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The influence of heparin resistance on postoperative complications in patients undergoing coronary surgery

Piotr Knapik[ACDEFG], Daniel Cieśla[ABCDE], Roman Przybylski[ADEFG], Tomasz Knapik[ABDEF]

Silesian Centre for Heart Diseases, Zabrze, Poland

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Summary

Background: Heparin resistance is relatively frequent in patients undergoing coronary surgery. We aimed to assess the impact of heparin resistance on the outcome of patients undergoing coronary surgery with cardiopulmonary bypass (CABG). Three definitions of heparin resistance were adopted.

Material/Methods: We performed a retrospective review of 756 consecutive patients undergoing isolated CABG. All anaesthesia records were reviewed manually. Heparin resistance was recognized if: ACT was less than 400 seconds after 300 U/kg heparin (local criteria), ACT was less than 480 seconds after 400 U/kg or more heparin (stringent criteria), or if heparin sensitivity index was lower than 1.3. Postoperative assessment included perioperative morbidity and mortality. A multiple logistic regression model was used to investigate the influence of all demographic, preoperative and surgical variables, as well as heparin resistance (variably defined) on hospital mortality and postoperative complications.

Results: Heparin sensitivity index, local criteria and stringent criteria identified 64.8%, 12.0% and 4.3% heparin resistant patients, respectively. Heparin-resistant patients more frequently had preoperative heparin administration, unstable course of coronary artery disease, and higher coronary symptoms scoring. Severe form of heparin resistance (expressed by the ACT less than 480 seconds after 400 U/kg heparin) was an independent predictor of death (OR 4.92; CI 1.11–21.89).

Conclusions: Mild forms of heparin resistance are relatively frequent and are not associated with increased morbidity and mortality. The isolation of severe heparin resistance as an independent predictor of death in our large cohort of coronary patients suggests that this phenomenon should be given more attention in future studies.

key words: cardiopulmonary bypass (CPB) • coronary artery bypass grafts (CABG) • heparin resistance

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Author's address: Piotr Knapik, Silesian Centre for Heart Diseases, M. Curie-Sklodowskiej 9 St., 41-800 Zabrze, Poland, e-mail: pknapik@sum.edu.pl

Background

Aspirin resistance is a documented unfavorable factor for patients undergoing percutaneous coronary interventions [1] or coronary revascularization [2], while the impact of resistance to heparin is unclear.

Heparin resistance is reported in up to 22% of patients undergoing cardiopulmonary bypass [3–5]. It is usually defined as failure to reach a certain activated clotting time (ACT) value after a certain bolus administration of heparin; however, there are varying proposals as to what those given values are [3,5–8]. Another approach was introduced by Ranucci et al, who proposed the use of a heparin sensitivity index (HSI), with values less than 1.3 indicating heparin resistance [9].

There is general agreement that heparin resistance is more common in patients receiving unfractionated heparin preoperatively [5,6,10,11]; however, this may be extended also to patients treated with low molecular weight heparin [12,13]. It is not clear whether heparin resistance is of significant clinical relevance. Nicholson et al. proved that despite the ACT being frequently less than 400 seconds, no coagulation was seen in their group of heparin-pretreated patients, and suggested that a standard heparin dose should always be safe and sufficient [14].

Decreased AT III activity (usually associated with heparin resistance) is more common in certain subgroups of patients. It has been confirmed that decreased postoperative AT III activity at the end of a cardiac operation is more common in patients with decreased preoperative AT III activity, advanced age and diabetes, as well as following a combined operation or prolonged cardiopulmonary bypass [9]. However, in some cases decreased AT III activity is not associated with heparin resistance [4].

The impact of heparin resistance on the outcome of cardiac surgical patients is unclear. The only study that addressed this issue was published by the Ranucci group in the European Journal of Anesthesiology – the authors found that heparin resistance (and heparin pretreatment) was associated with increased incidence of postoperative fatal myocardial infarction [9].

Our study aimed to assess the impact of intraoperative heparin resistance on the outcome of patients undergoing cardiopulmonary bypass. Three frequently cited definitions of heparin resistance were used in the study.

Material and Methods

The retrospective study material involved 916 consecutive patients undergoing isolated coronary artery bypass surgery with cardiopulmonary bypass graft (CABG) in our prospectively collected departmental cardiac surgical database over a 2-year period (2008–2009). Patients in a critical preoperative state (cardiogenic shock) and patients requiring conversion from off-pump coronary artery surgery (OPCAB) to CABG were excluded.

All anesthesia records were reviewed manually to identify patients with heparin resistance. We excluded 160 patients who received <290 U/kg and >310 U/kg heparin as the initial dose. The remaining 756 patients underwent statistical analysis.

