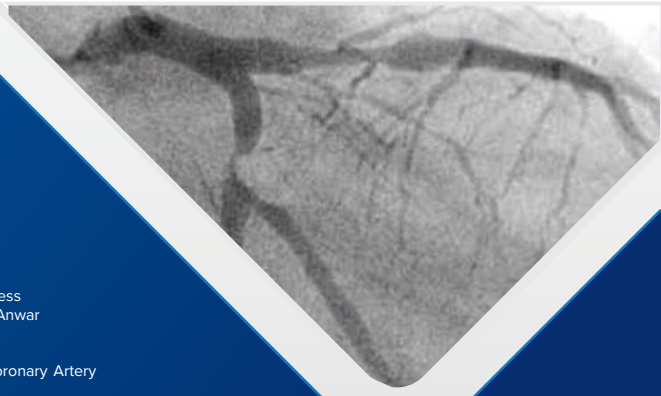
Volume 03 | Issue 04
1st October 2022
p-ISSN 2721 - 9984
e-ISSN 2721 - 9976
heartscience.ub.ac.id

Heart Science Journal



Prevention, Screening and Rehabilitation : The Back Bone of Quality Care Improvement in CVD Management

Universitas Brawijaya

p-ISSN 2721 - 9984
e-ISSN 2721 - 9976

Heart Science Journal

Official Open Access Journal of Brawijaya Cardiovascular Research Center

Volume 3 • Issue 4 • October 2022 • page 1–43 DOI: http://dx.doi.org/10.21776/ub.hsj.2022.003.04

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p-ISSN 2721 - 9984
e-ISSN 2721 - 9976

Heart Science Journal

Official Open Access Journal of Brawijaya Cardiovascular Research Center
Volume 3 • Issue 4 • October 2022 • page 1–43 DOI: http://dx.doi.org/10.21776/ub.hsj.2022.003.04

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Contents list available at www.heartscience.ub.ac.id

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Journal Homepage : www.heartscience.ub.ac.id

Editorial

Overcoming High Cardiovascular Disease Burden in Indonesia: The Importance of Massive Cardiovascular Disease Risk Factor Screening, Aggressive Guideline-Directed Treatment, and Community-Based Programs

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ARTICLE INFO

Keywords:
Cardiovascular Disease;
High-Risk Cardiovascular Disease.

ABSTRACT

Indonesia is a developing country with a large number of populations. Cardiovascular disease (CVD) is a serious public health concern in Indonesia because of its high burden. Moreover, the high-risk CVD patients were under treatment. Optimal CVD prevention can be the solution to this issue. In this paper, we are talking mainly about the role of massive CVD risk factor screening, precise risk stratification, aggressive guideline-directed treatment, and community-based programs in reducing the CVD burden.

Indonesia, with a population of 271.6 million, is the fourth most populous country in the world and has witnessed remarkable economic expansion over the past few decades.[1] Indonesia is undergoing a rapid epidemiological change in terms of its existing and predicted disease burden as a likely consequence of its economic development. The burden of non-communicable diseases is a serious public health concern in Indonesia. In Indonesia, approximately one-third of all deaths are attributed to cardiovascular diseases (CVD), with coronary artery disease (CAD) and stroke as the major causes of death.[2] Like most low- and middle-income countries in the Asia-Pacific region, the prevalence of major risk factors for CVD, such as obesity, diabetes, and hypertension, has increased in the Indonesian population.[3] High CVD risk is prevalent in over-40-year-old Indonesian adults, and rates of preventative treatment are low.[4] The other important issue is the high mortality rate for acute coronary syndromes (ACS). In Indonesia, all patients diagnosed with ACS had an in-hospital death rate of 10.6%.[5] Nonetheless, this figure is more than the in-hospital death rate in other Asia-Pacific countries (5%),[6] as well as Western countries (2.6% to 6.2%).[7]

CVD prevention is described as a population-level or individual-level coordinated collection of interventions to avoid or decrease the impact of CVD and its related disabilities. Prevention should be provided at two levels. First, prevention can be delivered at the population level by promoting healthy lifestyles. Second, at the individual level, for example, in people at moderate to high risk of CVD or in patients with established CVD, prevention can be conducted by stopping unhealthy lifestyles (smoking, physical inactivity, atherogenic diet) and optimizing risk factors. At least 80% of CVDs could be prevented by eliminating health-risk behaviors.[8] Some demographic interventions have effectively altered people's lifestyles. For instance, a greater understanding of how healthy lifestyles prevent CVD has reduced smoking and cholesterol levels. Before or in conjunction with pharmacological therapy, lifestyle modifications targeting several CV risk factors should be utilized. In addition, regulations targeted at cigarette smoking and reducing the trans-fatty acid and sodium content in food products are cost-effective in preventing CVD.[9,10]

Screening and managing risk factors for CVD are crucial components in preventing CVD.[11] Numerous studies have proven the benefits of risk factor management and have significantly influenced national and international health strategies for CVD prevention.[12–14] Generally, CVD risk factors are classified into modifiable and non-modifiable risk factors. The non-modifiable risk factors include older age, male gender, and family history of CVD. We cannot do anything about these risk factors. However, well-controlled modifiable risk factors can alter the natural history of CVD itself. Cigarette smoking, high-cholesterol diet, physical inactivity, hypertension, diabetes mellitus, hyperlipidemia, and overweight/obesity belong to the modifiable CVD risk factors.[8] This CVD risk factor screening should be completed by all physicians as part of a thorough patient evaluation.

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https://doi.org/10.21776/ub.hsj.2022.003.04.1
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022

Various CVD risk evaluation tools are available for use in apparently healthy persons, such as Framingham,[15] CUORE,[16] PROCAM,[17] QRISK1,[18] QRISK2,[19] ASSIGN,[20] and SCORE.[21] However, the current guideline from the European Society of Cardiology (ESC) strongly recommends total CVD risk assessment using SCORE for individuals aged at least 40 years old unless they have been classified as high-risk or very high-risk according to the documented CVD, kidney disease, diabetes mellitus, or a significantly higher risk factor.[8] The SCORE system assesses the first fatal atherosclerotic event risk occurring within 10 years. The components of the SCORE system include gender, total cholesterol level, systolic blood pressure, cigarette smoking status, and age.[21] This scoring system is user-friendly and can be applied by all physicians in daily clinical practice from primary to tertiary healthcare centers in Indonesia. The patients can be classified into low-, moderate-, high-, and- very high-risk persons if the total SCORE is less than 1%, between 1% to 5%, between 5 to 10%, and more than equal to 10%, respectively.[8,22]

Aggressive guideline-directed treatment for CVD risk factors is mandatory and has to be well-recognized by all physicians in Indonesia. The dangers of cigarette smoking exhibit a dose-response association with no minimum threshold for adverse effects. Current guidelines recommend no active or passive exposure to any form of tobacco. A diet low in saturated fat that emphasizes wholegrain items, vegetables, fruit, and seafood is strongly advised. A minimum of 75 minutes a week of vigorous aerobic exercise (15 minutes for 5 days/week), 150 minutes a week of moderate aerobic exercise (30 minutes for 5 days/week), or a combination of both has to be performed in a routine manner. Waist circumference has to be maintained below 80 cm and 94 cm for females and males, respectively. Moreover, keeping body mass index (BMI) around 20 to 25 kg/m2 is strongly recommended. The blood pressure and glycated hemoglobin (HbA1c) have to be maintained below 140/90 and 7%, respectively.[8,22,23] However, for managing hyperlipidemia, individual and specific lipid panel-based approaches are needed. Actually, for triglycerides and high-density lipoprotein cholesterol (HDL-C), there are no specific targets. However, achieving a high HDL-C level above 40mg/dL for male and above 45 mg/dL in females show a lower risk. Below 150 mg/dL, triglyceride level suggests a lesser risk, while levels above 150 mg/dL indicate the need to investigate additional risk factors.[8] The low-density lipoprotein cholesterol (LDL-C) has to be decreased to <116 mg/dL, <100 mg/dL, <70 mg/dL, and <55 mg/dL for persons with low-, moderate-, high-, and very high- risk for CVD.[22]

The role of community-based prevention-rehabilitation programs and the CVD community needs to be appreciated. Community-based interventions have successfully improved CVD risk factors, specifically by decreasing blood pressure, LDL-C level, triglyceride level, BMI, and blood sugar level. The effect of these programs on CVD varies by intervention type, cultural, and physical context.[24] By joining the CVD community, people can share information and their own experience with each other regarding their experiences having CVD. A cohort study including CAD patients revealed that community-based cardiac rehabilitation programs provided better adherence to the treatment and quality of life and reduced rehospitalization rate.[25]

In conclusion, CVD is still the leading public health issue in Indonesia because of its high burden. The massive CVD risk factor screening, precise risk stratification, aggressive guideline-directed treatment, and community-based programs can be the way to solve this problem. All physicians, nurses, healthcare workers, patients, and stakeholders have to work together to resolve this problem.

Conflict of Interest

There is no conflict o interest

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Heart Sci J 2022; 3(4): 4-8

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Review Article

Phase I Cardiac Rehabilitation Intervention in Patients Undergoing Coronary Artery Bypass Grafting

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ARTICLE INFO

Keywords:
Cardiac Rehabilitation Phase I;
Coronary Artery Bypass Grafting.

ABSTRACT

Patients undergoing coronary artery bypass grafting (CABG) have a risk of postoperative complications that result in prolonged hospitalization and even death. Interventions in the form of phase I cardiac rehabilitation are needed to help speed up the postoperative recovery process and prevent complications after CABG. Although a lot of research has been carried out, it is necessary to conduct further studies of research articles regarding interventions that can be carried out in cardiac rehabilitation programs that are safe and easy to perform in postoperative CABG patients. The purpose of this literature review was to examine safe and effective interventions in phase I cardiac rehabilitation in patients undergoing CABG. The implementation of phase I cardiac rehabilitation in patients undergoing CABG started from the preoperative phase and continued postoperatively until the patient was discharged. Phase I cardiac rehabilitation interventions, both pre and postoperative, consist of education and counselling, physical exercise, breathing exercises, effective coughing exercises, inspiratory muscle training, and chest physiotherapy. The results of this literature review can be used as a basis for determining standard operating procedures for the implementation of phase I cardiac rehabilitation for hospitals that provide CABG services.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke. Over three quarters of CVD deaths take place in low- and middle-income countries, including Indonesia. Out of the 17 million premature deaths (under the age of 70) due to noncommunicable diseases in 2019, 38% were caused by CVDs.[1] Given the growing number of deaths from Coronary Heart Disease (CHD), it is critical to provide effective management. One of these is through performing revascularization intervention called Coronary Artery Bypass Grafting (CABG).

Coronary Artery Bypass Grafting (CABG) is a treatment for CHD patients that uses blood vessels taken from other parts of the body and cuts or "bypasses" blocked or narrowed coronary arteries.[2] The purpose of CABG is to reduce angina, reduce the risk of recurrent attacks, help prolong life expectancy, optimize heart function, and improve quality of life. In addition to having a positive impact on the condition of CHD patients, patients undergoing CABG is also at risk for postoperative complications that can affect outcomes including length of stay and increased postoperative mortality.

Research conducted by Soares, et al. stated that 58% of postoperative cardiac patients experience complications such as the pulmonary system (31%), the cardiovascular system (15.8%), and the nervous system (13.9%). Complications that occur include infection, bleeding, heart attack, decreased heart function, phrenic nerve paralysis, and disorders of the respiratory system such as atelectasis, pneumonia, pulmonary oedema, haemothorax, and bronchospasm.[3]

Patients undergoing CABG are not only at risk for operative-related complications but also experience physical and psychological problems such as pain, decreased heart muscle strength, anxiety, stress, depression, changes in response to spirituality that can affect the patient's quality of life and even experience depression that increase risk of death.[4-5] Therefore, it is necessary to intervene for prevent and reduce these problems, as well as to help speed up the recovery process after CABG surgery. Interventions that can be done are cardiac rehabilitation programs. Cardiac rehabilitation is a program that combines several interventions, either physical, psychological, or educational. This program aims to optimize both physical and psychological, also social functions so that it is expected to reduce morbidity and mortality, as well as improve the quality of life of CHD patients.[6]

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https://doi.org/10.21776/ub.hsj.2022.003.04.2
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022

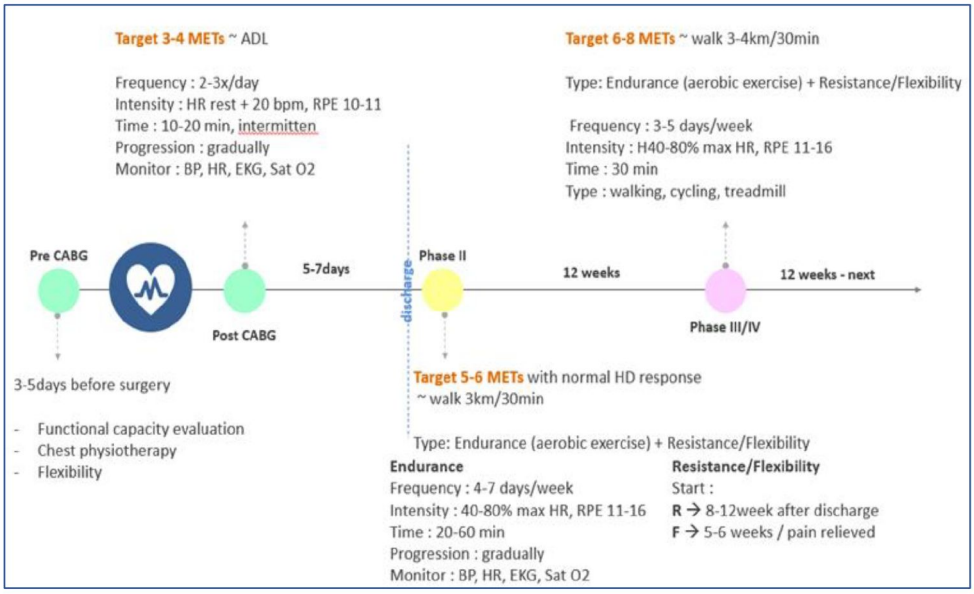

Figure 1. The timeline exercise-based rehabilitation phase in patient undergoing CABG11 Phase I is carried out during the hospitalization. A mix of physical activity of moderate intensity and stress control strategies and risk factors education is performed to ensure that the patient is discharged in the best psychological and physical state.[11]

Cardiac rehabilitation consists of three phases and all phases of cardiac rehabilitation are important in patients undergoing CABG surgery. This cardiac rehabilitation program starts from phase I in patients undergoing heart surgery starting preoperatively and continuing postoperatively. Phase I cardiac rehabilitation is cardiac rehabilitation that is carried out in hospital until they are discharged by performing mobilization, physical and respiratory activities, providing education regarding risk factors for heart disease, as well as stress and anxiety management.[7]

Several studies on phase I cardiac rehabilitation stated that patients undergoing the program showed an increase blood oxygen circulation in the body, as well as functional capacity.[8-9] Systematic reviews also stated that early mobilization after cardiac surgery has a positive impact such as length of stay, functional capacity, and prevention of postoperative complications.[10]

Phase I cardiac rehabilitation interventions in patients undergoing CABG surgery differ from those in patients undergoing percutaneous coronary intervention or fibrinolytic therapy. This happens because CABG surgery is a major surgical intervention with a long duration and has a higher risk of complications than other methods.[12] Cardiac rehabilitation intervention in patients undergoing CABG surgery already performed in all hospital, although the protocol still vary depending on the policies of each hospital. The research conducted by Cassina et al stated that early postoperative mobilization interventions are safe to do as long as the patient's hemodynamic status is stable and monitoring is still carried out during the intervention.[13]

Although cardiac rehabilitation interventions are safe for CABG patients, the method of intervention in phase I cardiac rehabilitation programs is still varies. Integrating several interventions included in a phase I cardiac rehabilitation program will have a positive impact on outcomes, especially those undergoing CABG surgery. Therefore, we are interested in conducting a literature review regarding any interventions that can be performed in phase I cardiac rehabilitation that are safe and easy to perform in postoperative CABG patients.

2. Discussion

In general, the intervention in the phase I cardiac rehabilitation program in patients undergoing CABG surgery is divided into two groups, namely preoperative and postoperative.

2.1 Preoperative Cardiac Rehabilitation Intervention.

Phase I cardiac rehabilitation interventions that can be performed preoperatively include education, breathing exercises, breathing exercises with inspiratory muscle training, psychological counselling, effective coughing exercises, and physical exercises.[11]

2.2 Education.

The education provided in the preoperative phase includes provide information about the activities that will be carried out when the patient has finished undergoing surgery, the care that will be carried out postoperatively, as well as information about diet, nutrition, drugs that will be used for urinary catheter care and drainage tubes, and how to change positions and physical activities to be carried out postoperatively.[14-15] Patients who are given preoperative education can reduce anxiety and increase the functional capacity of postoperative CABG patients.[15]

2.3 Breathing Exercises.

Breathing exercise is the key process in the preoperative preparation. Abdominal breathing exercises, purse lip, and deep breathing are recommended for patients undergoing CABG surgery. This is supported by Shakuri, et al. regarding giving breathing exercises including abdominal, purse lip breathing and deep breathing can improve postoperative respiratory function.[16] A similar study was also conducted by Sobrinho et al, who provided preoperative physiotherapy interventions in the form of breathing exercises consisting of deep breathing, then exhalation and long inspiration, breathing using the diaphragm and combined with mobilization of lower extremities,

as well as breathing exercises with a threshold-inspirational muscle trainer.[17] The conclusion of this study is that the exercise given preoperatively can increase the maximum inspiratory and expiratory pressure, so that the patient is better prepared to undergo the recovery process for respiratory function and reduce the length of stay which that has an impact on more effective treatment costs. Another study examining the effects of a pulmonary rehabilitation (PR) program applied to patients undergoing coronary artery bypass grafting (CABG) surgery with open heart technique on respiratory functions, functional capacity, and quality of life (QoL), showed the mean FVC and FEV1 values of the patients in the intervention group on the 4th day of clinical care were significantly higher with a medium level size effect than the control group ($p = 0.027$; effect size (d) = 0.643; $p < 0.024$; effect size (d) = 0.658, respectively).[18]

2.4 Psychological counselling.

Preoperative anxiety is linked to uncertainty and a lack of information. Increased preoperative anxiety has been linked to postoperative problems in coronary artery bypass graft (CABG) patients, including atrial fibrillation, myocardial infarction, higher readmission rates, increased healthcare use, and higher mortality rates. Giving patients beforehand information or instruction is a strategy to reduce preoperative anxiety.

Preoperative education includes giving patients pertinent information about the procedure and the recovery period (e.g., via a pamphlet, video, audiotape, or discussion). Healthcare workers work to reduce patients' worries, anxieties, and uncertainties by helping them understand the surgical procedure. In individualized or group sessions, educational content includes details about anticipated feelings (like fear), anticipated sensations (like pain), and likely outcomes. This might aid in minimizing the disparity between anticipated and actual feelings or occurrences. Patients may find it easier to deal with discomfort if they understand that it is a typical aspect of surgery and not a sign that something went wrong.[19]

2.5 Effective Cough exercises.

Effective coughing exercises is very important for patients undergoing CABG, because during surgery the patient has an endotracheal tube attached which can trigger secretions in the respiratory tract.[15] This exercise encourages expectoration of mucus and secretions that accumulate in the airways after general anaesthesia and immobility. Effective coughing exercises is one of the techniques in pulmonary care that is safe to use in CABG patients. Performing these exercises every 2 to 3 hours will facilitate pulmonary ventilation and promote airway clearance without overtiring the patients.[20]

(A) (B)

Figure 2. Effective cough exercise. (A) Instruct patient to hold pillow firmly over chest/incision; (B). Encourage patient to splint with pillow during coughing.[20]

2.6 Physical exercise.

Physical exercises performed preoperatively include mobilization, muscle stretching exercises and muscle strength training that can improve respiratory function and increase respiratory muscle strength. This is proven by the several research which stated that patients who were given physical exercise preoperatively and then continued postoperatively could improve respiratory function, functional capacity, and accelerate extubation.[16,21]

2.7 Postoperative Cardiac Rehabilitation Intervention.

Phase I cardiac rehabilitation interventions after surgery include physical exercise, breathing exercises, effective coughing exercises, and education.

2.8 Physical training.

Several articles state that postoperative physical exercise has a positive impact in reducing the occurrence of postoperative complications. Physical exercises performed in postoperative phase I cardiac rehabilitation include mobilization, range of motion (ROM), upper and lower extremity active exercises, and transfer exercises. The exercise is carried out gradually according to the patient's condition. In Iran, Moradian et al conducted a study by providing physical exercise in the form of early mobilization gradually starting 2 hours after extubation. The results of the study stated that the patients with the intervention had a better oxygenation status and the occurrence of complications (atelectasis and pleural effusion) was less than in the non-intervention group.[22]

2.9 Breathing exercises.

Breathing exercises performed postoperatively immediately after the patient is extubated can help to reduce chest pain and increase lung functional capacity.[23]

2.10 Cough exercises are effective.

Coughing exercises are effective on the first postoperative day (after extubation) to help remove secretions/phlegm in the respiratory tract. Increase tracheal secretion along with ineffective cough can lead to mucus stasis and even respiratory tract infection and extubation failure. Effective coughing can reduce this risk.[14]

2.11 Education.

The education provided after CABG surgery includes heart anatomy, disease, acute coronary syndrome, signs and symptoms of heart disease and modification of risk factors as well as providing re-information about pain management, controlling blood pressure and pulse rate, diet, and determine the next activity to be done at home.[19,24]

3. Additional Interventions

Additional interventions that can be performed on patients undergoing phase I cardiac rehabilitation program include respiratory muscle stretch gymnastics (RMSG) and increased exercise intensity that can improve outcomes after CABG surgery. This is evidenced by the study of Modi et al which compared postoperative patients undergoing phase I cardiac rehabilitation only with patients undergoing cardiac rehabilitation plus moderate intensity exercise on the results of the distance of 6MWT and quality of life. The results of the study indicated that moderate intensity exercise can improve outcomes, namely the 6MWT test results and quality of life so that it can accelerate the cardiac rehabilitation process and shorten the length of stay25. Subsequent research provides additional interventions in the phase I cardiac rehabilitation program in the form of respiratory muscle stretch gymnastics (RMSG) which is carried out on days 3-7 after CABG surgery. RMSG is a stretching exercise technique that is performed sequentially to stretch the muscles involved in breathing which consists of 5 exercise patterns. The exercise pattern consists of shoulder elevation, slowly stretching the upper chest, back and lower chest muscles, and elbow elevation. The conclusion of this study is that the addition of RMSG in cardiac rehabilitation can help reduce pain in both the scapula muscle and postoperative CPC pain.[26]

4. Time and Duration of Phase I Cardiac Rehabilitation

Preoperative phase I cardiac rehabilitation in the form of providing education regarding lung care techniques including abdominal breathing and effective coughing, postoperative actions that will include mobilization, drainage treatment, and urinary catheters, as well as psychological counselling started when the patient was admitted to the hospital or 2–3 days before surgery.[15] Physical exercise starting 2-3 days preoperatively and then continued for 5 days postoperatively can accelerate the recovery of respiratory muscle strength, increase functional capacity, quality of life, and psychosocial status of the patient21. The duration of breathing exercises and breathing exercises with a threshold-inspiratory muscle trainer is carried out 3–10 times for 2–30 minutes.[16,17,21]

Postoperative phase I cardiac rehabilitation begins on the first postoperative day or after extubation until the fifth postoperative day22. The duration of cardiac rehabilitation depends on the type of exercise such as breathing muscle exercises performed for 30 minutes, gradual mobilization includes repositioning from supination to sitting, from sitting to standing, from standing to walking 2 times a day. Walking exercises are carried out for about 1-45 minutes gradually according to the patient's ability.[14,21,27]

5. Conclusion

Cardiac rehabilitation interventions in patients undergoing CABG surgery are generally divided into two, namely interventions that start from preoperative and continue postoperatively until the patient returns home. Interventions both preoperatively and postoperatively consisted of education and counselling, physical exercise, breathing exercises, effective coughing, inspiratory muscle training, chest physiotherapy, and respiratory muscle stretch gymnastics. When these interventions are combined in a program, namely cardiac rehabilitation phase I, it is expected to improve outcomes optimally which has an impact on improving the patient's quality of life. The results of this literature review can be used as a basis for determining standard operating procedures for the implementation of phase I cardiac rehabilitation for hospitals that provide CABG services.

