10.8%) | (1.422-6.348) | |
| <92 minutes | 63(73.3%) | 107(89.2%) | | |
| Mechanical Ventilaton Duration | | | | 0.083 |
| Median | 0.00 | 0.00 | | |
| IQR (Q1-Q3) | 1.00(0.00-1.00) | 1.00(0.00-1.00) | | |
| Hospital LOS | | | | <0.001 |
| Median | 8.00 | 5.50 | | |
| IQR (Q1-Q3) | 6.00(7.00-13.00) | 2.00(5.00-7.00) | | |
| Hospital LOS Category | | | 13.103 | <0.001 |
| >6 days | 73(84.9%) | 36(30.0%) | (6.458-26.584) | |
| <6 days | 13(15.1%) | 84(70.0%) | | |
| Mortality | | | 2.175 | 0.326 |
| Yes | 6(7.0%) | 4(3.3%) | (0.595-7.955) | |
| No | 80(93.0%) | 116(96.7%) | | |

smoking habits. (COPD) is defined by an FEV1/FVC ratio of ≤0.7 from spirometry. Renal insufficiency is indicated by serum creatinine >1.24 mg/dL or a prior diagnosis. The creatinine level and estimated glomerular filtration rate (eGFR) were calculated one day prior to surgery. Early postoperative albumin refers to the serum albumin levels measured within the first 24 hours following surgery. The area under the curve in the receiver operating characteristic plot is utilized as a cutoff point for analysis.

Statistical analysis was performed using SPSS (IBM SPSS Statistics, version 26). Patients with and without POP were compared by univariate analysis using the Chi-Square test for categorical variables and the Fisher exact test for discrete variables. Variables with a p-value <0.25 on univariate analysis were entered into a multivariate logistic regression analysis to identify the independent risk factors. Significance was considered at a p-value <0.05.

## Results

From June 2020 to June 2024, 256 CABG procedures were performed. Fifty patients were excluded from the analysis: thirty patients underwent combination cardiac surgery besides CABG (valvular surgery, closure defects intracardiac, repair septal rupture), sixteen patients died during the first 48 hours, and four patients got pneumonia before surgery. The remaining 206 patients underwent isolated CABG procedures instituted by the cohort. POP was diagnosed in the 86 patients (41.7%). Table 1 shows the baseline characteristics of patients.

The most common microorganism isolated in this study was *Klebsiella pneumoniae* (16%), followed by *Staphylococcus epidermidis, Pseudomonas aeruginosa,* and *Staphylococcus haemolyticus* (9%). Polymicrobial POP was detected in 14% of cases. However, in 54% of cases, no microorganism growth was found in culture

**Table 3.** Multivariate analysis of risk factors of POP.

| | | B | S.E. | Wald | Nilai P | OR | CI 95% | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| INITIAL MODEL | Sex | 0.805 | 0.575 | 1.962 | 0.161 | 2.238 | 0.725 | 6.905 |
| | Creatinin | 1.429 | 0.712 | 4.024 | 0.045 | 4.176 | 1.033 | 16.873 |
| | eGFR Category | 2.131 | 0.722 | 8.720 | 0.003 | 8.427 | 2.048 | 34.682 |
| | Early Postoperative Albumin Category | 1.111 | 0.388 | 8.191 | 0.004 | 3.037 | 1.419 | 6.501 |
| | NLR | 0.176 | 0.114 | 2.386 | 0.122 | 1.192 | 0.954 | 1.491 |
| | RDW-CV | 0.007 | 0.151 | 0.002 | 0.961 | 1.007 | 0.749 | 1.355 |
| | Clincial Presentation Preoperative | 0.247 | 0.465 | 0.283 | 0.595 | 1.280 | 0.515 | 3.185 |
| | CPB Time Category | 0.527 | 0.485 | 1.182 | 0.277 | 1.694 | 0.655 | 4.384 |
| | Mechanical Ventilation Duration | 0.018 | 0.144 | 0.016 | 0.899 | 1.019 | 0.767 | 1.352 |
| | Hospital LOS Category | 2.427 | 0.412 | 34.669 | <0.001 | 11.320 | 5.047 | 25.388 |
| FINAL MODEL | Creatinin | 1.357 | 0.670 | 4.101 | 0.043 | 3.883 | 1.045 | 14.434 |
| | eGFR Category | 1.937 | 0.669 | 8.379 | 0.004 | 6.935 | 1.869 | 25.734 |
| | Early Postoperative Albumin Category | 1.168 | 0.375 | 9.713 | 0.002 | 3.215 | 1.542 | 6.700 |
| | Hospital LOS Category | 2.568 | 0.385 | 44.450 | <0.001 | 13.043 | 6.130 | 27.751 |

examination. The prophylactic antibiotic administered to patients is ceftriaxone 2 grams. According to the antibiotic resistance data gathered from our hospital, *Klebsiella pneumoniae* has been identified as the second most prevalent microorganism isolated from sputum cultures, following *Acinetobacter baumannii*, in the intensive care unit. This organism demonstrates the highest level of sensitivity to amikacin (>64%). Sensitivity to ceftriaxone has been documented to vary between 15% and 30%. *Pseudomonas aeruginosa* ranks as the third most prevalent microorganism isolated from sputum cultures within our hospital, exhibiting the highest sensitivity level recorded towards amikacin (>64%). Currently, there is no available data concerning pseudomonas sensitivity to the aforementioned antibiotic ceftriaxone.

No statistically significant differences were observed in univariate analysis between POP and non-POP patients, except for estimated GFR <60 (32.6% in the POP group vs. 18.3% in the non-POP group; p=0.019), early postoperative albumin (2.73 ± 0.49 in the POP group vs. 3.07 ± 0.58 in the non-POP group; p<0.001), acute clinical presentation preoperatively (29.1% in the POP group vs. 12.5% in the non-POP group; p=0.003), cardiopulmonary bypass duration (26.7% in the POP group vs. 10.8% in the non-POP group; p=0.003), and hospital length of stay (84.9% in the POP group vs. 30% in the non-POP group; p<0.001).

Univariate analysis of risk factors for POP is presented in Table 2. Some variables had a p-value of less than 0.25: sex, COPD, creatinine, eGFR < 60 ml/min/1.73 m², early postoperative albumin, NLR value, RDW-CV value, preoperative clinical presentation, CPB time, duration of mechanical ventilation, and hospital LOS. Chronic obstructive pulmonary disease has a p-value of less than 0.25, but it has missing data of more than 5%; therefore, to prevent substantial bias that may weaken the integrity of multivariate analysis, this variable cannot be processed further into multivariate analysis.

Multivariate analysis identified three independent risk factors for POP (Table 3): creatinine level (odds ratio [OR], 3.88; 95% CI, 1.04–14.43), eGFR < 60 ml/min/1.73 m² (odds ratio [OR], 6.93; 95% CI, 1.87–25.73), and early postoperative albumin < 2.93 g/dL (OR, 3.22; 95% CI, 1.54–6.7). POP occurrence has a strong association with prolonged hospital stays (odds ratio [OR], 13.04; 95% CI 6.13-27.75).

## Discussion

Predictive models for postoperative pneumonia (POP) after cardiac surgery exist, but data on CABG-only procedures are limited, especially in Southeast Asia. CABG is the most common cardiac surgery globally, making it vital to explore unique risk factors for POP in these cases. Independent risk factors for

POP differ across studies due to variations in population characteristics and diagnostic definitions. This study offers insights into POP risk factors for CABG-only procedures, addressing a regional gap and enhancing global understanding of this complication. Identified patient characteristics align with previous research, underscoring the need for tailored risk assessment and management approaches to prevention.

Kilic et al. developed a validated 33-point risk score for POP from 6,222 patients (2005–2012), noting a 4.5% incidence. Their model identified six key perioperative predictors: advanced age, chronic lung disease, peripheral vascular disease, prolonged cardiopulmonary bypass (CPB) time, intraoperative blood transfusion, and use of an intra-aortic balloon pump period.[8] Wang et al. reported a higher incidence of POP (9.96%) among 5,323 patients and developed a 32-point risk score incorporating 13 independent risk factors, including age > 60 years, hypertension, diabetes mellitus, smoking, COPD, BMI > 24 kg/m², renal insufficiency, NYHA class III-IV, preoperative anemia, hypoalbuminemia, CPB time > 120 minutes, and blood transfusion.[9] Allou et al. proposed a scoring system from a study of 5,582 patients with a 3.1% incidence of POP. Their model identified four key risk factors: advanced age, COPD, low preoperative LVEF, and the interaction of RBC transfusion with prolonged CPB duration.[10] These studies underscore the multifactorial nature of POP risk and the importance of identifying patient-specific and procedure-specific factors to guide preventive strategies.

This study identified three independent risk factors for postoperative pneumonia (POP) following CABG: elevated creatinine levels, eGFR <60 ml/min/1.73 m², and early postoperative albumin <2.93 g/dL. The observed POP rate of 41.7% was significantly higher than previously reported rates (2–24%).[11–15] Gram-negative bacteria were the predominant pathogens, with *Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus epidermidis,* and *Staphylococcus haemolyticus* as the most frequently isolated species. These findings align with prior studies in which K. pneumoniae and P. aeruginosa were common causes of POP after cardiac surgery.[9,10,16] Mortality among patients with POP was significantly higher compared to that of those without pneumonia, underscoring the severe impact of POP on outcomes. While the overall mortality rate was consistent with previous studies, these findings highlight the critical need for effective prevention and management of POP to reduce associated mortality risks.[11]

In the present study, both elevated creatinine levels and reduced eGFR were identified as independent risk factors for POP after cardiac surgery. Elevated creatinine levels were significantly associated with POP, with an odds ratio (OR) of 3.883 (95% CI: 1.045–14.434, p = 0.043) in the final model. Similarly, reduced eGFR <60 ml/min/1.73m² showed an even stronger association, with an OR of 6.935 (95% CI: 1.869–25.734, p = 0.004). Impaired renal function, indicated by these markers, likely contributes to systemic inflammation, immune dysfunction, and fluid imbalances, increasing susceptibility to pulmonary infections. Research by Wang et al. and Kilic et al. highlighted similar associations, with creatinine and eGFR serving as robust predictors of postoperative complications, particularly infections.[8,9] Estimated GFR <60 ml/min/1.73 m² was observed in 24.3% of patients, predisposing them to infection due to systemic inflammation, fluid imbalance, and impaired immune function. Studies have consistently shown that renal dysfunction is a strong predictor of postoperative complications, including pneumonia.[9,14,17] Improving renal function preoperatively may reduce complications and enhance prognosis in renal dysfunction patients.

In the early postoperative period, albumin levels at or below 2.93 g/dL were observed in 57.8% of patients, thereby indicating nutritional deficiencies. Hypoalbuminemia undermines wound healing, reduces immune responses, and increases infection susceptibility. Malnutrition adversely affects surgical outcomes, leading to higher complication rates, longer recovery, and extended hospitalization. Albumin, the main human protein, is a key nutritional status marker and predicts surgical outcomes. Its quick decline post-surgery indicates surgical stress and metabolic response. Hubner et al. showed that postoperative serum albumin reductions correlate with surgical stress and predict a more complicated recovery course.[18] Perioperative nutritional support, including immune-modulating formulas, has been shown to reduce infectious complications and hospital stays after major surgeries.[19]

The mean age of patients with POP in this study was 58.29 ± 7.633 years, which is lower than the mean age reported in previous studies (68 ± 13 years).[10] Older patients face higher complication risks due to weakened

immune function, reduced pulmonary reserve, and age-related comorbidities. However, the lower POP rate in earlier studies suggests other influential factors. In this research, younger patients might have had greater comorbidity burdens, indicated by renal impairment, smoking history, and hypoalbuminemia—strong risk factors for POP. These conditions likely outweigh the benefits of youth. In contrast, older populations in prior studies might have had fewer risk factors or benefited from improved perioperative care, resulting in lower complication rates age.

In this study, 87.2% of patients with POP were male compared to 65% in Allou et al.'s study. The higher proportion of male patients with POP compared to females suggests that gender may play a role in the increased incidence of pneumonia following surgery. Male patients also often have higher rates of smoking, which can impair lung function and increase vulnerability to respiratory infections.[21] In this study, 75.6% of patients with POP had a smoking history compared with 20% in the previous study. This behavior is strongly linked to increased risks of postoperative complications, including pneumonia.

This study found a lower occurrence of COPD among POP patients compared to Allou's study; however, missing data exceeding 5% rendered it inappropriate for multivariate analysis. This limitation restricts the ability to fully evaluate the impact of COPD on POP rates within this study. However, the univariate analysis indicated a COPD prevalence of 13.3% among POP patients, with an OR of 3.846 (95% CI: 0.736–20.111, p = 0.139). Although not statistically significant, these findings suggest that COPD remains a relevant factor influencing POP risk. However, the inability to analyze COPD data in the multivariate model underscores the challenge of accurately assessing its independent contribution to POP in this cohort.

In this study, neither the neutrophil-to-lymphocyte ratio (NLR) nor the red cell distribution width (RDW) significantly influenced postoperative pneumonia (POP). Univariate analysis revealed median NLR values of 2.02 in POP patients and 2.42 in non-POP patients (p = 0.126). Similarly, the median RDW-CV was 13.20 in POP patients and 13.10 in non-POP patients (p = 0.244). These findings indicate that NLR and RDW failed to differentiate between POP and non-POP patients in this cohort. NLR and RDW are nonspecific markers of systemic inflammation, influenced by factors like infections, comorbidities, and perioperative stress. The lack of significant differences in comorbidities between POP and non-POP groups limits variability in baseline inflammation, reducing NLR and RDW's predictive power.

Left Ventricular Ejection Fraction of less than 40% is a widely recognized indicator of heart failure with reduced ejection fraction (HFrEF), which is significantly correlated with postoperative complications, particularly pulmonary infections. Research conducted by Hosseini et al. revealed an odds ratio (OR) of 2.95 (95% CI: 1.2–7.6) for pneumonia among patients exhibiting LVEF below 40%, thereby underscoring its predictive value strength.[22] In a similar vein, Pieri et al. identified LVEF <40% as a significant predictor of complications following cardiac procedures surgery.[23] In this study, however, LVEF was not significantly correlated with POP occurrence. The median LVEF was comparable between POP and non-POP groups: 49% (38–59.25%) vs. 53% (38–60%) (p = 0.699). The prevalence of LVEF ≤40% was nearly identical (30.2% vs. 30.8%, OR = 0.972, p = 0.926). Unlike prior studies with higher proportions of patients with severe heart failure, such as Allou et al., this cohort had a moderate proportion of reduced LVEF cases (30.6%), with most patients presenting LVEF >40% (69.4%). This discrepancy highlights cohort variations, where fewer reduced heart failure cases may have weakened the statistical power to confirm LVEF <40% as an independent risk factor for POP. More research with higher reduced heart failure proportions is needed to clarify its predictive value.

This study found no significant correlation between mechanical ventilation duration and POP occurrence, unlike previous studies that identified prolonged ventilation as a major predictor, particularly for VAP. The lack of significance might be due to shorter ventilation in this cohort or improvements in respiratory therapy and early extubation. Larger studies with clinically relevant ventilation thresholds are needed to clarify this impact on POP.

Patients who developed POP had a substantially higher likelihood of requiring extended hospitalization. Specifically, 84.9% of POP patients had a hospital stay longer than 6 days, compared to only 30.0% of non-POP patients. The odds ratio (OR) for extended LOS

among POP patients in the final analysis was 13.043 (95% CI: 6.130–27.751, p<0.001), indicating a strong association between the occurrence of POP and longer hospital stays.

## Study Limitations

This study has several limitations. The lack of data on COPD over 5% prevented its inclusion in the multivariate analysis and may have affected the assessment of its link to POP. Additionally, inadequate preoperative albumin data hindered the analysis of delta albumin. The single-center design and small sample size limit the generalizability of the findings. Unmeasured confounding factors, such as infection control practices, intraoperative transfusions, provider performance, and postoperative care quality, were not addressed and might have influenced POP incidence. Future research should further explore these variables using multi-center designs to validate and enhance these findings.

## Conclusions

This study identifies renal impairment and hypoalbuminemia as key risk factors for POP after isolated CABG, providing insights for perioperative risk stratification. It emphasizes the importance of institutional practices and patient-specific factors, highlighting the need for tailored interventions to optimize outcomes. Additionally, it lays a groundwork for future research to explore unmeasured variables and improve preventive strategies, thus enhancing care for CABG patients.