Heparin resistance was diagnosed based on 3 different criteria:

- ACT less than 400 seconds after 300 U/kg heparin (local criteria);
- ACT less than 480 seconds after 400 U/kg (or more) heparin (stringent criteria) [3]; and
- HSI lower than 1.3 [9].

Cardiopulmonary bypass was performed under normothermia or moderate hypothermia (34°C) with topical cooling and was initiated after the confirmation of satisfactory ACT. Heparinization with 300 IU kg^{-1} of unfractionated heparin was used to reach the target value of ACT at 400 seconds. ACT was measured with the use of a Hemochron 401 coagulation monitoring instrument (Technidyne Corp., Edison, NJ, USA). During cardiopulmonary bypass, ACT measurements were repeated every 30 minutes and 50–100 IU of heparin were administered if ACT dropped below 460 seconds. After the termination of cardiopulmonary bypass, protamine sulfate was given to reverse the initial heparin dose at a 1:1 ratio.

Heparin sensitivity index (HSI) was calculated on the basis of ACT after the overall loading dose of heparin according to the following formula: HSI = (ACT after heparin – baseline ACT)/overall loading dose of heparin (IU kg^{-1}). The value of 1.3 was considered an adequate cutoff point for diagnosing heparin resistance for the initial loading dose of 300 Iu kg^{-1}, hence patients with HSI values less than 1.3 were considered to be heparin resistant [9,15].

Demographic and surgical data were identified in all patients. Preoperative risk assessment was performed on the basis of standard (additive) EuroSCORE, and patients were classified as having low (0–2 points), moderate (3–5 points) and high risk (6 or more points). Additionally, logistic EuroSCORE was calculated for each patient [16].

Demographic and preoperative data included: age, sex, body mass index (BMI), standard and logistic EuroSCORE, Canadian Coronary Score (CCS), left ventricular ejection fraction, and preoperative co-morbidities including diabetes, arterial hypertension, renal insufficiency, chronic obstructive pulmonary disease, pulmonary hypertension, previous stroke or TIA, extracardiac vascular disease, previous PTCA/stent, previous myocardial infarction, left main coronary artery disease, unstable course of coronary artery disease and mode of operation (elective, urgent, emergent), as well as particular preoperative medications including nitrate infusion and heparin administration (unfractionated heparin, fractionated heparin and any type of heparin).

The mode of operation was classified according to standard ACC/AHA definitions. Urgent category indicated that patients were required to stay in the hospital but could be planned and operated on within a normal schedule. Emergent operations were those with ongoing refractory cardiac compromise, unresponsive to other forms of therapy except for cardiac surgery [17]. Patients who did not fulfill any of the above definitions were considered elective.

Surgical data included cardiopulmonary bypass time, aortic crossclamp time, overall number of coronary grafts per patient and the number of arterial grafts per patient.

Postoperative assessment included the assessment of perioperative morbidity and mortality, as well as ICU and hospital stay. The outcomes were hospital mortality and morbidity (defined as any temporary or serious postoperative complications that could be theoretically linked to heparin resistance). Temporary perioperative complications included perioperative ischemia, significant inotropic support, use of intra-aortic balloon pump and reoperation due to bleeding. Serious perioperative complications included cerebral stroke, renal failure, perioperative myocardial infarction, ventilation >24 hours and mesenteric ischemia. In addition, lengths of ICU and hospital stays were analyzed.

Perioperative ischemia was diagnosed in cases of horizontal or oblique downward depression of the ST segment of more than 1 mm, or horizontal elevation of the ST segment of more than 2 mm in at least 1 ECG lead. Significant inotropic support was noted when noradrenaline or adrenaline (or both) were used in a dose higher than 0.1 mcg/kg/min.

Cerebral stroke was defined as a new focal or global cerebral dysfunction lasting longer than 24 hours. Renal failure was defined as renal dysfunction requiring renal replacement therapy. Perioperative myocardial infarction (CABG-related, type 5) was defined as CABG-related increase of troponin 5×99^{th} percentile of the upper reference limit plus either new Q waves of new left bundle branch block or angiographically verified new graft or native coronary occlusion within 24 h of the operation [18].

Patients with and without heparin resistance were compared with regard to their demographic and surgical data, as well as early postoperative mortality and morbidity.

Finally, a multiple logistic regression model was used to investigate the influence of all demographic, preoperative and surgical variables, and heparin resistance (variably defined) on hospital mortality and postoperative complications. The effect of demographic, preoperative and surgical variables on hospital mortality and postoperative complications was first calculated by means of univariate logistic regression. Variables with p value <0.05 were then included in the multivariate logistic regression analysis, where $p<0.05$ was again considered significant. Multivariate analysis was performed only if any form of heparin resistance was found to be a significant variable (for postoperative complications or death) in a univariate analysis.