6. Declarations

6.1. Ethics Approval and Consent to participate
Not applicable.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: AG, CT. Design: AG, CT. Control/supervision: CT, AR, HM. Data collection/processing: DAI. Analysis/interpretation: AG, CT, AR, HM. Literature review: CT, AR, HM. Writing the article: DAI. Critical review: CT, AR, HM. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

10.7 *Acknowledgements*
We thank to Brawijaya Cardiovascular Research Center.

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Heart Sci J 2022; 3(4): 9-15

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

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Original Article

Correlation of Urine Albumin Creatinine Ratio and C-Reactive Protein Levels on Carotid Artery Intima-Media Thickness and Flow-Mediated Dilatation Response in Children and Adolescent with Type 1 Diabetes Mellitus at Dr Saiful Anwar Hospital Malang

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ARTICLE INFO

Keywords:
Albumin to Creatinine Ratio;
High Sensitivity CRP;
Carotid Artery Intima-Media Thickness;
Flow-Mediated Dilatation;
Type 1 Diabetes.

ABSTRACT

Background: Early and accelerated atherosclerosis is a major cause of cardiovascular disease and often causes premature death in T1DM patients. In T1DM, atherosclerosis can be detected since adolescence. The initial association between urinary albumin to creatinine ratio (ACR) and c-reactive protein (hs-CRP) with subclinical cardiovascular disease in children and adolescents with T1DM supported findings from previous studies. Imaging tests using ultrasound can detect subclinical atherosclerosis in this patient population. Carotid artery intima-media thickness (cIMT) and flow-mediated dilatation response (FMD) have been frequently used to detect subclinical atherosclerosis.

Objectives: To find correlation between ACR and hsCRP on the thickness values of cIMT and FMD in children and adolescent T1DM patients at Dr Saiful Anwar Hospital Malang

Methods: This is a cross-sectional study with 82 subjects of T1DM patients who routinely control the pediatric outpatient clinic of RSUD Dr. Saiful Anwar Malang, with the research period January – July 2019 and December 2021 – March 2022. Subjects were undergone valcuras ultrasound examination for measurements of cIMT and FMD. Blood sample from subjects were also collected to detect level of ACR and hsCRP. Associations between the study variables were estimated by calculating the Pearson's rank correlation.

Result: There was correlation between ACR with FMD and cIMT (r=-0.593; p=0.000 and r=0.339; p=0.002, respectively). ACR was negatively correlated with FMD and positively correlated with cIMT. There was also correlation between hsCRP with FMD and cIMT (p=-0.375; p=0.001 and r= 0.414; p=0.023, respectively). hsCRP was negatively correlated with FMD and positively correlated with cIMT.

Conclusion: ACR and hsCRP have a correlation with increasing CIMT values and decreasing FMD values in children and adolescents with T1DM patients. Preadolescent children with T1DM displayed evidence of increased low-intensity vascular inflammation, increased cIMT and attenuated FMD measurements. These data suggest that endothelial dysfunction and systemic inflammation are present even in preadolescent children with T1DM

1. Introduction

Atherosclerosis in T1DM can be detected since adolescence. The first important stage towards the development of atherosclerosis is endothelial dysfunction. Microalbuminuria and proteinuria are preceded by an early increase in urinary albumin excretion. The early increase in urinary albumin excretion during adolescence is critical, not only for identifying the risk of developing microalbuminuria and diabetic nephropathy, but may also signal an increased risk of cardiovascular disease to the clinician. The initial association between urinary albumin to creatinine ratio and subclinical cardiovascular disease in adolescents with T1DM supports findings concluded from a cohort study in Australia.[1]

Many epidemiological and clinical studies have revealed that circulating inflammatory biomarkers may influence the likelihood of future cardiovascular events since the inflammatory process involved in the development of atherosclerosis was first postulated. High sensitivity C-Reactive Protein (hsCRP) has been demonstrated to be one of the most significant and useful clinically relevant markers for increased cardiovascular risk among the acute phase proteins examined so far.[2] The study by Babar et al. supports previous clinical research by showing that oxidative stress and atherosclerosis in T1DM begin in childhood.[3]

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https://doi.org/10.21776/ub.hsj.2022.003.04.3
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022

Imaging tests can detect subclinical atherosclerosis in patient populations at risk for cardiovascular complications, such as T1DM patients. This test can be used as a reference for primary prevention of cardiovascular complications and reclassification of risk categories, especially in patients with low or moderate risk of cardiovascular complications in the future. Carotid artery intima-media thickness and flow-mediated dilatation response have been frequently used to detect subclinical atherosclerosis.[4]

The purpose of this cross-sectional study was to assess the correlation of urine albumin creatinin ratio (ACR) and high sensitivity CRP (hsCRP) on Carotid Intima-Media Thickness (cIMT) and Flow Mediated Dilation (FMD) values in children and adolescents with T1DM at Saiful Anwar Hospital Malang.

2. Subject and Methods

The Research Ethical Committee of the Faculty of Medicine at Universitas Brawijaya (No. 400/039/K.3/302/2022) approved the procedures utilized in this study. From January to July 2019 and December 2021 to March 2022, 82 research participants were enrolled using the consecutive sampling method, with each participant who met the inclusion criteria being enrolled in the study. All individuals were tested with a complete blood count, ACR, hsCRP, lipid profile, renal and liver function tests, and clinically, followed by cIMT and FMD evaluations. This study was carried out at the outpatient clinic of the Paediatric Endocrinology and Cardiovascular Department at the Saiful Anwar Hospital in Malang, Indonesia.

The T1DM group's inclusion criteria were as follows: has been diagnosed with T1D, is between the ages of 3 and 18, with positif GAD65 immunoassay, and his or her parents/guardians consented to the child's involvement in this study after being informed (informed consent). Exclusion criteria included local and systemic infections, liver dysfunction, impaired renal function, malignancy, and anemia, as well as a three-week history of Vitamin D supplementation, also history taking antihypertensive, anti-inflammatory, or cholesterol-lowering drugs. Using an indirect enzyme-linked immune-absorbent assay (ELISA), the GAD65 assay was used to validate the presence of T1DM in participant.

2.1 Measurement of ACR

Albumin can be found in the urine of patients with early-stage renal impairment. The method used in this study to evaluate albuminuria was to measure urine ACR in spot urine samples. ACR is calculated by dividing the albumin concentration in milligrams by the creatinine concentration in grams.

2.2 Measurement of hsCRP

hsCRP test is more sensitive than the standard CRP test. The high-sensitivity test can detect a slight increase in the normal range of standard CRP levels. Examination using blood serum, then processed by the method of the immunoturbidimetric system.

2.3 Measurement of FMD

Measurement of FMD response of the brachial artery using a Phillips Affinity echocardiography machine with a high resolution L12-5 linear transducer probe. The forearm is equipped with a blood pressure cuff, 5 to 10 cm below the elbow, the brachial artery is scanned longitudinally. The transducer was positioned in the same position to ensure image consistency after the clearest B-mode image of the anterior and posterior intima interfaces between the lumen and the vessel wall was obtained. To optimize the arterial lumen wall interface image, the depth and gain settings were adjusted. The cuff blood pressure was raised to 50 mm Hg above the systolic pressure and maintained for 5 minutes after obtaining a baseline longitudinal image for 30 seconds before the cuff pressure was raised. Longitudinal images of the arteries were recorded continuously for up to 3 minutes after the cuff was deflated. The direct brachial artery diameter change was expressed as a percentage change compared to the vessel diameter before cuff inflation. The percentage change in peak vessel diameter from baseline was used to calculate FMD. FMD percentage is obtained from [(peak diameter - baseline diameter)/baseline diameter] x 100%.[5]

2.4 Measurement of cIMT

European Association of Pediatric Cardiology, American Heart Association, and American Society of Echocardiography Carotid Intima-Media Thickness Task Force all have guidelines for measuring intima-media thickness.[6] The carotid arteries are imaged in a cardiovascular ultrasound facility. After the research partisipants rested for 10 minutes, measurements were taken. The examination is performed with the patient lying comfortably in a supine position. The patient's neck is slightly stretched, and the head is rotated 45 degrees to the opposite side of the side being examined. The carotid arteries were imaged using a high-frequency 12-MHz linear-array transducer (Philips Affinity, L12-5 linear transducer).

To ensure optimal imaging of the vessel wall, ensure that the vessel is as perpendicular to the ultrasound plane as possible. The common carotid artery, carotid bulb, and internal carotid artery in the far wall were all measured when the carotid artery was examined on its longitudinal axis using various scanning angles (anterior and lateral). The focus should be around 30–40 mm, the frame rate should be at least 25 Hz, and the gain should be at least 60 dB. On each side, a measurement is made, and the average of both sides can be measured. Measurements were made using calipers to manually measure the distance between the two interfaces on standard B mode ultrasound. Measurement of cIMT was performed using a 3-lead ECG in the end-diastolic period.

2.5 Statistical Analysis

Version 24.0 of SPSS for Windows was used for statistical analysis. In descriptive data, patient demographics such as age, gender, IMT, and laboratory test results are presented. The data were then examined for normality by means of the Kolmogorov–Smirnov and variance homogeneity tests. This research yielded normally distributed and homogeneous data. Pearson's correlation test was used to examine the correlation between ACR and hsCRP on FMD and cIMT; $p<0.05$ is regarded as statistical significance. After conducting a bivariate test to identify the correlation between variables, a multivariate analysis with linear regression was conducted for the statistical analysis.

3. Results

3.1 Characteristics of research subjects

From all 82 research subjects, the majority were female (45 subjects (54.9%)), with an average age of 13.28±4.32 years. The mean BMI was 18.45±4.17 kg/m2. The mean systolic blood pressure was 111.67±9.73 mmHg and the average diastolic blood pressure was 73.9±4.8 mmHg. The mean ACR value was 28.94±17.64 mg/g. The mean value of hsCRP was 1.55±1.36 mmHg. From the lipid profile examination, the mean cholesterol level was 163±37.11 mg/dL, the mean HDL cholesterol level was 56.57±13.24 mg/dL, the mean LDL cholesterol level was 114.32±34.19 mg/dL, and triglyceride levels of 101.71±42.23 mg/dL.

Table 1. Baseline characteristic of research partisipants.

Variable		Total (n=82)	
		n/mean	%/SD
Demography			
	Age	13.28	4.32
	Sex		
	Male	37	45.1
	Female	45	54.9
	BMI (kg/m2)	18.45	4.17
	Sistole (mmHg)	111.67	9.782
	Diastole (mmHg)	73.9	4.806
Biomarker			
	Ureum (mg/dL)	21.7805	9.4145
	Creatinin (mg/dL)	0.5929	0.2798
	SGOT (U/L)	33.05	4.716
	SGPT (U/L)	32.89	4.751
	ACR (mg/g)	28.94	17.64
	hsCRP (mg/dL)	1.55	1.36
	HDL-C (mg/dL)	56.57	13.24
	LDL-C (mg/dL)	114.32	34.196
	TG (mg/dL)	101.71	42.23
	Kolesterol Total (mg/dL)	168.91	37.11
	Hb (g/dL)	14.11	1.22
	WBC (103/μL)	8.27	2.76
Variabilitas	Variabilitas HbA1C		
	HbA1C	43.90	34.14
	HVS	0.78	0.71
	HbA1c-SD	0.086	0.076
	HbA1c-CV	0.47	0.11
IMT (mm)		16	16
FMD (%)			

Note. All data were presented by mean SD; BMI = Body Mass Index; hsCRP = High Sensitivity CRP; HbA1C = Hemoglobin A1C; HVS = HbA1c Variability Score; ACR = Albumin to Creatinine Ratio.

HbA1c variability was calculated using 3 methods, namely the HbA1c variability score (HbA1c Variability Score/HVS), the HbA1c standard deviation (HbA1c-SD), and the HbA1c coefficient of variability (HbA1c-CV). From the examination, the mean HVS value was 43.90±34.14, the HbA1c-SD average was 0.78±0.71, and the HbA1c-CV average was 0.086±0.076). The mean thickness of the carotid artery intima-media (cIMT) for all examination subjects was 0.47 mm±0.11 mm. The mean flow-mediated Dilatation Response (FMD) of all subjects showed a mean of 16±16%.

Table 2. Data normality test with Kolmogorov-Smirnov

Variable		P
		0.134
Variable	IMT	0.075
	ACR	0.061
	hsCRP	0.826
	HDL-C	0.329
	LDL-C	0.430
	TG	0.414
	Total Kolesterol	0.177
	HVS	0.062
	HbA1c-SD	0.147
	HbA1c-CV	

Note. significant if the p-value is 0.05 or lower

3.2 Data Normality Test

Based on the Kolmogorov-Smirnov data normality test, all variables were normally distributed. BMI (p=0.134), HDL-C (p=0.826), LDL-C (p=0.329), triglycerides (p=0.430), total cholesterol (p=0.414), ACR (p=0.075), hsCRP (p=0.061), HVS (p=0.117), HbA1c-SD (p=0.062), and HbA1c-CV (p=0.147). The normality test of the data is shown in table 2.

3.3 Correlation between ACR with FMD and cIMT

Correlation test to determine the relationship between ACR and FMD. In this test, it was found that there was a statistically significant moderate correlation between ACR and FMD (r=-0.593; p=0.000). In table 5.3, based on the results of the correlation test, it was found that there was a statistically significant weak correlation between ACR and cIMT (r=0.339; p=0.002).

3.4 Correlation between hsCRP with FMD and cIMT

Meanwhile, the results of the correlation test between hsCRP and FMD showed a weak but statistically significant correlation (p=-0.375; p=0.001). There was also a statistically significant moderate correlation (r= 0.414; p=0.023) between hsCRP and and cIMT.

Table 3. Pearson's Test correlation test results.

Independent Variable	FMD		cIMT	
	r	p	r	p
Sex	0.647	0.421	0.180	0.671
Age	-0.098	0.383	0.120	0.284
ACR	-0.593	0.000	0.339	0.002
hsCRP	-0.375	0.001	0.414	0.023
Cholesterol Total	-0.167	0.134	0.240	0.030
HDL-C	0.064	0.569	0.011	0.922
LDL-C	-0.210	0.058	0.340	0.002
TG	-0.201	0.071	0.237	0.032
HVS	-0.312	0.004	0.410	0.000
HbA1c-SD	-0.339	0.002	0.279	0.011
HbA1c-CV	-0.276	0.012	0.193	0.082

Note. significant if the p-value is 0.05 or lower

From the results of the linear regression test, it was found that ACR was negatively correlated with FMD value (β=-0.360, 95%CI -0.005 - 0.000, p=0.028) and positively correlated with cIMT (β =0.442, 95%CI 0.030 - 0.623), p=0.039). Meanwhile, hsCRP was negatively correlated with FMD value (β=-0.269, 95%CI -0.036 to 0.019, p=0.043) and positively correlated with cIMT (β=0.412, 95%CI 0.021 - 0.517, p=0., 017).

Table 4. Linear regression test results

Variabel bebas	Variabel Terikat					
	FMD			cIMT		
	Beta	95% CI	p	Beta	95% CI	p
ACR	-0.360	-0.005 to 0.000	0.028	0.442	0.030 to 0.623	0.039
hsCRP	-0.269	-0.036 to .019	0.043	0.412	0.021 to 0.517	0.017

Note. significant if the p-value is 0.05 or lower; FMD = Fibromuscular dysplasia; CIMT = A carotid intima-media thickness test

4. Discussion

4.1 Correlation between ACR on FMD and cIMT

Even when ACR levels are within the normal range, microalbuminuria is the most frequently used risk marker for early renal failure in adults with T1DM. A higher ACR, even within the normal range, is associated with early atherosclerosis, according to the Adolescent Type 1 Diabetes Cardiorenal Intervention Trial (AdDIT). Adolescents enrolled in the AdDIT study with urinary albumin excretion rates in the upper tertile of the normal range showed a small but substantial increase in arterial stiffness, which predicts microalbuminuria in 85 percent of cases.[7] An early association between urinary albumin excretion and subclinical cardiovascular disease is supported. by the results of this Australian AdDIT cohort.

In this study, there was a statistically significant moderate correlation between ACR and FMD (r=-0.593; p=0.000). This finding is in line with research by El Dayem et. al. in 61 adolescents with T1DM (mean age 16.3 ± 1.5 years), showed a negative correlation between ACR and FMD (r= -0.55, p=0.0001).(8) A study on T1DM adolescents with T1DM duration of less than 5 years , T1DM had a lower mean FMD than the control group (P = 0.023), regardless of age, smoking, hypertension, or dyslipidemia. Endothelial dysfunction was found in 28 of 57 T1DM patients. FMD was lower in microalbuminuric patients (4.1%) compared to normoalbuminuric patients (10.1%, p=0.01) and controls (14.6%, p<0.001).[9] in the T1DM population, it was found that the ACR in the T1DM group with microalbuminuria was higher and statistically significant compared to the T1DM group without microalbuminuria and the control group (73.45mg/g vs 4.42mg/g vs 4.42mg/g, p<0.001). FMD in the T1DM group with and without microalbuminuria was lower and statistically significant compared to the control group (p<0.001). ACR was negatively and statistically significant correlated with FMD (r= -0.47 ± 0.22, p=0.036).[10]

Ladeia et. al. conducted a study on adolescents with T1DM (mean age 13.4 ± 3.3 years), found that microalbuminuria (ACR>30mg/g) had a negative correlation with FMD (r = -0.5, p = 0.049) even though the duration of T1DM was less than 5 years.[11] This study highlights the importance of ACR as an early marker of microalbuminuria as an early indicator of vascular disease. Consequently, the correlation between microalbuminuria and endothelial dysfunction may explain why microalbuminuria is associated with the development of extrarenal complications in T1DM patients.

This study found a statistically significant weak correlation between ACR and cIMT (r=0.339; p=0.002). In another study of 62 adolescents with T1DM with a mean age of 16.3±1.5, and a duration of 9.4±2.9 years, found that ACR, which is an early indicator of diabetic nephropathy and thus a sign of microvascular disease, is positively correlated with cIMT, which is an early sign of atherosclerosis and thus a sign of macrovascular disease.[12] The findings of this study are also consistent with the findings of Gül et. al., who found that patients with T1DM had a significantly higher cIMT than the control group, and a significant positive correlation between cIMT and microvascular problems, either nephropathy (beta=0.043, 95% CI 0.019-0.068, p=0.001) and/or retinopathy (beta=0.037, 95%CI 0.010-0.065, p=0.008).[13]

Follow-up data from the AdDIT study in adolescents with T1DM reported that higher ACR values, even within the normal range, were associated with a higher risk of developing microalbuminuria, and a poorer cardiovascular profile, as indicated by thicker cIMT during 2-4 years of follow-up in a cohort study of 546 adolescents with T1DM, assessed at ages 10-16 years.[14] Another study also found a correlation between ACR levels and increased cIMT in 60 adolescents

with T1DM with a mean age of 11.5 ± 3.5 years. (β=0.0051±0.0024, p=0.031).[15]

The presence of microalbuminuria was positively correlated with increased cIMT in adolescent patients (mean age 12±2.7 years) with T1DM. From the entire group of patients, using a univariate linear regression model, it was found that the factor that significantly correlated with cIMT was the presence of microalbuminuria (beta ± SE: 0.050 ± 0.021, p = 0.035).[16] Of the 1229 patients with T1DM who underwent ultrasound examination in the internal and common carotid arteries in 1994-1996 and again in 1998-2000 as part of the EDIC project, a long-term follow-up to the DCCT study. The group receiving intensive therapy during DCCT showed significantly less development of average cIMT than the group receiving conventional therapy. During DCCT follow-up (6.5 years), the development of cIMT thickness was associated with age, systolic blood pressure at the start of the EDIC study, smoking, LDL-C to HDL-C ratio, urinary albumin excretion rate (β=0.0912±0.0308, p= 0.003), and the mean value of glycosylated hemoglobin.[17]

Microalbuminuria is a strong and independent risk factor for cardiovascular disease in diabetics. So far, studies have contributed to establishing the association between microalbuminuria and cardiovascular disease. First, the association between urinary albumin excretion and cardiovascular disease risk did not begin at traditional microalbuminuria thresholds (i.e., ACR 2.5 mg/mmol in men and 3.5 mg/mmol in women, or equivalent urinary albumin excretion rates), but in much lower levels, ranging from ACR of 1 mg/mmol or even lower.[18] Second, the presence of microalbuminuria in diabetics has been associated with an increased risk of cardiovascular disease in a manner that is independent of urinary albumin excretion.[19]

4.2 Correlation between hsCRP on FMD and cIMT

Endothelial dysfunction, which occurs before the anatomic and clinical structural changes of atherosclerosis appear, is thought to play a role in atherogenesis. It has been demonstrated in several studies that endothelial dysfunction developed in T1DM at a young age is likely to occur before the increase in cIMT.[20-22] Gökşen et. al., studied 55 adolescents (mean age 17.7±4.0 years) with T1DM (mean duration of DM 10.4 years) found that FMD in adolescents with T1DM was lower than the healthy group of adolescents. One of the conclusions of this study is that hsCRP is an independent factor that is negatively correlated with FMD (r=-286, p=0.03).[23]

In this study, a negative correlation was found between hsCRP and FMD. hsCRP and FMD showed a weak but statistically significant correlation (p=-0.375; p=0.001). This finding is in line with the results of a study by Ohsugi et. al., who stated that in adolescents and young adults with T1DM and T2DM (age range 12 to 20 years), hsCRP was negatively correlated with FMD (β=-2.48, 95% CI (-4.6 to -0.39), p= 0.02).[24]

In this study, there was a positive correlation between hsCRP and cIMT (r= 0.414; p=0.023). Okano et. al., evaluated whether a low-grade inflammatory state contributes to the early stages of advanced carotid artery atherosclerosis in young adult T1DM patients. The results of 55 T1DM patients (22 males and 33 females, age 22.1 ± 3.6 years, duration of diabetes 14.2 ± 5.7 years) found that hsCRP levels were independently and positively correlated with mean cIMT (r = 0.429, p = 0.002).[25] This correlation finding is also in line with findings in another study where 60 T1DM patients with an average age of 14.1±2.6 years found a moderately significant positive correlation between hsCRP values and cIMT (r=0.534, p<0.001).[26]

Evidence of a correlation between hsCRP and early atherosclerotic processes in T1DM patients was also demonstrated by Atabek et al. al., where 65 children and adolescents with T1DM (33 girls and 32 boys, average age 12.7±3.8 years, with diabetes duration 6.9±3.6 years) were research subjects. From this study, it was found that hsCRP was positively and significantly correlated with CIMT (r=0.49, p=0.001).[27] In line with Atabek et. al., Research conducted by El-Asrar et. al., also found a significant correlation between hsCRP and an increase in cIMT(β= 3.020 ±0.917, p=0.001).[15]

Obesity and diabetes are associated with chronic low-grade systemic inflammatory states, which drive a vicious cycle of insulin resistance, oxidative stress, and endothelial dysfunction, which form the basis for an early and accelerated atherosclerotic process. In lean children with T1DM, low-grade systemic inflammation was also seen, which was seen in elevated levels of pro-inflammatory cytokines. Chronic systemic inflammation that begins in childhood accelerates the formation of atherosclerotic plaques and contributes to its development. Previous studies have found that children and adolescents with diabetes have higher levels of CRP, IL-6, TNF-, and leptin. In fact, levels of pro-inflammatory markers appear to be higher in lean adolescents with diabetes who have good glycemic control than in healthy adolescents.[28]

Limitation

This study has several limitations. First, the form of this research is a cross-sectional study, which cannot prove the existence of causality between the variables studied. Second, this study is a single center study, the research subjects were obtained only at the Saiful Anwar regional hospital in Malang where the subject could not represent the population of T1DM patients as a whole. Third, the number of research samples is small because the number of T1DM patients undergoing treatment both inpatient and outpatient at the Saiful Anwar Regional Hospital in Malang is still limited. Additional information can be obtained by prospective studies with a larger number of research subjects. The increase in ACR and hsCRP in T1DM patients should be investigated further in longitudinal studies with repeated samples from each patient to see if these factors are associated with the presence of endothelial dysfunction and macrovascular damage.