## List of Abbreviations

| | |
|---|---|
| CABG | Coronary artery bypass grafting |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPB | Cardiopulmonary bypass |
| eGFR | Estimated glomerular filtration rate |
| LOS | Length of Stay |
| LVEF | Left Ventricle Ejection Fraction |
| NLR | Peripheral Artery Disease |
| PCI | Percutaneous coronary intervention |
| POP | Postoperative pneumonia |
| RDW | Red cell distribution width |
| WBC | White Blood Cell. |

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# Novel Echocardiographic Parameter Assessing Pulmonary Vascular Resistance in Patients with Acyanotic Congenital Heart Disease

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**Abstract**

**Background:** Pulmonary vascular resistance (PVR) is an important variable in the management of acyanotic congenital heart disease. Right heart catheterization (RHC) using an impedance catheter remains the gold standard for pulmonary vascular resistance (PVR) measurement. The ratio of peak tricuspid regurgitant velocity to the right ventricular outflow tract time-velocity integral (TRVmax/RVOTVTI) was presented as a reliable non-invasive method of estimating PVR. Recently, right ventricular 2-dimensional speckle tracking strain (RVGLS) was proven as a new promising parameter to evaluate PVR. This study was performed to examine whether this new non-invasive variable ratio (TRVmax/RVGLS) provides a clinically reliable method to determine pulmonary vascular resistance (PVR) obtained by echocardiography.

**Methods:** The cross-sectional observational study was performed on 56 patients with acyanotic congenital heart disease. All subjects underwent cardiac catheterization and echocardiography data was obtained within 24 hours. The ratio of TRVmax/RVOTVTI and TRVmax/RVGLS analysis was performed using receiver-operating characteristic curve analysis, and a cutoff value for the ratio was generated to determine PVR more than 5 WU.

**Results:** A TRVmax/RVOTVTI cutoff value of 0.21 provided a sensitivity of 77.1% and a specificity of 81% (CI 81% to 97.5%) and a TRVmax/RVGLS cutoff value of -23.16 provided a sensitivity of 74.3% and a specificity of 90.5% to determine PVR > 5 WU (CI 79.6% to 98.2%).

**Conclusion:** The echocardiography parameter (TRVmax/RVGLS) could serve as a dependable noninvasive method to predict PVR greater than 5 WU in acyanotic congenital heart disease patients.

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**Keywords:** *Congenital heart disease, Echocardiography, Pulmonary hypertension, Pulmonary vascular resistance, Right ventricle global longitudinal strain.*

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## Introduction

Right heart catheterization (RHC) is the gold standard method for assessing the hemodynamics of individuals with pulmonary hypertension (PH), including determining pulmonary vascular resistance (PVR). Pulmonary vascular resistance is a hemodynamic variable that contributes to the management of patients with acyanotic congenital heart disease (CHD). It plays a critical role in guiding decisions regarding defect closure and evaluating clinical response to pharmacological therapy. However, RHC is considered an invasive procedure and not always available in several hospitals.[1–3]

Doppler echocardiography has significantly impacted clinical medicine by its ability to estimate intracardiac hemodynamics non-invasively. The estimation of pulmonary artery systolic pressure (PASP) using trans tricuspid flow velocity (TTFV) is a fundamental aspect of echocardiographic assessment for suspected pulmonary hypertension (PH). However, pulmonary artery systolic pressure (PASP) does not provide a definition for pulmonary vascular resistance (PVR). Since flow and pressure variables can be estimated by echocardiography, we hypothesized that a measure of PVR might be accurately obtained by Doppler-derived variables. Echocardiographic estimation of PVR using the ratio of peak tricuspid regurgitant velocity (TRV) to the right ventricular outflow tract time-velocity integral (RVOT VTI) was presented as a reliable and widely-known non-invasive method to determine PVR (Abbas Formula).[4–6] PVR is directly related to pressure difference (Δp) and inversely related to pulmonary flow (Qp). TRV can be used as a surrogate of Δp, while RVOT VTI correlates with pulmonary flow (Qp) which is influenced by RV function. However, doppler ultrasound beam alignment remains a crucial factor in acquiring adequate measurement of TRV and RVOT VTI. Right ventricular 2-dimensional speckle tracking strain is a promising parameter, as it is angle-independent, less load-dependent, and highly reproducible to assess RV function. Recent study shows that RV global longitudinal strain (RVGLS) correlates strongly with mean pulmonary arterial pressure (mPAP) and PVR in pulmonary arterial hypertension (PAH) patients.[7–9] In acyanotic CHD, it is crucial to determine the timing of management, especially for closure decisions. From previous studies and guidelines, PVR with a cut-off of 5 WU is commonly used for closure decisions.[1]

Based on recent advancements in echocardiography measurement of RV function and its relation to haemodynamics, we hypothesized that a new echocardiography parameter can be proposed to predict PVR > 5 WU in acyanotic congenital heart disease patients.

## Methods

This study is a cross-sectional observational study aimed at investigating echocardiography parameters and right heart catheterization results. The study protocol received approval from the Ethics Committee of Hasan Sadikin Hospital (DP.04.03/D.XIV.5.5/164/2024) and all the subjects gave informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki. We investigated all patients with CHD of different types, undergoing right heart catheterization (RHC). This study included patients visited our Grown Up Congenital Heart Disease Clinic who underwent RHC between August 2023 – August 2024. All subjects underwent echocardiographic examination with a maximum time interval of 24 hours before or after right heart catheterization. The inclusion criteria for this study were adults aged > 18 years with acyanotic CHD. Patients were excluded from the study if they had complex CHD, severe valvular heart disease, pregnancy, LVEF <50% by echocardiography, or poor echo window and right ventricular 2-dimensional speckle tracking strain cannot be performed. Potential sources of bias were managed by performing the echocardiography by different cardiologists and blinded for cardiac catheterization results.

### Echocardiographic Examination

An echocardiographic examination was conducted using a Phillips Epic CVx. The device was equipped with an adult 1.5 – 4.3 MHz phased array transducer. The parasternal long and short axis views, as well as the apical four-chamber image, were employed as standard imaging techniques. Flow velocities were acquired via pulsed and continuous wave Doppler techniques. The measurement of pulmonary artery flow was conducted

**Table 1.** Baseline Demographics.

| | Total (n=56) | PVR > 5 WU (n=35) | PVR < 5 WU (n=21) | P |
|---|---|---|---|---|
| Male/Female | 13/43 | 6/26 | 7/14 | 0.165 |
| Age (year) | 31 (18–71) | 30.00 (18 – 55) | 39 (19 – 71) | 0.009 |
| Aetiology of CHD, n | | | | |
| ASD | 38 | 16 | 22 | - |
| VSD | 11 | 4 | 7 | |
| PDA | 6 | 0 | 6 | |
| Other (ASD+VSD+PDA) | 1 | 1 | 0 | |
| NTproBNP | 738 (35 – 25000) | 961 (40-10729) | 481 (35 – 25000) | 0.178 |
| Echocardiography | | | | |
| LVEF (%) | 62.45 ± 7.89 | 62.26 ± 8.42 | 62.76 ±7.10 | 0.819 |
| RVOTVTI (cm) | 17.6 (7-68) | 14 (7-33) | 23 (12-68) | <0.001 |
| TRVmax (m/s) | 3.8 (1.3 – 5.4) | 4.3 (1.74 – 5.4) | 3.4 (1.3 – 4.8) | 0.001 |
| TRmeanPG (mmHg) | 40.60 ± 19.09 | 44.79 ± 20.65 | 33.62 ± 13.97 | 0.033 |
| $PASP_{ECHO}$ (mmHg) | 65.5 (9.76 – 127.36) | 78.04 (15.11 – 127.36) | 51.44 (9.76 – 95.16) | <0.001 |
| $mPAP_{ECHO}$ (mmHg) | 56.50 (21 – 97) | 48 (10.30 – 99) | 38 (8.6 – 61) | 0.028 |
| RVGLS (%) | -17.25 ± 7.03 | -14.26 ± 5.84 | -22.23 ± 6.99 | <0.001 |
| RV basal diameter (mm) | 50.50 ± 8.13 | 49.62 ± 7.17 | 51.95 ± 9.53 | 0.305 |
| RV FAC (%) | 34.5 (12.8 – 54) | 24 (12.8 – 45) | 40 (27.2 – 54.0) | <0.001 |
| RVS' (m/s) | 11.7 (4 – 18) | 11 (4 – 18) | 12 (10 – 17) | 0.007 |
| TAPSE (mm) | 19.48 ± 5.05 | 17.41 ± 4.38 | 22.95 ± 4.17 | <0.001 |
| RA area (mm2) | 20.15 (10 – 50) | 19.45 (10 – 41) | 23 (10 – 50) | 0.089 |
| MPA (mm) | 36.16 ± 7.50 | 47.63 ± 8.04 | 33.71±5.90 | 0.058 |
| TAPSE/PASP | 0.27 (0.11 – 2.04) | 0.20 (0.11 – 0.99) | 0.47 (0.20 – 2.04) | <0.001 |
| Right Heart Catheterization | | | | |
| $PASP_{CATH}$ (mmHg) | 91.46 ± 31.35 | 110.14 ± 20.27 | 60.33 ± 19.42 | <0.001 |
| $mPAP_{CATH}$ (mmHg) | 56.48 ± 23.15 | 70.46 ± 16.52 | 33.19 ± 9.92 | <0.001 |
| $PVR_{CATH}$ (WU) | 8.74 (0.82 – 69.16) | 16.18 (5.35 – 69.16) | 2.37 (0.82 – 4.63) | <0.001 |
| $PARI_{CATH}$ (WU/m2) | 10.84 (0.22 – 64.40) | 20.18 (8.75 – 64.40) | 3.17 (0.22 – 7.75) | <0.001 |

PVR: Pulmonary Vascular Resistance; CHD: Congenital Heart Disease; ASD: Atrial Septal Defect; VSD: Ventricular Septal Defect; PDA: Patent Ductus Arteriosus; LVEF: Left Ventricle Ejection Fraction; RVOTVTI: Right Ventricular Outflow Tract Velocity Time Integral; TRVmax: Tricuspid regurgitant peak velocity; TRmeanPG: Tricuspid regurgitation mean pressure gradient; PASP: Pulmonary artery systolic pressure; mPAP: mean pulmonary artery pressure; RVGLS: Right ventricle global longitudinal strain; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; RA area: Right atrial

by positioning the pulsed wave Doppler sample volume precisely at the midpoint of the transpulmonary valve jet, which was acquired from the short-axis view. Continuous wave Doppler was used to measure the peak tricuspid pressure drop by obtaining retrograde systolic trans tricuspid flow from either the parasternal right ventricular input view or the apical four-chamber view. The Doppler recordings were conducted at a sweep speed of 50 - 100 mm/s, accompanied by an ECG (lead II) overlay. The study focused on assessing the strain of the right ventricular long-axis function using the speckle-tracking echocardiography technique (STE). Pulmonary artery systolic pressure (PASP) calculated by 4 x (TRVmax)2 + estimated RA pressure. Variable RA pressure of 3/8/15 mmHg is determined based on IVC diameter and collapsibility. Mean pulmonary arterial pressure (mPAP) is calculated by the Aduen formula.[10] All measurement was obtained as recommended by the American Society of Echocardiography.[11]

**Table 2.** Echocardiographic parameters ratio between two groups.

| Echocardiographic Parameters | PVR > 5 (n=35) | PVR < 5 (n=21) | p | AUC |
|---|---|---|---|---|
| TRVmax/RVOTVTI | 0.24 (0.08 – 0.59) | 0.12 (0.04-0.24) | 0.001 | 0.893 |
| TRVmax/RVGLS | -30.95 [-75 – (-10.81)] | -16.51 [-42 – (-5.67)] | 0.001 | 0.889 |
| TRmeanPG/RVGLS | -307.44 [-1043.48 - (55.53)] | -148.69 [-500 – (-20.67)] | 0.001 | 0.822 |
| PASPECHO/RVGLS | -574.59 [-1400 – (-93.85)] | -231.90 [-627.34 – (-48.53)] | 0.001 | 0.884 |
| mPAPECHO/RVGLS | -328.76 [-1076.09 – (74.16)] | -161.73 [-536.59 – (-30.67)] | 0.001 | 0.833 |

RVOTVTI: Right Ventricular Outflow Tract Velocity Time Integral; TRVmax: Tricuspid regurgitant peak velocity; TRmeanPG: Tricuspid regurgitation mean pressure gradient; PASP: Pulmonary artery systolic pressure; mPAP: mean pulmonary artery pressure; RVGLS: Right ventricle global longitudinal strain.

### Right Heart Catheterization

Cardiac interventionists who performed the invasive measurements were blinded to the echocardiographic findings. Venous access was achieved by putting an introducer sheath into the femoral vein. Subsequently, a catheterization was conducted using an MP-2 Catheter. The mean pulmonary arterial pressure (mPAP) was directly measured using a catheter placed in the pulmonary artery. Similarly, the mean left atrial pressure (mLAp) was recorded directly using a catheter implanted in the left atrium in a patient with an IAS defect (Atrial Septal Defect or Patent Foramen Ovale). Meanwhile, in patients without an IAS defect and no evidence of mitral stenosis, LVEDP measurement was performed with a pigtail catheter. The measurements were automatically derived from the pressure graphics. Blood samples were collected from the superior and inferior cava veins, right atrium, pulmonary artery, four pulmonary veins, and left atrium to determine oxygen saturation. Pulmonary flow (Qp) is measured by individual O2 consumption divided by delta of pulmonary vein oxygen saturation (PVO2) and pulmonary artery oxygen saturation (PAO2). The pulmonary vascular resistance (PVR) was calculated using Indirect Fick's method.[2,3]

### Statistical Analysis

In the demographic data section, continuous variables were presented as mean ± standard deviation (SD) for normally distributed data, median-interquartile range (IQR) for nonnormally distributed data, and categorical data presented as percentages or frequencies. Normality was evaluated using the 1-sample Kolmogorov–Smirnov test. The difference between invasive PVR as the gold standard and echocardiography variables as independent variables was assessed by an independent t-test for normally distributed data and the Mann Whitney U test for nonnormally distributed data.

To assess the diagnostic value of the novel parameters, using $PVR^{CATH}$ as the gold standard, receiver operating characteristic curves were plotted using a dichotomized function of PVR and a cut-off value of 5 wood units (WU). Confidence intervals of sensitivity and specificity were assessed. All analyses were performed on software (SPSS 25.0, SPSS Inc, Chicago, IL) and $p<0.05$ was considered statistically significant.

## Results

There are 56 patients that remained in the final analysis. Baseline demography and standard echocardiographic parameters are presented in Table 1. The majority of patients were female, with most cases of ASD as aetiology of acyanotic congenital heart disease. There was no difference in LVEF, gender, RV basal diameter, RA Area, and MPA diameter between both groups. A total of 35 patients had $PVR^{CATH}$ > 5 WU, while 21 patients had $PVR^{CATH}$ < 5 WU. Median $PVR^{CATH}$ was 8.74 (0.82 – 69.16) WU measured by RHC with significant differences between two groups.

TRVmax, RVOT VTI, TRmeanPG, PASP, mPAP (Aduen Formula), RVGLS, FAC, RVS', TAPSE, and TAPSE/PASP show significant differences between groups. RVGLS was significantly more impaired in patients who had PVR > 5 WU. Based on a previous study, TRVmax/RVOTVTI shows an excellent correlation in predicting PVR. We perform analysis on several echocardiography parameters for predicting PVR

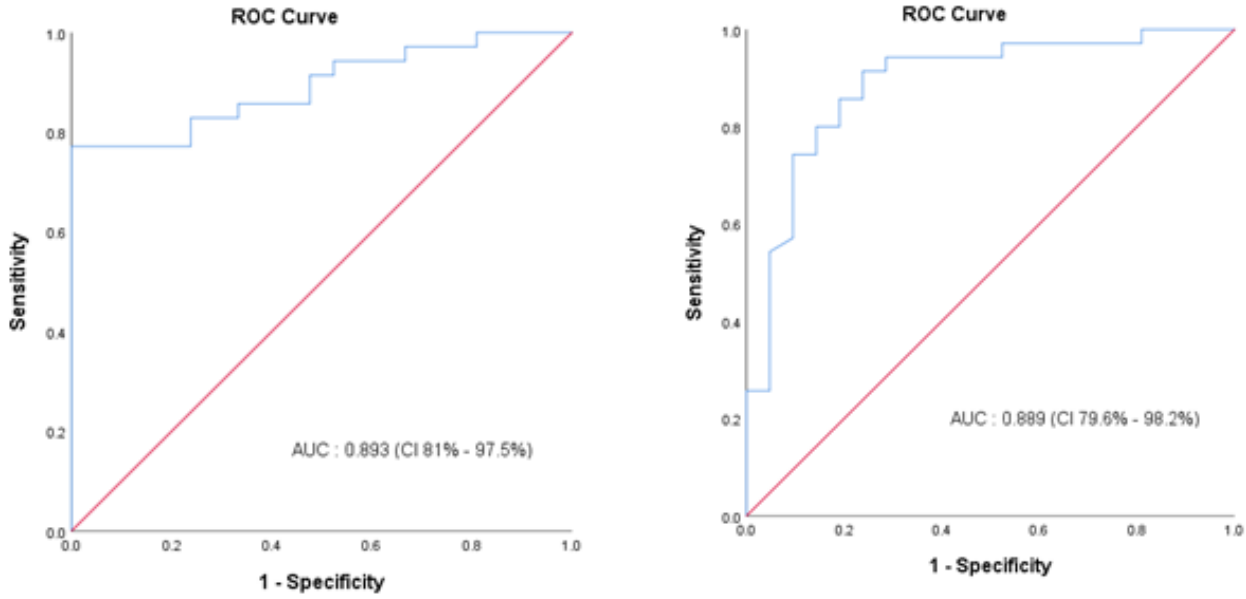


**Figure 1.** (a) receiver-operating characteristic curve for TRVmax/RVOTVTI with AUC 0.893 (CI 81% - 97.5%), (b) receiver-operating characteristic curve for TRVmax/RVGLS with AUC 0.889 (CI 79.6% - 98.2%).

