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Role of Aspirin Resistance, Mechanical Factors and Inflammation on Early Saphenous Vein Graft Thrombosis After CABG

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Abstract

Objectives: This study was carried out to determine the role of pre-operative and transient aspirin resistance in the formation of early saphenous vein graft (SVG) thrombosis six weeks after coronary artery bypass graft (CABG) surgery and to analyze the other factors, such as mechanical and inflammation factors, that are also suspected of contributing to the formation of early thrombosis.

Methods: Pre- and post-operative blood samples were taken from 99 subjects, whom 74 patients were undergoing elective on-pump CABG and receiving aspirin as monotherapy, for evaluation of inflammation parameters and the state of aspirin resistance using a Platelet Function Analyzer-200 (PFA-200). Transit time flow measurements (TTFM) were performed intra-operatively to determine mechanical factors. Multi-sliced computed tomography (MSCT) was done six weeks after surgery to determine the patency of the vein grafts.

Result: In the 222 vein conduits, aspirin resistance was related to early vein graft failure due to thrombosis ($p < 0.001$; relative risk (RR) = 3.69). The massive increase of interleukin 6 (IL-6) levels after surgery were related to the existence of post-operative transient aspirin resistance ($p < 0.001$). Transient aspirin resistance (IL-6 > 122.5) was associated with early graft failure ($p = 0.029$; RR = 8.6) compared to the aspirin-sensitive group (IL-6 > 122.5).

Conclusion: Aspirin resistance plays a primary role in early vein graft thrombosis. Transient aspirin resistance accompanied by an increase of inflammation factor (IL-6) significantly increases the risk of early vein graft thrombosis after CABG.

Background

Coronary artery bypass grafting (CABG) surgery is a revascularization modality used in patients with coronary artery disease (CAD). In this procedure, saphenous vein grafts (SVGs) are the most frequently used conduits because they are easy to harvest, have a large diameter, convenient anatomy, and technical features, and can be used for multiple grafts. However, SVG conduits are more susceptible to thrombosis during the first postoperative year (15–18%), which increases the risk of repeat revascularization, myocardial infarction, and death.[1,2]

Aspirin is believed to reduce the incidence of post-CABG thrombosis by suppressing platelet function through cyclooxygenase (COX)-1 inhibition.[3] COX-1 is an enzyme that acts as a catalyst in regulating thromboxane A2 (TXA2) from arachidonic acid (AA). Nonetheless, routine aspirin administration has not been shown to reduce the incidence of early SVG thrombosis after CABG. It is suspected that this phenomenon is closely related to aspirin resistance.[4,5]

Aspirin resistance is defined as inappropriate platelet inhibition that correlates to the persistence of thromboxane formation and high ex-vivo platelet reactivity. In clinical settings, it has been shown that platelet activation and aggregation are not being inhibited, so the formation of thrombosis is ongoing.

There are two types of aspirin resistance: the resistance found before the CABG procedure and the temporary resistance that occurs after CABG, which usually lasts up to 30 days in subjects who were previously sensitive to aspirin. These events could occur as a result of the inflammatory response during CABG (e.g., from the use of a cardiopulmonary bypass (CPB) machine), which includes the increasing platelet count, endothelial cells, leukocyte, complement, and coagulation cascade activation.[1,4,6]

Besides aspirin resistance, early SVG thrombosis post-CABG could also be caused by mechanical factors, such as native vessel diameter and conduit blood flow, or by inflammation factors that occur through the formation of transient aspirin resistance post-CABG or directly by influencing thrombus formation. This SVG thrombosis could trigger future major and minor cardiovascular events. Therefore, this study evaluated the relationship between pre-operative aspirin resistance, transient aspirin resistance, inflammation, and mechanical factors related to the incidence of early SVG thrombosis after CABG.

