

Inotropic Requirement in Patients Undergoing Coronary Artery Bypass Grafting (CABG) in RSUP Dr. Hasan Sadikin Bandung in 2014-2016

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How to cite this paper: Sudjud, R.W., Catriona, A. and Kadarsah, R.K. (2020) Inotropic Requirement in Patients Undergoing Coronary Artery Bypass Grafting (CABG) in RSUP Dr. Hasan Sadikin Bandung in 2014-2016. *World Journal of Cardiovascular Surgery*, 10, 41-49.
<https://doi.org/10.4236/wjcs.2020.104006>

Received: November 4, 2019

Accepted: April 10, 2020

Published: April 13, 2020

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Abstract

Inotropic agents are indicated to treat ventricular dysfunction that frequently found post-CABG surgery. However, the use of inotropic isn't free from disadvantageous side effects and is related to higher morbidity and mortality in post-CABG surgery patients. Several risk factors are known to affect higher need for inotropic agents' post-CABG surgery. This study aims to discover the inotropic requirement in patients undergoing CABG surgery based on age, sex, preoperative left ventricular ejection fraction (LVEF), comorbidities, cross clamping time (CCT), and cardiopulmonary bypass (CPB) duration in Hasan Sadikin General Hospital Bandung in 2014-2016. This study is a descriptive cross-sectional study done retrospectively through medical records. This study found the inotropic requirement post-CABG surgery was 130 patients (74.3%). The inotropic requirement based on age was 28 patients (80.0%) > 65 years old, 112 patients (75.7%) were male, 18 patients (66.7%) were female, 19 patients (100%) with <40% LVEF, 41 patients (85.4%) with DM, 20 patients (90.9%) with CKD, 44 patients (93.6%) with >90 minute CCT, 37 patients (90.2%) with >120 minute duration CPB. In conclusion, there was a higher inotropic requirement in patients with age > 65 years old, preoperative LVEF < 40%, DM and CKD comorbidities, CPB duration > 120 minutes and CCT > 90 minutes.

Keywords

Coronary Artery Bypass Grafting, Inotropic Requirement, Risk Factors

1. Preliminary

Coronary Artery Bypass Grafting (CABG) is an open cardiac surgery that is of-

ten reserved due to the high number of the incidence of coronary heart disease of the world population. Based on UN data in 2008, the number of morbidity caused by ischaemic cardiac disease has reached 12.7% of the total number of morbidity worldwide. Coronary artery bypass grafting (CABG) is a recommended therapy to improve patients' survival suffering from coronary artery three-vessel disease (CAD 3VD) with or without the involvement of the proximal left anterior descending (LAD) artery [1] [2].

Ventricular dysfunction is one of the CABG complications most commonly found. Although there has already been a rapid progress in the protection of the myocardium, the surgical technique, and perioperative treatment, yet some studies reported the incidence of biventricular dysfunction rate of 90% in the early postoperative period [3]. One of the causes of low cardiac output syndrome is severe ventricular dysfunction. In general, low cardiac output syndrome is defined by low rates of the cardiac index (CI) (less than 2.2, 5 L/min/m²), systolic blood pressure less than 90 mmHg. Also, dysfunction of organs (e.g. the production of urine is less than 0.5 mL/kg body weight/hour) or other signs of hypoperfusion without hypovolemia are found. This syndrome is characterized by a decrease in the heart pump function which causes a decrease in the delivery of oxygen (DO₂) resulting in tissue hypoxia. Low cardiac output syndrome is associated with an increase in postoperative morbidity and mortality, increased length of stay, increased use of hospital resources, and the accumulative cost of health care [4].

The causes of ventricular dysfunction involve a variety of factors, including surgical tissue trauma, ischemic myocardial injury-reperfusion, regulation disturbance of beta-adrenergic receptors, coronary embolization, cascade activation of inflammation and coagulation, as well as heart disease that is not improved previously. The administering of inotropic agents aimed to improve the dysfunction of systolic ventricular and maintain the cardiac adequacy of patients after the use of the cardiopulmonary bypass machine (CPB) and cardioplegia. Inotropic agents are given as selective as to improve the risk of tachycardia and dysrhythmias thus increasing the consumption of oxygen of the myocardium, which in turn leads to myocardial ischemia [4] [5].

Knowledge of the specific risk factors of the occurrence of ventricular dysfunction after CPB machine weaning is essential to plan the intervention prophylaxis cardio-protection and supportive therapy by administering of cardiovascular medications and even the use of supportive circulation machine (e.g. intra-aortic ballooning pump). According to previous researches, factors of ventricular dysfunction risk which require inotropic agents consist of two factors, namely the preoperative risk factor and intraoperative risk factors. Preoperative risk factors cover elderly age, female gender, decrease in left ventricular ejection fraction, and the comorbidity (DM and CKD). Whilst the intraoperative risk factor is cross-clamping time (CCT), duration of CPB, the complexity of the surgery associated with the ischemic myocardium injury, the emergency surgery,

and imperfect revascularization [4] [5] [6] [7].