> 5 WU. As the results, TRVmax/RVOTVTI, TRVmax/RVGLS, TRmeanPG/RVGLS, PASP/RVGLS, and mPAP/RVGLS show significant differences among both groups. (Table 2). Receiver operating characteristic (ROC) curves were calculated to evaluate the prediction of PVR > 5 WU by several echocardiographic parameters.

The area under the receiver-operating characteristic curve for TRVmax/RVOTVTI was calculated at 0.893. A TRVmax/RVOTVTI cutoff value of 0.13 provided a sensitivity of 91.4% and a specificity of 52.4% to determine PVR > 5 WU, meanwhile, a cutoff value of 0.21 provided a sensitivity of 77.1% and a specificity of 81% (CI 81% to 97.5%). The area under the receiver-operating characteristics curve for TRVmax/RVGLS was calculated at 0.889. This result was comparable with the previous formula in predicting PVR (TRVmax/RVOTVTI). A TRVmax/RVGLS cutoff value of -19.61 provided a sensitivity of 91.4% and a specificity of 76.2 % to determine PVR > 5 WU, meanwhile, a cutoff value of -23.16 provided a sensitivity of 74.3% and a specificity of 90.5% to determine PVR > 5 WU (CI 79.6% to 98.2%).

## Discussion

Previous studies have attempted to obtain a non-invasive measurement of PVR. The ratio of TRVmax to RVOT VTI was the most studied to predict PVR.[4–6,12–22] However, certain limitations was found to predict PVR in certain conditions such as unreliable formula in high PVR subjects. Recent advancement of RV function assessment shows RV GLS measurement can be performed to measure RV function and several studies shows excellent relationship to mPAP and PVR.[7–9,23,24] We present the process of developing novel echocardiography parameter to predict PVR. Our study shows, TRVmax/RVGLS have excellent performance in predicting PVR > 5 WU in patient with acyanotic congenital heart disease with cut-off point of -19.61 provided sensitivity 91.4% and specificity 76.2%.

Volume and/or pressure overload lead to alteration in RV physiology and function. Increase of RV pressure and wall stress results in RV dysfunction including RV dilatation, reduced RV wall motion, intraventricular, and interventricular RV dyssynchrony. Conventional RV functional parameters such as TAPSE, RV S' and RVFAC in early stages of PH can remain normal, consequently RV strain analysis is favourable for detecting subtle hemodynamic changes. Standard

echocardiographic parameters (TAPSE, S', RVFAC, etc) are used for evaluation of RV function but they are affected by some factors such as image quality, angle dependent, heart motion or ventricular loading condition. RV strain has several advantages such as angle independency, less load dependency, accuracy in measurement of regional myocardial deformation, high availability, low cost, and high reproducibility. [9,11,25,26]

Right ventricular function has an important prognostic role in various condition, especially patient with pulmonary arterial hypertension (PAH). Changes in RVGLS value in congenital heart disease is not well defined in patient whom had chronic volume or pressure overload, but RVGLS has been shown to be a robust marker of RV function in patients with PAH and was proved to be strong predictor of mortality. However, there are several limitation or issues regarding the use of RVGLS such as no agreement about cut off normal values, demand high temporal resolution, visualization of RV endocardial border, and sometimes problem with window in term of poor visualization of RV free wall. [9,11,23–27]

Pulmonary hypertension in adult acyanotic congenital heart disease should be evaluated particularly and determination of PVR is mandatory. PVR was associated with outcome of closure intervention in congenital heart disease and patients with PVR > 5 are likely to have worse clinical outcome.[28–32] Previous study by Abbas et. al. shows TRVmax/RVOTVTI has excellent performance in predicting PVR value.[4,6] In this study, TRVmax/RVOTVTI shows similar results with cutoff value of 0.13 provided a sensitivity of 91.4% and a specificity of 52.4% in predicting PVR > 5 WU. Abbas et. al. provided 0.175 as cutoff value for TRVmax/RVOTVTI with good sensitivity of 77% and specificity of 81% in predicting PVR > 2 WU.[4] Our result show similar area under the curve but with slightly differences in sensitivity and specificity cutoff value in predicting PVR (> 5 WU vs > 2 WU).

Prior researchers have documented the utilization of different doppler parameters for the assessment of pulmonary vascular resistance. The primary focus of these work has been on determining the timing of events such as the duration of right ventricular pre-ejection and ejection, the acceleration time of the right ventricular outflow tract velocity, and the velocities of flow propagation. Other studies show decent correlation between echocardiographic parameter estimation of PVR with PVR by RHC, but none of them using global longitudinal strain in their parameters.[4,6,19–22,33] Our study shows significant correlation between TRVmax/RVGLS and $PVR^{CATH}$ and cut-off point of -19.61 provided sensitivity 91.4% and specificity 76.2% in terms of predicting PVR > 5 WU.

Our study has showed that our novel parameter TRVmax/RVGLS may have better performance in determining PVR in adult acyanotic congenital heart disease with pulmonary hypertension. We hope our models can be applied in centre that with no catheterization laboratory, in addition to start, evaluating medical therapy, and determine definite management in adult patients with acyanotic congenital heart disease and pulmonary hypertension. If the patient had estimated PVR > 5 WU, we can start medical therapy and refers to cardiac catheterization centre for invasive evaluation. Conversely, if the patient had estimated PVR < 5 WU, prompt referral to cardiac catheterization centre for closure management is a priority.

## Limitation

Limitations inherent to the doppler technique are related to proper alignment of the ultrasound beam and have been reported elsewhere. Inability to obtain the tricuspid regurgitation jet is also a concern and has been addressed in the respective publications. Also, the peak TRV may vary with respiration, so using an average of multiple beats, rather than the maximum velocity obtained during sinus rhythm, may be a more appropriate representation of this parameter. RV GLS measurement have several weaknesses such as demand high temporal resolution, visualization of RV endocardial border, and sometimes have problem with window in term of poor visualization of RV free wall, leading to improper measurement of RV GLS.

All patient in this study had mPAP >20 mmHg thus this new method represents PH population in acyanotic congenital heart disease should be interpret cautiousl.

## Conclusion

The novel echocardiography parameters TRVmax/RVGLS, which are based on a non-invasive formula for

predicting PVR, have a significant correlation with the gold standard measure and demonstrate high accuracy with excellent sensitivity and specificity in detecting individuals with elevated pulmonary vascular resistance (PVR > 5 WU) for patient with acyanotic congenital heart disease. A cut-off point of -19.61 was proposed as a predictor of PVR > 5 WU.

## Ethics approval and consent to participate

The research was performed in accordance with the Declaration of Helsinki and was approved by the Hasan Sadikin Hospital Ethics Committee.

## Informed consent

Written informed consent was obtained from each participant.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Competing interest

I have nothing to declare.

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## Author Contributions

All authors write and review the manuscript. MRRN and CJC took part on conceptualization. MRRN, CJC, and AFK took part on data curation. CJC and AFK took part on investigation. MRRN, JWM, and CJC took part on project administration. MRRN, CJC, and NS took part on data analysis. JWM, CJC, and AFK took part on supervision. MRRN, CJC, JWM, AFK, and NS took part on methodology.

## List of Abbreviations

| | |
|---|---|
| CHD | Congenital Heart Disease |
| mPAp | Mean pulmonary arterial pressure |
| mLAP | Mean left atrial pressure |
| PAO2 | Pulmonary Artery Oxygen Saturation |
| PASP | Pulmonary artery systolic pressure |
| PVR | Pulmonary vascular resistance |
| PH | Pulmonary hypertension |
| PVO2 | Pulmonary vein oxygen saturation |
| RHC | Right heart catheterization |
| RVGLS | Right ventricle global lingutudinal strain |
| TTFV | Trans tricuspid flow velocity |
| TRVmax | Tricuspid regurgitant peak velocity |
| TRmeanPG | Tricuspid regurgitation mean pressure gradient |
| RVOTVTI | Right Ventricular Outflow Tract Velocity Time Integral |

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Original Article

# Outcome Analysis and Determinants of Major Adverse Cardiac Events in Young Adults After Coronary Artery Bypass Graft Surgery Who Participated in Early Phase II Cardiac Rehabilitation Program: A single–center study

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**Abstract**

**Background:** Cardiac rehabilitation (CR) program is proven to reduce mortality after coronary artery bypass surgery (CABG). Our study aimed to investigate the determinants of survival in young adult patients after CABG.

**Methods:** This was a single-center, longitudinal study with a survival analysis method from MACE of consecutive patients under 55 years old who underwent CABG and participated in the early phase II CR program between January 2017 and December 2018. The major adverse cardiac events (MACE) rates were determined over a 2-year follow-up time. Cox regression and Kaplan-Meier analysis were used to determine the predictors of the events.

**Results:** 279 patients who fulfilled the inclusion criteria were recruited in this study. MACE happened to 23 (8.45%) of them (3 patients died, 20 patients were hospitalized). Patients who dropped out (12%) from the CR program had a higher risk of developing events (HR 3.86, 95% CI 1.36-10.99). Of those who completed the CR program (245 patients), beta-blocker usage, chronotropic index, resting heart rate, and functional capacity after the CR program independently correlated with MACE. Six-minute walk distance (6-MWD) ≤376 meters was a significant predictor (p=0.001), with a shorter mean survival time of 6 months.

**Discussions:** The early phase II CR program after CABG in young adult patients reduced the risk for cardiovascular mortality, major adverse events, and related readmission. It also increased the survival rate and mean survival time for participants who completed the CR program compared to dropouts. Optimum beta blocker medication, chronotropic index, resting heart rate, and functional capacity after the CR program are essential predictors of survival after CABG in young adults.

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**Keywords:** *Cardiac Rehabilitation, Young adult, Mortality, Major advevse cardiac event, Predictor.*

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## Background

Coronary artery bypass graft (CABG) surgery becomes an option for myocardial revascularisation, especially for patients with more complex coronary anatomy and comorbidities such as diabetes mellitus and renal failure.[1] Compared to percutaneous transluminal coronary angioplasty, CABG is a more invasive procedure with more difficulties. It is associated with potential complications, so it usually needs 2 to 6 weeks of convalescence to recover.[2]

Patients need a full and prompt physical recovery after surgery to allow a fast return to daily life activities, especially at younger and more productive ages. A cardiac rehabilitation (CR) program was recommended for early post-CABG patients and was classified as a class IA recommendation.[3,4] Supervised exercise-based CR is crucial to secondary prevention and reduces hospital admissions and all-cause mortality by 15%–28% in moderate to long-term studies.[5-6]

Furthermore, traditionally, most institutions do not deliver outpatient supervised CR exercise (CR phase II) until 6 weeks after CABG, so functional capacity may decline gradually.[7] In several cardiovascular rehabilitation facilities in Indonesia, the phase II CR program for patients after CABG is implemented earlier, starting within 1 week after hospital discharge. However, there is still a lack of evidence of the benefit of midterm follow-up.

Among the key clinical endpoints in cardiovascular research, major adverse cardiac events (MACE) have emerged as critical markers for evaluating disease progression and therapeutic efficacy. MACE, which encompasses events such as myocardial infarction, stroke, and cardiovascular death, provides a comprehensive framework for assessing patient outcomes beyond traditional measures. Understanding the factors influencing the occurrence of MACE and their implications on overall patient outcomes is essential for improving cardiovascular care. Mortality, as a component of MACE, underscores the severity of these events and highlights the need for integrative approaches in cardiovascular risk management.

From our knowledge, no published study evaluated the effect of early phase II CR program post-CABG in young adults and the determinants of the outcome in this population, especially in Indonesia. This study aimed to investigate the benefit of early phase II CR programs in midterm outcomes and the determinants of event-free survival from MACE in young adult patients after CABG. By emphasizing MACE, including mortality, the study seeks to provide a comprehensive understanding of cardiovascular risk factors and their impact on patient prognosis.

## Methods

### Study design and population

This was a single-center, longitudinal study with a survival analysis. The subjects were patients under 55 years old who underwent CABG at the National Cardiovascular Center Harapan Kita and participated in the early phase 2 CR program between January 2017 and December 2018. The clinical data were obtained from medical records and a registry. The patients were excluded if they underwent combined cardiac surgeries or were contraindicated for exercise programs. Patients who attended less than ten sessions of the CR program were classified as dropouts but still included in the follow-up study. Meanwhile, the survival analysis study included patients who attended at least ten sessions.

We reviewed medical records and database to obtain basic data (sex, age, height, weight, length of stay), clinical characteristics (CAD risk factors, resting blood pressure and heart rate, preoperative left ventricular ejection fraction (LVEF), coronary stenosis severity (number of stenotic coronary arteries), critical events (life-threatening complication during surgery and morbidity during hospitalization), history of CAD medication, functional capacity before and after CR program by 6-minute walk distance (6-MWD) and treadmill test (TMT) parameters (maximum heart rate and blood pressure, 1-minute heart rate recovery abnormality, and chronotropic index). We also evaluate physical activity levels after the CR program by using an international physical activity questionnaire (IPAQ) using telephone interviews at the sixth-month follow-up and the end of 2 years follow-up duration.

### Early phase II cardiac rehabilitation program

Patients registered and started the CR program within the first week after discharge. They attended a

**Table 1.** Baseline characteristics and comparison between drop-out and complete groups.

| Variables | All population N=279 | Cardiac Rehabilitation Program Groups | | p |
|---|---|---|---|---|
| | | Drop out (<10 times) n=34 | Complete (≥ 10 times) n=245 | |
| Demographic: | | | | |
| Age, year (IQR) | 51 (7) | 51 (7) | 51 (6) | 0.92 |
| Male, n (%) | 243 (87%) | 26 (78.1%) | 217 (88.7%) | 0.161 |
| Clinical characteristic: | | | | |
| Malignant arrhythmia, n (%) | 37 (13.2%) | 6 (17.6%) | 31 (12.6%) | 0.181 |
| Shock or massive bleeding, n (%) | 13 (4.8 %) | 2 (5.8%) | 11 (4.6%) | 0.403 |
| In hospital complications, n (%) | 34 (12.1%) | 1 (2.9%) | 33 (13.4%) | 0.166 |
| length of stay, day (IQR) | 6 (3) | 6 (6) | 6 (3) | 0.451 |
| body mass index, kg/m2 (IQR) | 25 (4) | 23.9 (1.6) | 25.5 (4) | 0.412 |
| symptomatic HF, n (%) | 210 (75.1%) | 23 (67.6%) | 187 76.1%) | 0.497 |
| LV EF, % (IQR) | 57 (23) | 58 (15) | 56 (24) | 0.335 |
| Hypertension, n (%) | 154 (55.1%) | 21 (61.7%) | 133 (54.5%) | 0.604 |
| Diabetes, n (%) | 117 (42.6%) | 11 (32.35%) | 106 (43.5%) | 0.395 |
| Medication: | | | | |
| Aspirin, n (%) | 261 (93.7%) | 29 (85.3%) | 232 (94.7%) | 0.236 |
| Clopidogrel, n (%) | 23 (8.2%) | 3 (8.8%) | 20 (8.2%) | 0.737 |
| ACE-inhibitor, n (%) | 254 (91.1%) | 32 (94.1%) | 222 (90.8%) | 0.750 |
| Calcium channel blocker, n (%) | 11 (4.0%) | 1 (2.9%) | 10 (4.2%) | 0.313 |
| Beta blocker, n (%) | 251 (90.0%) | 31 (91.1%) | 220 (89.8%) | 0.900 |
| Statin, n (%) | 256 (91.8%) | 31 (91.1%) | 225 (91.8%) | 0.733 |
| Nitrate, n (%) | 9 (3.2%) | 1 (2.9%) | 8 (3.3%) | 0.944 |
| Phase II CR program | | | | |
| Duration phase II CR, day (IQR) | 20 (12) | | 20 (12) | |
| 6-MWD pre-CR, meter (SD) | 311 (74.3) | 302 (65.8) | 318 (66) | 0.622 |
| 6-MWD post-CR, meter (SD) | 393 (55.9) | - | 394 (56) | - |
| Treadmill test | | | | |
| Resting heart rate, bpm (IQR) | 78 (14) | 75 (18) | 78 (15) | 0.892 |
| Resting SBP, mmHg (IQR) | 107 (20) | 107 (16) | 107 (18) | 0.911 |
| Resting DBP, mmHg (IQR) | 66 (12) | 68 (16) | 66 (11) | 0.956 |
| Max. heart rate, bpm (IQR) | 125 (32) | - | 125 (32) | - |
| Maximum SBP, mmHg (IQR) | 140 (20) | - | 140 (20) | - |
| Maximum DBP, mmHg (IQR) | 80 (10) | - | 80 (10) | - |
| chronotropic index, % (IQR) | 51.7 (27.8) | - | 51.7 (27.8) | - |
| HRR-1, bpm (IQR) | 14 (14) | - | 14 (14) | - |
| Predicted Mets, Mets (IQR) | 7.2 (2.8) | - | 7.2 (2.8) | - |
| Follow up IPAQ | | | | |
| 6-month moderate-high PA (%) | 55.6% | 55.2% | 56.3% | |
| End follow up moderate-high PA(%) | 56.8% | 56.5% | 58.8% | |

Note: IQR: interquartile range; LVEF: left ventricle ejection fraction; ACE: angiotensin-converting enzyme; 6-MWD: six-minute walk distance; SBP: systolic blood pressure; DBP: diastolic blood pressure; HRR-1: heart rate recovery minute 1; TMT: treadmill test; IPAQ: International physical activity questionnaire; PA: physical activity, p: for comparison between Dropout group and Complete group.