Subjects And Methods

The study design is an observational cohort study with a repeated measurement conducted in Harapan Kita National Cardiovascular Centre from January 2014 until March 2015. This study has been ethically reviewed and approved by the ethics committee of the National Cardiovascular Centre Harapan Kita. The populations of this study are CAD patients undergoing elective on-pump CABG procedures. Non-probability consecutive sampling method was used in subjects that meet the inclusion and exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria included subjects with CAD undergoing elective conventional CABG surgery, a creatinine clearance time (CCT) of more than 50 ml/minute, signed informed consent to participate in the study, and a willingness to be monitored for six weeks after surgery. The exclusion criteria were subjects with CAD complicated by heart valve surgery, indications of another procedure beside CABG, intraoperative coronary endarterectomy, a mean graft flow (MGF) of less than 10 ml/sec and/or a pulsatility index (PI) of more than 5, allergies to contrast media, a target vessel diameter of less than 1.0 mm, a CPB duration of more than 120 min, an aortic cross-clamp duration longer than 90 min, the presence of cardiovascular complications after surgery, and the use of extracorporeal membrane oxygenation (ECMO) and/or continuous veno-venous hemofiltration (CVVH) after surgery. This study was conducted on subjects that fulfilled all inclusion and exclusion criteria, had been informed about the objectives and the risk of the study and had signed the informed consent.

Aspirin administration and pre-operative assessment

All subjects were given 100 mg aspirin once daily as the only anticoagulant for a minimum of seven days before a laboratory test of aspirin sensitivity was done using a PFA-200. The PFA cut-off point was 193 seconds. A value of < 193 seconds was considered as resistant to aspirin while a value of ≥ 193 seconds was considered as sensitive to aspirin. Other pre-operative laboratory tests, such as IL-6, CRP, leukocyte, and other routine hospital tests, were performed simultaneously to obtain baseline data. The aspirin administration was discontinued seven days before surgery.

Intra-operative assessment

The subjects underwent conventional CABG surgery following standard procedures. TTFM, which include MGF and PI, were measured in each SVG intra-operatively to evaluate the quality of the flow and the patency of the conduit.

Post-operative assessment

At six hours, post-operative, IL-6, CRP, and leukocyte levels were measured, and aspirin was continued when there was no evidence of significant bleeding. At 48 hours post-operative, additional leukocyte and CRP measurements were performed. Three days after surgery, the PFA test for aspirin sensitivity was repeated to reassess aspirin resistance status. The subjects were further classified into three groups: aspirin resistant, transient aspirin resistant, and aspirin-sensitive. Upon hospital discharge, the subjects were given 100 mg aspirin once daily as the only anticoagulant for a period of weeks. Pill counts were performed in each post-operative appointment. After six weeks, MSCT was performed to assess SVG patency.

Statistical analysis

Statistical analyses were performed using IBM SPSS V22.0. Logistic regression was used to assess the relations among the high levels of platelet reactivity, inflammatory response, and early SVG thrombosis. Results were considered significant with a p-value < 0.05. Univariate analyses were performed on a per-graft basis for the odds of occlusion versus patency. A categorical variable was analyzed using chi-square or Fischer's exact tests and was presented in frequency and percentage. Meanwhile, continuous variables were calculated using a T-test or non-parametric test (Mann–Whitney U test).

Result

Subject characteristics

A total of 99 subjects and 222 SVGs were included in this study. There were 79 male subjects and 20 female subjects. There were no differences with regards to demographic characteristics or pre-operative risk factors between the patients who had occluded grafts and patents. Intraoperative data, such as ejection fraction, CBP, and cross-clamp time, were also similar (Table 1). Based on aspirin sensitivity, the subjects were then further classified into three different subgroups: resistant (83 conduits), transient (65 conduits), and sensitive (74 conduits).