Depending on statistical distribution, numerical data were shown by either mean and standard deviation or median values and their range, and then compared with the Mann-Whitney test result. Binary data were shown as numbers and percentages, and compared with the use of χ^2 test. Yates corrected χ^2 was used if the expected cell frequencies were below 6. $P<0.05$ was considered significant.

Results

The implementation of various definitions of heparin resistance created various percentages of heparin-resistant patients. The largest heparin-resistant group was created with the use of the heparin sensitivity index (490 patients, 64.8% of the entire group). Local criteria identified 91 heparin-resistant patients (12.0%). The smallest heparin-resistant group, containing only 31 patients (4.3%), was created with the use of the most stringent criteria.

Frequency of various demographic and preoperative characteristics of heparin-resistant patients in comparison to the remaining patients are shown in Table 1. Significantly higher percentage of patients with preoperative heparin administration, unstable course of coronary artery disease, and higher CCS scores was found among all heparin-resistant groups.

Frequencies of various demographic and preoperative characteristics of patients with postoperative complications in comparison to the remaining patients are shown in Table 2. An exceptionally high incidence of patients with the most severe form of heparin resistance was found among patients who died in the postoperative period.

Overall hospital mortality in the entire studied group was 1.7% (n=13). As predicted from the preoperative EuroSCORE, patients at low risk (0-2 points) had 0% mortality, patients at moderate risk (3–5 points) had 2.1% mortality, while patients at high risk (>5 points) had 4.7% mortality. Deaths in the entire studied group were due either to mesenteric ischemia (n=8), perioperative myocardial infarction (n=3), rupture of the ascending aorta (n=1), or anoxemic brain injury (n=1). Deaths in the group created on the basis of the most stringent criteria were due to mesenteric ischaemia (n=2) or anoxemic brain injury (n=1).

Univariate analysis revealed that patients who developed any complications in the postoperative period differed from the remaining patients in terms of demographic, preoperative and surgical data, but not in the frequency of variably defined heparin resistance (Table 2). Patients who died additionally differed with regard to frequency of heparin resistance according to the stringent criteria (Table 2).

No multivariate analysis for postoperative complications was carried out as there were no differences in the univariate analysis in the percentage of patients with variably defined heparin resistance between patients who developed and who did not develop postoperative complications.

Multivariate analysis for hospital mortality was performed, as the most severe form of heparin resistance was found to be a significant factor affecting mortality in univariate analysis (Figure 1). Multivariate analysis revealed that fatal outcome was significantly associated with 4 variables: heparin resistance expressed by the ACT less than 480 seconds after 400 U/kg heparin (OR 4.92; CI 1.11–21.89), non-elective mode of operation (OR 3.73; CI 1.18–11.79), cardiopulmonary bypass time exceeding 120 min (OR 3.55; CI 1.04–12.13), and age (OR 1.53/5 year; CI 1.03–2.27).

Discussion

Heparin resistance is defined as the inability to raise the blood ACT to expected levels despite an adequate heparin dose and plasma concentration [6,19]. As the determination of heparin plasma concentration is not a routine practice, heparin

Table 1. Comparison of patients with heparin resistance with the remaining patients (%).