**Table 2.** Mid-term outcome of post-CABG patients.

| Outcomes | Total N=279 | Drop out (<10 times) n=34 | Complete (≥ 10 times n=245 |
|---|---|---|---|
| Major adverse cardiac events (composite endpoint) | 23 (8.2%) | 7 (20.5%) | 16 (6.5%) |
| Acute HF | 10 (3.5%) | 4 (11.8%) | 6 (2.4%) |
| NSTEMI | 4 (1.4%) | 1 (2.9%) | 3 (1.2%) |
| Unstable angina pectoris | 5 (1.8%) | 1 (2.9%) | 4 (1.6%) |
| Re-PCI | 2 (0.7%) | 0 (0 %) | 2 (0.8%) |
| Stroke | 2 (0.7%) | 1 (2.9%) | 1 (0.4%) |
| Cardiovascular mortality | 5 (1.8%) | 1 (2.9%) | 4 (1.6%) |

HF: Heart Failure; NSTEMI: Non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention.

pre-participation orientation, and medical assessment and underwent a pre-participation six-minute walk test (6-MWT). This early phase II CR program was carried out for a maximum of 12 sessions with 3 to 5 sessions per week. It consisted of several counseling and education sessions regarding risk factor prevention and control, self-care, and supervised exercise program sessions.

Each exercise session took about 60 minutes and consisted of warming up, stretching, and aerobic exercise. The exercise took 30 – 40 minutes on an ergocycle, corridor walk, and/ or treadmill. Warming up and stretching were performed for the first 10 minutes, and relaxation in the last 10 minutes of each exercise session. Exercise intensity was adjusted individually to the increase of 10-20 beats per minute from their resting heart rate and subjective symptoms. The walking distance, ergo cycle workload, and treadmill speed were adjusted gradually for every consecutive exercise session. The exercise sessions were supervised by trained nurses, physiotherapists, and a cardiologist. Post-participation functional capacity tests were performed at the last session using 6-MWT and TMT the next day with standardized protocols.

### Endpoints

The incidence of major adverse cardiovascular events (MACE), including stroke and cardiac-related emergency re-hospitalization, percutaneous transluminal coronary angioplasty (PTCA), repeat CABG, cardiac-related mortality, and all-cause mortality was recorded as an outcome in the 2-year follow-up. All outcome data were collected from the hospital database, medical records, and telephone calls made directly to the patients, their relatives, or caregivers. For these analyses, the time at risk began on the last day of the CR program and ended on the date of the outcome event or on January 31, 2020.

### Statistical Analysis

Continuous data of baseline characteristics and clinical data are reported as mean (SD) if the data distribution is normal, median (IQR) if the distribution is not normal, or proportions by % for categorical data. For bivariate analysis, the Chi-Square test was used to analyze categorical data, and an independent T-Test or Mann-Whitney U test was used to compare the mean of continuous data. Survival was described using the event-free rate by plotting cumulative incidence estimates using a single Kaplan–Meier curve for all patients and a separate Kaplan–Meier curve for patients who complete the CR program and drop out. The Cox proportional multivariate hazard regression model was used to determine the predictors of events and the hazard ratio of each variable and to develop risk score models to predict major cardiovascular events of patients who finished the CR program after CABG. All statistical analysis was conducted using SPSS 20.0.

## Results

The baseline characteristics of all subjects and the comparison between the patients who completed the program (Complete group) and those who dropped out (Drop Out group) are shown in Table 1. Both groups

**Table 3.** Univariate and Multivariate Analysis of Survival from MACE in CABG Patients Under 55 Years Old Completed Early Phase II Cardiac Rehabilitation Program.

| Variable | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Male | 0.98 | 0.22 □ 4.29 | 0.979 | 0.63 | 0.13 – 3.16 | 0.572 |
| Age | 0.95 | 0.87 – 1.04 | 0.274 | | | |
| Smoker | 1.05 | 0.39 – 2.84 | 0.914 | | | |
| Diabetes Mellitus | 3.10 | 0.88 – 10.88 | 0.077 | 0.31 | 0.08 – 1.16 | 0.083 |
| Hypertension | 0.91 | 0.35 – 2.36 | 0.851 | | | |
| Dyslipidemia | 0.51 | 0.19 – 4.10 | 0.194 | 0.57 | 0.17 – 1.78 | 0.328 |
| Aspirin | 0.64 | 0.08 – 4.85 | 0.668 | | | |
| P2Y12 inhibitor | 1.70 | 0.38 – 7.51 | 0.482 | | | |
| Statin | 0.37 | 0.10 – 1.28 | 0.161 | 0.21 | 0.04 – 1.09 | 0.512 |
| ACE Inhibitor | 0.59 | 0.19 – 1.82 | 0.359 | | | |
| CCB | 2.52 | 0.58 – 11.24 | 0.212 | 4.32 | 0.61 – 31.08 | 0.146 |
| Beta-blocker | 0.20 | 0.07 – 0.54 | 0.002 | 0.15 | 0.31 – 0.72 | 0.018 |
| Diuretic | 0.64 | 0.24 – 1.69 | 0.369 | | | |
| BMI | | | | | | |
| Normal | | | 0.996 | | | |
| Underweight | 0.03 | 0.01– 0.06 | 0.987 | | | |
| Overweight | 0.87 | 0.26 – 2.90 | 0.825 | | | |
| Obesity | 1.01 | 0.33 – 3.10 | 0.978 | | | |
| Malignant arrhythmia complication | 3.42 | 1.10 – 10.57 | 0.033 | 4.52 | 0.96 – 17.58 | 0.079 |
| Shock and massive bleeding | 3.45 | 0.78 – 15.31 | 0.102 | 3.94 | 0.70 – 22.10 | 0.120 |
| In-hospital co-morbid | 1.81 | 0.52 – 6.32 | 0.348 | | | |
| Length of stay | 0.99 | 0.98 – 1.01 | 0.821 | | | |
| % LVEF | 0.98 | 0.96 – 1.02 | 0.635 | | | |
| Higher resting HR | 1.04 | 0.99 – 1.07 | 0.055 | 1.04 | 1.01 – 1.08 | 0.020 |
| Higher maximum HR | 0.98 | 0.95 – 1.01 | 0.196 | | | |
| Abnormal HR recovery min-1 | 1.67 | 0.56 – 4.98 | 0.354 | | | |
| Higher chronotropic index | 0.96 | 0.93 – 0.99 | 0.020 | 0.95 | 0.92 – 0.98 | 0.011 |
| 6-MWD pre-CR | 0.98 | 0.97 – 1.03 | 0.284 | | | |
| 6-MWD post-CR | 0.99 | 0.98 – 1.00 | 0.050 | 0.99 | 0.98 – 1.00 | 0.052 |
| Low physical activity IPAQ | 7.86 | 1.74 – 35.53 | 0.037 | 0.048 | 0.004 – 1.072 | 0.062 |

CI: confidence interval; ACE: angiotensin-converting enzyme; CCB: calcium channel blockers; BMI: body mass index; LVEF: left ventricle ejection fraction; HR: heart rate; 6-MWD: six-minute walk distance; CR: cardiac rehabilitation; IPAQ: International Physical Activity Questionnaire.

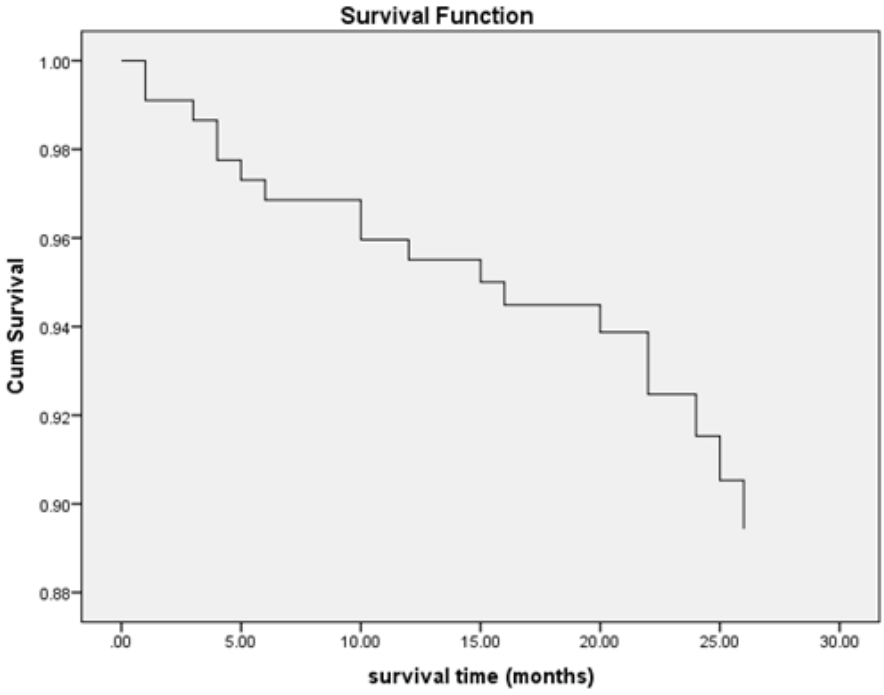


**Figure 1.** MACE Survival Cox regression analysis plot of young adult CABG patients.

had similar demographic, clinical, and medication characteristics. Table 1 also presents 6-MWD, the treadmill test results, and the results of IPAQ of subjects in the Complete group.

This study collected data from 279 patients who met the criteria and 245 (88%) who completed the CR program. The median age of all patients was 51 years old, and the majority were male (87.4%). The median duration of participation in the early phase II CR program was 20 days.

## Outcomes

During the follow-up time (median 25 months), composite MACE occurred in 23 patients (8.2%), consisting of acute heart failure (acute lung oedema or acute decompensated heart failure), acute coronary syndrome, angioplasty, stroke, and cardiovascular mortality in 5 (1.8%) patients (1,8%). Table 2).

## Effect of CR on survival and functional capacity

The survival rate for the composite end-point (all major adverse cardiac events) in 25 months of median follow-up was 91.8% (Figure 1). The Estimated mean survival time/event-free time of the total population of this study was 33.7 months (95% CI: 32.6-34.7 months).

The effect of the CR program on survival was analyzed using Cox regression. Patients who dropped out from the program had a hazard risk of MACE 3.75 (95% CI 1.3 – 10.5, p=0.012) compared to patients who completed the CR program. Kaplan-Meier survival analysis revealed that the mean survival time for the complete CR group was 4 months longer than that of the dropout group. (34 vs 30 months) (figure 2).

The effect of the early exercise-based CR program in 245 patients who completed the CR program was represented by the improvement of 6-MWD, which increased from 318±66 meters to 394±56 meters after the CR program (p<0.001).

## Multivariate analysis of survival predictors in patients who completed CR program

The predictors of survival of patients who completed the CR program were analyzed using univariate and multivariate logistic regression analysis. Variables with p-value <0.25 in the univariate analysis were included in the multivariate logistic regression model. Univariate

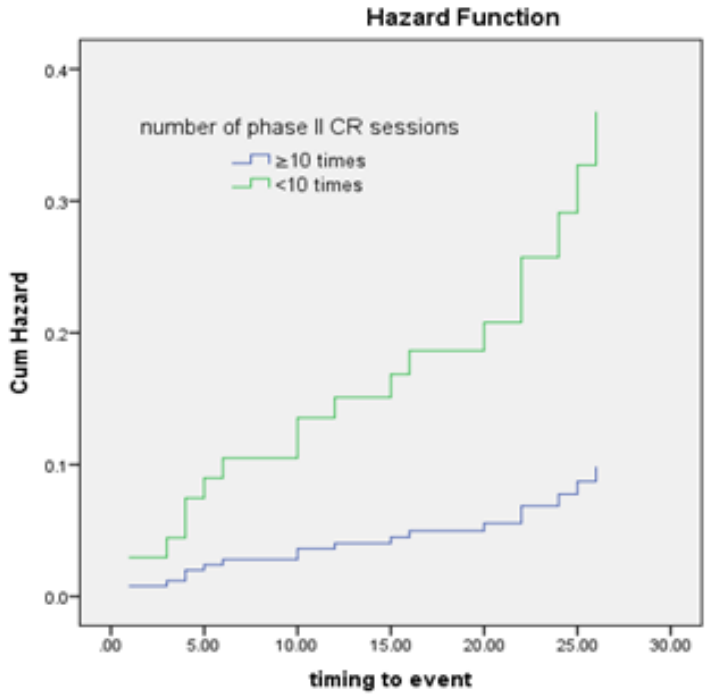


**Figure 2.** Hazard function plot of CR program status between drop out (<10 times) vs complete (≥ 10 times) on MACE outcome.

analysis revealed that diabetes mellitus, dyslipidemia, absence of statin and beta-blocker usage, arrhythmia, shock, massive bleeding, higher resting heart rate, lower chronotropic index, and lower functional capacity were associated with higher adverse cardiac event rates. The model from multivariate Cox regression revealed that only beta-blocker usage, chronotropic index, resting heart rate, and functional capacity (6-MWD) after the CR program were independently correlated with the event (Table 3) with p model=0.009, and good fitness of the data (Hosmer and Lemeshow test p=0.478). The new model explained 79.8% (Nagelkerke R2) of the variance in CAD and correctly re-classified 92.7% of cases.

### Functional capacity and survival outcome

As presented in Table 3, functional capacity, represented by 6-MWD post-CR, was identified as an independent predictor of event-free. The 6-MWD post-CR positively discriminated composite MACE outcome and survival in 25 months follow-up period based on the ROC curve with area under the curve (AUC) 0.65 (P=0.043) with the best cut-off at 376 meters with sensitivity 71% and specificity 65%. (Figure 3) After controlling other confounding factors, 6-MWD post-CR <376 meters had a hazard ratio of 6.2 (1.8 – 11.0, 95% CI, p = 0.001) to develop the event in follow-up duration compared to those with 6-MWD post-CR≥ 376 meters (29 months vs 35 months). The Kaplan-Meier survival function plot can be seen in Figure 4.