5. Conclusion

ACR and hsCRP correlate with the increase in cIMT and a decrease in brachial artery FMD in children and adolescent with T1DM. We conclude that initial atherosclerotic alterations may occur with altered vascular endothelial dysfunction caused by T1DM. We advise early and careful monitoring of children with T1DM to detect any changes in vascular endothelial dysfunction.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: SW. Design: SW, NK . Control/supervision: NK, IP, CT, BS. Literature search: NK, IP, CT, BS. Data extraction: SW, NK. Statistical analysis: RP, MSR. Results interpretation: SW, NK. Critical review/discussion: NK, IP, CT, BS. Writing the article: SW, NK. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.

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Heart Sci J 2022; 3(4):16-20

Contents list available at www.heartscience.ub.ac.id

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Original Article

The Relationship of Heart Rate Recovery Post Exercise Stress Test to Syntax Values in Patients with Stable Coronary Artery Disease

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ARTICLE INFO

Keywords:
Coronary Artery Disease (CAD);
Heart Rate Recovery (HRR);
Syntax.

ABSTRACT

Background: The prognostic usefulness of abnormal heart rate recovery (HRR) as a predictor of death has been discovered 1–3. Abnormal HRR results from inadequate vagal activation after exercise 4,5. The association between HRR and angiography in CAD (coronary artery disease) has been studied, however the conclusions are still being contested due to a lack of data 6–8.
Objectives: The purpose of this study is to see if HRR after an EST (exercise stress test) may predict the severity of syntax values in individuals with stable CAD at Saiful Anwar Hospital Malang (RSSA).
Methods: This study is an analytic observational study. It was held in Saful anwar, Malang Hospital during January 2017–December 2019, including 366 patients. All patients underwent exercise stress test for CAD screening and coroner angiography. Those were divided into two groups, which included syntax score < 23 (n=148) and syntax score ≥ 23 (n= 218). Chi-square analysis was used to analyze the relationship correlation between HRR1, HRR2 and Syntax Score, and was used to compared between HRR1 (heart rate recovery first minutes), HRR2 (heart rate recovery second minute) and Syntax Score group. The confounding factor was adjusted with multivariate logistic regression analysis and AUC curve.
Results: There was a significant negatif correlation between abnormal HRR1 and HRR2 after exercise and Syntax score, with strong correlation (HRR1 ; OR = -2.11, p = 0.00 AUC :90,8%, HRR2 ; OR = -1,6, p = 0,48, AUC : 70,4%).
Conclusion: Decrease HRR at first and second minutes after exercise stress test in stable CAD patient related to higher Syntax Score (>1).

1. Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and death globally, and its incidence is constantly rising9. In 2020, CAD contributed 26.4% of the total death rate in Indonesia. This figure is 4x higher than deaths from cancer (6%). Based on the diagnosis and symptoms, the highest estimated number of patients with CAD in 2013 was in East Java Province, with as many as 375,127 people (1.3%).[10]

The costs of diagnosing and treating CAD after symptoms manifestation are very high. Even when MSCT, MRI, and nuclear facilities improve, East Java still lacks a significant number of them. Therefore, it is crucial to eliminate risk factors before disease progression and to identify the presence of CAD through simple and applicable methods before the onset of symptoms.

Abnormal HRR (heart rate recovery) is caused by inadequate vagal activity during exercise, and its predictive significance for death has been shown.

Several studies have shown that an abnormal heart rate recovery cannot indicate the existence or severity of CAD based on the association between heart rate recovery and angiography in CAD. Nonetheless, Ghaffari et al. have revealed findings that contradict earlier research and imply that an aberrant HRR after exercise does predict the severity and prevalence of CAD. According to Lipinski et al., HRR2, defined as the decrease in heart rate from peak exercise speed to a rate two minutes after training stop, might indicate the occurrence of CAD.[6,8,11]

Coronary angiography is an important tool for quantifying the severity of coronary lesions. Several scoring systems were created to quantitatively assess the severity of coronary lesions angiographically.[12] One of the most widely used scoring systems in the literature today is the syntax score. A higher syntax score indicates the presence of a more complex lesion and is associated with more difficult management of the lesion. A higher syntax score is also associated with a poorer prognosis.[13]

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https://doi.org/10.21776/ub.hsj.2022.003.04.4
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022

Table 1. Characteristic data of all subjects.

Variable	Syntax score		
Sex	< 23, N : 148	**≥ 23, N : 218**	**P**
Male	80,40%	**84.4%**	**0,33**
Smoker	54,70%	**50,90%**	**0,52**
HT	59,50%	**63,30%**	**0,51**
DM	29.7%	**26.1%**	**0,47**
CKD	4,90%	**2.3%**	**0,32**
Dyslipidemia	7%	**7.1%**	**0,32**
Age	52,9 ±19,5	**54,9 ± 18,72**	**0,051**
BMI	28.4 ± 3.8	**28.9 ± 28.3**	**0,12**
METs	8,32 ± 2,32	**6,91 ± 2,28**	**0,00**
DTS	0,5 ± 7,43	**-4,42 ± 6,75**	**0,00**
HRR1	16,96 ± 4,93	**8,39 ± 3,83**	**0,00**
HRR2	31,69± 8,13	**19,58 ± 5,57**	**0,00**
Resting systole	123,02 ± 13,18	**122,61 ± 14,60**	**0,78**
Resting diastole	76,65 ± 10,49	**75,85 ± 9,72**	**0,45**
Peak systole	170,44 ± 23,27	**151,10 ± 17,39**	**0,77**
Peak diastole	93,98 ± 11,93	**88,81 ± 8,77**	**0,85**
Peak HR	144,26 ± 15,29	**128,41 ± 20,30**	**0,93**
ASA	17 (4,7%)	**29 (7,9%)**	
CPG	5 (1,4%)	**12 (3,3%)**	
TCG	6 (1,6%)	**0**	
ASA/CPG	97 (26%)	**141 (38,6%)**	
ASA/TCG	19 (5,2%)	**35 (9,6%)**	
ACEI/ARB	148 (40,4%)	**218 (59,6%)**	
B-blocker	138 (40,1%)	**206 (59,9%)**	
Statin	147 (40,8 %)	**213 (59,2 %)**	
LM			
Yes	33 (9 %)	**82 (20,5%)**	
No	115 (31,5%)	**146 (39,9%)**	
LAD			
Yes	109 (29,8%)	**204 (55,8%)**	
No	39 (10,6%)	**14 (3,8%)**	
LCx			
Yes	81 (22,1%)	**170 (46,4%)**	
No	67 (18,3%)	**48 (13,1%)**	
RCA			
Yes	86 (23,4%)	**182 (73,2%)**	
No	62 (16,9%)	**36 (9,4%)**	

Note. significant p value <0.05. HT = hypertension, DM = diabetes mellitus, CKD = Chronic kidney disease, BMI = Body mass index, Mets = Metabolic equivalent of task, DTS = Duke treadmill score, HRR1 = Heart rate recovery at first minute, HRR2 = Heart rate recovery at second minute, HR = Heart rate, ASA = Aspilet, CPG = Clopidogrel, TCG = Ticagerol, ACEI = Ace inhibitor, ARB = Angiotensin receptor blocker, B-blocker = Beta blocker, LM = Left main, LAD = Left anterior descending, LCx = Left circumflex, RCA = Right coronary arteries

This study aims to determine the relationship between heart rate recovery after EST as a predictor of the severity of syntax values in stable CAD patient at Saiful Anwar Hospital Malang (RSSA).

2. Methods

2.1 Study Design and Population

This research is a retrospective cross-sectional analytic observational study. From January 2017 to December 2019, medical record data was used to identify patients who underwent exercise stress test and coronary angiography. The target population in this study were all patients who underwent EST (exercise stress test) at dr. Saiful Anwar Malang's hospital. The affordable population in this study were patients who underwent EST and coronary angiography at Dr. Saiful Anwar Malang. The data was taken consecutively according to the sample selection criteria. Inclusion criteria included, age 18 – 74 years who underwent exercise stress test for CAD screening and coronary angiography at Saiful Anwar Hospital Malang with result of exercise stress test positive ischemic response, and patients 3 months post ACS who were not revascularized. The data was validated by consultant cardiologist of prevention and rehabilitation Exclusion criteria were patients dies during hospitalization, anemia, heart block, heart rate < 50 beats per minute, moderate to severe valvular disorders, post CABG patients, patient with pacemaker implantation.

2.2 Ethics

Management of research permits and the use of secondary data from patient medical records and coronary angiography in accordance with the procedures for research ethics permits and medical record services at RSUD dr. Saiful Anwar Malang.

2.3 Statistical Analysis

The data will be analyzed by the Statistical Package for the Social Science (SPSS) ver 25 software to determine the differences between variables.

Baseline characteristics were presented by means and standard deviation. Categorical variables were presented as percentages and frequencies and compared using Chi-square. Multivariate analysis using the logistic regression method and ROC curve was used to assess the strength of the relationship between variables.

3. Results

There were a total of 366 subjects who met the inclusion criteria, followed by data collection using medical record data and coronary angiography data at Dr. Hospital. Saiful Anwar Malang. This study evaluated the results of coronary angiography assessed using the SYNTAX score and compared the HRR after the exercise stress test at the first minute and at the second minute.

3.1 Baseline Characteristic

There were 303 (82%) subjects were male and 63 (18%) subjects were female. The mean age of the study population was 53.2 ± 18.6 years with an age range of 29 - 77 years. Population anthropometric data showed a mean BMI of 28.4 ± 3.8 kg/m2 (overweight mean). The highest risk factor was hypertension (61.7%) followed by smoking (52.5%). Most of the patients had syntax ≥ 23 with 218 patients and 148 patients had syntax <23.

Clinical and demographic data of patients with high and low SYNTAX scores are shown in Table 1. There were 303 (82%) subjects were male and 63 (18%) subjects were female. The mean age of the study population was 53.2 ± 18.6 years with an age range of 29 - 77 years. Population anthropometric data showed a mean BMI of 28.4 ± 3.8 kg/m2 (overweight mean). The highest risk factor was hypertension (61.7%) followed by smoking (52.5%). Most of the patients had syntax 23 with 218 patients and 148 patients had syntax <23.
Clinical and demographic data patients with high and low SYNTAX scores are shown in Table 3. DTS, HRR1, HRR2 and resting diastole were higher in the group with high SYNTAX scores ($p < 0.05$).

3.2 Multivariate analysis

Univariate analysis for METS, DTS, HRRI and HRR2 showed a significant association with high SYNTAX scores (6.91 ± 2.28 p=0.00, -4.42 ± 6.75 p=0.00, 8.39 ± 3.83 p=0.00, 19.58 ± 5.57 p=0.00, respectively) and there was also a significant relationship with a low SYNTAX score (8.32 ± 2.32 p= 0.00, 0.5 ± 7.43 p= 0.00, 16.96 ± 4.93 p=0.00, 31.69 ± 8.13 p = 0.00). The multivariate predictors of the SYNTAX score are presented in Table 2.

Table 2. Characteristics in groups with normal and abnormal FMD

	p	OR	95,0% C.I. Lower	Upper
HRR1	.000	2.110	1.648	2.637
DTS	.024	2.038	1.100	2.776
HRR2	.027	1.604	1.118	1.967
Mets	.048	1.070	1.008	1.426

Note. *) significant if the p-value is 0.05 or lower

In the multivariate logistic regression analysis, it was found that HRR1, HRR2, mets and DTS had a negative relationship with the syntax score.

3.3 ROC Analysis Results

Figure 1 describes the ROC curve for predictive values of HRRI, HRR2 and DTS in detecting the severity of CAD which was evaluated by the SYNTAX score. At different threshold levels, the ROC

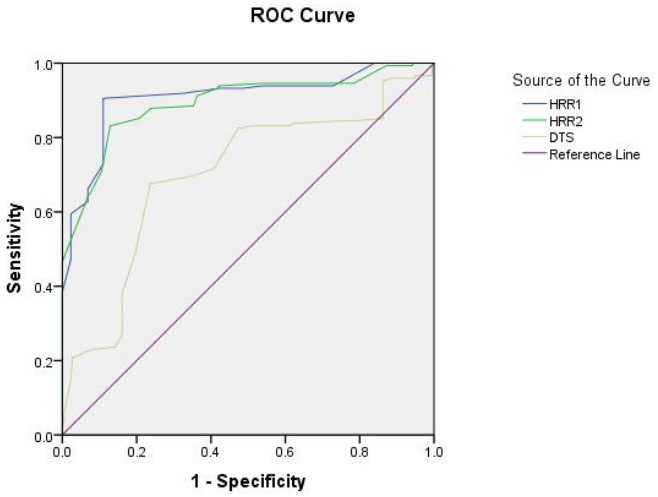

Figure 1. ROC curve of the relationship between HRR 1, HRR 2 and the Syntax score.

analysis plotted sensitivity on the y-axis and 1-specificity (false negative) on the x-axis.If the curve is near to the top vertical and horizontal axis lines, it represents high sensitivity and low false negative (1-specificity) or high specificity.

Table 3. AUC values of HRR1, HRR2 and DTS on syntax scores

Test Result Variable(s)	AUC	p	95% Confidence Interval Lower Bound	Upper Bound
HRR1	.908	.000	.873	.942
HRR2	.704	.000	.644	.757
DTS	.893	.000	..857	.929

Note. *) significant if the p-value is 0.05 or lower

Based on the ROC curve, it shows that the first minute recovery heart rate (HRR1) and second minute recovery heart rate (HRR2) have good diagnostic value, because the curve is far from the 50% line and close to 100%. The AUC values for HRR1, HRR2 and DTS obtained from the ROC method were 90.8% (95% CI: 87.3%-94.2%, p=0.000), 70% (95% CI: 64 ,4%-76.7%, with p=0.000), 89.3% (95% CI: 85.7%-92.9%, with p=0.000) respectively. Statistically, AUC values above 80% are considered significant, so HRR1 and DTS have significant values for predicting syntax scores in patients with stable coronary artery disease, while HRR2 has moderate values for predicting syntax scores.

4. Discussion

Coronary heart disease is a leading cause of morbidity and death in a number of affluent nations.[14] Scientists and researchers are always trying to reduce the burden of treating this disease by finding new ways to identify and treat coronary artery disease. Exercise stress test is not only inexpensive and non-invasive, but also has a high level of accuracy, so this test is often used as an initial test to diagnose CAD. Cardiac exercise testing is also frequently performed to assess risk stratification in patients with CAD. First minute recovery heart rate (HRR1) is one of the variables measured in the exercise stress test, and has been shown to be a predictor of mortality. Recent studies have shown that HRR1 can also be a predictor of coronary lesion severity.

From the demographic data in this study, it was found that the largest population was 82.4% male with an average a

ge of 53.2 ± 68 years with the highest risk factor being hypertension. These data are consistent with research from Hata et al., they found that in the Asian population per 100,000 people there were 348 cases of CAD in men while in women there were 181 cases per 100,000 people, and hypertension was the largest risk factor.[15] The mean BMI in this population 28.4 ± 3.8 kg/m2 (obesity). In the study, Sadik et al also showed that the average BMI of patients undergoing exercise stress tests was overweight (27.8 for syntax score < 23 and 27.9 for syntax score 23).[16,17]

In this study, we found that HRR1 had a significant relationship with syntax scores. In this study we used a cut off of 12 bpm as a reference for heart rate recovery in the first minute and we got a p value < 0.000. Samad et al, conducted a study on 208 people (146 men, 66 women). They found that HRR1 had a significant relationship value (p<0.001).[18] Another study conducted by Sadik et al using a larger population of 406 patients, they also found that HRR1 had a significant relationship with the syntax score (p<0.001)16. The study of Lipinski et al, found that the heart rate recovery was significantly affected by coronary artery stenosis, but that the heart rate recovery did not depend on the location of the coronary lesion.[18]

In multivariate analysis of HRR1 on syntax scores, we found that HRR1 had a significant negative relationship on syntax scores (OR – 2.11, p 0.00). Sadik et al's research also found that HRR1 also had a significant negative value on syntax (OR=0.78, p=0.001).[16] Cole et al showed that the decrease in heart rate after exercise stress test in the first minute was dominated by vagal activation. This is also reinforced by another study by Laurino et al, they found that there was a decrease in heart rate after the first minute of exercise which was suspected as a decrease in vagal activity in patients with stable coronary artery disease.

In this study, we also found that the second minute recovery heart rate after exercise had a significant relationship with the syntax value (p 0.000). This is in accordance with research conducted by Uzunget et al. They conducted a study on 346 people and found that the second minute recovery heart rate had a significant relationship with syntax (p<0.001).[17] Chen et al. also conducted a study of heart rate recovery from the first to the fifth minute in patients with stable coronary artery disease as assessed by the Genesis score. They found that heart rate from the first minute to the fifth minute heart rate had a significant relationship with the genesis score (HRR1 : p 0.005, HRR2 : p 0.008, HRR3 : p 0.001, HRR4 : p 0.002, HRR5 : p0.006).[19]

In the multivariate analysis of the second minute recovery heart rate on syntax, we found that there was a significant negative relationship (OR=-1.60 p=0.027 95% CI 11.1%-19.8%). Chen et al also found the same relationship (OR = -1.39 p = 0.019). They found heart rate recovery was significantly different in patients with >70% stenosis.[19] This result is also in line with the research conducted by Ghaffari et al.

The Duke treadmill score is one of the noninvasive modalities that has been known to be a predictor of coronary artery severity.[8,20] In this study, we found that the duke treadmill score had a significant negative relationship with the syntax value (OR: -2.03 p = 0.024 95% CI 11%-27.7%). This is also in line with other studies. Vilma et al. conducted a study of duke treadmill scores on syntax in 258 patients and found that the duke treadmill score predicts coronary artery severity (r=-0.181 ; p=0.005)8. Similar studies by Almeida et al also confirm this. In their study using 525 patients, the odds ratio of patients with abnormal angiography was 1.92.[21,22]

Based on the analysis of the ROC and AUC curves in this study, we found that the first minute recovery heart rate and the duke treadmill score both had strong values for predicting syntax scores (HRR1 ; 90.8% (95% CI: 87.3%) -94.2%, with p=0.000), DTS 89.3% (95% CI: 85.7%-92.9%, with p=0.000) This is in accordance with research conducted by Choi et al, they measured the heart rate recovery in the first and second minutes and the duke treadmill score on syntax-.They found that the heart rate recovery in the first minute and the duke treadmill score had a positive linear relationship (R=0.281, p<0.05)23.

This study has several limitations. First, this research is a cross-sectional study, which cannot prove the existence of causality between the variables studied. Second, this study is a single center study, the research subjects were obtained only at the Saiful Anwar regional hospital in Malang where the subject could not represent the population of stable coronary artery disease patients as a whole. Third, other factors that influence heart rate recovery such as hormonal disturbances, dyslipidemia, PAD, uric acid are difficult for us to obtain due to lack of data, so the results of this study require prospective studies to confirm the results of this study.

5. Conclusion

In summary, the HRR1 and HRR2 has a significant negative relationship to the syntax value in patients with stable coronary artery disease. HRR in the first minute after the exercise stress test has the same predictive value as the DTS in assessing the magnitude of the syntax value in patients with stable CAD.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: II, SA. Design: II, SA. Control/supervision: SA, CT, BS, VYP. Literature search: SA, CT, BS, VYP. Study quality assessment: SA, CT, BS, VYP. Data extraction: II, SA. Statistical analysis: II, SA. Results interpretation: DAI. Critical review/discussion: SA, CT, BS, VYP. Writing the article: II, SA. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.

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Heart Sci J 2022; 3(3): 21-28

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

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Case Report

Provisional Technique for Bifurcation Left Main In-Stent Restenosis Lesion: A Case Report

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ARTICLE INFO

Keywords:
Bifurcation Lesion;
Provisional Technique;
Kissing Balloon Inflation.