Table 1
Baseline Characteristic of this study

Variable		Occluded (n = 47)	Patent (n = 175)	p
Sex				
Male (79 Subjects)		37 (20.7%)	139 (79.3%)	0.916
Female (20 Subjects)		10 (21.7%)	39 (78.3%)	
Age (Years)	Median	56	59	0.147
	Min-Max	(50–74)	(40–74)	
Risk Factors				
Hypertension		39 (83.0%)	145 (82.9%)	0.984
Dyslipidemia		39 (83.0%)	136 (77.7%)	0.433
Diabetes Mellitus		29 (61.7%)	103 (58.9%)	0.724
Smoking		31 (66.0%)	123 (70.3%)	0.568
Ejection Fraction (%)	Median	54	52	0.111
	Min-Max	(43–71)	(40–71)	
CPB Times (Minutes)	Median	87 Minutes	79 Minutes	0.127
	Min-Max	(47–114)	(39–118)	
Cross Clamp Time (Minutes)	Median	55 Minutes	50 Minutes	0.128
	Min-Max	(31–84)	(29–89)	

Role of aspirin resistance in early SVG failure

Of the 222 vein conduits, 175 (78.8%) were patent, and 47 (21.2%) were occluded. It was found that 83 conduits were resistant to aspirin while 139 conduits were sensitive to aspirin. In the sensitive group, 65 subjects (46.8%) transformed into a resistant state on the third day after surgery (transient group). In the resistant group, 34.9% of the total graft was occluded, which was higher compared to values in the transient (16.9%) and sensitive (9.5%) groups. Bivariate analysis was performed to assess the relations in each group about the early SVG thrombosis rate. A strong correlation was seen. It was found that the aspirin resistant group had a significantly increased risk of SVG thrombosis post-CABG (RR = 3.69 (1.72–7.93) and $p < 0.001$). However, transient aspirin resistance also increased the risk of SVG thrombosis post-CABG (RR = 1.79 (0.74–4.34) and $p = 0.191$), although the result was not statistically significant (Table 2).

Table 2
Vein Graft Patency in Each PFA Subgroup

	Occluded (n = 47)	Patent (n = 175)	Total (n = 222)	RR (95% CI)	p
Resistant	29 (34.9%)	54 (65.1%)	83 (100%)	3.69 (1.72–7.93)	P < 0.001
Transient	11 (16.9%)	54 (83.1%)	65 (100%)	1.79 (0.74–4.34)	P = 0.191
Sensitive	7 (9.5%)	67 (90.5%)	74 (100%)	1.00	
PFA = Platelet Function Analyzer					

Role of inflammation factors in early SVG thrombosis

In this study, IL-6, CRP, and leucocyte were evaluated as representative inflammation factors that contribute to early SVG thrombosis formation.

IL-6

The median pre-operative values of IL-6 were insignificantly different in each group (patent or occluded; p = 0.204) and subgroup (Table 3). Post-operatively, the mean values in each group and subgroup also increased insignificantly (p = 0.582) (Table 3).

Table 3 The Influence of Inflammation Factors towards the formation of early

graft failure

Inflammation Factors		Occluded	Patent	P
IL-6				
Pre-operative	Median	4.90	4.77	0.204
	Min–Max	(1.10–13.40)	(1.10–13.40)	
6 Hrs Post-operative		107.20	121.00	0.582
		(67.00–292.00)	(59.28–223.00)	
Delta IL-6		103.27	114.29	0.350
		(60.90–287.78)	(55.49–216.90)	
CRP				
Pre-operative		2.00	2.00	0.483
		(1.00–13.00)	(1.00–18.00)	
48 Hrs Post-operative		89.00	87.00	0.267
		(38.00–155.00)	(34.00–31.00)	
Delta CRP		87.00	80.00	0.252
		(32.00–154.00)	(31.00–229.00)	
Leukocyte				
Pre-operative		7540	6990	0.272
		(5940–10430)	(4120–14320)	
48 Hrs Post-operative		18.600	18.780	0.547
		(13.790–26.100)	(13.420–29.000)	
Delta Leucocyte		1.0530,00	12.280	0.277
		(6690–18.770)	(6690–16.750)	
IL-6 = Interleukin 6; CRP = C-Reactive Protein				

CRP

In the pre-operative analysis, the median CRP values were insignificant (p = 0.483) in each group (Table 3). However, these median values also increased insignificantly in each group and subgroup. These results were further analyzed by plotting a receiver operating characteristics 6t (ROC) curve. The graph analysis showed that the validity of the analysis was 55.3% (45.1–65.5%; p = 0.267), and the cross-section coordinate was 101.5, with 48.9% sensitivity and 80% specificity. The analysis showed that a CRP value of more than 101.5 plays a significant role (p = 0.004) in the formation of early SVG thrombosis, with a relative risk of 2.11 (Table 4).