## Discussion

In this study, young adults with sufficient CR participation after CABG were associated with a lower hazard ratio or longer adverse event-free than the dropout group. Similar to other studies that suggested patients with good compliance in the CR program obtained similar outcomes in 1-3 years, lower adverse events and mortality, and longer mean survival time.8-11 For young adults, compliance with a hospital-based CR program is a problem because they are at a productive age, and returning to work is one of the barriers. However, the critical consideration for analyzing CR studies is the variety of programs among centers and population characteristics.[12]

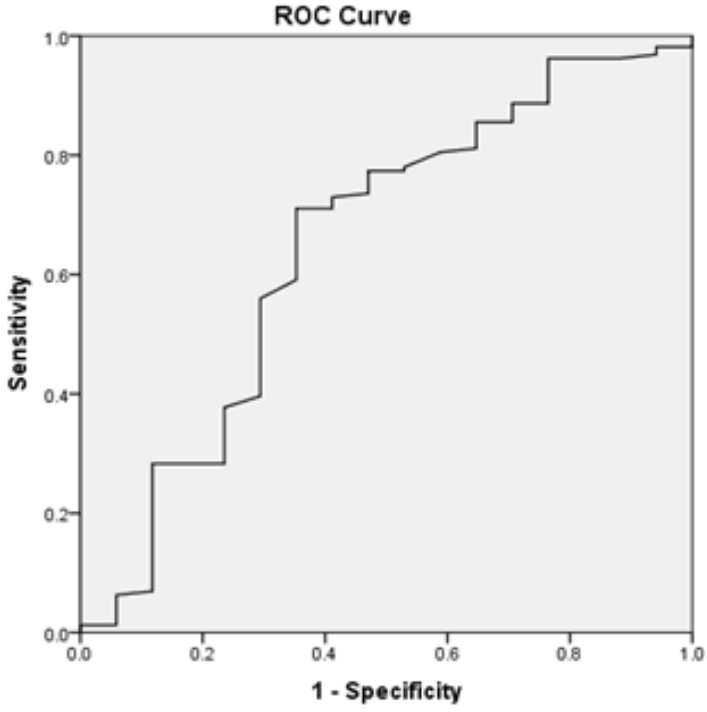


**Figure 3.** ROC curve of 6MWD post-CR cut-off as a predictor of MACE survival.

Our study is the first to analyze the outcome of the CR program after the CABG procedure in Indonesia, particularly in young adults, in which CABG patients are less studied than MI patients. The cut-off is ten sessions as minimum completion (80% of total sessions available) to get greater exposure to educational and exercise benefits in this program. Early phase II CR program enrollment is within 1-2 weeks of hospital discharge rather than 3 months after discharge, as in other centers.[13] The duration of the hospital-based supervised exercise CR program for CABG patients in this study is also shorter, with only 12 sessions and a median duration of only 20 days, compared to other similar studies with a duration of 6 to 12 weeks.[14-17] This shorter period of hospital-based CR will ensure more patient compliance, especially for those referred from remote places. This will also benefit young adult patients who are still employed because lack of time is one of the most common reasons for withdrawing from the CR program.[18]

## Effect of CR on secondary prevention and health behavior

Compliance with medication as a secondary prevention in patients after CABG and PCI is essential, and there is usually a difference between those groups.[19] An analysis to verify if the CR program affected long-term compliance with medication and regular consultation revealed that patients who attended a minimum of 10 sessions of the CR program 1.34 times (OR 1.01 – 1.87, p-0.013) more complied with regular medication consumption and regular check-ups compared to those who drop out in CR (compliance rate 92.2% vs 68.8%). This result suggests that CR benefits not only physical and functional capacity but also health awareness and behavior in the patients, which will help reduce morbidity after CABG in the long term. The multivariate survival analysis revealed that beta-blocker usage, chronotropic index, resting heart rate, and functional capacity were significantly related to composite events.

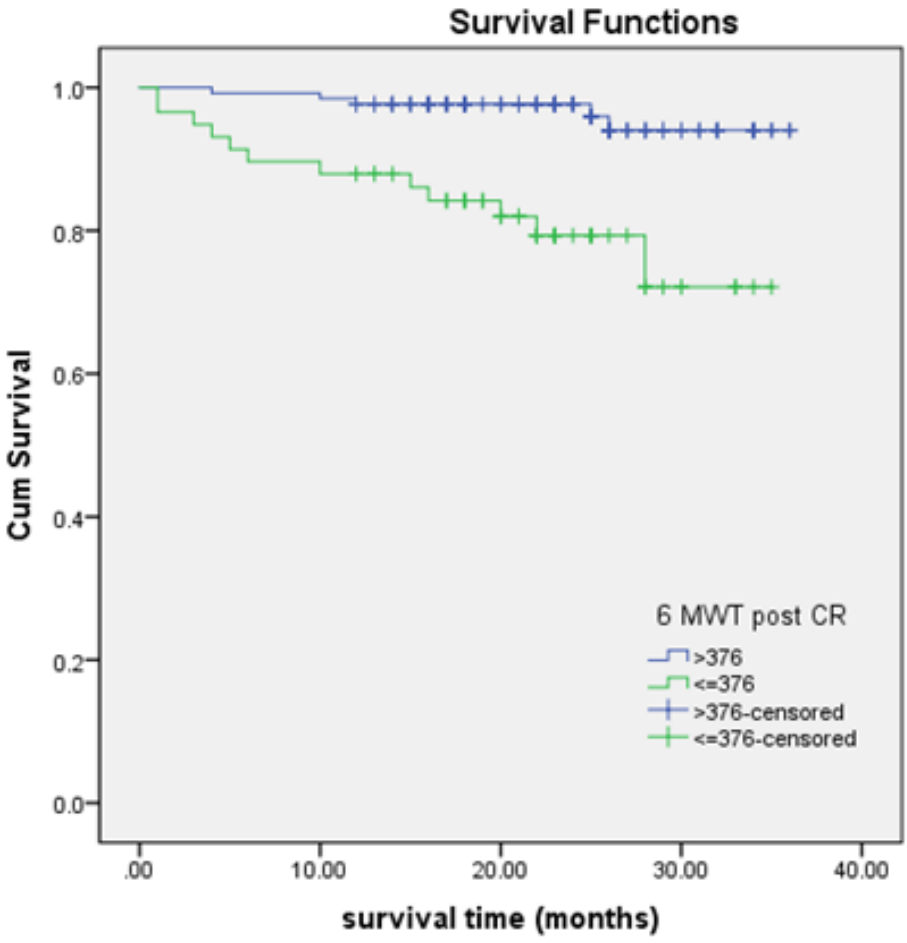


**Figure 4.** Kaplan Meier Survival Curve Analysis for 6 MWT distance post-CR.

### Beta-blocker usage

Our finding suggested that beta-blockers were protective in midterm survival after CABG. This result is consistent with a large cohort study of 5926 patients by Zhang et al., which proved that using beta blockers was associated with a lower risk of long-term mortality and adverse cardiovascular events in patients with or without previous MI undergoing CABG.[20] An observational study by Dayan et al. also revealed that stable angina patients who underwent CABG with preoperative beta-blocker therapy had better overall survival than those without it.[21] This study supports the current guidelines regarding beta-blocker use in CABG patients, including young adults.[4,22]

### Chronotropic index

The chronotropic index (CI) was defined as an index of the maximum predicted HR reserve achieved.[23] This study revealed a higher chronotropic index as an independent protective predictor of survival from composite end-points. With an increment of CI by 1 unit, the risk for the event was reduced by 4%. Our finding was consistent with previous studies that showed impaired chronotropic index or chronotropic response as a risk predictor of cardiovascular mortality or hospitalization,[24-26] including an insight study from an HF-ACTION trial that disclosed a decrease in CI <0.6 was associated with adverse clinical outcomes in HF patients receiving optimal medical therapy.[13] CR programs are also essential in improving recovery from

impaired chronotropic response and contributing to better cardiovascular outcomes.[27]

### Resting heart rate

Another factor that significantly predicted adverse outcomes was resting heart rate. For each bpm resting heart rate increase, the risk of adverse outcomes increased by 4%. This finding was supported by a meta-analysis of 46 studies, which revealed that a higher resting heart rate was independently associated with increased risks of all-cause and cardiovascular mortality.[28] Menown et al., also suggested that a resting heart rate <70 bpm is the target to reduce cardiovascular risk as part of secondary prevention.[29]

### Functional capacity

Good functional capacity has been well known as a protective predictor of medium to long-term cardiovascular mortality and morbidity after CABG, with variation of age dependencies.[9,30,31] In this study, 6-MWD was confirmed as an independent predictor of survival from mid-term composite adverse outcomes in young adults under 55. What made our finding interesting is that the 6-MWD, which was proven to be significantly important is after early CR sessions, rather than the pre-surgery or immediately after surgery 6MWT like in other studies.[30-31] This suggests that exercise-based early phase II CR in our study affects midterm survival prognosis by improving the functional capacity after cardiac surgery. It was also proved by the significant increase in 6-MWD after CR programs (mean difference 76 meters). A study also confirmed that supervised exercise training in CR improved hemodynamic responses and functional capacity in CABG patients.[32] The 6-MWD cut-off in our study was also higher than in the previous study (376 meters vs 300 meters).[31] The difference between these results can be caused by the difference in the age population of the study, which is younger. Thus, younger adults usually have better functional capacity and should aim to achieve higher 6-MWD after the CR program.

### Strengths and Limitations

The study was limited to a single center and only included young adult patients who underwent CABG and participated in the CR program, and the population number was relatively small. Since the follow-up includes phone calls, the accuracy needs to be verified. However, despite the limitations, to our knowledge, this is the first survival analysis study of the CR program, which focuses on young adult patients after CABG in Indonesia and could further emphasize the use of the CR program in Asian populations with unique characteristics.

### Future Implications

As discussed previously, the CR program has been beneficial for short-term, mid-term, and long-term benefits. Early enrollment in an exercise-based CR program after CABG for only 10-12 sessions in young adults has the same positive effect on patient adherence. Thus, it could be implemented as an option for CR after CABG, especially in Indonesia, where the CR program is still underused. Healthcare providers are encouraged to refer patients and to urge patients to attend CR until program completion is accomplished regularly.

## Conclusion

Early phase II CR program after CABG in young adult patients reduced the risk for cardiovascular mortality, major adverse events, related readmission, and an increase in survival rate and mean survival time for participants who completed the CR program. Optimum beta blocker medication, chronotropic index, resting heart rate, and functional capacity after the CR program are essential predictors for survival after CABG in young adults. Further study is needed to prove these findings with a larger population and longer follow-up duration.

## List of Abbreviations

| | |
|---|---|
| CHD | Congenital Heart Disease |
| mPAp | Mean pulmonary arterial pressure |
| mLAP | Mean left atrial pressure |
| PAO2 | Pulmonary Artery Oxygen Saturation |
| PASP | Pulmonary artery systolic pressure |
| PVR | Pulmonary vascular resistance |
| PH | Pulmonary hypertension |
| PVO2 | Pulmonary vein oxygen saturation |
| RHC | Right heart catheterization |
| RVGLS | Right ventricle global lingutudinal strain |

| | |
|---|---|
| TTFV | Trans tricuspid flow velocity |
| TRVmax | Tricuspid regurgitant peak velocity |
| TRmeanPG | Tricuspid regurgitation mean pressure gradient |
| RVOTVTI | Right Ventricular Outflow Tract Velocity Time Integral |

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Review

# Collagen–Based Hydrogel Encapsulated Cardiosphere–Derived Cell (CDC): Potential of Stem Cells as Tissue Repair Therapy Post–Acute Myocardial Infarction.

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**Abstract**

**Background:** Acute myocardial infarction (AMI) is a global health issue that is the leading cause of morbidity and mortality. Post-AMI management currently has therapeutic and side-effect limitations and has not been able to repair damage to myocardial tissue caused by AMI. The development and discovery of therapeutic modalities with the potential for a more optimal therapeutic effect remains a challenge in this post-AMI treatment. The purpose of this literature review is to collect and analyze various sources related to collagen-based hydrogel encapsulated cardiosphere-derived cells (CDC). This literature review is written systematically by gathering library sources from various databases, such as Google Scholar, PubMed, and Research Gate. According to the findings of the study, the CDC has the potential to be used as a post-AMI therapy because it can promote regeneration of the heart, which has lost function as a result of the AMI. To achieve the greatest effect, this modality is administered intracoronary. This treatment will be encapsulated with collagen hydrogel, which has a cardioprotective effect, to increase the survival and effectiveness of CDC. The use of collagen-based hydrogel encapsulated CDC can provide post-AMI cell regeneration effects comparable to existing modalities while having minimal side effects. Further investigation in larger and more definitive trials is needed to elucidate the potential use of CDC therapy in AMI.

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**Keywords:** *acute myocardial infarction, cardiosphere-derived cell, collagen, hydrogel.*

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## Introduction

Acute myocardial infarction (AMI), commonly referred to as a heart attack, is one of the main causes of morbidity and mortality that is still a global challenge. AMI is commonly caused by a decrease or cessation of blood flow to parts of the heart, resulting in heart muscle necrosis.[1] This condition causes more than 15% of deaths each year.[2] Ischemic heart disease also remains the number one cause of death and illness in Indonesia with the number of disability-adjusted life years (DALYs) increasing by 10.5% from 5.9 million in 2006 to 6.52 million in 2016.[3]

As secondary prevention, patients who had suffered AMI were given a variety of therapies, both pharmacological and non-pharmacological. To reduce mortality and cardiovascular morbidity, patients were given aspirin, β blockers, statins, and angiotensin-converting enzyme inhibitors (ACEi). Lifestyle modification and cardiac rehabilitation are also recommended for this group of patients. This group of therapy is an ongoing and lifelong process that allows the patient to return to a normal life.[4] The complexity and side effects of this treatment regimen can reduce patient compliance, resulting in a poor outcome. This modality is also less effective because it doesn't repair tissue damage caused by AMI.[5]

Research shows that cardiosphere-derived cells (CDC) have the potential to be used as post-AMI therapy.[6] These cells can promote heart regeneration, reduce scarring, and improve heart function.[7] CDC also provide advantages such as improved cardiac function, faster cell turnover, increased myogenic differentiation, improved cardiac morphology, and lowered apoptosis of cells when compared to stem cells derived from bone marrow or adipose.[8] This modality must be administered correctly for CDC to reside in infarcted tissue and provide a long-lasting therapeutic effect. The CDC will achieve consistent therapeutic success and effectiveness with good cell retention. The use of biomaterials can improve cell retention at the infarct site.[9]

Biomaterials can act as an extracellular matrix replacement for encapsulated cells thereby increasing cellular viability of the cells. This biomaterial aids in the delivery of more cells to the target site, the maintenance of cell localization and viability, and the enhancement of the continuous production of beneficial paracrine factors at the target site. One of the biomaterial approaches that can be provided to achieve cellular delivery to the myocardium is a collagen-based hydrogel. Collagen itself is the main component of the myocardial extracellular matrix, so the administration of collagen-based hydrogel can support the attachment and elongation of cardiomyocytes. Based on the description above, the collagen-based hydrogel encapsulated CDC injection approach has the potential to be used as a tissue repair therapy in post-myocardial infarct conditions.[9–11] This literature review aims to discuss the potential use of collagen-based hydrogel encapsulated CDC as a post-AMI tissue repair therapeutic modality. The authors hope that this review can provide a new theoretical basis for treating post-myocardial infarction patients.

## Methods

This review is prepared using the literature synthesis method. The literature was searched using the keywords "*acute myocardial infarction*", "*cardiosphere-derived cell*", "*collagen*", "*hydrogel*" and "*collagen-based hydrogel*" on numerous electrical databases—ScienceDirect, PubMed, and Research Gate— from inception up to August 2024, without imposing any restrictions on publication years. There are 52 relevant and appropriate publications. Information from these sources is reviewed, analyzed, and compiled into a comprehensive scientific literature review.

## Results and Discussion

### Pathogenesis of Acute Myocardial Infarction (AMI)

Myocardial infarction (MI) begins with the accumulation or blockage of atherosclerotic plaques in the coronary arteries, which supply blood to the myocardial muscle. Chronic endothelial injury caused by cardiovascular risk factors such as chronic hyperlipidemia, long-term hypertension, or smoking initiates atherosclerosis. This process starts at a young age and takes a long time to cause significant obstructions. Due to hemodynamic disturbances, this plaque can rupture, fissure, or ulcerate, and the body responds by

**Table 1.** The role of CDC as a therapeutic agent for cardiac tissue repair.[18,19,24–26]

| CDC's Multiple Roles in Cardiac Regeneration |
|---|
| - Myogenesis |
| - Cardiogenesis |
| - Angiogenesis |
| - Improved cell engraftment |
| - Releases paracrine factors |
| - Prolongs the survival of cardiomyocytes |
| - Activates endogenous cardiac stem cells |
| - Mediates the process of scar reduction due to myocardial infarction |
| - Increases capillary density |
| - Improve work function and improve heart morphology |
| - Stops detrimental tissue reconstruction |
| - Increase the differentiation of heart cells |
| - Mediates the process of reducing fibrosis |
| - Secretes pro-angiogenic and pro-cardiogenic cytokines |
| - Increase myogenic differentiation |
| - Reducing the levels of apoptotic cells |

forming a thrombus to heal the wound in the plaque. However, the thrombus can grow in size, causing plaque to clog blood vessels more severely.[12–14]

Acute myocardial infarction (AMI) results from a sudden blockage of one or more epicardial coronary arteries for more than 20 to 40 minutes. The occlusion is usually thrombotic and occurs as a result of rupture or erosion of the atherosclerotic plaque in the coronary artery, thereby the myocardium to be deprived of oxygen. This condition results in disruption of the sarcolemma and relaxation of myofibrils, followed by mitochondrial change.[15] Ischemia for an extended period of time results in liquefactive necrosis of the myocardium. Necrosis progresses in a predictable pattern, starting from the subendocardial layer, and then progressing to the subepicardial layer. The location of the infarct determines whether or not cardiac function is impaired as a result of this process. This infarcted area then heals and undergoes remodeling, which is characterized by scar tissue formation, dilatation, segmental hypertrophy of the remaining tissue, and cardiac dysfunction.[16]

## Cardiosphere-Derived Cells (CDC)

Various new therapeutic strategies have been developed in an effort to repair damaged cardiac myocardium after myocardial infarction, including the use of stem cell transplantation.[17] Types of stem cell modalities that have the potential to be used in cardiac cell therapy are bone marrow-derived stem cells (BMC), and adipose-derived stem cells. cells (ADSC), mesenchymal stem cells (MSC), and cardiosphere-derived cells (CDC).[6,18] Various studies that have been conducted previously indicate that CDC is a cardiac cell therapy agent that has a higher efficacy level than BMC and ADSC in increasing cardiac function, improvement of cardiac morphology, cell engraftment, myogenic differentiation, and reduction of apoptotic cells.[19] On the other hand, a comparative study between the CDC and MSCs conducted by Walravens et al. found that the CDC had a better capacity to reduce wound size due to myocardial infarction.[20]

CDC is a cell that has a high rate of proliferation rate and is derived from cultured percutaneous endomyocardial tissue biopsy samples.[8] In addition, CDC has also been isolated from cadaveric myocardium and canine heart organs.[21,22] CDC meet the criteria as a stem cell modality because it is clonogenic and has multilineage potential.[23] Specifically, CDC belongs to a heterogeneous population of stem cells because it expresses the TGF-β subunit (CD105), c-kit, markers of MSCs (CD90 and CD73), hematopoietic markers (CD45, CD34, and CD133), and markers of endothelial cells (CD31 and CD34).[8] Several studies have shown that CDC plays a role in the regeneration of cardiac organs that have decreased function due to disease/abnormalities (Table 1).