ABSTRACT

Background: Percutaneous coronary intervention for bifurcation lesions remains challenging because of its complexity and the lack of trials to guide decision-making. It also comes with several debatable issues, including the requirement for kissing balloon inflation as the post-dilation produces.
Case Illustration: A 64-year-old male with some coronary risk factors of hypertension, passive smoker, and family history of CAD presented with recurring exertional chest pain for the last 4 months. He was hospitalized to undergo DCA-Adhoc after the ECG stress test revealed a positive result. The coronary angiography revealed a 95% ISR in the osteal LAD and 20% ISR of the proximal LCx. Since the patient refused to undergo coronary bypass surgery, the team decided to perform catheter intervention to the LM bifurcation of LAD-LCx. The procedure begins with the insertion of IABP through the access of the left femoral artery. We performed a provisional approach with the main vessel stenting of LM-LAD. At the end of the procedure, we performed simultaneous kissing balloon inflation of LAD-LCx followed by POT in LM stent as the post-dilation produces.
Discussion: When considering intervention on a bifurcation lesion, there are two general strategies i.e the more conservative or provisional technique that intent to only use one stent and the two-stent approach. The provisional technique is considered to offer advantages in terms of reducing procedure complexity, reducing fluoroscopic time, requiring less contrast volume, and reducing resource (stent) use compared by 2 stent strategy.
Conclusion: Coronary bifurcation lesions are fairly frequent, and their management is associated with an increased risk of MACE, increased complexity, and prolonged treatment times.

1. Introduction

Coronary artery intervention for bifurcation lesions continues to be an issue of contention. Regardless of traditional cardiovascular risk factors, high turbulence and shear stress leads to a high prevalence of stenosis in the bifurcation of about 10-15% from all percutaneous coronary intervention (PCI). The heterogeneity of bifurcation lesions anatomy and the paucity of large randomized trials make decision making need certain consideration.[20] As the clinical outcomes following PCI have notably improved due to improvements in drug-eluting stent (DES) technologies, there still several debatable issues including the techniques to approach the bifurcation lesion. The requirement for post-dilatation was one issue that has been making PCI for bifurcation lesions remains challenging.

Even while provisional procedure can treat most patients with bifurcation lesions, a small percentage of them have different bifurcation architecture, making provisional technique risky in the event of side branch occlusion.[5]

The complexity of performing PCI in coronary bifurcation lesions is simply due to the operator efforts to maintain optimal patency of the side branch (SB) while optimally treating the main vessel (MV). From several trials there is no disadvantage to a provisional approach in terms of clinical outcomes. This case report tried to explain the provisional stenting approach in patients with LM bifurcation lesion.

2. Case Illustration

A 64-year-old male was diagnosed with coronary artery disease (CAD) in 2013. Hypertension, being a passive smoker, and having a family history of CAD were both risk factors for atherosclerosis in this patient. In the last three years, the patient has undergone PCI treatments. It is also known that patients experience incidents of in-stent restenosis (ISR) despite having good medication adherence and having followed a healthy lifestyle. In May 2018, he undergo PCI in LM bifurcation since the CAG revealed 70% distal LM stenosis, 90% ostial

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https://doi.org/10.21776/ub.hsj.2022.003.04.5
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022

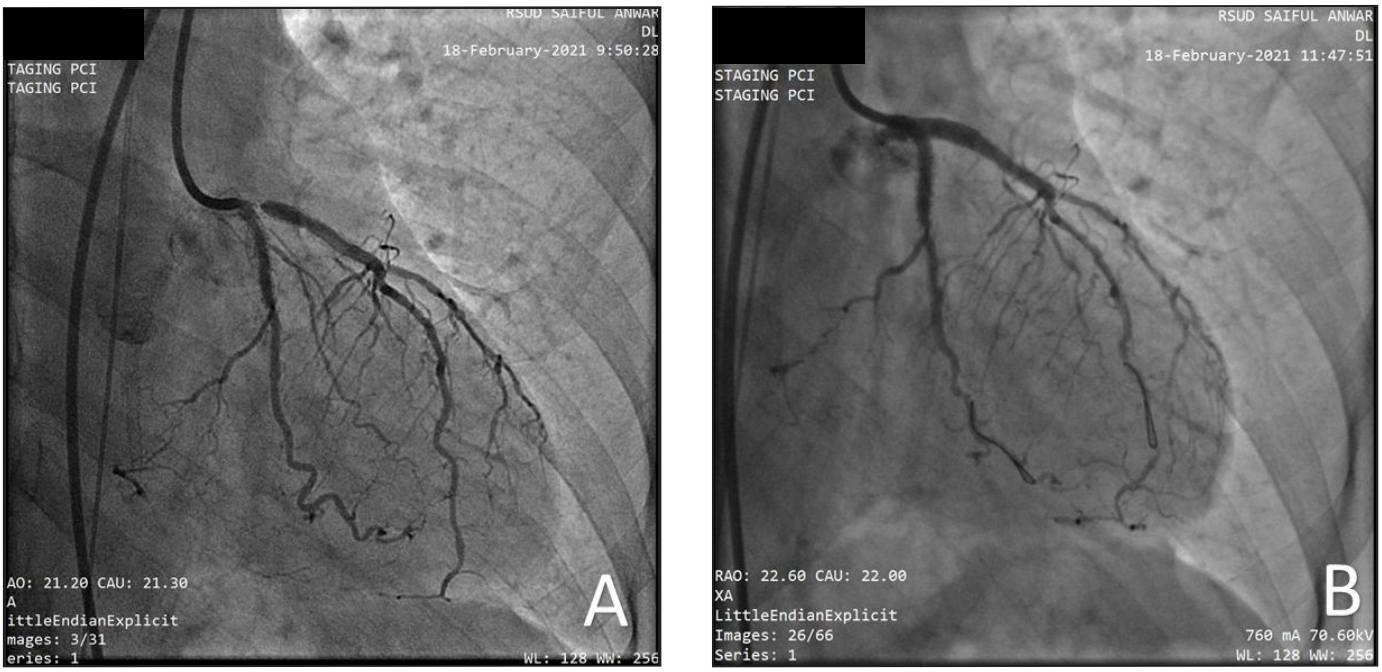

Figure 1. A. The diagnostic angiography revealed an ISR of 95% in the osteal LAD and an ISR of 20% in the proximal LCx (RAO 20, CAU 20 view); B. Successful provisional stenting with final KBI shows remarkable result of bifurcational intervention.

LAD stenosis, and 80% proximal LCx ISR. There was a complex procedure using 2 stents strategy of culotte technique with implantation of DES in LM-LAD and LM-LCx.

Patients receive 1x100mg CardioAspirin, 1x40mg Atorvastatin, 1x10mg Ramipril, 1x2.5mg bisoprolol, and 3x5mg ISDN in cardiac outpatient clinic. The patient reported that he already had diminished symptoms of chest pain since receiving this treatment. He also was able to carry out his everyday household chores without difficulties.

Unfortunately since last 4 months, the patient has had complaints of angina triggered by moderate activity. Angina is felt more frequently with lesser triggers despite it still relieved by rest. The patient has never experienced an episode of acute coronary syndrome or hospitalization due to other causes of an acute cardiac event. The ECG stress test was came with the result a positive ischemic response. We saw a horizontal ST depression in leads II, III, aVF, and episodes of PVC trigeminy. The patient then underwent coronary angiography and obtained an ISR of 95% in the osteal LAD and an ISR of 20% in the proximal LCx. The patient was planned to undergo a PCI procedure on the LM bifurcation with several preparations to achieve optimal results. Action will be taken with IABP backups followed by provisional technique approach.

Pre-procedural preparation showed that the patient was hemodynamically stable. He was fully alert, the BP was 125/65 mmHg, HR 69 x / min, RR 20 x / min, and the peripheral oxygen saturation was 96% on room air. The procedure begins with the insertion of the IABP through the access of the left femoral artery. The 40 cc IABP balloon was inserted and set 1: 1, with an ECG trigger.

We used right femoral artery access using a 7F sheath with a JL 3.5 6F and JR 3.5 6F diagnostic catheter. Coronary artery diagnostic revealed a CAD Three Vessel Disease + LM disease with ISR 95% in osteal LAD, ISR 100% proximal to RCA, ISR 20% proximal to LCx. The target lesion was the ostial LAD. The procedure started by administration of a 5000 IU IV heparin bolus and continued by intravenous infusion 2000 IU / hour. The guiding catheter (GC) BL 3.5 7F was engaged in ostial LMCA. We delivered the first Guiding Wire (GW) Runthrough NS Floppy to distal LAD. Then followed by the Asahi Sion GW as a protection wire to the distal LCx. The 3.0 x 10 mm NC Saphire II balloon was entered through the GW Runthrough NS Floppy towards the LM-proximal LAD. We inflated the Balloon several times with a maximum pressure of 14 atm for 9 seconds. Pull out the balloon then we performed a sine-angiographic evaluation.

The Stent Combo Plus 4.0x18 mm was delivered through the first GW towards LM - proximal LAD. Inflate the stent with a pressure of 9 atm for 8 seconds. Post dilation at the distal to the stent was performed with a pressure of 10 atm for 7 seconds. Proximal optimalization was performed with a pressure of 12 atm for 6 seconds precisely at the proximal of the carina. Asahi Sion GW became jailed wire afterwards. Pull out balloon ex-stent then cine-angiographic evaluation performed. We deliver the third GW, by recrossing to distal LCx using GW Runthrough Hypercoat, but failed. We directed the GW Runthrough Hypercoat to distal LAD followed by pulling the GW Runthrough NS Floppy from the distal LAD then directed towards the distal LCx through the strout stent at the LM-proximal LAD. GW Runthrough NS Floppy made it to distal LCx, followed by delivering the NC Sapphire II Balloon 3.5x15 mm towards LM - proximal LCx. Inflate the balloon several times with a maximum pressure of 12 atm for 8 seconds. The Balloon NC Sapphire II 4.5x12 mm entered via GW Runtrough Hypercoat towards LM - proximal LAD. We inflate the NC Saphhire 3.5x12 mm balloon in LM - proximal LCx several times with maximum pressure of 20 atm for 10 seconds. The NC Saphhire balloon 4.5x12 mm was inflated at LM - proximal LAD with a maximum pressure of 14 atm for 8 seconds. We repeated the inflation of the NC Saphhire 3.5x12 mm balloon at LM - LCx several times with a maximum pressure of 20 atm for 5 seconds.

Simultaneous double kissing of balloons was performed at the LM - LAD and LM-LCx. We inflate both NC balloons simultaneously

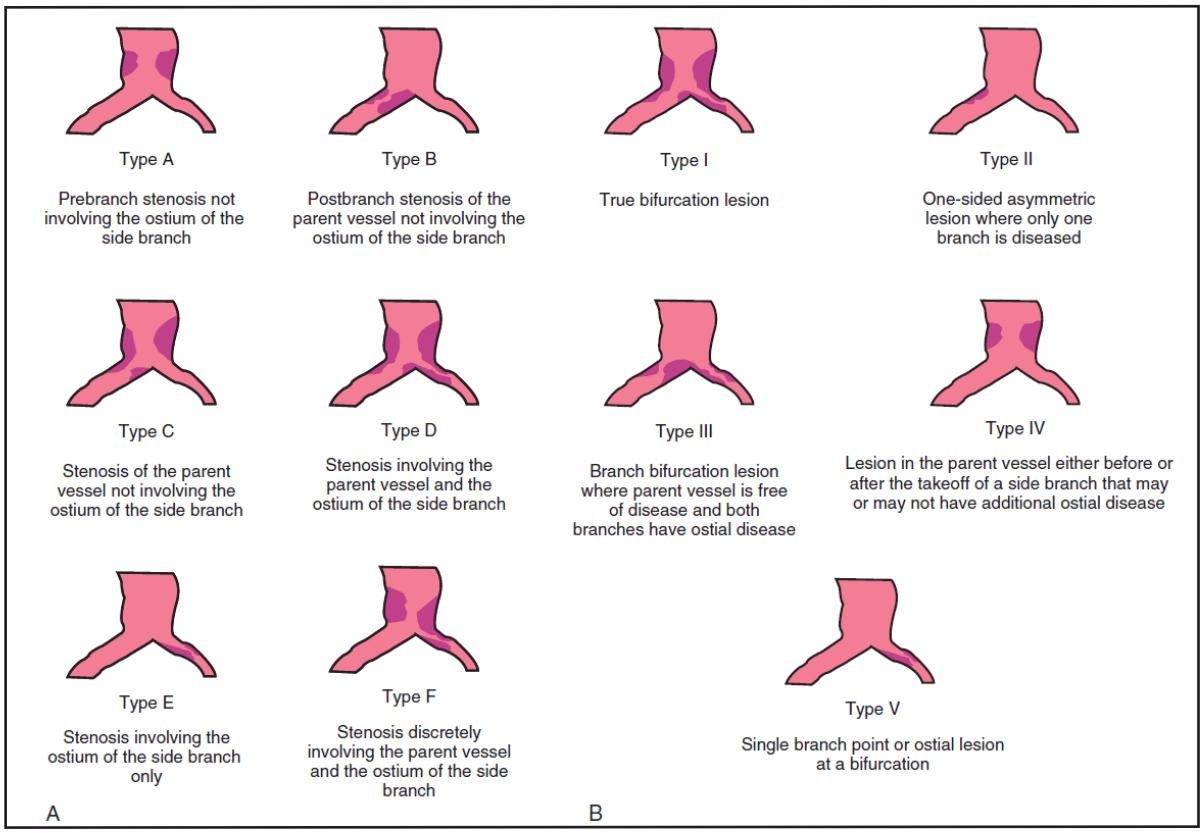

Figure 2. Various classifications of bifurcations according to plaque distribution. A, Duke. B, Sanborn.[4]

several times with a maximum pressure of 14 atm in LM-LAD and 20 atm in LM-LCx for 8 seconds. Final kissing balloon was performed with a pressure of 14 atm in LM-LAD and 20 atm in LM-LCx for 7 seconds. Finally, the NC Saphhire 4.5x12 mm balloon was inflated in LM - LAD carina several times with maximum pressure of 26 for 6 seconds, followed by proximal optimization with a pressure of 26 atm for 7 seconds. Pull out both balloons, followed by sine-angiography evaluation. We sought a TIMI Flow 3 without residual stenosis (figure 1). The procedure is complete, then the patient was transferred to the recovery room. For further observation in the CVCU room, we still maintain the IABP support for the next 24 hours. During the observation there were no complications, the IABP was weaned and removed on the second day of treatment. The patient was discharged on day 5 of treatment, with continued therapy and control as an outpatient clinic.

The follow-up, which was carried out 2 months after the procedure, found that the patient had returned complaint-free and was able to carry out his daily activities properly. The patient continues to live a healthy lifestyle and adheres to the routine therapy given, namely 1x80mg aspilet, 2x90mg brilinta, 1x40mg atorvastatin, 1x10mg Ramipril, 1x5mg bisoprolol, and ISDN 3x5mg.

3. Discusion

A coronary bifurcation lesion is a lesion that occurs at or adjacent to a significant division of a major epicardial coronary artery.[3] Functionally, coronary bifurcation lesions are defined as angiographically significant lesions which involve a branch point or the immediate vicinity of a branch point between two coronary arteries larger than 2 mm in diameter. Consensus societies have simplified this definition to “a coronary artery narrowing adjacent to and/or involving a significant side branch.” The larger of the two vessels (either in size or territory supplied) is referred to as the parent or main branch, while the smaller vessel is designated as the side branch.

Various techniques involving complex angioplasty plus one or more stents can be employed for treating bifurcation lesions, making the development of a standardized approach difficult. High complexity and lesion variability, high rates of restenosis and thrombosis, and a myriad of approaches to treating bifurcation lesions have left the field with many unanswered questions. Small trials, case series, and registries have reported on specialized techniques including dedicated bifurcation-specific stents, but for now interventional cardiologists are left choosing an approach based on personal preference and anecdotal experience rather than rigorous randomized data.

On the LM bifurcation lesion, our patient was approached using the provisional technique. It is expected that by preparing mechanical circulatory support with IABP before the high risk PCI procedure, the outcome would be optimal, regarding the complexity of the patient's lesion. There was an unprotected left coronary artery in this patient, due to the existing 100% ISR in the RCA. Previous studies have proven the benefits of IABP in complex PCI procedures, it is in line with the procedures performed in these patients.[13,14]

Patients with ISR, as our patient, commonly present with a current presentation of recurrent angina. Following the 2018 ESC guidelines regarding myocardial revascularization, repeat PCI is a procedure that should be performed in patients with ISR with clinical presentation of progressive or recurrent angina. DES are shown to be superior compared with balloon angioplasty, BMS implantation or brachytherapy. New-generation DES (everolimus, zotarolimus) are recommended as 1st line treatment of ISR of BMS/DES.[14]

Although DES significantly reduces the incidence of ISR, the multifactorial etiology of ISR still makes ISR a challenge in the world of interventional cardiology.[10]

3.1 Classification of Bifurcation Lession

Currently, six different classifications of bifurcation lesions have been defined. The most important distinction to make is to divide bifurcation lesions into true bifurcations, in which the main branch (MB) and the side branch (SB) are both significantly narrowed (>50% diameter stenosis), and non-true bifurcations, which include all the other lesions that involve a bifurcation.

In routine practice, the Medina classification is still the most simple and widely used approach to classify distribution of atherosclerotic plaque at a bifurcation site.

With the Medina classification system, lesions can be easily characterized using a three-number designation system where the first number represents the presence or absence of disease in the proximal main branch, the second number represents the presence or absence of disease in the distal main branch, and the third number represents the presence or absence of disease in the side branch. For each of the three locations, a zero (0) is designated for less than 50 % stenosis, and a one (1) is designated for a greater than or equal to a 50 % stenosis. Each of the three numbers is then listed in order separated by a comma to create a classification schema for the lesion.

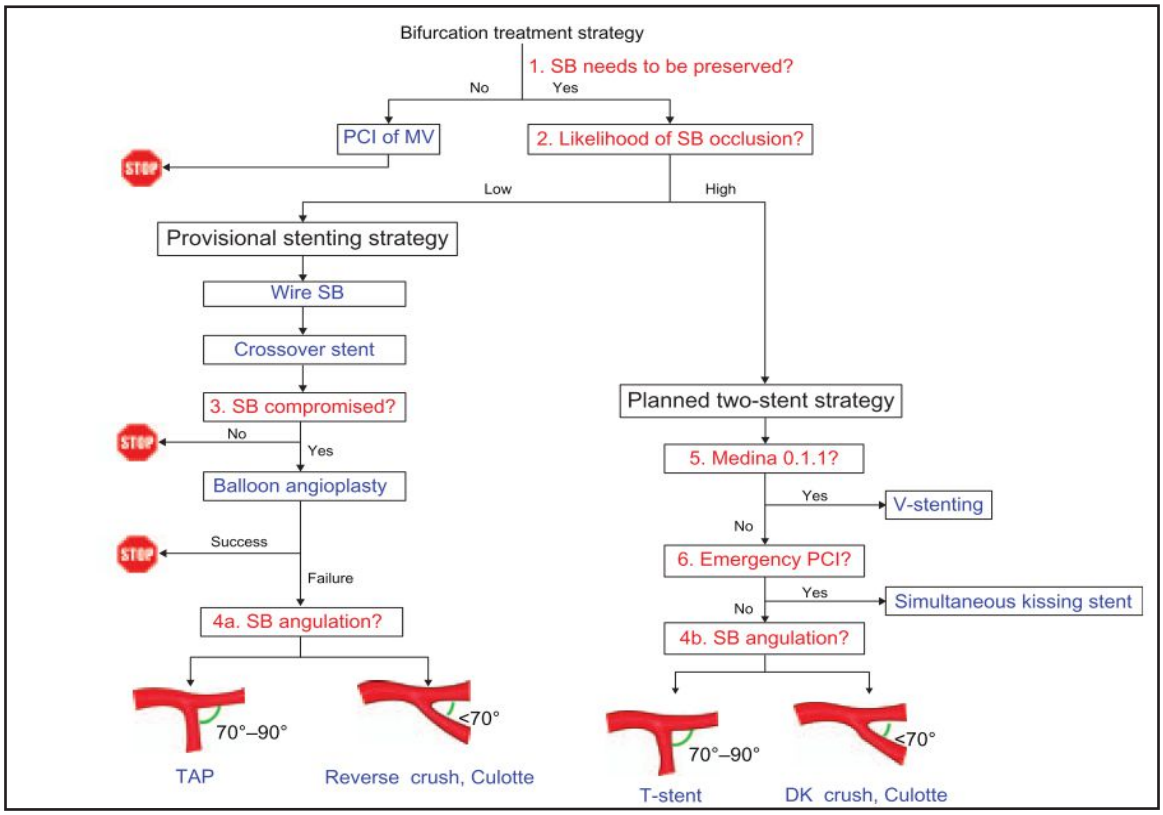

Figure 3. Algorithm for Bifurcation Lesion (modified from Rai et al., 2015).

In practice, the Medina system is both easy to calculate and has been shown to have excellent inter- observer agreement for classification of lesion subtypes. Despite its strengths, the Medina system has several weaknesses, including that it does not account for the side branch angle or side branch size, two factors which may impact an interventional approach and the number of stents which are utilized. Additionally, it does not quantify the percent stenosis, but uses a binary "present or not present" approach, which can lead to the same classification for a 50 % stenosis as a 99 % stenosis in a main vessel or side branch, despite the difference in interventional risks which may be present with these disparate lesions. Nevertheless, the trade-off in ease of use may be justified, especially when considering that complex lesion subsets are easily identified with the Medina classification despite its simplistic formulation.

3.2 Current Treatment Options for Bifurcation Lesions

When considering intervention on a bifurcation lesion, there are two general tactics that can be employed. The more conservative, or provisional, approach involves the intent to only use one stent to treat the stenosis (typically the main branch is stented).