The necessity of inotropic agents on patients who underwent CABG surgery may be one of the predictors of the output postoperatively. According to previous studies, the mortality rate of patients who received the inotropic agents within 30 days and that within 1 year is higher. The mortality number of patients who require postoperative and perioperative inotropic agents within 1 year is higher compared to patients who only require intraoperative inotropic agents. Besides, patients who consume the inotropic agents are found to increase in numbers of infarct myocardium, strokes, and require renal replacement therapy more frequently [8].

Data on patients' characteristics which necessitate postoperative CABG inotropic agents at Dr. Hasan Sadikin General Hospital Bandung has by far unavailable. This study aims to determine the number of postoperative CABG inotropic agents necessity based on factors that may increase the risk of inotropic agents needs such as age, gender, preoperative left ventricular ejection fraction, and comorbid disease (DM and CKD), duration of CPB, and CCT.

2. Subjects and Research Methods

This research is an observational descriptive cross-sectional study. The subject of the study was the patients' medical record with a diagnosis of coronary artery disease 3 vessel disease (CAD 3VD) who underwent CABG surgery at Dr. Hasan Sadikin General Hospital Bandung. After obtaining approval from the Health Research Ethics Committee of the Faculty of Medicine Padjadjaran University/Dr. Hasan Sadikin General Hospital Bandung, researchers conducted data observations in the medical records section of Dr. Hasan Sadikin General Hospital Bandung in June 2018.

The subject selection of research is done by inclusion criteria. They are patient medical records with 3VD CAD who underwent CABG surgery and were treated in the intensive care unit from January 2014 to December 2016. Whilst the exclusion criterion is the incomplete patient medical records. Sample taking technique is *total sampling* and the number of samples collected is 175 patient medical records. Data examined include age, gender, preoperatively left ventricular ejection fraction (LVEF), complementary disease (DM and CKD), duration of CPB, and CCT. Data from observations of medical records gathered are classified according to the operational definition of the study. The collective data is processed by computerized technique to transform the data into information through editing, coding, data entry, and cleaning.

Data analysis of this study is a descriptive analysis which depicts the necessity figures of inotropic agents, such as the frequency or the amount presented in the form of proportions. Univariable data analysis on categorical data is presented in numbers (n) and percentage (%). As for the numerical data analysis is presented in the form of *mean* and *median* for the data focusing extent. Whereas the extent of data prevalence is presented with minimum and maximum data and *range*.

3. Discussion

This retrospective study finds that in the medical records data of the medical years of 2014 up to 2016, most patients with a diagnosis of CAD 3VD require CABG postoperative inotropic agents (130 patients out of total 175 patients or 74.3%). The rate of inotropic needs in this study was higher compared to previous studies conducted in patients undergoing CABG surgery that was 32.4%. While in other studies, the number of inotropic needs was 52% in patients who underwent CABG surgery and aortic valve replacement. This might be due to differences in preoperative, intraoperative factors, the complexity of surgeries, and so on [7] [9].

Based on the data gathered, there was an increased need for inotropic agents in patients of 65 years old. Elderly age is one of the predictors of the use of postoperative CABG inotropic drugs [6] [7]. Aging is the process of physiology that occurs progressively and has the characteristics of a typical form of a decrease in the function of organs, a decrease in the functional capacity, imbalance mechanism of homeostasis, and an increase in the incidence of the pathological process. The structure and function of the heart weaken along with the increasing of age. Structure changes include a decrease in the number of myocytes and ventricular left hypertrophy. These structural changes led to a decrease in contractility, an increase in the stiffness of the myocardial muscle, and an increase in the filling pressure of ventricles. The increased activity of the sympathetics might occur in elderly patients and caused intraoperative hemodynamic vascular resistance lability increase occurred consequently. A decrease in response to receptor β on elderly patients occurred so that the rate of maximum pulse and the cumulative ejection fraction decreased. Subsequently, the needs of the metabolic to an increase in cardiac output were filled mainly with *preload* which led the elderly are likely to be prone to heart failure [10]. Elderly patients with high risk against complications postoperatively are due to a decrease in the functions of the organ as a whole, especially changes in the structure and function of the heart and vascular that affect the performance of the cardiovascular. Also, there was an increase on the prevalence of comorbidity in elderly patients [11].