Table 4
Postoperative CRP analysis based on ROC Cut off towards vein graft patency

CRP *Cut-Off*	Total Graft		p	RR (95% CI)
	Occluded	Patent		
>101.5	19	35	0.004	2.11 (1.29–3.46)
	35.2%	64.8%		
≤ 101.5	28	140		
	16.7%	83.3%		
CRP = C-Reactive Protein				

Table 5
Pre and Post operative IL-6 value in each PFA subgroups

		Transient	Sensitive	p
Pre-Operative IL-6	Median	4,50	5,50	0,242
	Min-Max	(1,10 – 7,89)	(2,00–12,50)	
Post-Operative IL-6	Median	166,70	102,95	< 0,001
	Min-Max	(88,00-223,00)	59,28–200,00	
IL-6 = Interleukin 6; PFA = Platelet Function Analyzer				

Leucocytes

The median pre-operative and post-operative leucocyte values were insignificantly different (p = 0.227 vs. p = 0.547) in each group (Table 3), although there was an increase in postoperative values. The highest increase was achieved 48 hours post-CABG.

Role of IL-6 in the transformation of aspirin sensitivity from sensitive to transient

Of the 222 vein conduits, 139 were categorized as aspirin-sensitive before the subject underwent CABG. However, 65 of these subjects transformed into a resistant state three days after the surgery, which was later called a transient group.

Table 5
Pre and Post operative IL-6 value in each PFA subgroups

		Transient	Sensitive	p
Pre-Operative IL-6	Median	4,50	5,50	0,242
	Min-Max	(1,10 – 7,89)	(2,00–12,50)	
Post-Operative IL-6	Median	166,70	102,95	< 0,001
	Min-Max	(88,00-223,00)	59,28–200,00	
IL-6 = Interleukin 6; PFA = Platelet Function Analyzer				

Table 6
Prevalence of post-operative IL-6 value in transient aspirin subgroup towards the occurrence of early graft failure in comparison with sensitive subgroup

IL-6 in Transient and Sensitive subgroup	Occluded	Patent	p	RR (95% CI)
IL-6 > 122,5				
Transient	9 (17.3%)	43 (82.7%)	0.029	8.6 (1.28–141.86)
Sensitive	0 (0.0%)	23 (100.0%)		
IL-6 ≤ 122,5				
Transient	2 (15.4%)	11 (84.6%)	0.589	1.12 (0.26–4.77)
Sensitive	7 (13.7%)	44 (86.3%)		
IL-6 = Interleukin 6				

As stated in the previous analysis, the pre-operative IL-6 values did not differ between the sensitive and transient subgroups (p = 0.242). However, a contrasting result was found postoperatively, with values of 102.95 (59.29–200.00) in the sensitive group and 166.70 (88.00–223.00; p < 0.001) in the transient group (Table 5). These median values in the sensitive and transient subgroups were significantly different. They were then plotted to the ROC curve to calculate the area under the curve (AUC) as the basis of a prognostic model. The result was an AUC of 75.3% (68.3%–82.1%; p < 0.001), with 80% sensitivity and 70.7% specificity.

A cut-off point of 122.5 was used to divide the IL-6 group into two new subgroups: IL-6 > 122.5 and IL-6 ≤ 122.5 (p = 0.210). According to the previous separated analysis, both IL-6 values >122.5 and ≤ 122.5 were not related to the occurrence of early vein graft occlusions. Furthermore, the transient subgroup alone was also not related to the occurrence of early graft patency (p = 0.191). However, this study sought to analyze both variables, and it was found that SVG occlusion was more prevalent in subjects in the transient group where IL-6 > 122.5 (RR = 8.6, p = 0.029) than in the group where IL-6 ≤ 122.5 (RR = 1.12; p = 0.589) when each was compared to the sensitive group with the same IL-6 values (Table 6).