Frequently, balloon angioplasty is used to "bail-out" the side branch using a KBI, which involves simultaneous inflation of two balloons in the coronary which are touching ("kissing"), with one in the main branch and one in the side branch. The operator can elect to use a second stent, but usually this would only be performed if there was significant compromise to the side branch (residual high-grade stenosis, dissection, or reduced distal flow) which could not be rectified with additional balloon angioplasty. The goal of the provisional approach is to minimize the complexity of the procedure, reduce the fluoroscopic time and contrast volume required, and reduce the resource (stent) utilization. In contradistinction to a provisional approach, a dedicated approach implies the planned use of two stents, one in the main branch and one in the side branch.[12,20] An algorithm may simplified decision making for bifurcation lesion as seen in figure 3.[11]

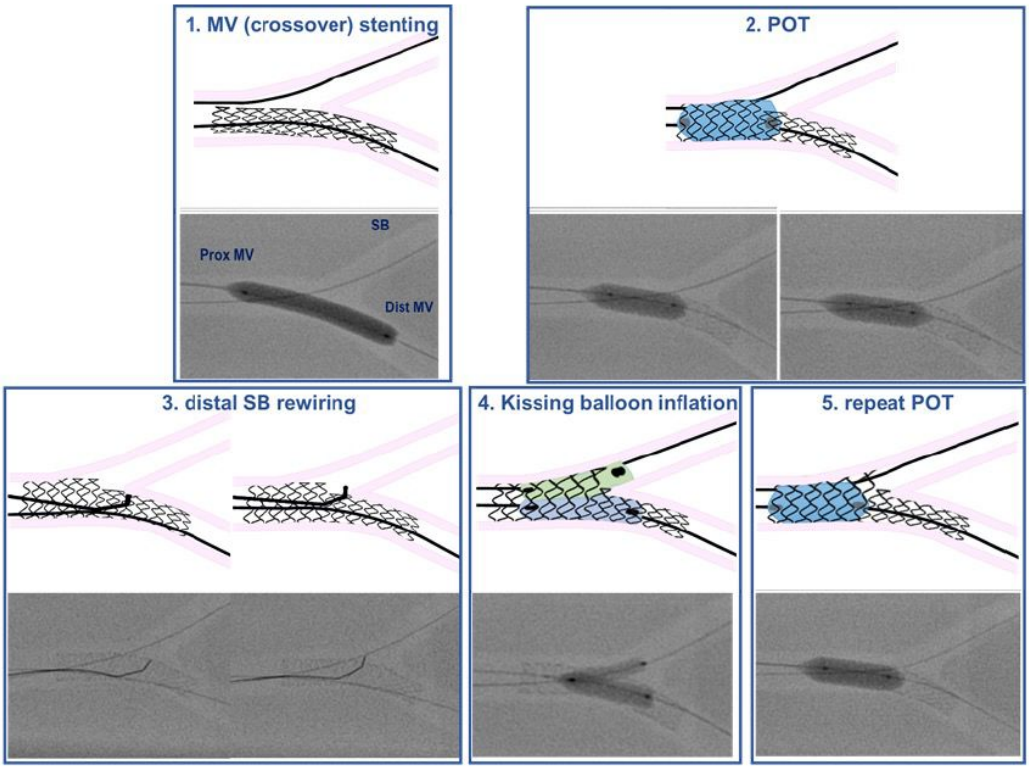

Figure 4. Sequential step for provisional technique.[2]

In our patient, the provisional technique approach was chosen regarding the existing risk and benefit considerations. The patient has borderline serum creatinine so that optimizing the procedure by calculating an efficient contrast agent to prevent worsening of the renal function is one of the considerations. In addition, as previously mentioned, the provisional technique allows a shorter procedural time so that radiation exposure for the operator is also minimal.

Recommended steps for provisional technique were described as follow in figure 4. (1) MV stenting across SB take-off with DES sized 1:1 according to distal MV diameter. (2) POT with balloon sized 1:1 to proximal MV. Note that, due to long stented area in the proximal MV, two inflations were needed to appropriately post-dilate the entire proximal MV stent segment. (3) Distal SB rewiring according to the pullback technique. Note the double bended guidewire tip shape that allows entering easily the distal part of SB ostium. (4) Simultaneous kissing balloon inflation with MV balloon sized 1:1 according to distal MV and SB balloon sized 1:1 according to SB diameter. (5) Repeat POT with balloon sized 1:1 to proximal MV.[5]

3.3 A General Outline when Treating a Bifurcation Lesion – SB protection

An important aspect when stenting bifurcations is the protection of the SB by insertion of a wire to be left until the stenting procedure on the MB has been completed, which includes high-pressure stent deployment or post dilation. These temporary “jailed” wires can be retrieved provided attention is paid to avoid any trauma to the ostium of the proximal coronary with the guiding catheter, which tends to be pulled in as the guidewire is withdrawn. In the provisional technique, wire crossing through the distal strut (the “carina strut”) following MB stenting is strongly suggested because it creates better SB scaffolding than proximal crossing.

To optimize SB access through the carina strut, the proximal optimization technique (POT) is proposed. Optimization of the stent deployment proximal to the carina using a short, bigger balloon may help to access the most distal strut during wire exchange. If the result remains unsatisfactory after MB stenting (>75% residual stenosis, dissection, TIMI flow grade <3 in an SB ≥2.5 mm, or FFR <0.75), SB stenting should be performed. SB stenting can be performed with T stenting or with T-and-protrusion (TAP) stenting, reverse/internal crush and culotte, followed by FKBI.[3] It is important to perform SB assessment after the MV stenting as seen in figure 5.

3.4 The Role of Final Kissing Balloon Inflation

Stenting only the main vessel (MV) in a bifurcation without further post-dilation produces incomplete stent apposition proximal to the side branch (SB), leaving stent struts malapposed at the SB ostium that disturb flow and increase the risk of stent thrombosis. Post-dilation is necessary to ensure full apposition of the stent. In bifurcation stenting practice, it is still controversial how post-dilation should be performed and whether the final kissing balloon inflation (FKBI) is mandatory when only the main vessel (MV) receives a stent.

Final kissing balloon inflation (FKBI) is proposed if the SB is dilated through the MB stent struts to correct MB stent distortion and proximal expansion and to provide better scaffolding of the SB ostium and facilitate future access to the SB. The long-term clinical benefit of FKBI, in cases of MV stenting alone, is still unproven. The Nordic-Baltic Bifurcation Study (Nordic III) and the Cordoba & Las Palmas (CORPAL-KISS) trial demonstrated that no systematic clinical advantage exists with a routine kissing strategy when a single stent treatment is used, and retrospective analysis of the COBIS registry showed that FKBI may even increase long-term TLR rate in the MV. However, angiographic follow-up at 8 months in the NORDIC III study showed a lower SB restenosis rate in patients with true bifurcation lesions when

FKBI was performed (7.6% vs. 20.0%, P = .024), and a study by Koo and colleagues showed that FKBI restores normal FFR in the SB in the majority of patients. Several criteria have been proposed to define lesions in which FKBI is required: these include greater than 75% residual stenosis at the SB, TIMI flow grade less than 3, or FFR below 0.75. Therefore two appropriate strategies are to use either a pressure wire to interrogate the significance of the SB lesion and treat or not accordingly or to simply do FKBI on all angiographically significant ostial SB lesions, which reduces the proportion of these lesions that are physiologically significant; in light of the information from Nordic III, there appears to be no penalty for doing so. A two-step sequential strategy has also been proposed as a simpler and more efficient alternative to an FKBI technique; this accomplishes SB dilation with a balloon at least the diameter of the SB, and final optimization of the MV stent is with a balloon sized per the proximal MV with the distal marker at the carina site. As a general approach, we favor performance of FKBI.[3,9]

Final KBI has been recommended repeatedly based on bench experiments and observational studies. From the study of Bondi-Zoccai et al., KBI appears beneficial in reducing the risk of side-branch repeat revascularization after using a two-stent strategy.[1] However, after provisional bifurcation stenting, sequential post-dilation of the SB and MV may offer a simpler alternative to final KBI. A multicentre study by Watanabe et al., PROPOT Trial, comparing proximal optimization technique (POT) versus KBI found that POT was not superior to KBI in terms of stent apposition.

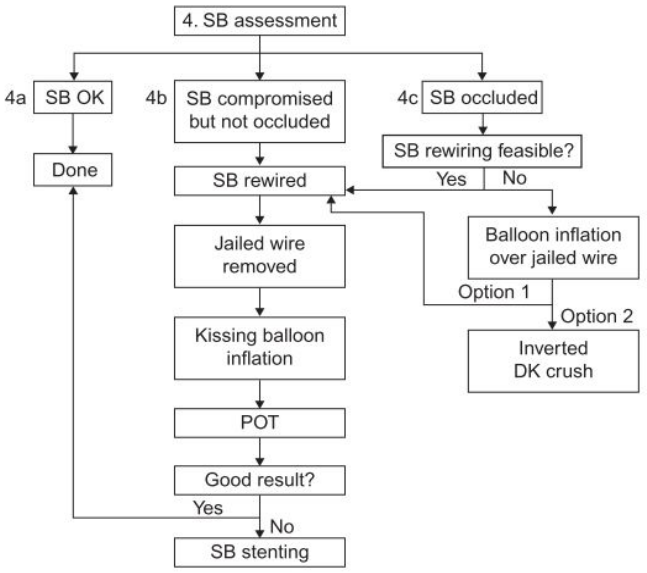

Figure 5. Algorithm for SB Assessment after Provisional Stenting.[11]

3.5 Randomized Data for Bifurcation Approaches

Studies and randomized trials have been conducted since the introduction of DES to determine the best treatment for bifurcation stenosis, especially comparing provisional and dedicated two-stent strategies. There is considerable variation in trial end points, stenting procedures, lesion characteristics, and side branch bailout approaches; nonetheless, for most bifurcations, a provisional approach has no detriment in terms of clinical results (fig. 6, table 1). The provisional approach of implanting one stent on the MV should be the default approach in most bifurcation lesions.[3]

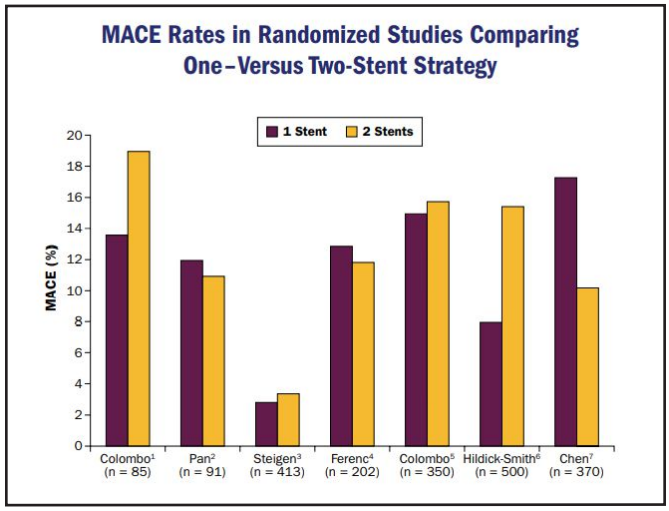

Figure 6. MACE Rates in Randomized Studies Comparing One- Versus Two-Stent Strategy.[3]

The Nordic trial enrolled 413 patients with bifurcation lesions were randomly assigned to either a two-stent technique or a dedicated approach in the first randomized trial comparing the two therapies. Patients assigned to a two-stent strategy underwent either culotte or crush stenting at the operator's choice. Cardiac mortality and stent thrombosis were the major outcomes after six months of follow-up in this study. No difference was found between the two groups at six months, with the provisional group reporting 2.9 percent and the dedicated group reporting 3.4 percent. An important "cost" of a dedicated method was a higher rate of biomarker elevation, as well as increased contrast volume, fluoroscopy time, and operation time in the group using a dedicated two-stent technique. Overall, the authors concluded that the data support a de facto provisional approach.[13,20]

Shortly after the publication of the Nordic and BBK trials, the Cactus trial was reported. In this randomized trial, 350 patients with bifurcation lesions were assigned to a dedicated crush-stenting approach or to a provisional strategy using sirolimus-eluting stents. The primary angiographic outcome measure was in-segment restenosis at 6 months, and the primary clinical outcome was MACE defined as cardiac death, myocardial infarction, or target vessel revascularization at 6 months. The results demonstrated a statistically identical, but numerically lower, rate of restenosis in the side branch of 13.2 % in patients who received the dedicated crush versus 14.7 % in those with provisional stenting. Clinical outcomes as measured by MACE at 6 months were also identical between the two approaches.[4,20]

The DK-Crush-II trial is the most recent randomized trial comparing a double kissing crush technique with provisional stenting. In this trial, 370 patients were assigned to either the double kissing crush technique or the provisional technique. Of the patients assigned to the provisional technique, about 28 % crossed over to a 2-stent technique. Double kissing crush technique involves deploying the side branch stent, balloon crushing that stent, then performing a kissing balloon inflation in the side branch and main vessel. Next, the main vessel stent is deployed and a final kissing balloon angioplasty is performed. In the DK-Crush trial, the primary end point was MACE at 12 months and the secondary end point was angiographic restenosis at 8 months. Results of the study demonstrated a lower rate of target-lesion revascularization in the two-stent group (4.3 % vs. 13.0 %, p = 0.005) and lower target-vessel revascularization in the two-stent

Table 1. Baseline characteristic of research partisipants.

Study	NORDIC [7] Elective (N = 206)	NORDIC [7] Provisional (N = 207)	BBK [8] Elective (N = 101)	BBK [8] Provisional (N = 101)	CACTUS [9] Elective (N = 177)	CACTUS [9] Provisional (N = 173)	BBC-ONE [10] Elective (N = 250)	BBC-ONE [10] Provisional (N = 250)
Clinical Outcome	6 months		1 year		6 months		9 months	
Primary end point	Death, MI, TVR, or Stent thrombosis		% DS of the SB		Death, MI, TVR		Death, MI, TVF	
	3.4 %	2.9 %	27.7 ± 24.8 1	23.0 ± 20.2 2	15.8 %	15 %	15.2 %*	8 %*
Death (%)	1.5	1	1	1	0.0	0.5	0.8	0.4
Non- fatal MI (%)	0.5	0.0	2	NA	10.7	8.6	11.2*	3.6*
Peri-procedure	18	8	NA	10.9	8.5	6.9	6.8	1.6
TVR (%)	1.9	1.9	8.9	1	7.9	7.5	6.8	5.6
Stent thrombosis (%)	0.0	0.5	2		1.7	1.1	2.4	0.4
Angiographic outcome	8 months		9 months		6 months		NA	
Re stenosis (%)								
MV	5.1	4.6	3.1	7.3	4.6	6.7	NA	NA
SB		19.2	12.5	9.4	13.2	14.7	NA	NA
%DS in SB	24 ± 21*	31 ± 22*	27.7 ± 24.8	23.0 ± 20.2	30 ± 19	31 ± 22	NA	NA

From Moussa [15], with permission
The CACTUS trial: Peri-procedural and non-Q-wave MI was defined as an elevation of postprocedural CK levels >2 times normal levels with elevated CK-MB in the absence of pathological Q waves.
The NORDIC trial: Peri-procedural cardiac biomarker elevation was defined as a CK-MB or troponin increase to ≥3 times the upper limit of nor- mal with or without clinical manifestations.
BBC ONE: Peri-procedure non-Q-wave myocardial infarction was defined as a CK-MB or troponin increase to ≥3 times the upper limit of normal.
BBK: Peri-procedure Non-Q-wave myocardial infarction was defined as. an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of normal in two samples during hospitalization.
*$p < 0.05$

approach (6.5 % vs .14.6 %, p = 0.017). Moreover, the restenosis in the side branch was 4.9 vs. 22.2 % (p = 0.001) when comparing the two stent approach to the provisional approach, respectively.[3]

4. Conslusions

Coronary bifurcation lesions are fairly frequent, and their management is associated with an increased risk of MACE, increased complexity, and prolonged treatment times. Cardiologists have gotten more active in their treatment of these tough lesions over the last decade, with the introduction of drug-eluting stents. With the exception of the DKCRUSH trial, the majority of randomized studies have indicated equality in outcomes employing a provisional technique to bifurcation treatment. Nonetheless, there are several circumstances in which a two-stent technique appears to be appropriate, including big side branch, severe stenosis in either branch of the bifurcation, and strongly angulated lesions. More information regarding the newer bifurcation-specific stent designs and their performance in comparison to current choices will become accessible in the future years. Until that happens, interventional cardiologists must rely on common sense and clinical expertise judgment to guide decision making about the treatment of bifurcation lesions.

5. Declarations

5.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

5.2. Consent for publication
Not applicable.

5.3. Availability of data and materials
Data used in our study were presented in the main text.

5.4. Competing interests
Not applicable.

5.5. Funding source
Not applicable.

5.6. Authors contributions
Idea/concept: KAN, SW. Design: KAN, SW. Control/supervision: SW, BS, NK. Literature search: KAN, SW. Data extraction: KAN, AW. Statistical analysis: KAN SW. Results interpretation: KAN, W, BS, NK. Critical review/discussion: W, BS, NK. Writing the article: KAN, SW. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.

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Heart Sci J 2022; 3(4): 29-34

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

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Case Report

Symptomatic Bradycardia In CAD Patient: Which One First To Treat?

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ARTICLE INFO

Keywords:
Sinus Node Dysfunction;
Coronary Arterial Disease;
Permanent Pacemaker.

ABSTRACT

Background: The incidence of sinus node dysfunction (SND) increases with age. Likewise, the incidence of coronary artery disease (CAD) has increased from year to year in Indonesia. When doctors are faced SND patients with CAD, it can be confusing in determining initial treatment options.
Objective: This study aimed to describe the diagnosis and management of SND in CAD patient.
Case Presentation: We will discuss a 75 years old male who had schedule to management of bradycardia symptomatic related to SND. Five month before admission, he had acute coronary syndrome, and had 2 DES implantation at left main (LM) to proximal left anterior descendent (LAD) artery and mid LAD. Two months after PCI he felt near syncope with bradycardia. Evaluation with ambulatory EKG was performed with result of SND, and correction of reversible cause related to SND already done. Eventually, symptom still exist and PPM insertion was decided to perform.
Conclusion: Patients with SND and CAD have a higher risk of complications and death. Correction of reversible factors, one of which is CAD, can be done as an initial step in the treatment of SND. When symptomatic signs still appear after correction of reversible causes, PPM implantation is the modality of choice in management.

1. Introduction

Sinus node dysfunction (SND) is a condition with heart rate < 50 bpm and/or a sinus pause > 3 seconds.[1] SND is one of classification of bradycardia, instead of atrioventricular block. The electrocardiographic findings in patients with SND are varied.[2] Sinus node dysfunction is caused by intrinsic/idiopathic factors (49%), treatable extrinsic factor (51%) or mix factor.[3] Incidence of SND with coronary arterial disease (CAD) is increasing with age.[2,4] There are about 0.03% patient with SND in UK, and much more common in elderly.[3] Data showed that SND with CAD account for 10 - 15%.[2] In 2013, prevalence of coronary disease in East Java is 1,3% people (375.127) and 0,5% (883.447) nationally.[5] While, elderly population in Indonesia is increasing each year.[6,7] With increasing incidence of coronary heart disease and increasing of elderly population in Indonesia, the incidence of SND could be increasing either.

Patient with SND tend to have high mortality rates, high risk of heart failure, and atrial fibrillation (AF).[2,8,9] This situation can reduce quality of life. Therefore, good early management can make a good prognostic to patient. In situation with symptomatic bradycardia related to SND and with existing CAD, physician may get confuse which one to be treated first? Do we need to do early pacemaker insertion or revascularization? We realize that proper treatment and good decision can maximize the outcome.

2. Case Illustration

Male 74 years old came to Saiful Anwar Hospital scheduled with complaints of weakness and near syncope with slow heart rate that happen since two months before admission. This situation happen approximately three - twice a week for less than 10 minutes, and said disturbed his daily activity. The symptom was often preceded by palpitation, but not triggered by an angry or emotional state, not because of urinating, nor coughing. The patient was also not experiencing diarrhea. No complaint of sleep apnea from his family while patient sleeping at noon or night. After the symptom relieved by itself, there was no unilateral weakness at patient extremities. In admission, there was no chest pain, heavy chest sensation, or radiating pain.

Five months before presentation, the patient had had severe shortness of breath and felling like falling followed by chest pain, 7-8/10 VAS and cold sweats. Because the complaints did not resolve, the patient was taken to private hospital. Patient was diagnosed with acute coronary syndrome and received injection at the abdomen. He was treated for 4 days in the ICU. After discharge the patient was routinely controlled to cardiologist and was planned for elective cardiac catheterization at the Hospital.

Five months before presentation, the patient had had severe shortness of breath and felling like falling followed by chest pain, 7-8/10 VAS and cold sweats.

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https://doi.org/10.21776/ub.hsj.2022.003.04.6
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022

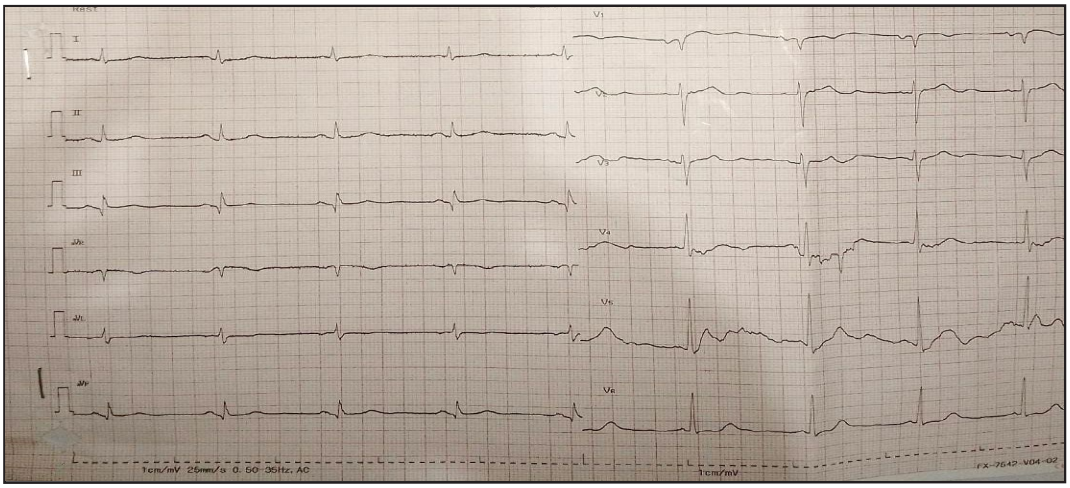

Figure 1. ECG on admission showed Sinus rhythm, HR 55 bpm, FA N, HA N, QRS 80ms ST Change (-) pathological q at III; T inverted aVL with conclusion : Sinus bradycardia.

Because the complaints did not resolve, the patient was taken to private hospital. Patient was diagnosed with acute coronary syndrome and received injection at the abdomen. He was treated for 4 days in the ICU. After discharge the patient was routinely controlled to cardiologist and was planned for elective cardiac catheterization at the Hospital.

A month after that, patient had catheterization with diagnose CAD 3VD post 2 DES implantation in Mid LAD and Proximal LM-LAD. After catheterization, patient felt better activity with less shortness of breath. Patient was planned to do next catheterization for distal LAD and RCA.

Two months before admission, the patient complained of chest palpitations with slow heart rate, accompanied by weakness and near syncope. There were no emotional state change prior to palpitation nor urinating or coughing. This sensation was never happen before. Holter procedure was performed with the results : basic sinus rhythm with frequent episodes of sinus arrest (conclusion: SND, suggestion of permanent pacemaker).

Patient also complained of swelling at both feet with pitting +2 at ankle level. Patient was diagnose with new onset CKD and underwent hemodialysis twice a week.