However, direct administration to the infarcted area would result in the CDC having low cell retention and poor cell engraftment mechanism. This is caused by cellular apoptosis events induced by an ischemic local environment and the presence of physical pressure from the contracting heart.[27] The low retention of CDC will have implications for decreasing the efficiency of the therapy given so it is necessary to increase retention to maximize the potential of modalities such as cardiac cell therapy. In response to this problem, Selvakumar et al. used hydrogel encapsulation as a carrier for stem cells to optimize their performance as therapy. In addition,

**Table 2.** Clinical Trial of CDC Efficacy.

| Clinical Trials and Stages | Method of Application | Dosage of CDCs | Duration of Measurement | Adverse Effect | Author, Year |
|---|---|---|---|---|---|
| Intracoronary Cardiosphere-Derived Cells after Myocardial Infarction: Evidence for Therapeutic Regeneration in the Final 1-Year Results of the CADUCEUS (CArdiosphere-derived aUtologous stem Cells to Reverse Ventricular Dysfunction) Trial | Clinical Trial Phase I (NCT00893360) | A prospective, randomized, dose escalation study with CDC administration via post-AMI arterial infusion using autologous stem cells from endomyocardial biopsy. | 31 post-AMI participants with moderate left ventricular dysfunction (Ejection fraction 25 to 45%) due to coronary artery atherosclerotic disease. (23 participants in the CDCs group and 8 participants in the control group) | Significant reduction in scar tissue increased viability of myocardium and improvement of regional contractility. | Malliaras et al, 2014[50] |
| Safety and Efficacy of Intracoronary Infusion of Allogeneic Human Cardiac Stem Cells in Patients With ST-Segment Elevation Myocardial Infarction and Left Ventricular Dysfunction: A Multicenter Randomized, Double-Blind, and Placebo-Controlled Clinical Trial | Clinical Trial Phase I/II (NCT02439398) | A randomized double-blind placebo-controlled study with a suspension of allogeneic cardiac stem cells (CSC) administration via intracoronary infusion in the acute phase of first AMI. | 49 post-AMI participants with left ventricular dysfunction (ejection fraction ≤45%), infarct size ≥25% of left ventricular mass, and high risk of developing chronic heart failure | No significant differences in infarct size reduction by -2,3% (95% CI, −6.5% to 1.9%), indices of left ventricle remodeling, laboratory assessments, functional class, quality of life scores, and immunologic events. | Aviles et al, 2018[51] |
| Administration of Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy (the SCIPIO Trial): Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance | Clinical Trial Phase I (NCT00474461) | A randomized study with administration of CSC via intravenous infusion post-AMI | 33 participants with heart failure (HF) with an LVEF ≤ 40%, evidence of a previous myocardial infarction (MI), and need for coronary artery bypass graft surgery (CABG) | Increased cardiomyocyte levels, reduced scarring of the infark, and significantly improved left ventricular function | Chugh et al, 2012[52] |
| Intracoronary ALLogeneic heart STem cells to Achieve Myocardial Regeneration (ALLSTAR): a randomized, placebo-controlled, double-blinded trial | Clinical Trial Phase II (NCT01458405 | Randomized study placebo-controlled with CDC administration via intracoronary infusion | 142 post-AMI participants with left ventricular (LV) ejection fraction <45% and LV scar size ≥15% | Improves segmental myocardial function especially segmental myocardial circumferential strain (Ecc) in segments containing scars post-AMI. | Makkar et al, 2020 and Ostonoveh et al, 2021[53,54] |

**Table 3.** ClinClinical Trial of CDC Safety.

| Study | Stages of Clinical Trial | Methodology of the Study | Number of Participants | Efficacy (Study Outcome) |
|---|---|---|---|---|
| Intracoronary Cardiosphere-Derived Cells after Myocardial Infarction: Evidence for Therapeutic Regeneration in the Final 1-Year Results of the CADUCEUS (CArdiosphere-derived aUtologous stem Cells to Reverse Ventricular Dysfunction) Trial | Intracoronary infusion 1.5-3 months post MI | First group: 12.5 x 106 autologous cells<br>Second group: 25 x 106 autologous cells<br>Third group (control): usual medical management | 6-12 months | No serious adverse effect (SAE) related to the biopsy with the only SAE related to the study is a non-ST segment elevation MI (NSTEMI) in 1 patient of the CDC group occurring 7 months post-infusion. No other event including death, major adverse cardiac events (composite of death and hospital admission for heart failure or nonfatal recurrent MI), or tumor formation seen on MRI. |
| Safety and Efficacy of Intracoronary Infusion of Allogeneic Human Cardiac Stem Cells in Patients With ST-Segment Elevation Myocardial Infarction and Left Ventricular Dysfunction: A Multicenter Randomized, Double-Blind, and Placebo-Controlled Clinical Trial | Intracoronary infusion with 2-phase including open dose-escalation phase and double-blind randomized phase. | Escalation-dose phase: 10 × 106 allogeneic CSCs, 20 × 106 allogeneic CSCs, and 35 × 106 allogeneic CSCs<br>Double-blind randomized phase: 35 × 106 allogeneic CSCs | 8 months | No adverse effects linked to CSC administration in 12 months post-treatment including ischemia, anaphylaxis, hemodynamic instability, or ventricular arrhythmias, deaths, or major adverse cardiac events-MACE (all-cause death, reinfarction, hospitalization because of HF, sustained ventricular tachycardia, ventricular fibrillation, and stroke) |
| Administration of Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy (the SCIPIO Trial): Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance | Intracoronary injection of cardiac stem cells through expanded autologous c-kit positive cardiac stem cells. | Infarct region:<br>Anterior Left Ventricle Wall:<br>1 × 106 CSCs were injected into the graft supplying the left anterior descending artery<br>Other regions:<br>5 × 105 CSCs were injected into the graft(s) supplying those regions | 4 months | Minimal complications such as left internal mammary artery (LIMA) dissection repaired with covered stent and elevated cardiac enzymes after balloon inflation consistent with peri-procedural MI appears in this research. |
| ALLogeneic Heart Stem Cells to Achieve Myocardial Regeneration (ALLSTAR Trial) (Clinical Trial Phase II) | Intracoronary infusion into the infarct-related artery using stop-flow technique. The infusion included three cycles: 2.15 mins of balloon inflation, 15 s of wash, 1.45 mins of cell infusion, and followed by 15 s of wash | 25 million of CAP-1002 Allogeneic Cardiosphere-Derived Cells | 6- and 12-months post-infusion | No adverse events led to early removal of any patient from the study; however, two serious events were linked to the intracoronary infusion procedure: acute myocardial infarction and femoral artery pseudoaneurysm. |

the study conducted by Li et al. explained that the retention of stem cells in an environment with high reactive oxygen species (ROS) levels can be increased by using hydrogel encapsulation.[29] Therefore, to optimize the function of the CDC in regenerating the heart, it is necessary to protect and maintain retention by using a hydrogel-mediated encapsulation method.

In addition, the research conducted by Ottersbach et al. implemented the use of superparamagnetic microspheres (SPM) to increase the localization capability of CDC to be able to demonstrate its effectiveness in global myocyte cell repair in patients with ischemic heart disease such as myocardial infarction.[30] Utilization of SPM is also able to increase retention of CDC so that it can survive blood flow and heart contractions, as well as improve the quality of therapeutic outcomes because it increases cell engraftment in the long-term use.

## Collagen-Based Hydrogel

Hydrogel is a porous biomaterial with a three-dimensional structure that has a high hydration status and can encapsulate living cells.[27,31] The high hydration status of hydrogels can assist in facilitating the mechanism of exchange of nutrients and metabolic waste products, as well as providing a hydrated and immune-protected environment. for the encapsulated cells.[27] On the other hand, the soft nature, biodegradability, and high biocompatibility as well as the ownership of structures that resemble macromolecular components of the body support the use of hydrogels as an ideal therapeutic delivery medium.[32] There are two groups of hydrogels based on the type of base material used, namely natural hydrogels (natural hydrogels) and synthetic hydrogels (synthetic hydrogels).[27,31] Synthetic hydrogels are a group of hydrogels whose basic ingredients are in the form of modified natural biopolymers or artificial biopolymers. Meanwhile, natural hydrogel is a hydrogel group with basic ingredients derived from natural biopolymers. Some of the characteristics that can be found in natural hydrogels are that they can be biodegraded by cellular enzymes, good biocompatibility, and can maintain their biochemical and biological properties.[27,31] Most of the compositions of these natural biopolymers consist of protein and polysaccharides, thus enabling the water absorption process., nutrient exchange, and elimination of metabolic products.[31,33] Therefore, natural biopolymers can facilitate increased cell survivability and facilitate the motility of the cells they carry. Several types of hydrogels based on natural biopolymers have been used in several clinical applications as cell carriers for cardiac tissue repair therapy, one of which is collagen.

Collagen is a protein that is the main component of the extracellular matrix of the heart.[31] Collagen is composed of a combination of chains that are folded into a tight left-handed helix, where the chain has the characteristic of having an unbroken sequence consisting of the repetition of glycine-proline-hydroxyproline amino acid.[34] Within each of the three left-handed helices of collagen there will be right-handed folds.[34] Collagen can be obtained by implementing decellularization methods, preserving the original tissue structure, or using extraction methods.[31] The use of collagen as a hydrogel base material has also been studied extensively, in vivo and in vitro. Based on several studies that have been carried out, there are several benefits such as stimulating myocardial cytokine profile, angiogenesis, reducing fibrosis and preventing cell death, having a cardioprotective effect, increasing stem cell adhesion, and increasing the delivery of bioactive molecules for myocardial repair and regeneration.[35] In addition, collagen can also be degraded by the body with the help of the enzyme collagenase. Natural biopolymers such as collagen are pH-responsive in the acidic category so that they can be used as the basis of therapeutic agents with a target in the form of low-pH infarct tissue.

Up to this point, 28 types of collagens have been identified based on their polypeptide sequence.[34] One of the types of collagen found to have high levels in the heart is type I collagen (±85% of the total collagen).[36] Type I collagen can be used as a base material hydrogel because it has a high level of permeability and biocompatibility behavior. In addition, type I collagen can facilitate the transport of stem cells to the microenvironment to maintain cell survival and proliferation, as well as mediate the extension of cell retention.[37,38] The use of type I collagen-based hydrogels has also been applied clinically in experimental animals induced by myocardial infarction.[11]

However, there are some disadvantages of hydrogels based on natural biopolymers such as experiencing a rapid degradation process and having poor mechanical strength.[31,39] As an effort to slow down the degradation process of hydrogels mediated by matrix metalloproteinase (MMP)-type proteases, it can be done

by mixing doxycycline, which plays a role in an MMP inhibitor, in the hydrogel matrix.[40] On the other hand, the study conducted by Efraim et al. stated that the genipin cross-linking approach accompanied by a low dose of chitosan on the collagen-based hydrogel could be implemented to increase the mechanical strength of the hydrogel up to 36.8 kPa.[41]

## CDC Extraction and Modification Procedure

The CDC extraction process is initiated by taking percutaneous endomyocardial tissue specimens, approximately 276 mg, from an individual with AMI within the last 30 days by the biopsy method.[8,24,42] To maintain tissue viability before processing, the biopsy specimens are stored on ice in a cardioplegic solution with a high potassium content.[43]

Processing of biopsy specimens begins with cutting the specimen into fragments with a size of <1 mm3, then the preparation is cleaned and given trypsin. The fragments as cardiac explants were then cultured on Petri dishes that had been coated with fibronectin and placed in cardiac explant media (CEM). After 3-4 days of exposure to 5% CO2 gas and a temperature of 37°C, there was a growth of a layer of explants with the characteristics of cells similar to the stroma. Cells that are loosely attached to the area around the explants (called cardiac outgrowth cells) are then isolated using an enzymatic process with trypsin. Cardiac outgrowth cells that have been successfully harvested will be cultured in Petri dishes coated with poly-D-lysine and placed in the cardiosphere growing media (CGM). Cardiosphere is estimated to be formed after 2-3 days and harvested. To obtain CDC, the harvested cardiosphere will be placed in an Erlenmeyer tube containing fibronectin and cultured at CEM.[24,43] The extracted CDC will be modified by implementing magnetic labeling using SPM. Based on the research by Ashur et al., SPM particles were utilized at CDC with the coincubation technique in culture for 24 hours.[8]

## CDC Encapsulation Procedure with Collagen-Based Hydrogel

The procedure for making collagen-based hydrogel, especially type I collagen, is carried out by adding 1.1 ml of saline solution to 0.9 ml of type I collagen (derived from sterilized rat tails) in acetic acid.[11,44] This process will produce a liquid mixture. of 2 ml of collagen-saline and then the pH was adjusted to 7.4 using 0.1 M NaOH.[15] After the hydrogel was formed, modifications were made with the incorporation of an MMP inhibitor, namely doxycycline to slow down the biodegradation of the modality.[40] Furthermore, the addition of a reinforcing biomaterial in the form of genipin (0.1 gr/gr hydrogel) and chitosan (0.2 gr/gr hydrogel) was purposely to control the mechanical strength of the hydrogel.[41]

The hydrogel-based encapsulation method will be based on the methods proposed by Li et al. (2016).[29] The encapsulation procedure was initiated by thoroughly mixing the CDC suspension ratio of 0.5 ml and 1 ml of hydrogel solution at 4°C temperature. Then it was incubated at 37°C for 20-30 minutes to produce the CDC modality encapsulated by a collagen-based hydrogel.[29]

## Method of Administration, Dosage, and Recipient Eligibility Criteria

The administration method of a therapeutic modality is an important consideration when discussing the most effective use of stem cell-based therapies for tissue repair after myocardial infarction. The aspects that need to be considered in determining the method of administration from the CDC are the risk of side effects, retention of stem cells, and the usefulness of therapy for patients.[8]

Administration of collagen-based hydrogel encapsulated CDC will be carried out using the intracoronary infusion method with continuous flow in the three main coronary arteries.[45] This method was chosen as the intracoronary approach can prevent the formation of CDC aggregation in vivo and can be carried out simultaneously when carrying out the percutaneous coronary intervention (PCI).[46] Research by Gallet et al. also stated that there were no side effects associated with the intracoronary administration of stem cells for post-AMI therapy.[47] In addition, this method is also useful in reducing the size of the infarct wound effectively, preventing adverse tissue reconstruction, and improving neovascularization and cardiac function.[47] Approaches to the disadvantages that can be encountered through the intracoronary infusion method such as low cell retention have also been carried out by encapsulating CDC using collagen-based hydrogel.