Role of mechanical factors in the formation of early vein graft occlusion

The lower intra-operative blood flow group had a greater prevalence of early graft occlusion than those with the higher flow. However, the differences did not reach statistical significance (24.4% vs. 17.5%; p = 0.210). The pulsatility index and native vessel diameter also failed to discriminate between the occluded and patent grafts (pulsatility index < 3 with 18.2% occlusion vs. PI 3–5 with 25.9%, p = 0.176; diameter 1–1.5mm with 20.5% vs. D >1.5mm with 21.6%, p = 0.846) (Table 7).

Table 7
Role of Mechanical Factors in the formation of early vein graft occlusion

Mechanical Factors	Occluded	Patent	p	RR (95% CI)
Native Vessel Diameter (mm)				
1.00–1.50	17 (20.5%)	66 (79.5%)	0.846	0.95 (0.56–1.61)
> 1.50	30 (21.6%)	109 78.4%)		
Mean Graft Flow (MGF) (mL/Sec)				
10–30	29 (24.4%)	90 (75.6%)	0.210	1.39 (0.82–2.36)
> 30	18 (17.5%)	85 (82.5%)		
Pulsatility Index (PI)				
3–5	22 (25.9%)	63 (74.1%)	0.176	1.42 (0.86–2.35)
< 3	25 (18.2%)	112 (81.8%)		
PI = Pulsatility Index; MGF = Mean Graft Flow				

Multivariate analysis

Cox regression was used in performing the multivariate statistical analysis, following the backward stepwise method. There were 10 included variables with $p \leq 0.25$, which were suspected of contributing to the occurrence of early vein graft occlusion.

Based on the Wald test results, when the p-value of a variable was > 0.10, the variable had to be eliminated in the next step. However, if the p-value were < 0.10, the corresponding variable would be included in the next step.

As a result, there were two critical variables: PFA category resistant, with p<0.001, and PFA category transient, with p = 0.191, regarding the occurrence of early vein graft failure six weeks after CABG. In this study, the formula used to calculate the probability of early vein graft occlusion six weeks after CABG was as follows:

$$\text{P (Probability of early vein graft occlusion 6 weeks after CABG)} = \frac{1}{1+\exp(-y)}$$

y = -2.259 + 1.637 × PFA Category Resistant + 0.668 × PFA Category Transient

The probabilities of early vein graft occlusion six weeks after CABG were 34.9% in the resistant group, 16.9% in the transient group, and 9.5% in the sensitive group. The relative risk of the occurrence of early vein graft thrombosis was calculated by comparing the probabilities of the resistant and sensitive groups, and the result was 3.69 times more likely to develop early graft failure.

Discussion

CABG is a common revascularization modality in patients with advanced CAD that is performed following a standardized general technique.[7] Aspirin is a routine oral antiplatelet given in patients who have undergone CABG in order to prevent/reduce the risk of developing other cardiovascular events.[8] Despite the advances in surgical technique and postoperative management, including the routine administration of acetylsalicylic acid (ASA), the rate of early SVG occlusion remains high, especially in the first year after surgery (15%).[9,10] Although graft failure in the first post-operative week is frequently blamed on surgical technique, we minimized this issue as a confounding variable by the routine use of intraoperative flow measurements (TTFM).[3,11–13] Moreover, there is an aspirin non-responsive trait in this study population, which has raised a fundamental question regarding the existence of the relationship between aspirin resistance and the prevalence of early SVG occlusion in patients who have undergone CABG.[14–16] The findings of this study have answered this question and show that there is a strong association between aspirin resistance and early SVG failure. Specifically, we found that aspirin resistance was significantly related to the occurrence of early graft failure, with a relative risk of 3.69 (CI 95% 1.72–7.93). In addition, the transient group was 1.79 times more likely to develop early graft failure compared to the sensitive group, although the result was not statistically significant (p = 0.191).

PFA-200 was used in this study because it is simple and reliable; however, there are no laboratory parameters or measurements that have been identified as a gold standard to assess aspirin resistance. It is also not included as a standard pre-operative screening because there is not enough evidence to describe its role. Therefore, its specificity and ultimate usefulness are still debatable.[3,13] Furthermore, this study did not assess the potential genetic contribution to the aspirin resistance trait and the formation of early SVG thrombosis.