One month before admission, patient still complained of chest palpitation with slow heart rate that happened intermittently. Patient was performed catheterization at mid-distal LAD. Percutaneous trans luminal coronary angioplasty (PTCA) was done at chronic total occlusion (CTO) RCA. There was no event during procedure. No further revascularization was needed and medical optimization was suggested.

Patient had hypertension since 35 years ago. He didn't regularly take medication before, but had started consuming medication regularly since 20 years ago. No history of diabetes or stroke. Patient had hemodialysis (HD) since 1 month ago for newly diagnose chronic kidney disease and had been scheduled twice per week.

Patient regularly consumed Aspilet 0-0-80mg, Clopidogrel 75mg-0-0, Atorvastatin 0-0-20mg, Lansoprazol 1x30mg, Valsartan (Diovan) 0-0-160mg, Spironolactone 0-25mg-0, ISDN 3x10mg. Previously, patient had Bisoprolol 2,5mg for his heart failure medication, but already stopped since palpitation with slow heart rate occurred two months ago.

Patient was retired from local government civil servant. The patient can perform light daily activities independently.

From family history, his father died at age of 80 due to complications from kidney stones and had history of hypertension (HTN). The his mother died at age of 56 due to heart disease and had history of HTN. The patient is the first among 10 siblings. His sister (6th child) has HTN and cardiovascular disease that already done catheterization. All patient's siblings have HTN.

On physical examination we found GCS E4 V5 M6, BP: 139/75 mmHg, HR: 45 x/minute regular-strong pulse, RR: 20 x/minute, SpO2 : 98% on RA. Body weight: 60 kg, height: 169 cm, BMI: 21.0 kg/m2 (normo-weight), urine output: 800cc/24Jam, fluid balance: +50cc/24 hours on routine hemodialysis (HD) for twice per week.

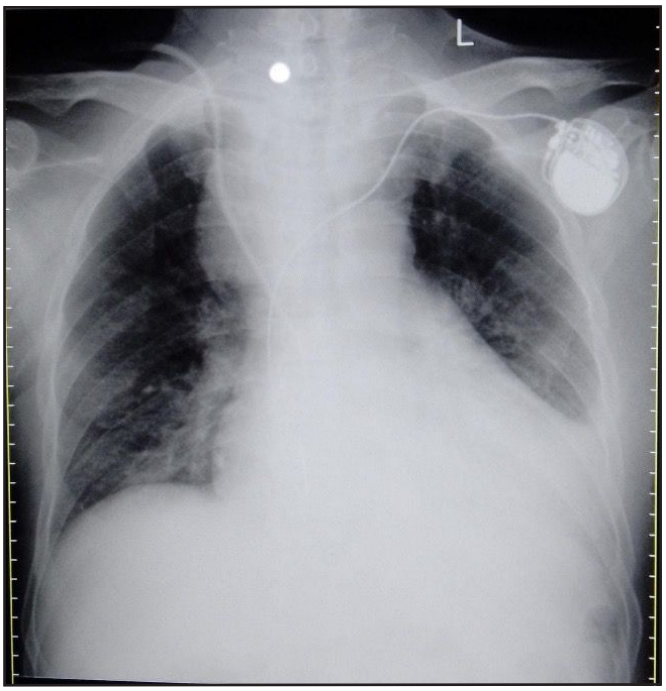

Figure 2. Chest X-Ray post PPM implantation

Table 1. Laboratory finding at admission

	Value		Normal Range
Hb	8,40	g/dL	13.4 – 17.7 g/dL
Leukocytes	4,26	/μL	4300-10300/μL
Hematocrit	27,80	%	40 – 47 %
Thrombocytes	133	/μL	142000-424000/μL
MCV	94,60	fL	80 – 93 fL
MCH	28,60	pg	27 – 31 pg
MCHC	32,20	g/dL	32-36 g/dL
Differential count	9,2/0,2/51,9/22,3/16,3		0-4/0-1/51-67/25-33/2-5 %
Random Blood Sugar	77	g/dL	<200 mg /dl
Urea	155,8	mg/dl	16.6 – 48.5 mg/dL
Creatinine	7,26	mg/dl	16.6 – 48.5 mg/dL
eGFR (CKD-EPI)	6,718	mg/dl	136 – 145 mmol/L
Sodium (Na)	140	mmol/L	3.5 – 5.0 mmol/L
Potassium (K)	3,49	mmol/L	98 – 106 mmol/L
Chloride (Cl)	106	mmol/L	3.5 – 5.5
Albumin	3,51	g/dL	Non reactive
Anti SARS COV-2	Non reactive		9.4-11.3
PPT	10,70	sec	24.6-30.6
APTT	28,10	sec	<1.5
INR	1,03		136 – 145 mmol/L

Head and neck examination showed conjunctiva pale +/+, icteric sclera -/- , JVP R+2 cmH2O (45deg), no palpable mass around neck examination. Thorax examination showed cardiac: ictus cordis invisible, palpable at ICS V 2 cm lateral MCL left, S1 S2 , murmur (-) and gallop (-) left, S1 S2 , murmur (-) and gallop (-). Pulmonology auscultation within normal limit, abdomen soefl, bowel sound normal, extremities warm acral, CRT < 2 seconds, with leg edema +/+ at level of ankle.

On ECG examination we found sinus rhythm, HR 55 bpm, frontal axis normal, horizontal axis normal, QRS 80ms ST Change (-), q pathologies at III, T inverted at aVL. Laboratory finding showed normocytic normochromic anemia and increased renal function test related to CKD. Serum electrolyte was within normal limit. Other finding was within normal limit. CXR at postero-anterior view examination showed cardiomegaly with CTR 64%, flattening cardiac waist, and apex embedded.
Echocardiography on June 12th 2021 showed mild MR, moderate TR, reduced LV Function with EF 47%, with RMWA hypokinetic at anterior segment.

4. Discussion

4.1 Differential Diagnosis

The patient came to the Saiful Anwar hospital after previously experiencing a near syncope accompanied by slow heart rate. Prior to feeling of near syncope, the patient did not complain of any emotional changes, diarrhea, or standing for a long time. As a first step in evaluating the patient, we re-evaluate whether the patient is hemodynamically stable or not.[10] Signs of hypotension, loss of consciousness, shock, ischemic chest pain, and acute heart failure were absent at presentation. The patient does not complain of typical chest pain, and palpitations was relieved in < 10 minutes. In this case, the patient is in a stable condition. Syncope or near syncope is included in the Transient Loss of Consciousness (TLOC) group, which is defined as a state of actually passing out or about to lose consciousness. The clinical picture can be amnesia during periods of unconsciousness, abnormal motor control, loss of responsiveness, and happen in a short period of time. Initial screening for TLOC was divided into 2 groups: those caused by head trauma or non-trauma.[11] In patients, nearly syncope are caused by non-trauma.

Etiologically, syncope/near syncope can be divided into 3 groups, such as reflex (neurally mediated syncope), orthostatic hypotension, and cardiac syncope. These three groups have their own characteristics. In our patient, the symptom was not preceded by emotional changes, eating activities, excessive physical activity, urinating, or standing for a long time. The patient felt palpitations when about to pass out. The patient had a history of acute coronary syndrome who underwent catheterization and stent implantation at LM to proximal LAD coronary artery and mid LAD. On physical examination, the patient showed bradycardia and the ECG showed sinus rhythm, HR 55 bpm, frontal axis normal, horizontal axis normal, QRS 80ms, ST Change (-), q pathologies at III, T inverted at aVL . From the history and physical examination, it can be concluded that the syncope/near syncope experienced by the patient tend most likely to a group of cardiac syncope.[11]

Table 2. Reversible Cause inducing SND1

Factors	Description
Acute myocardial ischemia or infarction	
Athletic training	
Atrial fibrillation	
Cardiac surgery	Valve replacement, maze procedure, coronary artery bypass graft
Drugs or toxins	Toluene, organophosphates, Tetrodotoxin, Hypoglycemia
Heart Transplant	
Hypervagotonia	Therapeutic hypothermia (exp. post cardiac arrest) Environmental exposure
Hypothermia	
Hypothyroidism	
Hypovolemic shock	
Hypoxmeia, hypercarbia, acidosis	Sleep apnea, respiratory insufficiency (suffocation, drowing), stroke, drug overdose
Infection	Lyme disease, Legionella, Psittacosis, Thypoid fever, thyhus, listeria, malaria, leptospirosis, dengue fever, viral hemorrhagic fever, Gullain-Barre
Medication	Beta blocker, non-dihidrophyridine calcium channel blockers, digoxin, antiarrhythmic drugs, lithium, methyldopa, risperidone, cisplatin, interferon.

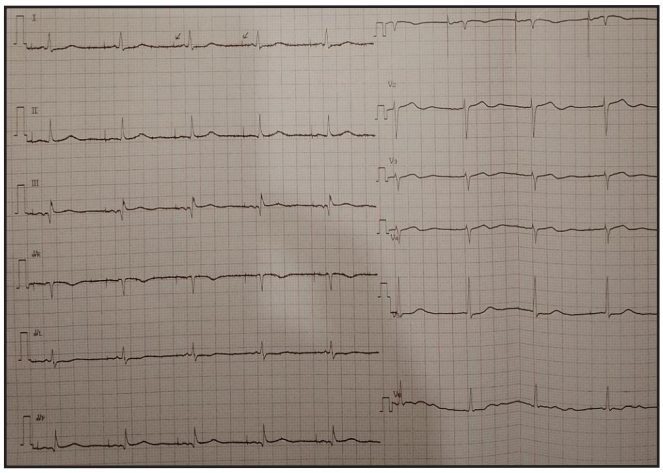

Figure 3. EKG after PPM insertion showed Pacing rhythm, HR 60 bpm, FA N, HA CWR, QRS 80ms.

In addition to conduction problems, other cardiac causes that can cause syncope include structural problems (e.g. valvular heart disease, myocardial heart disease, pericardial disease) and vascular causes. The patient had mild mitral regurgitation (MR) and moderate tricuspid regurgitation (TR), accompanied by decreasing left ventricular ejection fraction (LVEF) 47% which was probably caused by coronary heart disease.

After evaluating the possibility of cardiac syncope, further evaluation needs to be done to find the etiology of syncope. From the patient's presentation, the pulse was <60 bpm when a feeling of near syncope appeared. A pulse below 60 bpm is a sign of bradycardia. The feeling of near syncope that occurs incidentally related to decreased heart rate is a picture of symptomatic bradycardia.[1,12] Bradycardia can be classified into two groups: sinus node dysfunction (SDN) and atrioventricular (AV) block. A history and physical evaluation will assist in identifying the etiology of bradycardia. It is also necessary to obtain information about the frequency of symptomatic events, their duration, severity, circumstances accompanying the appearance of symptoms, and factors that reduce the severity of symptoms. In addition, we should evaluate the routine drugs consumed by the patient regarding the possibility of induction of bradycardia. In patients with bradycardia or conduction disturbances, screening for a 12-lead ECG, screening for structural heart defects and systemic disease is recommended. ECG abnormalities at the beginning of the examination provide predictive results and the possibility of structural disorders of the heart. Echocardiography is useful in evaluating patients with symptoms suspected to be of cardiac origin, e.g. aortic stenosis, hypertrophic cardiomyopathy or heart failure. Furthermore, investigations to evaluate metabolic disorders such as acidosis, hyperkalemia, hypokalemia, hypothermia, hypothyroidism, and hypoxia and cardiac structural disorders also support the search for the etiology of the disease.[1,12,13]

In the patient, near syncope symptom with bradycardia occurred at least 2-3 times per week with duration of < 10 minutes. After the incidence, there was no weakness at one side of the body. This incidence reduced the patient's quality of life. The patient did not have any emotional changes, diarrhea, or standing for long periods of time. One of the drugs consumed by the patient is bisoprolol, which has the possibility of induction of bradycardia. However, bisoprolol was discontinued after the first symptomatic appearance.

Physical examination showed normal blood pressure and bradycardia. The temperature and saturation were within normal limit. On examination of the neck, there was no palpable mass that led to an enlarged thyroid gland. There was swelling in the right and left legs at ankle level. From laboratory finding, no hypokalemia/hyperkalemia were found. Blood gas analysis and thyroid function tests were not performed. A 12 lead ECG showed a sinus rhythm with a heart rate of 55 bpm and a pathological q in lead III and an inverted T in aVL. The CXR image showed cardiomegaly with a CTR of 64%, cardiac waist flattening, and apex embedded. Echo examination showed a mild MR and moderate TR, accompanied by an LVEF of 47% (decreased) which was probably caused by coronary heart disease. From the results of the patient's evaluation, it appeared that the heart rhythm disturbances were bradycardia without metabolic disorders and without significant structural disturbances in the heart.

In the case of patients experiencing syncope/near syncope whose etiology is unclear or in patients who have repeated palpitations, the implementation of an ambulatory ECG becomes a class I choice.[1,14–16] There are 3 types of ambulatory ECG : Holter, event recorder (loop and non-loop) and real time continuous event recorder. The consideration of choosing any type of ambulatory ECG is based on the patient's symptoms on arrival, the frequency of complaints, and the degree of suspicion of a malignant arrhythmia.[14,15] Other considerations such as the availability of equipment, the capability to use the equipment, and financial coverage should also be considered in the choice of an ambulatory ECG modality. In patients with a dominant presentation of syncope, a continuous recording or loop recording is selected to overcome the patient's inability to activate the device when syncope occurs. Meanwhile, in patients with a dominant presentation of palpitations, the choice of non-loop recording can be considered. With the relatively high frequency of occurrences in daily activities, the selection of short duration recordings is deemed adequate. However, with the frequency of complaints being rare, the choice of a longer duration should be considered. In patients with suspected malignant arrhythmias, the choice of real time recording to monitor the condition continuously is recommended.[14,15]

Our patient had a near syncope presentation accompanied by palpitations with a frequency two to three times per week and the ECG showed sinus rhythm. The selected ambulatory ECG to support diagnosis is continuous ambulatory. A Holter monitor was set for 24 hours, by stopping bisoprolol prior to examination, and advice to do activities as usual. The results of the Holter monitor showed a basic sinus rhythm, good AV node conduction, no ST-T wave changes, bradycardia episodes, a maximum heart rate of 65 – a heart rate of at least 18 bpm, with the longest sinus arrest being 5.6 seconds.

SND is associated with increasing age (with the highest proportion found in the age of 70 – 80), progressive, degenerative fibrosis in the SAN and around the atrial myocardium.[1,3,17] By definition, SND can be expressed as:

1. Sinus rhythm with rate <50 bpm;
2. Atrial depolarization caused by an atrial pacemaker other than the sinus node at <50 bpm;
3. Sinoatrial block with evidence of obstruction of conduction between the sinus node and adjacent atrial tissue;
4. Sinus pause: sinus node depolarizes >3 seconds after last atrial depolarization;
5. Tachycardia-bradycardia syndrome ("tachy-brady"): sinus bradycardia, ectopic atrial bradycardia, or sinus pauses alternating with periods of abnormal atrial tachycardia, atrial flatter, or atrial fibrillation (S2.2-6). Tachycardia may be associated with sinus suppression of node automation and sinus pauses of varying duration as the tachycardia ends;
6. Chronotropic incompetence: defined as the inability of the heart to increase its rate according to increased activity, as a percentage defined as failure to achieve 80% of the expected HRR during exercise;
7. Isorrhythmic dissociation: atrial depolarization (from either the sinus node or ectopic atrial site) is slower than ventricular depolarization (from the atrioventricular node, bundle of His, or ventricle).

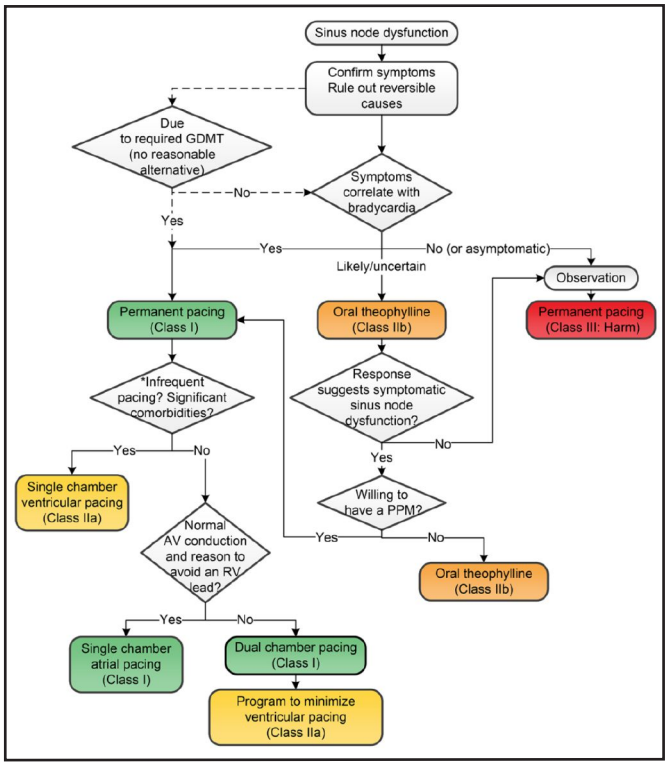

Figure 4. Diagram of Sinus Node Dysfunction management by ACC/AHA/HRS Guideline 2018. Note that different color showed different class of recommendation. First step to mention is to rule out reversible cause of SND.

From the 24-hour Holter, 74-year-old patient was found to have a sinus rhythm with a minimum rate of 18 bpm – a maximum rate of 65 bpm and a sinus arrest with a longest time of 5.6 seconds. These pictures support the diagnosis of SND in cases of symptomatic bradycardia.

4.2 Clinical Diagnosis

Sinus Node Dysfunction

The pathophysiology of SND varies from conduction problems to structural problems. Patients with symptomatic bradycardia that correlateso with SND have a high risk of cardiovascular events such as syncope, AF, heart failure and in ther hand increases the risk of cardiovascular death.[1,2,18] Clinical manifestations that often appear in patients with SND include syncope, dyspnea on effort, lightheadedness, and chronic fatigue. In SND patient with stable symptomatic bradycardia, evaluation and treatment of reversible causes is important to assess the trigger factors for reversible SND (recommended class I) such as acute myocardial infarction, atrial tachyarrhythmias, medications, electrolyte abnormalities, hypothyroidism, metabolic abnormalities and infections.[1]

The use of bradycardia-inducing drugs such as beta-blockers and calcium channel blockers has a fatal systemic toxicity effect by inducing negative chonotropic and inotropic.[1,19] The bradycardia-inducing drug that was routinely used (bisoprolol) was discontinued at the onset of the complaint of bradycardia. The patient did not have electrolyte disturbances despite having associated chronic kidney disease and had routine HD 2 times per week.

Acute myocardial ischemia affects cardiac conduction pathways through mechanisms of abnormal autonomic tone, decreased perfusion or injury to the SAN tissue.[3] Meanwhile, in the context of chronic ischemia, the correlation with the incidence of SND is not clear. Several studies have shown that patients with a history of inferior myocardial infarction who have SAN artery stenosis >75% have lower intrinsic heart rates, longer corrected sinus node recovery times (cSNRTs) and longer sinoatrial conduction times (SACTs) compared to moderate to no stenosis (< 75%).[20,21] This is possible due to inducing of reflex cardio-inhibition phenomena caused by chemical stimulation or mechanical stretch in the ischemic dilated right heart.[21,22] Meanwhile, in another study, patients with SND rarely had sinus node artery disease, there was even severe stenosis of the sinus node artery that still showed normal SAN function. Disorders of the coronary arteries, especially the proximal RCA, increase the incidence of bradyarrhythmia and hypotension.[21–23] This is anatomically related to 61% of patients had SAN vascularization branches originating from the right coronary artery (RCA), 37% branches from left coronary artery (LCx), and about 2% from both branches (RCA and LCx). Thus, there is a high probability of impaired vascularization if there is stenosis of the proximal RCA.

From the coronary view after the first PCI procedure, with clinical signs of acute coronary syndrome (ACS) in the form of sudden weakness, near syncope and palpitation, the culprit coronary lesions were found in RCA and LAD. Catheterization and stenting were performed on the Proximal and Mid LAD with the remaining lesions on the distal LAD and CTO in the RCA. It was planned to scheduled revascularization of the residual lesion. After the revascularization procedure, the ACS complaint was relive and patient'condition was better. Complaints of palpitation with slow pulse started to appear two months after the first PCI. Holter has been performed and got results. The presence of residual coronary lesions is one of reversible cause of SND. In patients with stable hemodynamic with symptomatic, it may still be considered to correct the reversible cause through revascularization.

A month after Holter, a stent was placed in the mid-distal LAD due to diffuse stenosis. PTCA was performed on the proximal osteal portion of the RCA because CTO RCA was difficult to penetrate. It was decided that another revascularization was not necessary and medical optimization was carried out as a follow-up treatment for the patient.

From the evaluation after the second catheterization procedure, the patient still complained of near syncope with a low heart rate in almost the same frequency. Despite correction of reversible factors, electrolyte correction, discontinuation of drugs that induce bradycardia (bisoprolol), and revascularization, the patient still complained of the same symptoms. From the diagram of SND treatment, if efforts to correct the reversible cause factor have been made but the symptoms related to bradycardia are still felt, the next choice of action is the implantation of a permanent pacemaker (PPM).[1,13,24]

4.3 Clinical Procedures

Permanent Pacemaker Implantation

Permanent pacemaker Installation aims to improve the patient's symptoms, not to increase patient survival.[1,13,14] In October 2021, AAI mode PPM insertion was chosen because of good AV node function and consideration of the lower incidence of atrial fibrillation in the future. The setting of PPM AAI mode was a lower rate of 60x/minute, amplitude 3.5V, pulse width 0.04ms, sensitivity 2.8mV. The results of postoperative CXR evaluation showed the pacemaker was in the left subclavian position with the lead position in the right atrium, no signs of hematothorax and pneumothorax were found. Monitoring for 3 days in the ward showed a rate of 60 bpm with stable hemodynamics.

4.4 Follow Up

One month after the PPM installation, on evaluation and reprogramming of the PPM we found rate of 60 beat per minute with 62 atrial high-rate (AHR) events, good impression. Clinically, the symptom of near syncope was no longer felt and the heartbeat was regular. Daily activities can be done well without any problems. Patients still routinely have HD which was increased to 3 times per week. Patients also routinely control and take the drugs given.

5. Conclusion

Patients with SND and CAD have a higher risk of complications and death. Correction of reversible factors, one of which is CAD, can be done as an initial step in the treatment of SND. When symptomatic signs still appear after correction of reversible causes, PPM implantation is the modality of choice in management.

6. Declarations

6.1. Ethics Approval and Consent to participate
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: AYS, MRS. Design: AYS, MSR. Control/supervision: MSR, AR, SW. Data collection/processing: AYS, MSR. Analysis/interpretation: AYS, MSR. Literature review: MSR, AR, SW. Writing the article: AYS, MSR. Critical review: MSR, AR, SW. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7 *Acknowledgements*
We thank to Brawijaya Cardiovascular Research Center.