For many regenerative therapies, including those involving cardiac cells, precise timing and dosing are critical to enhance recovery and minimize further damage. Based on previously conducted trials, this stem cell-based therapy can be administered to patients with a myocardial infarction within 30 days up to the past 4 weeks post-AMI.[42] The dosage of CDC administered can be categorized into three distinct regimens: low dose (12.5 million cells), intermediate dose (17.3 million cells), and high dose (25 million cells). A safety review determined that a dose of 25 million cells is the maximum safe therapeutic amount. Furthermore, as proposed by previous studies, the recipients of this modality must meet several eligibility criteria: 1) must be over 18 years old; 2) have successfully undergone stent placement; 3) achieve a minimum Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 in the affected artery.[42]

### Pharmacokinetics of Collagen-Based Hydrogel Encapsulated CDC

Administration of CDC with type I collagen-based hydrogel encapsulation via intracoronary injection showed good absorption by the body where CDC could work optimally with minimum cell retention. Along with the increased absorption, CDC can be well distributed in the myocardium which undergoing AMI as well. This can happen because type I collagen-based hydrogel mediates cell engraftment and is immunoprotective towards CDC so that CDC can survive in an inflamed environment due to the AMI itself.[29] Based on clinical trials regarding the effectiveness of CDC as a therapy in previous heart disease, no significant side effects were found. However, studies on the effectiveness of the CDC are still ongoing to review the long-term effects of CDC administration to reshape the myocardium after AMI.

The metabolism of CDC encapsulated by type I collagen-based hydrogel in the body is also slowed by the addition of doxycycline so that it isn't easily degraded and can work optimally in target areas of the myocardium experiencing AMI. Naturally, collagen-based hydrogel degrades after 5-6 weeks of administration.[48]

### Pharmacodynamic of Collagen-Based Hydrogel Encapsulated CDC

In general, CDC-encapsulated type I collagen-based hydrogel with the addition of doxycycline reduces the risk of post-AMI scarring, increases myocardial viability, and improves myocardial function so that cardiac construction can be maintained. Intracoronary administration minimizes invasive effects on the body where the transport of CDC type I collagen-based hydrogel encapsulated via this intracoronary catheter can maintain coronary flow without disrupting the systolic and diastolic phases of the heart.[49]

### Clinical Trial of CDC Efficacy and Safety Outcomes in Post-AMI

Several clinical trials related to the efficacy and safety of CDC as a modality in the treatment of AMI have shown promising results. Based on the preclinical trial of type I collagen-based hydrogel encapsulated CDC administration, it showed a cardioprotective effect that increased the level of cardiomyocytes after AMI. The following is a table of several clinical trials related to CDC administration as post-AMI therapy (Table 2. and 3.).

## Conclusion

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide. Myocardial tissue damage following AMI increases the risk of recurrence, which current management strategies have not fully addressed. Stem-cell therapy utilizing type I collagen-based hydrogel encapsulated CDCs shows promise in advancing post-AMI management by promoting cardiomyocyte regeneration, thereby reducing the risk of recurrent AMI and improving both the functional and structural integrity of the heart. Moreover, safety data from existing trials have demonstrated no serious adverse effects, including the absence of MACE, arrhythmias, or mortality. This favorable safety profile underscores the potential of stem cell therapy as a viable and promising tissue repair agent, offering significant benefits without compromising patient safety.

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Nil.

## Conflict of Interest

There are no conflicts of interest.

## List of Abbreviations

| | |
|---|---|
| ACEi | Angiotensin-Converting Enzyme inhibitors |
| AMI | Acute myocardial infarction |
| CDC | Cardiosphere-Derived Cells |
| CEM | Cardiac Explant Media |
| CGM | Cardiosphere Growing Media |
| TIMI | Thrombolysis in Myocardial Infarction |

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Review

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# Effects of High–Intensity Interval Training on Cardiovascular Function and Risk Factors, Functional Impairments, and the Quality of Life in Coronary Artery Disease Patients: A Narrative Review

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**Abstract**

Coronary artery disease (CAD) causes damage to the cardiovascular system that leads to functional and quality of life (QoL) deterrence. Cardiac rehabilitation (CR) aims to improve cardiorespiratory fitness (CRF) to prevent disease progression and its risk factors. Aerobic exercise (AE) causes different physiological effects depending on the applied intensity. High-intensity interval training (HIIT) is being developed because of better effectivity than moderate-intensity continuous training (MICT). However, HIIT is generally not prescribed. This review aimed to describe the effects of HIIT on cardiovascular function and risk factors, functional impairments, and the QoL. Articles were searched using PubMed and CINAHL databases with the keywords "high-intensity interval training", "cardiac rehabilitation", "exercise-based cardiac rehabilitation", and "coronary artery disease". HIIT improves ventricular function, left ventricular ejection fraction (LVEF), heart contractility, and endothelial function, which further improves systolic and diastolic function. Improvement in cardiovascular risk factors was better in HIIT compared to AE in lower intensities. Studies recommend HIIT for CAD patients due to significant cardiovascular adaptation in this exercise. Compared with MICT, most studies have found that HIIT is better at improving CRF. HIIT also positively affects executive and affective functions. Research on the impact of HIIT on functional activity and QoL is still limited. However, one study found no differences in physical activity level and QoL in groups given HIIT or MICT. To conclude, HIIT is considered an alternative exercise that is more time-efficient than continuous exercise in CAD patients.

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**Keywords:** *Cardiorespiratory fitness, cardiovascular disease, coronary artery disease, exercise therapy, quality of life*.

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## Introduction

Coronary artery disease (CAD) remains one of the main causes of mortality worldwide, with a prevalence of 126 million people (1,655 per 100,000 population), accounting for 1.72% of the world's population. Approximately nine million deaths are caused by CAD, and it is estimated to exceed 1,845 in 2030.[1]

The cardiac rehabilitation (CR) program is one of the interventions given to CAD patients. It aims to improve cardiorespiratory fitness (CRF), functional abilities, and quality of life (QoL). The CR program is also provided as a secondary prevention program for cardiovascular disease (CVD).[2-4] Aerobic exercise (AE), which is a major component of the CR program, plays an important role in achieving these goals.[5,6]

Exercise intensity is linearly correlated with CRF improvement. Moderate-intensity continuous training (MICT) is the most widely used training protocol for CR programs. However, several obstacles were found in its implementation, including a lack of patient compliance and tolerance.[7-9] For this reason, a program that is more efficient and well-tolerated is needed.

High-intensity interval training (HIIT) is a form of intervention given in a CR program including patients with CAD.[10,11] This exercise protocol has been extensively developed because, in addition to being more effective than MICT, several studies have stated that this exercise is safe and does not cause significant adverse events.[11,12] However, many rehabilitation practitioners are concerned about the side effects and risks of HIIT.[13] Therefore, this review aimed to synthesize articles describing the use of HIIT in CAD patients regarding its effect on cardiovascular function and risk factors, functional impairments, and QoL to improve the knowledge of rehabilitation practitioners and expand the use of HIIT.

## Methods

We reviewed articles that were searched using PubMed and CINAHL databases. The inclusion criteria were original articles from any method of research, systematic review, and meta-analysis without limitation of publication year. The keywords used were "high-intensity interval training", "cardiac rehabilitation", "exercise-based cardiac rehabilitation", and "coronary artery disease". Non-full text and non-English articles were excluded. The results are presented in the form of text and tables.

## Results and Discussion

Twenty-two articles were identified and used to explain the subtopics. Nine articles were used to explain the implementation of HIIT in CAD patients consisting of exclusion criteria, protocols, and safety of exercise. Twelve articles explained the effect of HIIT on cardiovascular function and risk factors and 11 articles explained the effect of HIIT on CRF. The effects of this exercise on executive and affective functions were explained in one and three articles, respectively. Only one article has explained the effect of HIIT on Qo.

### HIIT in CAD Patients

HIIT is defined as high-intensity AE or >85% peak oxygen uptake (VO2 peak), repeated for short periods (10 seconds to 5 minutes) and separated by rest periods of low-intensity exercise or complete rest. This form of exercise allows the patient to accumulate more time at a higher intensity than can be done during continuous exercise.[14]

HIIT is indicated in patients with CAD who have undergone revascularization procedures with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), non-obstructive CAD as evidenced by angiography, and CAD with a left ventricular ejection fraction (LVEF) >40%. Another indication is CAD patients with stable symptoms and no medication changes for more than 2 weeks. 10 Several conditions that cause HIIT exercise not to be given to patients with CAD based on previous research exclusion criteria are listed in Table 1.[10,15,16]

Other conditions that prevented researchers from providing HIIT in patients with CAD include hospitalization due to CVD in less than 6 months, symptomatic aortic stenosis, uncontrolled diabetes, symptomatic cerebrovascular disease for <6 months, severe shortness of breath at rest, severe exercise intolerance, thrombophlebitis, recent embolism, symptomatic aortic stenosis or pulmonary infarction, acute myocarditis or pericarditis, active endocarditis, and other acute non-cardiac disorders that may impair

**Table 1.** Conditions that cause high-intensity interval training not to be given in coronary artery disease patients.

| | Research exclusion criteria |
|---|---|
| 1. | Presence of ischemic symptoms |
| 2. | Unstable angina pectoris |
| 3. | New or revascularized acute myocardial infarction <4 weeks |
| 4. | Significant (>50%) left main coronary artery stenosis |
| 5. | The presence of proximal left anterior descending artery stenosis >75% |
| 6. | Presence of vessel stenosis with minimal diameter (<2 mm) |
| 7. | Presence of chronic heart failure with symptoms according to New York Heart Association class III (symptoms at rest or light physical activity) |
| 8. | The presence of uncontrolled ventricular arrhythmias that cause hemodynamic disturbances |
| 9. | Presence of significant valvular heart disease or shortness of breath on light exertion |
| 10. | Use of pacemakers |
| 11. | Presence of chronic obstructive pulmonary disease |
| 12. | Presence of chronic renal failure |
| 13. | Uncontrolled hypertension with blood pressure >180/100 mmHg, |
| 14. | Pregnancy |
| 15. | Inability to participate in training or practice tests according to the guidelines |
| 16. | Presence of co-morbidities that preclude the patient from participating in exercise |

exercise performance or be exacerbated by exercise, life expectancy <1 year, and drug abuse or alcohol in the last six months.[15,17]

HIIT protocols given to patients with CAD vary widely based on several studies and a review of the literature as described in Table 2.[10,16-19] The most commonly used protocol is an exercise consisting of a 10-minute warm-up followed by 4x4 min of interval training with an intensity of 85% - 95% heart rate peak (HR peak) or rating of perceived exertion (RPE) 15-18 and an active recovery period of 3 min with an intensity of 70% HR peak (RPE <13).[14]

## Safety Issues of HIIT in CAD Patients

Most of the previous studies found no adverse events or significant adverse events that limited the ability of patients to perform HIIT programs. (15,17-19) A systematic review and meta-analysis of 17 studies found that only 1 study reported an incident of cardiac event, namely angina which caused the subject to leave the study and this occurred in both intervention groups who were given the HIIT or MICT. Compared to MICT or continuous training, other studies have found that cardiovascular events in both forms of exercise are very low.[15]

Adverse events that may occur during the HIIT program include death from all causes, hospitalization due to cardiovascular disease, atrial tachycardia, atrial fibrillation, or frequent ventricular arrhythmias. 15 Another study found one fatal event in 129,456 hours of MICT program and two non-fatal events in 23,182 hours of HIIT program.[20]

Data from 11 studies in stable CAD patients revealed three adverse cardiovascular events that were not clearly related to exercise. Two patients presented with angina and no arrhythmias were reported in any of the studies. It has been argued that HIIT is a safe exercise and does not differ in the frequency or increase in adverse cardiovascular events during exercise compared with continuous training. Before prescribing a HIIT program, the presence of angina symptoms, exercise intolerance, ischemic functional status, or arrhythmias during exercise should be carefully considered.[15]

Only a few studies reported additional adverse events, especially musculoskeletal and digestive problems, and these events were more frequent in the MICT-treated group. There were no deaths or cardiac events requiring hospitalization in the HIIT or MICT group. 15,20 The low fatality rate after the provision of supervised training is because the training is provided by officers who are trained in emergency management. It is said that the death rate will increase 6 times higher without proper management of cardiac arrest by trained personnel.[18]

Rognmo et al. obtained the adverse event rate was 1/129,456 hours of moderate-intensity exercise (one fatal cardiac arrest during moderate-intensity exercise) and one in 23,182 hours of vigorous-intensity exercise (two non-fatal cardiac arrests during HIIT). This

**Table 2.** HIIT Protocols and Its Effects of HIIT on Cardiovascular Function and Risk Factors, Functional Impairments, and the Quality of Life.

| Author, Study (Year)/Study Design/Study Groups | HIIT Protocol | Cardiovascular Function and Risk Factors | Functional Impairments | | Quality of Life |
|---|---|---|---|---|---|
| | | | CRF | Affective Function | |
| Madsen et al (2014)17/ Randomized controlled trial/HIIT vs usual program | • Frequency: 3 sessions of HIIT per week<br>• Intensity, Time:<br>• 4 x 4 min HIIT intervals (3 min active recovery between intervals)<br>• HIIT: 85–95% of HRmax<br>• Active recovery: 70% of HRmax<br>• Type<br>• Hospital: Walk or run on treadmills<br>• Home: Walking uphill, running, cross-country skiing, or bicycling<br>• Warm-Up: 8-10 min<br>• Cooldown: No data<br>• Program duration: 12 months. | • No changes in resting heart rate, heart rate recovery, and blood pressure in both groups<br>• No between-group difference in resting heart rate, heart rate recovery, and blood pressure after 12 months<br>• No changes in blood markers (serum glucose, total cholesterol, LDL cholesterol, HDL cholesterol, TG, Hs-CRP, and HbA1c) during follow-up in both groups | • No changes in VO2peak value from baseline to follow-up in both groups<br>• No between-group difference in VO2peak value | | There was an increase in quality of life (social domain) in the control group, but no be- |
| Maturana et al (2021)22/ Randomized controlled trial/HIIT vs MICT | • Frequency: 3 sessions per week<br>• Intensity, Time<br>• 4 x 4 min intervals (4 min active recovery between intervals)<br>• HIIT: 90% of HRmax<br>• Active recovery: 30 W<br>• Total: 43 min (inc. warm-up & cool-down)<br>• Type: Cycle ergometer<br>• Warm-Up: 10 min (70% of HRmax)<br>• Cooldown: 5 min (30 W)<br>• Program duration: 6 weeks. | • No significant morphological changes in the heart as measured by echocardiography<br>• A small change in the systolic and diastolic function especially in the right ventricle | • A significant increase in VO2max value in both groups with a greater increase in HIIT<br>• The variability in the ΔV-O2max was associated with initial lower cardiorespiratory fitness, higher arterial stiffness, lower left ventricular mass, and higher diastolic function in HIIT.<br>• The variability in the ΔV-O2max was associated with lower lower-limb microvascular responsiveness and higher right ventricular systolic function in MICT. | | |

| | | | |
|---|---|---|---|
| Cardozo et al (2015)29/ Randomized controlled trial/HIIT vs MICT vs non-exercise | • Frequency: 3 sessions per week<br>• Intensity, Time<br>• HIIT: 90% of HRpeak<br>• Active recovery: 60% of HRpeak every 2 min<br>• Total: 30 min<br>• Type: Treadmill aerobic<br>• Warm-Up: 5 min<br>• Cooldown: 5 min<br>• Program duration: 16 weeks | No differences in hemodynamic variables (HRpeak, SBP, and DBP) after the training program both within and between groups | • VO2peak and peak O2P decreased in CG, increased in HIIT, and remained stable in MICT.<br>• VE and VO2 at the ventilatory threshold and peak exercise were similar among groups.<br>• The ventilatory threshold was achieved at 61% VO2 peak<br>• The VE/VCO2 slope is maintained in trained groups and CG<br>• The OUES is maintained in trained groups and CG<br>• The O2P slope increased in HIIT, remained stable in MICT, and decreased in CG. |
| Prado et al (2016)30/ Randomized controlled trial/HIIT vs MICT | • Frequency: 3 sessions per week<br>• Intensity, Time<br>• HIIT: At respiratory compensation point (7 bouts)<br>• The active interval at the ventilatory anaerobic threshold every 3 min<br>• Total: 42 min<br>• Type: Treadmill<br>• Warm-Up: 5 min<br>• Cooldown: 5 min<br>• Program duration: 3 months | • No reduction in body weight in either group<br>• No between-group differences in left ventricular ejection fraction | • No differences in peak RER or HR in either group after the intervention<br>• There was a significant and similar increase in VO2 at VAT, peak VO2, and OUES in both groups |

| | | | | |
|---|---|---|---|---|
| Villelabeitia-Jaureguizar et al (2019)25/ Randomized controlled trial/HIIT vs MICT | • Frequency: 3 days per week<br>• Intensity, Time<br>• 1st month: 20 s repetitions of 50% maximum load reached with SRT (peak intervals)<br>• Recovery period: 40 s of 10% maximum load<br>• 2nd month: adjusted using the new SRT result<br>• Total: 40 min (inc. warm-up & cool down)<br>• Type: Bicycle ergometer<br>• Warm-Up<br>• Week 1 to 4: 12-10-7-5 min (25 W)<br>• Week 4 to 8: 5 min (25 W)<br>• Cooldown<br>• Week 1 to 4: 13-10-8-5 min (25 W)<br>• Week 4 to 8: 5 min (25 W)<br>• Program duration: 8 weeks | | • Both exercise programs significantly increase VO2peak with a higher increase in the HIIT group.<br>• ME at VO2peak and VT2 only significantly increased in the HIIT group<br>• ME at VT1, significantly increased in both groups, with a greater increase in the HIIT group | |
| Jung et al (2014)33/ Randomized controlled trial/HIIT vs VICT vs MICT | • Frequency: 4 visits<br>• Intensity, Time<br>• HIIT: ≈100% Wpeak (≈90 ± 7% HRmax)<br>• Recovery period: ≈20% Wpeak every 1 min<br>• Total: 20 min<br>• Type: Cycle ergometer<br>• Warm-Up: 3 min (Self-determined light intensity)<br>• Cooldown: 3 min (Self-determined light intensity)<br>• Program duration: 3 months | | | Participants reported greater enjoyment of HIIT as compared to VICT and MICT, with over 50% of participants reporting a preference to engage in HIIT as opposed to either VICT or MICT |
| Wu et al (2017)19/ Randomized controlled trial/ HIIT vs MICT | • Frequency: 5 days/week<br>• Intensity, Time<br>• HIIT: 80% VO2max<br>• Recovery period: 40% VO2max every 3 min<br>• Total: 30 min<br>• Type: Bicycle ergometer<br>• Warm-Up: 3 min (30% VO2max)<br>• Cooldown: 3 min (30% VO2max)<br>• Program duration: 6 weeks | HIIT simultaneously improves mitochondrial bioenergetics and suppresses dynamic thrombin generation in platelets undergoing hypoxia | | |

indicates that the incidence of adverse events is low.[18]