Based on a previous study by Poston et al., mechanical factors were considered as the most important factors in early SVG failure.[12] Inconsistent with this finding, our study found no difference between MGF and PI in the early SVG occlusion. The lower intra-operative blood flow group had a greater prevalence of early graft occlusion than those with higher flow. However, the differences did not reach statistical significance (24.4% vs. 17.5%; p = 0.210). The PI factor also failed to discriminate between the occluded and patent grafts (PI < 3 with 18.2% occlusion vs. PI 3 − 5 with 25.9%; p = 0.176).

With regard to the native vessel diameter factor, this study yielded different results than those of Gluckmann et al., as there was no significant difference between occluded and patent grafts (diameter 1–

1.5mm with 20.5% vs. D > 1.5mm with 21.6%; p = 0.846).

In addition to aspirin resistance and mechanical factors, this study also attempted to correlate inflammation factors with early graft failure. This review was based on the negative effect of a very high inflammation response from the use of a CPB machine during CABG that hypothetically contributed to this phenomenon.[17–19] The previous study by Arazi et al. described the influence of increasing inflammation markers on the transformation of aspirin resistance from sensitive to resistant after CABG.[20] Similarly, in this study, it was found that high post-operative IL-6 levels play a significant role in the transformation of aspirin resistance from sensitive to resistant. Moreover, the transient group had a higher prevalence of early graft occlusion. As a result, very high post-operative IL-6 levels > 122.5 in the transient compared to the sensitive group resulted in a risk up to 8.6 times higher (p = 0.029) compared to a risk 1.12 times higher (p = 0.589) in the group with IL-6 levels < 122.5 in terms of developing early graft failure. However, the result was insignificant when these factors were analyzed independently.

The other inflammation factor that was shown to have a role in early SVG occlusion was a high post-operative CRP value of > 101.5. Based on these results, the role of inflammation in early SVG occlusion remains inconclusive. Independently, each of the inflammation markers had no significant impact on early SVG occlusion. However, upon further analysis, a very high post-operative CRP had a significantly higher prevalence of early graft occlusion in comparison to a lower value; the increased prevalence was likely related to the post-operative IL-6 values because high post-operative IL-6 values and not CRP were associated with occlusion in the transient group.

Study limitations

A limitation of this study was not including other inflammation parameters, such as TNF-α and other cytokines, in the analysis. Additionally, this study did not include a genetic examination to determine the role of polymorphism in both the existence of aspirin resistance and the formation of early graft occlusion.

Now that aspirin resistance, IL-6 values, and CRP values have been identified as important parameters, additional studies will be needed to determine whether other inflammation and genetic factors also play a role. Further, future emphasis on the study of the effect of anti-inflammatory agents on preventing SVG thrombosis would be beneficial.

Conclusion

We have identified that aspirin resistance measured with PFA-200 plays a significant role in early vein graft occlusion six weeks after CABG. High levels of IL-6 post-CABG had a significant impact on the transformation of aspirin resistance from sensitive to resistant (the transient aspirin group). Post-operative CRP values > 101.5 were associated with early SVG failure. Post-operative IL-6 values of more than 122.5 in the transient subjects were associated with a higher risk of developing early graft occlusion six weeks after CABG.

Declarations

- **Ethics approval and consent to participate**

This Research already got ETICAL CLEREANCE CERTIFICATE No. 553/ UN2.F1/ETIK/2015 from Faculty of Medicine, Universitas Indonesia Research Ethical Clereance Commission. Informed consent was obtained from all participants and all methods were carried out in accordance with relevant guidelines and regulations The informed consent was written (File attached in Revision).

- **Consent for publication**

Not Applicable

- **Availability of data and materials**

The Authors declare that that all the data is Available. Anyone that need the data can one access by mail me at drdudyarmanhanafy@gmail.com or contact the publsiher BMC Public health or Nature

- **Competing interests**

The authors declare that they have no competing interests

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