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Heart Sci J 2022; 3(4): 35-39

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Case Report

Idiopathic Pulmonary Arterial Hypertension Newly Diagnosed in Pregnancy with Anemia and Threatened Preterm Labor

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ARTICLE INFO

Keywords:
Idiopathic Pulmonary Arterial Hypertension;
Pulmonary Hypertension;
Pregnancy;
Anemia;
Preterm Premature Rupture of Membrane.

ABSTRACT

Background: Pulmonary hypertension (PH) is a rare cardiovascular disorder that leads to right heart failure (RHF). Although most PH occurs secondary to congenital heart disease (CHD), PH can occur primarily due to pulmonary arterial vasculature abnormalities, known as Idiopathic pulmonary arterial hypertension (IPAH). In addition, the physiologic changes during pregnancy can potentially lead to worsening PAH and confer a poor prognosis. Therefore, when the mother refuses termination, a multidisciplinary team should manage the pregnancy and delivery to improve maternal and fetal outcomes.
Objectives: This case report aimed to describe the importance of early diagnosis and treatment in PAH.
Case reports: We reported a case of a 24-year-old woman with idiopathic pulmonary arterial hypertension (IPAH) that was newly diagnosed at 25 weeks of pregnancy and previously misdiagnosed with patent ductus arteriosus (PDA). This pregnancy was complicated with anemia and threatened preterm labor. Sildenafil was used as a vasodilator to reduce the symptoms of PAH. Unfortunately, the pregnancy was terminated at 29 weeks because of PPROM after considering giving lung maturation and neuroprotectant to the fetus. The patient was discharged without complication, but the baby died after eight days of intensive care due to HMD II, which led to respiratory failure.
Conclusion: PAH in pregnancy is a life-threatening condition if untreated. Continuous treatments can help control the symptoms and avoid further complications for both mother and baby.

1. Introduction

Pulmonary hypertension (PH) is a rare heart defect and can be fatal, causing maternal and fetal death. The most frequent causes of PH during pregnancy (64%) are congenital heart diseases (CHD) such as ventricular septal defect (VSD), atrial septal defect (ASD), or patent ductus arteriosus (PDA).[1] The incidence of pregnancy with PH is scarce for approximately 1.1:100,000 women (Obican et al., 2014). PH group 1 or known as primary Pulmonary arterial hypertension (PAH), is a condition that is rarely found, with an average survival rate of only 2.8 years if not treated.[2] Therefore, a woman with PH is not advised to get pregnant. The physician should offer termination when pregnancy occurs. Nevertheless, some mothers cannot accept the decision to terminate the pregnancy and choose to continue their pregnancy.[3]

Physiological changes that occur in pregnancy can aggravate the burden on the heart, especially in PAH conditions. The condition of anemia can also worsen the work of the heart in pregnant women with PAHs. Iron deficiency is one of the most frequent causes of anemia in pregnancy and also affects the pathogenesis of PAHs. Iron deficiency due to malnutrition underlies cardio-intestinal syndrome, which can worsen hypoxic conditions in pregnant women with PAHs.[4] Both anemia and decreased CO due to PH can increase morbidity in the mother and fetus. Pregnant women with PH and anemia require intensive, multidisciplinary treatment during pregnancy and childbirth.[2]

We will report cases of pregnancy with Idiopathic Pulmonary Arterial Hypertension (IPAH), which was newly diagnosed during pregnancy. The PAH condition is exacerbated by anemia in pregnancy which causes symptoms of acute shortness of breath and causes complications of preterm labor. Pregnancy management with PAH is carried out by a multidisciplinary team at Dr. Saiful Anwar Hospital Malang so that it can add insight to handling pregnancy cases with PAH. However, establishing a diagnosis that is not easy can lead to misdiagnosis and increase the risk of complications that occur in the mother and fetus. Therefore, the management of pregnancy with PAH is complicated and makes it a big challenge.

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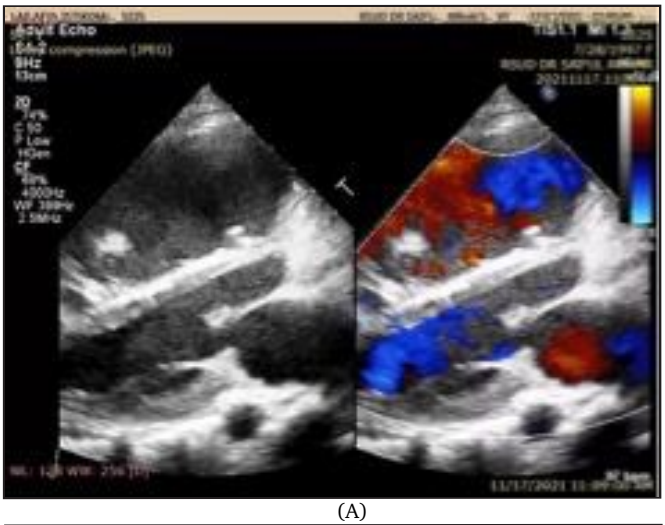
https://doi.org/10.21776/ub.hsj.2022.003.04.7
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022



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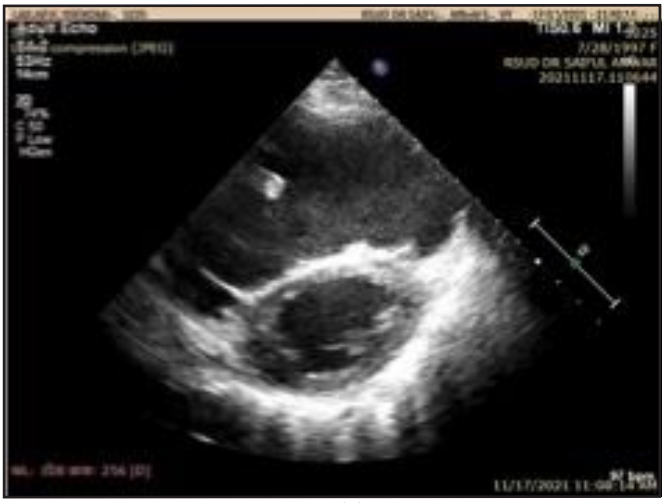

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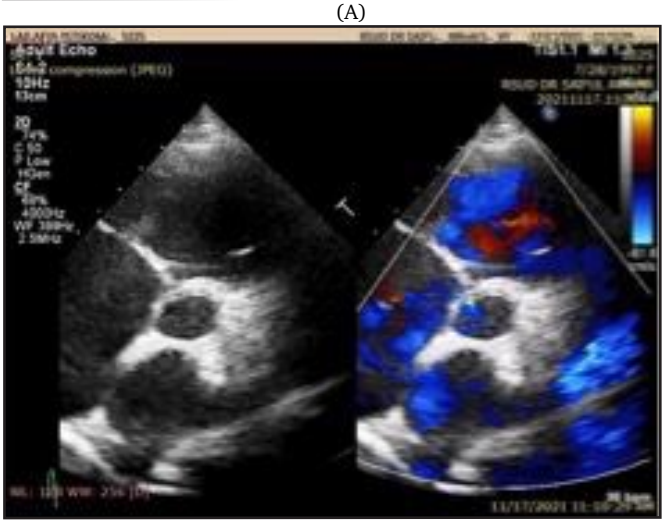

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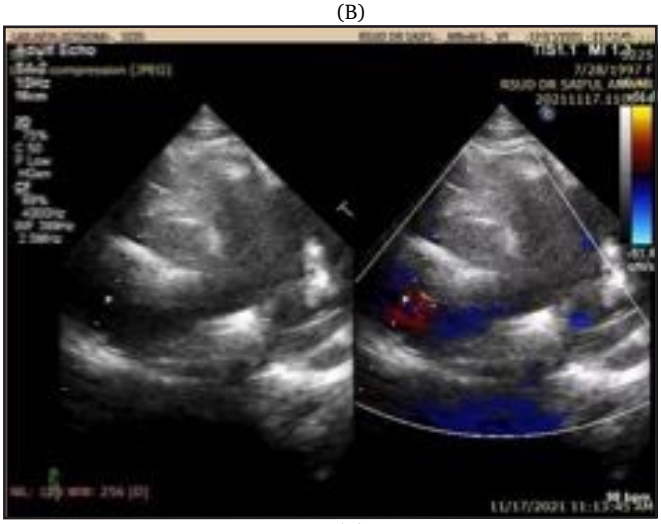

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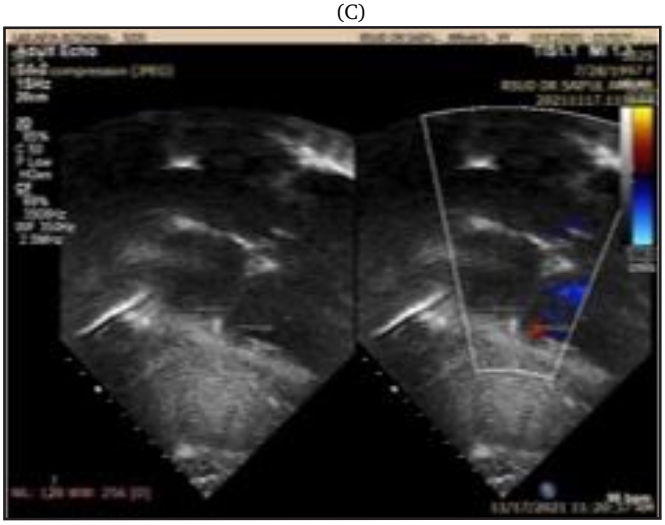

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Figure 1. Echocardiographic of idiopathic pulmonary arterial hypertension

A. Parasternal Long Axial image: RV dimension enlarged with LV geometric change; B. LV D-shaped in Parasternal short Axis (PSAx) image; C. PSAx- great artery level shows there is no interatrial shunt; D. Pulmonary Artery Enlargement; E. There is no interatrial shunt from sub-costal view

2. Case Report

A 24-years-old woman, primigravid, was referred to our emergency department by an Obstetrician at a private hospital with a chief complaint of shortness of breath after two times of PRC transfusions. The patient was hospitalized for two days and diagnosed with threatened preterm labor and anemia. The patient felt a frequent uterine contraction at 25 weeks of gestation, a day before being hospitalized. The hemoglobin level at visiting that private hospital was 7.4 gr/dL. Patient planned for dexamethasone-induced fetal lung maturation and PRC transfusion twice a day. After the second transfusion, the patient felt dyspnoea and palpitation. The patient was consulted by the Cardiologist and given digoxin 1x0,25 mg. The patient was diagnosed with ASD based on clinical appearance and electrocardiograph examination. After 24 hours of observation, the patient did not get better. Because lack of facilities, the Obstetrician referred the patient to our hospital.

The patient did antenatal care with the midwife and never came to Obstetrician. She did a triple elimination test in Public Medical Centre Jatisari, and the results were non-reactive. On admission, the patient's vital sign was blood pressure of 120/81 mmHg, heart rate of 107 bpm, respiratory rate of 28 breaths/min, pulse oxygenation of 99% on nasal cannula three L/min, and temperature of 36.2°C. Head and neck examination found conjunctiva anemia and JVP +1. Cor examination found murmur systolic 3/6 continuous at ICS II left parasternal line. The abdominal examination determined the fundal height of 18 cm, single intrauterine baby head below, fetal heart rate of 147 bpm,

and uterine contraction (+). In addition, we found two cm cervical dilatation, 50% effacement, head presentation at Hodge I, and no amniotic fluid leakage from the vaginal examination.

Her hemoglobin level at admission was 8.5 mg/dL. Patient has hypercoagulability condition that showed from increased D-dimer 1.32 mg/L FEU (normal range < 0.5 mg/L FEU) and fibrinogen 502 mg/dL (normal range 154.3-397.9 mg/dL). The patient was hospitalized in the Obstetrics High Care Unit for preterm delivery observation. Her shortness of breath was due to suspect congenital heart disease with a high probability of PH. The transfusion was continued with one PRC daily. Tocolytic ketoprofen suppositories were given to relieve uterine contraction. Treatment of pulmonary hypertension with oral sildenafil 20 mg daily improved the shortness of breath.

Echocardiographic evaluation was done after three days of hospitalization by a senior Cardiologist (Figure 1). Dilatation of the pulmonary artery was consistent with the prior echocardiogram with a diameter of MPA 3.26 cm, RPA 1.61 cm, and LPA 2.12 cm. The intracardiac shunt did not detect either an atrium or ventricle. Dilatation of the right heart, including atrium (RA length 7.25 cm and RA width 6.14 cm) and ventricle (RVDB 5.99 cm, RV mid 5.77 cm), were found. Moderate pulmonary regurgitation and moderate to severe tricuspid regurgitation were consistent with a high probability of pulmonary hypertension. Additional laboratory workup was done for lung disease, thromboembolic, and autoimmune disorders. The patient was counseled about her idiopathic pulmonary arterial hypertension and refused to terminate the pregnancy. A multidisciplinary team, including Obstetrician, Cardiologist, Pulmonologist, Anaesthesiologist, and Neonatologist, collaborated for comprehensive management. The patient showed improvement in symptoms and was discarded from the hospital after ten days of hospitalization.

Unfortunately, after two weeks of being discarded from the hospital, the patient got a water break. The patient visited the obstetrics outpatient unit at 28 weeks of gestation. Vital sign examination was blood pressure of 113/70 mmHg, heart rate of 101 bpm, respiratory rate of 20 breaths/min, pulse oxygenation of 98% on room air, and temperature of 36.3°C. Amniotic fluid flow was visible at the uterine external os on sterile speculum examination. The patient was planned for hospitalization, and antenatal dexamethasone 6 mg twice a day for two days was given for lung maturation of the fetus. Neuroprotectant with MgSO4 20% 4 gr IV slowly bolus continued with syringe MgSO4 40% 10 gr 1 gr/hours was given 24 hours before termination.

At 29 weeks of pregnancy, the patient delivered a male infant with Apgar scores of 6 in the first minute and 9 in the 5th minute by cesarean section under low-dose spinal anesthesia block (SAB). The infant's birth weight was 1126 gr, and birth length was 37 cm. Mechanic contraceptive with IUD T380A was inserted into the uterus post-placental delivery. A preventive B Lynch procedure was done to minimize the risk of hemorrhagic post-partum. The postoperative observation was done in the intensive care unit. The patient condition post-operation was good, without any complaints. The patient was allowed to pump her breast milk because her condition was not a complication. The patient was discarded three days after the cesarean section. Unfortunately, her baby died after eight days of intensive care due to HMD II, which led to respiratory failure.

3. Discussion

PH generally occurs secondary due to underlying medical conditions such as heart and lung disease. Primary PH is less common and is included in a condition called pulmonary arterial hypertension (PAH). Our patient has been diagnosed with idiopathic pulmonary arterial hypertension (IPAH). Primary PH is very rare and often idiopathic, with a life expectancy between 2.8-5 years, especially in young patients. PH can occur in connective tissue diseases such as lupus or systemic sclerosis.[1] This patient showed an ANA test examination result was negative. Clinical findings did not show any criteria consistent with the American College of Rheumatology (ACR) for lupus and systemic sclerosis.[5]

Based on the WHO functional class, this case is included in WHO FC II, characterized by mild physical activity limitations but no complaints when the patient is resting.[2] The patient is suspected of having an Atrial Septal Defect (ASD) due to the presence of RBBB images and "crochetage" signs on all three inferior leads on the electrocardiogram. Crochetage signs obtained in all inferior leads showed 100% specificity, 73.1% sensitivity, and 69% PPV to ASD diagnosis.[6] Nevertheless, the transthoracic echocardiogram did not indicate the presence of intracardiac shunt in these patients.

Pregnancy with a PAH is contraindicated because it causes serious heart failure that could result in morbidity and mortality.[7] Pregnancy causes physiological changes in all body organs, including the cardiovascular system. The volume of blood plasma increases by approximately 6-8L by the time of approaching labor.[8] Hormonal changes in pregnancy, progesterone, and estrogen, also play a role in causing a decrease in systemic vascular resistance (SVR) by up to 40%.[9] The physiologic process in pregnancy causes an increase in the heart size by up to 30% to increase cardiac output up to 30-50%, especially in the first trimester of pregnancy. Mothers with IPAH have idiopathic dilatation of the pulmonary artery as compensation for the high pressure. In this condition, the heart cannot increase CO and potentially cause right heart failure.[3] Physiological pregnancy hypercoagulability conditions increase the risk of thromboembolism which can worsen the condition of the patient with PAH.[7]

Anemia in pregnancy is still a major problem for maternal health in Indonesia. Anemia in pregnancy increases the risk of premature delivery, low birth weight babies, perinatal mortality, and post-partum bleeding.[10] Anemia in pregnant women can occur physiologically as a response to an increased plasma volume with a peak at 30-34 weeks of gestation.[11] Iron deficiency is the main cause of anemia in pregnancy.[12] The incidence of iron deficiency anemia in pulmonary hypertension is quite high, around 40-60%.[13] Iron is needed for hemoglobin synthesis in erythrocytes and myoglobin in the heart muscle and skeletal muscle to facilitate the diffusion and storage of oxygen.[14] Impaired iron homeostasis contributes to pulmonary vascular endothelial dysfunction. Hemoglobin scavenger transporter CD163 is a regulator of cellular function and proliferation of pulmonary arterial endothelial cells (PAECs), and pulmonary artery smooth muscle cells (PASMCs) needed for pulmonary vascular remodeling.[13] The management of anemia and iron deficiency in pregnancy can reduce vasoconstriction of the vascular lung and improve pulmonary hypertension.[4]

Anemia can increase the risk of infection in pregnancy. The infection causes a 2.4-fold increase in the risk of early rupture of the amniotic. A decrease in hemoglobin levels causes a decrease in oxygen transport to tissues, including the membrane amnion. Hypoxia causes an increase in serum norepinephrine which induces maternal and fetal stress. The incidence of anxiety in pregnancy will increase corticotrophin-releasing hormone (CRH). Increased CRH can improve premature labor, hypertension, preeclampsia, and PROM. Iron deficiency can affect the proliferation of T and B cells and reduce phagocytic activity, cell activity, and bactericidal ability, thereby increasing the risk of infection. Infection is one of the risk factors for the onset of premature labor.[15]

The administration of medications can control pulmonary hypertension in pregnancy. Pharmacological therapy for HAP in pregnancy can be divided into four groups: prostaglandins,

phosphodiesterase five inhibitors (PDE-5), endothelin receptor antagonists, and soluble guanylate cyclase stimulators.[9] Only the PDE-5 inhibitor group is available in our hospitals. PDE5 inhibitors as monotherapy can be recommended in patients with functional class FC I or II with normal right ventricular function. Sildenafil is a PDE5 inhibitor first used in pulmonary hypertension and is more widely recommended than the newly recommended tadalafil.[16] Around 2009, PDE5 inhibitors acted on the nitric oxide (NO) pathway as competitive inhibitors against cGMP degradation. Increased cGMP concentrations lead to the activation of protein kinase G through the potassium sarcolemma canal. This process triggers conditions of intracellular hyperpolarisation and inhibition of calcium canals that cause the relaxation of smooth muscles of pulmonary blood vessels.[17] Sildenafil is safe to use in pregnancy, as reported by a meta-analysis study in the Netherlands. Sildenafil in obstetrics is used as a therapy for intrauterine growth restriction (IUGR) in preeclampsia. The administration of sildenafil also positively lowers peripheral vascular resistance and improves uteroplacental flow, which is beneficial for fetal development.[18] In this case, the patient is given therapy with sildenafil 3x20 mg. Complaints of tightness gradually improved after the patient was given therapy with sildenafil. The administration of sildenafil is continued until the KRS patient.

Pregnant women with PH have a higher risk of post-partum bleeding, premature delivery, and cesarean delivery.[19] Childbirth is recommended to be scheduled immediately after fetal lung maturation. Delivery with cesarean section is highly recommended to avoid prolonged labor and prepare for hemodynamic optimization and better anesthesia techniques. Childbirth is associated with an extra increase in CO by 30-50%, with a total increase of 80%. PAP increased from 53.5 mmHg in pre-pregnancy conditions to 72.8 mmHg at 31 ± three weeks. Increased reverse blood flow from causing hemodynamic instability in pregnancy with PAHs. A multidisciplinary team must carry out the management of pregnancy with PAH.[20] Experts consisting of obstetricians, cardiologists, anesthesiologists, pulmonologists, and neonatologists play an important role in managing this case.

Post-partum bleeding can be controlled during surgery by administering oxytocin and the B-Lynch procedure. In addition, oxytocin administration as a preventive therapy for post-saline bleeding is also recommended. However, oxytocin is not allowed to be administered bolus intravenously because it can cause hypotension and reflex tachycardia.[3] The B-Lynch method has been known since 1997 as a suturing method that accommodates mechanical compression of the uterus during surgery to prevent and manage uterine atony.[21] Oxytocin administration, in this case, was given by intravenous drip at a dose of 20 IU in RL 500 cc at a rate of 28 drip/min to 12 hours postoperatively. Postoperative evaluation of this patient found a stable hemodynamic condition, no complaints of tightness were obtained, and the patient could be transferred to the HCU treatment room 24 hours after monitoring in the ICU.

The preoperative management carried out by TS Anesthesia includes the installation of a 2-lane IV line with an 18G needle, the administration of IVFD RL fluid 40 cc/hour during fasting, the fasting of 6 hours of pre-operation, the premedication of ranitidine 50 mg and metoclopramide 10 mg 1 hour of pre-operation and the installation of arterial line pre-operation. The key to managing intraoperative anesthesia in patients with pulmonary hypertension is the prevention of ischemia, especially in the right coronary artery.[22] The strategy that can be applied is to optimize the contractility of the right ventricle by keeping the preload safe and preventing an increase in afterload caused by mechanical, physiological, and pharmacological factors.[23] The installation of invasive arterial lines can be very useful for monitoring coronary perfusion pressure and analyzing diastolic pressure.[22] The administration of pharmacological agents such as norepinephrine and milrinone during surgery is recommended to maintain the perfusion of the coronary arteries. Norepinephrine is an alpha and beta-agonist that functions for inotropic augmentation while also being able to cause systemic vasoconstriction without affecting the pulmonary vascular. Meanwhile, milrinone is a phosphodiesterase III (PDE III) agent that directly affects the relaxation of smooth muscles of pulmonary blood vessels so that it can reduce vascular resistance of the lungs.[23]

Mothers with PAHs are recommended to use contraceptives to prevent unplanned pregnancies. Estrogen-containing contraceptives are not recommended because they will increase the risk of venous thromboembolism (VTE) and negatively affect pulmonary blood vessels. Estrogen also contributes to the pathogenesis of PAH in pregnant patients. Copper-containing intrauterine devices (IUDs) or progestin-releasing IUDs can be the recommended contraceptive options in PAHs.[9] In this case, the contraceptive chosen was a post-placental IUD installed during cesarean section because the patient was still of reproductive age. The IUD installation during surgery is safer because it does not manipulate the cervix so that it does not cause vasovagal reflexes that can harm the patient.