This study showed that all patients with preoperative LVEF < 40% needed inotropic agents. Previously conducted research found that patients with LVEF < 40% required an inotropic agent and intra-aortic ballooning pump (IABP) more frequently compared to patients who had LVEF > 40%. Low LVEF is the most important predictor in the morbidity and mortality postoperatively. Patients with decreased ventricular function are prone to postoperative low cardiac syndrome due to preoperative ventricular function impairment coupled with intraoperative myocardial injury (ischemic injury and reperfusion injury). Another study also showed that in the group of patients with inotropic agents, patients with LVEF \leq 40% were found as many as 46% while in the group of patients without inotropic agents the patients who had LVEF \leq 40% was of 32% [6] [12].

Other research showed that in elderly age group, low LVEF, the duration of

CPB, and repetitive surgeries helped play a role in long hospitalization in intensive care unit. Moreover, it was found in patients with LVEF less than 40% of the time required is much longer to achieve stable hemodynamics and weaned from mechanic ventilation so as to extend the period of treatment in the intensive care room [6] [13].

Pharmacology regimens to help the myocardium during the recovery must consider the pathophysiological process of the chronic failure of heart congestive. When dilated ventricles in chronic heart failure occur, compensated myocardium by the law of Laplace leads to an increase in the muscle mass. The increase in the muscle mass (hypertrophy) causes an increase of energy necessity so that the increase in the transport of metabolic substrates to the myocardium is necessary to increase the production of energy. Myocardial blood flow in ventricular hypertrophy remains normal in non-ischemic conditions but coronary blood flow in ischemic conditions will decrease. As a result, the reduction of cyclic adenosine monophosphate (CAMP) and slowing of the activity of myosin adenosine triphosphatase (ATPase) cause abnormal systolic contractions [12].

Accompanying DM and CKD are also preoperative risk factors that increase the risk of inotropic agent requirements. In this study, patients with DM and CKD had a higher incidence of inotropic needs compared to patients who did not have the concomitant disease. In the previous study, it is stated that patients with CKD and DM were found to have an increase in the risk of the syndrome of low cardiac output of as much as 50% [4]. Patients with diabetes had diffused coronary artery stenosis and more dysfunction of organs. Formerly conducted research in patients with DM who underwent CABG showed much higher complications of kidney compared to patients who did not suffer from diabetes (5, 5% compared to 1, 4%). Whereas another research found an increase in mortality within 30 days and morbidity as much as 23% - 37% compared to patients who did not suffer from DM. Heart disease is the most prevalent cause of death in DM patients [14].

Diabetes mellitus is one of the perioperative predictors against the incidence of lower cardiac output syndrome. Formerly conducted studies found that 13% of patients with diabetes experienced a lower cardiac output syndrome with an *odds ratio* of 1.6 and the value of $p < 0.001$. This is probably because the patients suffering from diabetes having the atherosclerosis disease are more prevalent so as to limit a complete revascularization. Furthermore, the protection of the myocardium on patients with cardioplegia experienced difficulty with multiple lesion coronaries. Proximal coronary lesions may disrupt the anterograde flow of cardioplegia fluid that it reduced the myocardial protection [11].

Earlier research resulted that patients with decreasing GFR until below 60 mL/min/1.73m² had a significant increase in the incidence of cardiovascular (coronary artery disease, heart failure, strokes, and peripheral arterial disease). This is probably associated with the function of regulation of kidney that was reducing, including the reduction of vitamin D 1.25 [OH] and the synthesis of

erythropoietin. Disruption in the production of the hormone regulation has led to changes in the environment that tends to increase calcification of vascular and decrease the capacity of transporting oxygen [15].

Changes in calcium/phosphate homeostasis due to a decrease in vitamin D of 1.25 [OH] and an increase in parathyroid hormone began to be detected when the GFR reached 60 mL/minute/1.73m² and became clearer when it reached GFR 45 mL/minute/1.73m². Improved calcium/phosphate products associated with the prevalence of calcification of vascular, arteriosclerosis, and mortality were caused by cardiovascular events. Other pivotal factors in the increase of the cardiovascular incidence in patients with CKD are a decrease in the production of erythropoietin and anemia. There is a clear reciprocal relationship between haemoglobin levels and the risk of cardiovascular events. Cardiovascular events and mortality, particularly the secondary on the heart failure at the levels of Hb < 13 g/dL was found to rise. Partial correction of Hb levels can reduce cardiovascular events [15]. CKD stage 3 to stage 5 with GFR < 60 mL/min/1.73m² is a free use predictor of inotropic use when weaning from CPB machines. While on another study, it is proven that eGFR is a factor of risk significantly to mortality operative in patients who underwent CABG and CKD stages 3, 4, 5 which are progressively associated with an increase in mortality [9].