A systematic review by Kolmos et al. found that HIIT is safe, time efficient, and well tolerated in healthy subjects and patients with cardiovascular disease. No studies have reported adverse events or evidence of vessel wall damage or negative effects on endothelial function after exercise, regardless of the intensity applied. In healthy people, it has been found that HIIT is safe and causes a variety of changes in endothelial function. One study examined serum nitric oxide production before and after exercise and found no significant differences.[21]

## The Effect of HIIT on Cardiovascular Function and Risk Factors

The cardiovascular benefits of AE are linearly related to intensity; the higher the intensity, the greater the cardiovascular benefits.[9,18] If the total energy expenditure from exercise is kept constant, high-intensity exercise shows a greater cardioprotective benefit than moderate-intensity exercise.[18]

Exercise for six weeks did not cause significant morphological changes in the heart, but there were small changes in systolic and diastolic function, especially in the right ventricle.[22] A systematic review by Kolmos et al. found that out of 17 studies, six studies showed no changes in endothelial function related to exercise, while 11 studies showed changes in endothelial function after moderate or high-intensity exercise.[21]

HIIT programs improve endothelial function like MICT or standard care. Improvement was independent of the interval training mode, patient population, and training duration. Not all studies have reported that HIIT improves endothelial function. One study found no significant changes in serum nitrate or nitrite; only an increase in nitric oxide concentration was found. Therefore, nitrate and nitrite are biomarkers that are not appropriate for determining endothelial function.[21]

The structure and function of the left ventricle also improved after being given HIIT. One study found that 36 sessions of HIIT reduced left ventricular dilatation and mass, increased ejection fraction, systolic or diastolic blood flow, and other systolic and diastolic parameters.[18] Variability in the changes in maximal oxygen uptake (VO2 max) was associated with greater arterial stiffness, lower left ventricular mass, and higher diastolic function in the HIIT group.[22]

In post-PCI patients, regular exercise is beneficial for increasing the LVEF and cardiac contractility. Less intensive training even when given at moderate intensity does not produce a better effect than HIIT in terms of increasing LVEF. This shows that exercise intensity has different effects on cardiovascular function.[23]

Madssen et al. obtained no difference in blood pressure and resting pulse, as well as blood gas analysis between the groups given the HIIT and MICT programs.[16] Previous clinical studies reported a higher increase in diastolic blood pressure after exercise with an intensity of >60% VO2 peak than after moderate-intensity exercise. There are no data regarding the effects of high-intensity exercise on systolic blood pressure.[18]

The benefits of HIIT on the cardiovascular system are two times greater than those of MICT, so this is the basis for administering HIIT programs to patients with cardiovascular disease.[18] The advantages of HIIT with short intervals in CAD patients include the following: 1) HIIT is an optimal protocol that allows patients to perform exercises with an intensity close to the VO2 peak value; 2) the number of exercise bouts can be increased to fulfill the required volume; and 3) the rest periods between exercise bouts resulting in a lesser frequency of fatigue and shortness of breath.[24]

The HIIT protocol with short intervals was well-tolerated in patients with CAD. This protocol was also safe and elicited the same physiological response as MICT, allowing increased exercise compliance. The HIIT protocol with longer active intervals was more intolerable, with a higher rating of perceived exertion (RPE). This protocol was also associated with poorer adherence; therefore, it should be administered to patients who are fit or at low risk. In patients who are less fit and/or at higher risk, the HIIT protocol is more appropriate for administration at short intervals.[15]

In addition to increasing the VO2 peak, Villelabeitia-Jaureguizar et al. also found an increase in glycolytic metabolism in type 2 muscle fibers, which causes an increase in energy efficiency in terms of increasing strength and muscle resistance to fatigue. This process indicates an increase in mechanical efficiency (ME). Mechanical efficiency is an individual's ability to transfer the energy consumed by external work, which provides important information about biomechanical adaptation and the use of energy resources related to exercise and functional capacity. The decrease in ME, which indicates that the energy consumed is higher at

a given work output, can represent the energy cost of breathing during exercise and the changes in production efficiency or ATP consumption per work output, which is higher. Individuals with lower ME scores are less efficient at exercising and have limited physical activity abilities. ME evaluation can be valuable for detecting muscle dysfunction and adaptation to exercise.[25]

Potential mechanisms that cause a greater increase in aerobic capacity with interval training include increased mitochondrial function and the maximal rate of calcium uptake into the sarcoplasmic reticulum, which in turn reduces the level of muscle fatigue.[26] Exercise causes an increase in oxygen delivery to the myocardial area but there is no certain explanation for the pathophysiology.[23]

Improved mitochondrial function is strongly associated with an increased VO2 peak. This supports the theory explaining the influence of mitochondrial function on cardiorespiratory capacity. Mitochondrial biogenesis is an important component in maintaining the structural integrity of skeletal muscles. Mitochondrial function is related to aerobic fitness and plays an important role in pathophysiological changes in patients with heart disease.[26]

Mitochondrial dysfunction is closely related to oxidative stress and is thought to be the most common mechanism underlying cardiovascular and metabolic diseases. Wu et al. found that exercise with 12% oxygen increased mitochondrial oxidative stress, which, in turn, led to hypoxia and thrombin generation. HIIT suppresses oxidative stress at the cellular level, thereby reducing the risk of thrombin generation due to hypoxia.[19]

The HIIT program is associated with a reduced risk of cardiovascular disease compared with AE at a lower intensity due to a greater cardioprotective effect. [18] A systematic review found that serum LDL and triglyceride levels did not increase significantly, whereas HDL and total cholesterol levels increased after administration of the HIIT program.[23] Findings by Abdelhalem et al. found different results on lipid and cholesterol profiles that varied widely with or without HIIT prescribing. This was caused by the insufficient number of samples, and the research samples continued pharmacological treatment, such as clopidogrel, aspirin, statins, and beta-blockers.[27] The increase in glucose control was higher after exercise with an intensity of >60% VO2 peak than after moderate-intensity exercise. There are no data regarding the lipid profile or loss of body fat following high-intensity exercise.[18]

## The Effect of HIIT on CRF

Peak oxygen uptake (VO2 peak) is the amount of oxygen absorbed by the body in 1 minute when cardiorespiratory function and the ability of muscles to use oxygen reach their limits during long-term strenuous activity involving several large muscle groups. The higher the VO2 peak, the stronger the aerobic metabolism and the better the cardiorespiratory function.[23] Interval training with an intensity of 85%-95% HR peak is more effective in increasing VO2 peak than exercise with an intensity of 60%-70% HR peak.[18]

The investigators recommend using HIIT in a CR program for patients with CAD because of the significant cardiovascular adaptations to this exercise program.[20] HIIT programs are effective for improving health and physical fitness.[15] Research has found that the HIIT program has a beneficial effect on increasing VO2 peaks, while peak HR and resting HR do not change significantly.[23] The variability in VO2 peak changes was associated with low cardiorespiratory fitness at the start of exercise.[22] Ventilatory threshold and maximum workload increased significantly in post-PCI patients undergoing the HIIT program.[23] Interval training also causes an increase in VO2 peak, which is a strong predictor of all-cause death and death related to cardiovascular events.[26]

The increase in VO2 max varies based on the training component. Variations in the increase in VO2 max include the following: 1) interval training causes a slightly greater increase in VO2 max than continuous exercise; 2) more intense exercise causes a greater increase in cardiorespiratory fitness (VO2 max); and 3) longer training intervals combined with continuous high-intensity exercise lead to a more marked increase in VO2 max in almost all relatively young subjects.[24]

The HIIT program resulted in an increase in VO2 peak within <8 weeks compared with that in the control group without intervention.[28] Clinically significant increase in VO2 peak is >1.5 milliliter/kg/minute. HIIT programs improve aspects of fitness in healthy young or older individuals (> 60 years).[29]

Compared to MICT, the HIIT program significantly increased cardiorespiratory fitness to a greater extent.

The mean increase in cardiorespiratory fitness was 1.53 – 1.78 milliliters/kg/minute. HITT programs of 7-12 weeks lead to greater increases in cardiorespiratory fitness; therefore, training for less than 7 weeks or more than 12 weeks will yield suboptimal results.[20]

Madssen et al. provided a rehabilitation program for 12 months after the patient underwent a CR phase II program for 12 weeks at the hospital. Patients were given HITT three sessions per week at home and a supervised exercise program in the hospital 1 time a month. This study found that there was no difference in VO2 peak between the groups that continued the exercise program for 12 months after discharge from the hospital and the control group. Supervised exercise once a month was not sufficient to increase the VO2 peak. Even though the patient was given home exercises three times a week, his adherence to these exercises was not good, as evidenced by the physical activity questionnaire. Only one-third of the patients in the intervention group underwent HIIT 2-3 times a week.[17]

Intervals of 3-5 min are effective in improving the effectiveness of the exercise. Several studies have found a greater increase in VO2 max, which is around 0.85 liters/minute with an interval of 3-5 min. A literature review and meta-analysis found that interval training alone or in combination with continuous exercise increased VO2 max by an average of 0.5 liters/minute. This result is higher than that obtained in previous studies with an average increase in VO2 max of 0.4 liters/minute in response to exercise for 20 weeks. An increase in VO2 max of 0.2-0.3 liters/minute has also been reported in other studies.[24]

The increase in VO2 max with exercise was due to cardiac output and peripheral oxygen extraction. The role of changes in stroke volume, blood volume, capillary density, muscle mitochondrial content, and several factors associated with an increase in VO2 max due to exercise vary among individuals and due to the interaction of the specific components of the exercise program.[24]

Cardozo et al. conducted a study to compare the effect of a 16-week program of HIIT and MICT on cardiorespiratory fitness in patients with CAD. This study found that cardiorespiratory fitness (VO2 peak) and ventricular function were better in the HIIT group than those in the MICT group.[29] Maturana et al. in their research found that the HIIT and MICT programs significantly increased VO2 max. Greater improvement was found in the HIIT group than in the MICT group.[22]

In their study of patients with CAD, Prado et al. found that cardiorespiratory function improved significantly from baseline in the two groups given the HIIT and MICT programs. The improvement in cardiorespiratory function was the same in both groups because the MICT group received training with a relatively higher volume and intensity. The MICT group exercised for 50 min with intensity at the ventilatory anaerobic threshold, which was around 70%-80% VO2 peak for 41 min with an episode of 10 weeks.[30]

## The Effect of HIIT on Executive Function

Acute HIIT programs tend to have a positive effect on overall executive function. Executive function refers to a specific category of cognitive control processes that operate in a top-down manner to support intentional and goal-oriented actions. Executive function later can be categorized into two sub-domains: 1) core executive functions, which include inhibition, shifting, and updating/working memory; and 2) higher-order EF, such as planning. The facilitation of executive functions is likely due to physiological changes induced by HIIT, such as heart rate, lactate, catecholamines, and blood flow. Executive function was assessed using several instruments including the Flanker task incongruent, Stroop test, Corsi block test, digit span test-backward, and several other instruments. These changes can lead to increased attention when performing activities that require executive function.[31]

Previous studies have found evidence that acute HIIT affects the prefrontal cortex and the area of the brain associated with executive function by increasing the activation and oxygenation of the prefrontal cortex. The facilitation of executive function is related to a biomarker that determines executive function, namely brain-derived neurotrophic factor (BDNF), which is induced by exercise.[31]

Exercise with an intensity of 95% maximum power output caused a decrease in overall cognitive performance improvement 30 min after stopping the exercise. This is associated with a higher neuromuscular fatigue during exercise. Acute HIIT interventions with a total time between 11 and 20 min or 21 and 30 min are likely to have a positive effect on executive function.

A total time of less than 10 min or more than 30 min did not consistently have a positive effect on executive functioning.[31]

Regardless of whether the intensity is submaximal or maximal, acute HIIT tends to have a positive effect on executive function. This is in contrast to previous findings that acute HIIT exercises lead to impaired executive function.[31]

### The Effect of HIIT on Affective Function

Most studies show the overall beneficial effect of HIIT programs on pleasure as measured during and after a workout session.[15] Studies that assess affective responses during exercise in overweight and inactive individuals have found a negative relationship between exercise intensity and affective functioning. When exercise intensity increases above the ventilatory threshold, the affective response to exercise becomes increasingly negative.[32] Several studies have found that affective responses decrease when exercise intensity increases above the anaerobic threshold.[15] Continuous exercise with vigorous intensity, such as cycling with an intensity of around 80% VO2 max for 30 min causes greater psychological distress and greater discomfort compared to moderate-intensity cycling of around 50% VO2 max.[33]

The relationship between the stimulus and duration of recovery is important for maintaining positive affect. HIIT sessions performed with a 120-second stimulus elicited lower affective responses compared to HIIT sessions with a stimulus for 60 s and 30 s, even though the stimulus-recovery ratio was maintained at 1:1 throughout the HIIT sessions.[15]

Oliveira et al. found that affective response and pleasure were dependent variables. Affect is a reflexive response to emotions, including the positive, neutral, and negative aspects. Pleasure is a more specific feeling characterized by cognition and evaluation. Both of these aspects are related to adherence to practice.[32]

Inactive individuals found that HIIT caused less discomfort than continuous exercise did at vigorous intensity. It was also reported that HIIT was more enjoyable and preferred than continuous vigorous-intensity exercise, and comparable to moderate-intensity continuous exercise.[33]

The affective experience experienced during exercise is influenced by metabolic needs related to intensity. The HIIT program induced the same health-promoting adaptations as the MICT, although the time required for HIIT was shorter. This shorter time is considered more promising for increasing physical activity levels. The feeling of pleasure when performing exercises consisting of 6 × 3 min of interval training with an intensity of 90% VO2 max is lower than that of continuous exercise with an intensity of 70% VO2 max for 50 min.[33]

### The Effect of HIIT on Functional Activity and the QoL

Research on the effect of HIIT on functional ability and QoL remains limited. In a study by Madssen et al., there was no difference in physical activity level and QoL between groups given the HIIT and MICT programs.[17]

## Conclusion

HIIT causes changes in ventricular structure and function, increases in LVEF and cardiac contractility, and improvement in endothelial function. These changes affect systolic and diastolic blood pressure. HIIT is also associated with a better reduction in the risk of CVD than AE at a lower intensity. Studies have recommended using HIIT in a CR program for patients with CAD because of the significant cardiovascular adaptability of this exercise. Studies have shown that HIIT has a beneficial effect on CRF; however, these improvements vary based on training protocols. Compared with MICT, most studies found that HIIT was better at improving CRF. Regarding executive function and affective function, it is known that HIIT has a positive effect on these two functions. Research on the effect of HIIT on functional activity and QoL is still very limited, but one study found no difference in physical activity levels and QoL between groups given HIIT or MICT programs. In patients with CAD, HIIT is considered an alternative exercise that is more efficient in terms of time compared to continuous training.

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## List of Abbreviations

| | |
|---|---|
| AE | Aerobic Exercise |
| CAD | Coronary artery disease |
| CABG | Coronary Artery Bypass Graft |
| CR | Cardiac rehabilitation |
| CRF | Cardiorespiratory Fitness |
| HIIT | High-intensity interval training |
| MICT | Moderate-intensity Continuous Training |
| QoL | Quality of Life |

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