4. Conclusion

We reported cases of 24-year-old women with idiopathic pulmonary arterial hypertension newly diagnosed at 25 weeks of pregnancy with threatened preterm labor and anemia. The patient was diagnosed with a congenital heart defect PDA at the referring hospital. After going through laboratory supporting examinations and echocardiography evaluations, the patient was diagnosed with IPAH. Cardiovascular physiological changes during pregnancy and conditions of anemia compromise heart function, causing manifestations of shortness of breath. Treatment with collaboration between divisions between obstetricians, cardiologists, pulmonologists, anesthesiologists, and neonatologists, in this case, is appropriate. Termination was performed with an elective cesarean section performed to reduce the risk of perioperative mortality. The patient's current condition is good and controlled with the administration of 20 mg of sildenafil three times daily. PAH in pregnancy is a life-threatening condition if untreated. Continuous treatments can help control the symptoms and avoid further complications for both mother and baby.

5. Declarations

5.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

5.2. Consent for publication
Not applicable.

5.3. Availability of data and materials
Data used in our study were presented in the main text.

5.4. Competing interests
Not applicable.

5.5. Funding source
Not applicable.

5.6. Authors contributions
Idea/concept: SH, BR. Design: SH, BR, NP, PMD, VYSP, MSR. Control/-supervision: BR, NP, PMD, VYSP, MSR. Data extraction: SH. Statistical analysis: SH, BR, NP, PMD, VYSP, MSR. Results interpretation: SH, BR, NP, PMD, VYSP, MSR. Critical review/discussion: SH, BR, NP, PMD, VYSP, MSR. Writing the article: SH, BR, NP, PMD, VYSP, MSR. All authors have critically reviewed and approved the final
draft and are responsible for the content and similarity index of the manuscript.

5.7. Acknowledgements
We thank to Department of Obstetrics and Gynecology, Universitas Brawijaya

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Heart Sci J 2022; 3(3): 40-43

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

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Case Report

Central Vein Stenosis in Patient with Routine Haemodialysis: From Diagnosis and Prompt Treatment

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ARTICLE INFO

Keywords:
Arm Edema;
Central Vein Stenosis;
Percutaneous Transluminal Venoplasty;
Arterio-Venous Fistula;
Graft.

ABSTRACT

Background: Central vein stenosis (CVS) is common in hemodialysis patients and is caused by the implantation of cardiac intravascular devices, venous access, and limited vascular access. The effect may develop until an arteriovenous fistula (AVF) or graft is established in the ipsilateral arm or forearm for hemodialysis. Arm edema, significant venous dilatation, and recurring infections are common complications of having an ipsilateral arteriovenous fistula or graft
Case Illustration: We present the case of a 50-year-old female who developed symptomatic CVS while being on regular hemodialysis. Venography using a catheter revealed significant stenosis of the subclavian vein. Due to central venous stenosis, this patient had substantial edema of her left arm after undergoing an ipsilateral arteriovenous graft. Multiple endovascular treatments have failed to alleviate the symptoms.
Discussion: The incidence and danger of central vein stenosis in hemodialysis patients are discussed, as well as the success of endovascular therapies. The initial line of therapy should be percutaneous balloon angioplasty.
Conclusion: Unfortunately, after angioplasty or stenting, primary patency is poor. If there is recurring stenosis, the procedure can be repeated.

1. Introduction

The incidence of Central Vein Obstruction (CVO) ranges between 25% and 40%. The previous history of venous catheterization is the most common cause and serious complication of CVO in hemodialysis access. For individuals with end-stage renal disease (ESRD), hemodialysis is the most commonly prescribed treatment. This treatment should be given through an arteriovenous fistula (AVF) whenever possible, as this affords the best vascular access. This procedure has fewer infection concerns, as well as a lower rate of morbidity and mortality when compared to other techniques of kidney replacement therapy. In the treatment of hemodialysis (HD) patients, central venous stenosis (CVS) and obstruction (CVOD) is a common and serious conditions. By producing venous hypertension with or without severe symptoms, CVD jeopardizes the integrity of the hemodialysis access circuit. This can lead to the access site being lost due to access malfunction or being ligated for symptom relief. In the literature, the incidence of CVD has been estimated to be in the 30 percent range. Stenoses develop in about 40% of patients who had previously undergone a subclavian vein hemodialysis catheter.[1]

Cannulation of the central venous system can lead to central venous stenosis. In dialysis patients, ipsilateral CVC placement is the most common cause. However, it can develop without prior catheter implantation history. While endovascular therapy has a high initial technical success rate, it is associated with a low primary patency rate and a high failure rate, both of which have adverse consequences (e.g., the development of upper limb edema). The therapy of CVS is changing, and the best management method is yet unknown. The findings of trials examining the safety and efficacy of endovascular methods such as balloon angioplasty and venous stenting in CVS were positive; nonetheless, aided primary patency rates tend to decline during the first 12 months, necessitating additional treatments to preserve AVF patency. This case study aimed to examine central venous thrombosis caused by a hemodialysis catheter from a clinical standpoint, from diagnosis through treatment.[2]

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https://doi.org/10.21776/ub.hsj.2022.003.04.8
Received 9 July 2022; Received in revised form 30 August 2022; Accepted 15 September 2022
Available online 1 October 2022

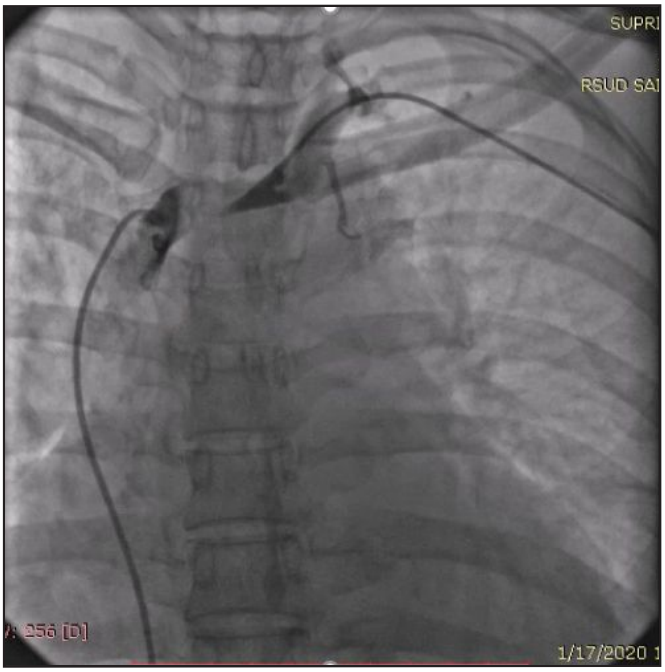

Figure 1. Venography before percutaneous transluminal venoplasty

2. Case Illustration

A 50-year-old woman with the chief complaint of a swollen left hand. She had Swollen on the left hand for 1.5 years before admission, accompanied by pain, the skin on the left hand was reddish, and sometimes felt pins and needles. She went to the nearest hospital. They performed an ultrasound examination of the left hand and continued with an imaging test of the left arm blood vessels. The result was a narrowing in the left arm vein. The patient was then referred to our hospital for further treatment. For the past medical history, she was suffered from Chronic Kidney Failure 2 years ago and routinely got dialysis two times a week. She had implantation of the double lumen in the left hand during the initial 5 months of dialysis. Because the left hand began to swell, then the patient performed AV-Shunt implantation 1.5 years ago. For the risk factors, she got no Diabetes mellitus. However, she has had hypertension since 4 years ago. Routine medications were Lisinopril 1x10 mg, Amlodipine 1x10 mg, Bisoprolol 1x2.5 mg, Atorvastatin 1x20 mg. From family history, her mother had hypertension.

Clinical Manifestation BP 160/95 mmHg HR 96 bpm RR 18 tpm SpO2 99% room air, Weight: 70 kg, Height: 155 cm, BMI 29.1 kg/m2, BSA 1.69 m2. JVP R+2 cmH2O, Ictus cordis was invisible, palpable at ICS VI MCL. S1-S2 normal, no murmur and gallop. Vesicular breath sound, no crackles or rales, no wheezing. Extremities edema at the left arm. Left arm locational status was arm circumference 36 cm with edema and redness. Chest X-ray showed Cardiomegaly. For the Duplex Ultrasound examination in August 2019, the result was suspicious of stenosis in anastomose AV-Shunt of the left ulnar artery – left cephalic vein, and there were no aneurysms or DVT along the upper left limb. Then we continued to perform Peripheral Arteriography in Sept 2019, the result was normal arteriography, AV – Shunt patent, and there was an enlargement in the proximal one-third radial vein up to the superior vein of upper left extremities. From all the examinations, we conclude that she got suspicious of central venous stenosis. Then we performed venography and continued with venoplasty. The venography upper left extremity revealed stenosis 100% at the Subclavian vein, irregularity at the axillary vein, and stenosis 70% at the radiochepalic shunt anastomosis (Figure 1).

We performed a percutaneous transluminal venoplasty procedure. The patient was laid on the operating table and disinfected with 10% povidone-iodine in the left radial region and right and left inguinal. The patient was closed with a sterile cover and given local anesthesia with 2% pehacaine in the left radial and right inguinal regions. The 6F radial sheath with the Selinger technique was inserted in the left radial artery. Then the MPA-1 5F diagnostic catheter was advanced to the Cephalic Vein via the AV Shunt with the guidance of Terumo hydrophilic wire J-stiff 260 cm. Wire Entering the left Subclavian vein, cine-angiography was performed. There was stenosis in the left subclavian vein. Another puncture was performed on the right femoral vein, and 7F femoral sheath was inserted. Then, JR 3.5 6F diagnostic catheter with a Guidewire Terumo hydrophilic wire J-stiff 260 cm directed towards the left subclavian vein for cine-angiography. There was stenosis in the left subclavian vein. Heparin 5000 IU IV was given, and a Mustang 5x40mm balloon was directed through the left radial artery to the left Subclavian vein. The balloon successfully penetrated the stenosis and was inflated several times with a pressure of 10 atm for 2 minutes. After that, cine-angiography revealed minimal flow in the left subclavian vein. The balloon was directed to radiocephalic shunt anastomosis and then inflated for 8 atm for 2 minutes, followed by 10 atm for 2 minutes. We changed the Mustang 5x40mm balloon with the Mustang 10x40mm balloon to the left Subclavian vein (Figure 2). The balloon was inflated gradually along the left Subclavian vein with 8 atm for 2-minute. After that, the cine-angiography showed adequate flow in the left Subclavian vein (Figure 2). All devices were removed, and the procedure was completed. We successfully performed percutaneous transluminal venoplasty at the stenosis left Subclavian vein with adequate flow and suggested optimal medical treatment.

3. Discussion

A pathophysiologic venous luminal narrowing that obstructs blood flow is referred to as venous obstruction. The obstruction could be partial or complete. Obstructions were further classified as central, which meant the obstruction was closer to the right atrium, BCVs or SVC, or peripheral, which was farther away from the right atrium, BCVs, and SVC, for example, SCV and IJV obstructions.[3] Fibrosis, organized mural thrombus, or De novo smooth muscle hyperplasia could cause venous wall thickening, as could stent, implanted cardiac rhythm device leads, stent graft, or catheter. Wall thickening could be caused by infection, tumor infiltration, inflammation, hematoma, or intramural dissection. The endoluminal obstruction, which is most commonly caused by a thrombus, could also be caused by the implanted endoluminal device (as mentioned above) or the secondary formation of fibrous or neointimal tissues.[4] Swelling and discomfort in the arm or neck and venous distension were common clinical features. In some cases, patients might experience unusual symptoms, such as jaw or shoulder pain.4 In our case, the patient had left arm swelling after having a double lumen for dialysis access implanted.

CVS remained a difficulty for doctors working in vascular access maintenance. It was frequent in HD patients and constituted a significant danger to the AVF's development and patency. Several different factors could cause catheter-related thrombosis (CRT). These factors are linked to Virchow's triad of hypercoagulability, stasis, and endothelial damage described as thrombus-forming components. In the HD population, CVS was thought to be caused by a combination of vein damage generated by central venous catheterization for temporary access and AVF formation causes higher flow and turbulence.[5]

Animal models of vein injury had shown that a "critical area" of injury was required for platelet microthrombi to form within 24 hours, followed by smooth muscle proliferation over the next 7–8 days. Subclavian vein atherectomy specimens from individuals with symptomatic stenosis or occlusion revealed intimal hyperplasia and

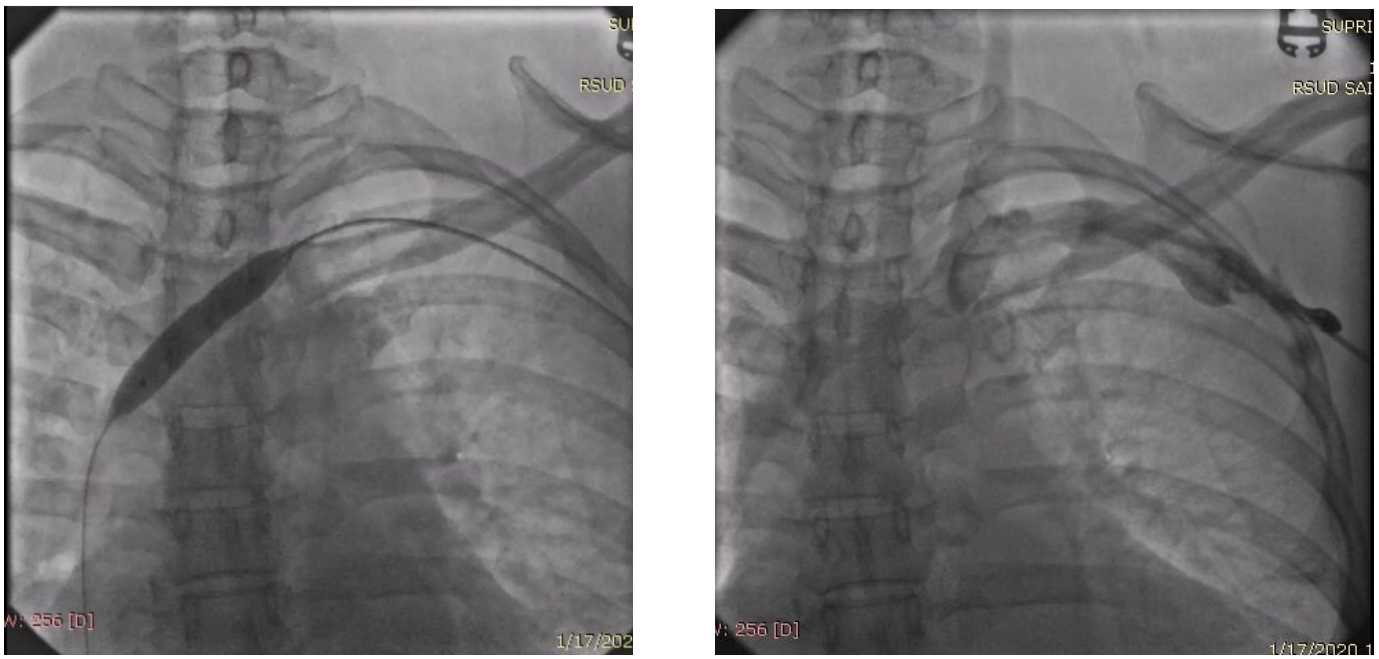

Figure 2. Venography during and after percutaneous transluminal venoplasty procedure

fibrous tissue alterations. Thrombus could form inside, around, or at the catheter's tip. Fibrin sheaths, sock-like structures that formed on the catheter's external surface within 24 hours of insertion, could obstruct flow into and out of the catheter. When blood refluxed into the catheter, an intraluminal thrombus was formed. These occlusions could be partial or complete and could occur because of insufficient flushing, low infusion rates, or a combination of these factors.[6,7] The link between the placement of a tunneled dialysis catheter in the upper limb and the development of CVS was well known. The risk of CVS was increased for those who have had subclavian vein catheters in the past, and recommendations were made to use the internal jugular vein instead of the subclavian vein for tunneled dialysis catheter placement. To limit the risk of thrombosis, CVCs should be put in the jugular vein on the right side of the body, with the tip near the intersection of the superior vena cava and the right atrium, according to the International Society of Thrombosis and Hemostasis recommendations.[7]

For the diagnosis of CRT, a venous duplex is recommended. If a suspicion of CRT is found from clinical presentation, or if lumen patency is not restored with simple measures, duplex ultrasound is the first imaging modality of choice. It is non-invasive and especially good at detecting thrombi in anatomically accessible veins like the axillary, jugular, arm, and distal subclavian. The left and right arm's superficial and deep venous systems might be evaluated from the wrist to the central veins if technically viable (axillary or distal subclavian vein).[6] Certain sonographic parameters for assessing veins prior to vascular access implantation were found by Silva et al. When using a tourniquet. An AVF requires a 2.5 mm venous luminal diameter and grafts require a diameter of 4.0 mm. The ipsilateral upper arm's deep venous system had to be connected, and there had to be no blocked segments or segmental stenoses. In ultrasound tests without the application of a tourniquet, a minimum diameter of the cephalic vein of >2.0 mm results in a much larger proportion of well-matured fistulas. Stenosis was also detected using parameters such as the presence of abnormal Doppler finding at the site of stenosis, post-stenotic turbulence, spontaneous contrast, slow flow, poor augmentation, vein dilatation, and contralateral asymmetry in the absence of superior vena cava (SVC) or inferior vena cava (IVC) obstruction, prior to the stenosis.[8] By comparing the smallest lumen to the usual lumen, planimetry was utilized to determine the vein diameter decrease. The luminal reduction was measured using B-mode, color, and power Doppler in both the longitudinal and transverse views. The diameter reduction was used to calculate a >50 percent stenosis and an area reduction of >75 percent. The preferred approach to CVS has been angioplasty with or without stent placement. The preferred treatment for CVS is the percutaneous intervention with transluminal angioplasty. The interval between the time of graft deployment and any intervention designed to maintain or reestablish the patency was defined as primary patency (intervention-free stent-graft patency). The interval between graft insertion and access abandonment or measurement of patency was defined as secondary patency, which included any intermediate treatments (surgical or endovascular procedures) to restore thrombosed access functioning (access survival till abandonment).[9, 10]

In angioplasty, we can use a variety of balloons, including "high-pressure," "ultrahigh-pressure (UHP)," "cutting," and "drug-eluting." We used Mustang balloons in this case, which are high-pressure, non-compliant balloons. They are dedicated to treat dialysis vascular access stenosis and have burst pressures ranging from 20 to 24 atm.[11] PTA had a high initial technical success rate, ranging from 70 to 90%. Primary and cumulative patency rates varied widely, with primary patency rates ranging from 23 to 63 percent at 6 months and 12 to 50 percent at 12 months and cumulative patency rates ranging from 29 to 100 percent at 6 months and 13 to 100 percent at 12 months. Following angioplasty, restenosis areas showed more aggressive neointimal hyperplasia and proliferative lesions than stenotic lesions.[11]

The fact that many central vein lesions were quite elastic was a major issue. With repeated angiography, secondary patency could be significantly improved. The central veins were much more likely than the peripheral veins to recoil, and the success of PTA was determined by the lesion's elastic or nonelastic nature. Cost considerations were important, as was the fact that we had no other option for effectively treating restenosis inside a stent. Even if we double the half-life of recurrent stenotic access (from every 3 months to every 6 months), it might appear to be a significant achievement, but it had little clinical significance.[12]

Endovascular procedures could be completed quickly and without the need for extensive preoperative planning. Second, hemodialysis could be resumed immediately if the AVF was successfully recanalized. Temporary hemodialysis catheter indwelling was not required during wound recovery following surgical thrombectomy. Because of these advantages, endovascular thrombectomy was suggested as the first line of therapy for individuals with thrombosed AVFs.[12]

In the case of CRT treatment, the consensus is that systemic anticoagulation should be used for at least three months. If the catheter remained in place after three consecutive months of anticoagulation, prophylaxis was advised until the line was removed. Due to a paucity of high-quality information, the duration of anticoagulation after removing a line in people with no persisting thrombotic risk factors is currently debated. Some doctors prescribed anticoagulants for three months, while others prescribed them for less time. Other potential thrombosis risks, the size of the clot, and the extent to which it occluded the vessel should all be factored into the decision-making process. If there were no risk factors and the clot was small and non-occlusive, six weeks of anticoagulation might be sufficient.[10-12]

4. Conclusion

A catheter-based hemodialysis is still a feasible option for many chronic kidney disease (CKD) patients. In addition to catheter-related infections, CRS development was responsible for a considerable share of catheter malfunction. The venous wall's reaction to the catheter and the thrombus it caused was dynamic and continuous. It involved biologically active cell types and bore many resemblances to the thrombus formation process. PTA was a relatively safe and effective treatment for CVS, with a high success rate, few side effects, and a good radiologic and clinical outcome.

5. Declarations

5.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

5.2. Consent for publication
Not applicable.

5.3. Availability of data and materials
Data used in our study were presented in the main text.

5.4. Competing interests
Not applicable.

5.5. Funding source
Not applicable.

5.6. Authors contributions
Idea/concept: YPA, NK. Design: YPA, NK. Control/supervision: NK. Literature search: YPA, NK. Data extraction: YPA, NK. Statistical analysis: YPA, NK. Results interpretation: YPA, NK. Critical review/discussion: NK. Writing the article: YPA. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

5.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.

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Volume 03 | Issue 04 | 1st October 2022
p-ISSN 2721 - 9984
e-ISSN 2721 - 9976
heartscience.ub.ac.id

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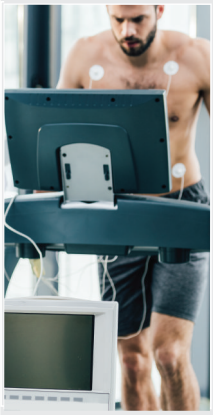

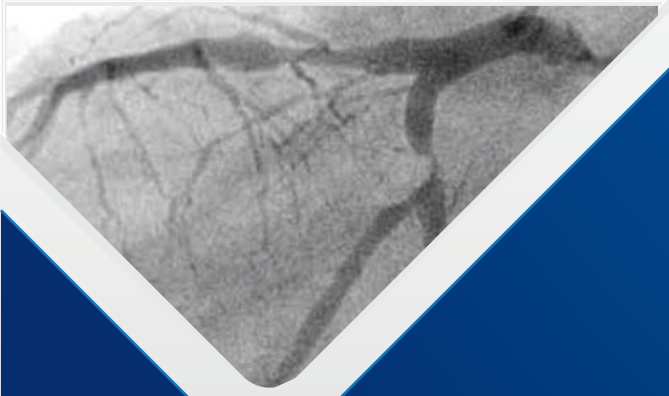

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