			Heparin Sensitivity Index <1.3		ACT <400 s after 3 mg/kg heparin		ACT <480 s after 4 mg/kg heparin	
			Yes (n=490)	No (n=266)	Yes (n=91)	No (n=665)	Yes (n=31)	No (n=725)
Demographic, preoperative and operative data		Female gender	23%	18%	18%	22%	26%	21%
		EuroSCORE >5	*19%	14%	25%	16%	13%	17%
		CCS >2	*51%	43%	*62%	47%	*68%	48%
		EF <35%	4%	2%	4%	2.9%	3%	3%
		Diabetes	*30%	37%	30%	37%	45%	32%
		Arterial hypertension	*83%	75%	87%	79%	87%	80%
		Renal insufficiency	12%	10%	14%	11%	*23%	11%
		COPD	7%	7%	7%	6.6%	7%	7%
		Pulmonary hypertension		0.4%		0.2%		0.1%
		Previous stroke or TIA	5%	6%	3%	5.1%	3%	5%
		Extracardiac vascular disease	24%	25%	24%	24%	19%	25%
		Previous PCI/stent	31%	32%	25%	32%	29%	31%
		Previous MI <3 months	26%	23%	*35%	23%	32%	24%
		Left main CAD	*37%	27%	*43%	32%	45%	33%
		Unstable course of CAD	*42%	32%	*62%	35%	*55%	37%
		Non elective mode of operation	22%	22%	25%	21%	26%	22%
		Emergent mode of operation	1%	2%	1%	1%		1%
		Nitrate infusion	2%	3%	6%	2%	7%	3%
		Preop. unfractionated heparin	*10%	5%	*15%	7%	*32%	7%
		Preop. fractionated heparin	16%	13%	*23%	14%	16%	15%
		Preop. heparin (any)	*25%	18%	*39%	21%	*48%	22%
		CPB > 120 min.	12%	10%	13%	11%	*29%	10%
Perioperative complications	Temporary	Perioperative ischaemia	2%	4%	2%	3%	*10%	2%
		Inotropic support	3%	3%	4%	2%	*13%	2%
		Use of IABP	3%	5%	4%	3%	*13%	3%
		Reoperation (bleeding)	3%	3%	4%	3%		3%
		Ventilation >24 hours	5%	4%	4%	5%	7%	5%
	Permanent	Cerebral stroke	2%	0.8%	3%	1%	3%	2%
		Renal failure	1%	2%	3%	1%	*10%	1%
		Perioperative MI	3%	3%	2%	3%	7%	3%
		Mesenteric ischaemia	0.6%	1%	2%	0.6%	3%	0.7%
		Any complication	37%	34%	34%	36%	48%	36%
		Hospital mortality	1%	3%	3%	2%	*10%	1%

* p<0.05. CCS – Canadian Cardiovascular Society score; EF – ejection fraction; COPD – chronic obstructive pulmonary disease; TIA – transient ischemic attack; MI – myocardial infarction; CAD – coronary artery disease; CPB – cardiopulmonary bypass; IABP - –ntra-aortic balloon pump.

response is usually defined on the basis of ACT. Most clinicians would agree that a safe minimum ACT value of 400 seconds is required for CPB; however, this belief is not evidence-based. Metz et al. proved that there were no thrombotic

Table 2. Comparison of patients with and without postoperative complications and of patients who died in the postoperative period to the remaining patients (%).

	Postoperative complications		Hospital deaths	
	Yes (n=272)	No (n=484)	Yes (n=13)	No (n=743)
Heparin Sens. Index <1.3	33%	36%	54%	35%
ACT <400 s after 3 mg/kg	11%	12%	23%	12%
ACT <480 s after 4 mg/kg	5%	3%	*23%	4%
Female gender	*28%	17%	31%	21%
EuroSCORE >5	*29%	10%	*46%	17%
CCS >2	*55%	44%	69%	48%
EF <35%	*7%	0.6%	8%	3%
Diabetes	34%	31%	46%	32%
Arterial hypertension	83%	79%	69%	80%
Renal insufficiency	*16%	9%	15%	11%
COPD	8%	6%	8%	7%
Pulmonary hypertension		0.2%		0.1%
Previous stroke or TIA	7%	4%	8%	5%
Extracardiac vascular disease	*31%	21%	39%	24%
Previous PTCA/stent	36%	29%	46%	31%
Previous MI <3 months	*35%	19%	46%	24%
Left main CAD	33%	34%	39%	33%
Unstable course of CAD	*44%	35%	46%	38%
Non elective mode of operation	*27%	19%	*54%	21%
Emergent mode of operation	1.8%	1%		1.4%
Nitrate infusion	3%	3%	8%	3%
Preop. unfractionated heparin	*12%	6%	*23%	8%
Preop. fractionated heparin	13%	16%	8%	15%
Preop. heparin (any)	25%	22%	31%	23%
CPB >120 min	*14%	9%	*39%	11%

* p<0.05. Abbreviations are explained in Table 1.

complications during cardiopulmonary bypass in 51 patients whose ACT was well below 400 seconds [20]. Nevertheless, our local ACT-based definition of heparin resistance (ACT less than 400 seconds after 300 U/kg heparin) may be considered a "mainstream" solution, which would probably be acceptable to most cardiothoracic centers. Therefore, it could be concluded that if the defined resistance to heparin is not associated with increased mortality (as was the case in our study), it is probably not dangerous to patients.

Such an approach, however, has a false assumption and is inherently wrong. Heparin resistance is not a typical binary variable (even if we consider it as such). We are usually able to finally achieve satisfactory ACT with increased doses of heparin; therefore the term "altered heparin responsiveness" seems to be more appropriate [19]. This term indicates that we are dealing with a continuous variable and the estimation of a predictive power should involve searching for an optimal cutoff point rather than opting for a fixed value.