In this study, patients with a duration of CPB > 120 minutes had higher rates of inotropic agent needs compared to patients with a duration of CPB ≤ 120 minutes. CPB activates the coagulation system and also the fibrinolytic system, the complement system, leukocytes which cause degranulation and release of cytotoxic enzymes, and inflammatory mediators such as tumor necrosis factor- α (TNF- α), interleukin (IL) -1, IL-6, and IL -8. The activation of various cascades of inflammation caused by the release of mediators of inflammation is believed to be the cause of the dysfunction of organs. CPB may also have negative effects on the immune system so that it can increase the risk of postoperative infection complications such as multiple organ failure. The longer the duration of CPB and the more exposure to the surface of the artificial, the worse the effect will be [16].

Ever since the beginning of the modern cardiac surgery, perioperative myocardial dysfunction associated with morbidity and mortality has been reported. Evidence terms for the subendocardial necrotic cells lead to a conclusion that the injury is due to inadequate supply to metabolically active myocardium. Basic protection of myocardium particularly uses the technique of hypothermia and the maintenance of stopping the heart by giving cardioplegia that contains potassium. The consequences of metabolic deficiency of oxygen become clear in seconds when an occlusive arterial coronary happens with the depletion of highly rapid phosphate energy, accumulation of intracellular acidosis and intracellular acidosis in myocytes, and subsequently followed by dysfunction contractility. When the levels of ATP in myocyte decreases in at the critical level, inability to maintain gradients of electrolytes that require active transport occurs (e.g. Na⁺,

K⁺, Ca²⁺) and incited intracellular edema, an overload of Ca²⁺, as well as the disappearance of integrity of the membrane of cells [17].

The mechanism of the potential occurrence of myocardium dysfunction related with the use of CPB is associated with disorders of acute transduction of β -adrenergic signals. Acute desensitization and downregulation of myocardial β -adrenergic receptors during CPB may occur after cardiac surgery. This emphasized that the effects have helped play a role in the increase of syndrome incidence of low cardiac output after CPB and the decrease in the response to inotropic drugs [17]. The duration of CPB and CCT during operations are correlative to the needs of inotropic support postoperatively. Earlier research has proven that the duration of CPB of more than 120 minutes is one of the predictors of the incidence of cardiac complications (arrhythmia, infarct myocardium, congestive heart failure). The longer duration of CPB may also be caused by the technical difficulty in the scheduled surgery plan. Normally, it was due to anatomic difficulty or intraoperative complications that can affect the output postoperatively. Furthermore, the complex procedure is one of the CPB extensive predictors [12] [18].

This study has proven that the need for inotropic agents was higher in patients with CCT > 90 minutes compared to patients who had CCT \geq 90 minutes. Damage to myocardial perioperative is considered the determinant of the major output on patients who undergo heart surgery. CCT prolongation is associated with the release of myocardial enzymes in response to significant myocardial ischemia. Previous study proved that the old CCT aorta is a risk factor of myocardial infarction during CABG surgery [17]. Another research showcased that CCT > 90 minutes is the highest variable in increasing the risk of the need for inotropic agents after the CPB machine weaning (*odds ratio* 2.32). Myocardium preoperative infarct along with other variables such as age of >65 years and NYHA class 2 is an independent predictor ventricular dysfunction after the CPB which requires inotropic agents. Inotropic agent requirements which were more substantial in the extensive CCT were also found in another study. In a retrospective study of 1280 patients, an increase in the necessity for inotropes, the levels of the enzyme creatinine kinase, the levels of the CKMB enzyme, and extensive health care elderly patients being hospitalized in the group with much longer CCT have been proven [7] [19].

Earlier studies conducted comparative of the effects of CCT on the higher and lower risk patients showcased that the elongation of the CCT increases morbidity and mortality rates in patients. The study divided CCT into 3 groups, namely CCT group of <60 minutes, CCT group of 60 - 90 minutes, and CCT group of >90 minutes. In the group of patients with lower risk, the incidence of postoperative low cardiac output syndrome increases in CCT groups > 90 minutes (OR 3.2). Whilst on the higher risk group of patients, an increased incidence of the syndrome of low cardiac output postoperatively in the CCT group > 90 minutes. Upon conducting any 1 minute CCT extension (OR 3.0), there found

an increase of in the risk of mortality of as much as 2% in patients with higher risk and lower risk [20].

4. Conclusion

The inotropic requirement is increased on patients with CAD 3VD who underwent CABG with age more than 65 years old, with preoperative LVEF < 40% and with diabetes and CKD morbidities, the requirement also increased on patients who had CPB duration more than 120 minutes and CCT more than 90 minutes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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