The problem is not that easy, however, as the assessment of heparin response involves a combination of 2 continuous variables (heparin dose and ACT). This means that a typical single "cutoff point" cannot be easily identified by statistical analysis. Instead, at least a few different definitions of "altered heparin responsiveness" should be tested to identify high-risk groups. Accordingly, in our study we decided to use local (but widely accepted) definition of "heparin resistance" and, additionally, 2 other definitions cited in the literature [3,9].

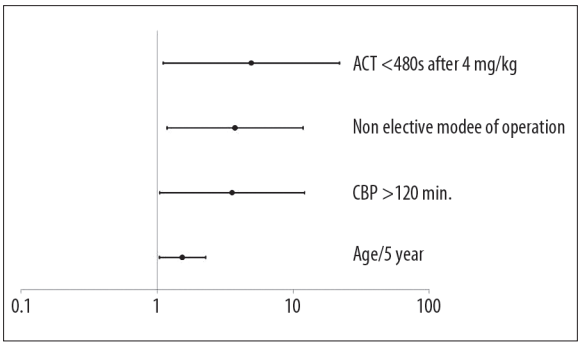

Figure 1. Independent predictors of hospital death.

The Results section shows that different definitions created variable percentages of heparin-resistant patients, with only 4.3% of patients meeting the criteria used by Avidan et al. [3]. This is much lower than the original data of the Avidan group, where 18.2% of patients (54 out of 296 consented) were found to be heparin-resistant; however, even the authors themselves stated that this percentage was surprisingly high.

The paper presented by the Avidan group was primarily aimed at evaluating the efficacy of recombinant human antithrombin, but the criteria used in their study created a subgroup that may be directly compared to our high-risk group. Unfortunately, no details on postoperative complications are provided in Avidan's study, except for the fact that 2 patients in the heparin-resistant group died in the postoperative period, with a resulting mortality rate of 3.7% [3].

There is little data in the literature to support the hypothetical association between altered heparin responsiveness and adverse outcomes. It has been suggested that thrombotic risk increases in patients with heparin resistance [15]. The early closure of a native coronary vessel has been described in a patient with antithrombin-III deficiency in 1 case report [21]. The only study in which heparin resistance was clearly linked to any postoperative complications is that by Ranucci et al. [9]. In their study, the authors proved that heparin resistance (defined as heparin sensitivity index <1.3) was an independent risk factor for perioperative myocardial infarction.

Heparin response reflects a "3-player game" – antithrombin III (AT III), thrombin and heparin [4]. Therefore, heparin resistance may result from decreased AT III availability as well as increased thrombin formation. A decreased concentration of AT III after preoperative therapeutic heparin does not necessarily cause heparin resistance [22] and some heparin-resistant patients may have entirely normal AT III activity [4].

In general, heparin exerts its anticoagulant effect by binding to and activating AT III. The major anticoagulant effect is achieved by inactivation of thrombin and activated factor X (factor Xa) through an antithrombin (AT)-dependent mechanism. The resulting heparin-antithrombin complex inactivates thrombin, activated factor X and other activated clotting factors. Heparin is highly negatively charged and it easily binds to positively charged plasma proteins and surfaces. As many heparin-binding proteins are acute-phase reactants, heparin resistance is frequently associated with acute illness [6]. Therefore, many clinical conditions such as sepsis or multiorgan failure are also associated with heparin resistance [19].

The aim of our study was to assess heparin resistance before cardiopulmonary bypass. This is important, as the cardiopulmonary bypass circuit triggers the unique activation of inflammation [23] and coagulation, which is not yet fully elucidated [6]. In addition, hemodilution is responsible for decreasing concentrations of circulating physiological anticoagulation factors, such as AT III, protein C and protein S, leading to an increased risk of blood clotting [24]. As all patients in our study underwent cardiopulmonary bypass, the use of extracorporeal circulation was entirely eliminated from the variables.

As already mentioned, in 1 study heparin resistance (and heparin pretreatment) was associated with increased incidence of postoperative fatal myocardial infarction [9]. Surprisingly, our results are contradictory – a similar percentage of heparin-resistant patients was found among patients with perioperative myocardial infarction, even if heparin resistance was identically defined.

An important limitation of our study is its retrospective design. Furthermore, because of the relatively small absolute number of deaths (only 13 patients) in a population of 756 patients, definite conclusions cannot be drawn. It has to be mentioned however, that the creation of such a homogeneous group in a busy cardiothoracic center required a period of 2 entire years. We also have not analyzed the timing of postoperative complications, while it has been already confirmed that the highest risk of cardiovascular events is in the morning, due to circadian changes in hemostasis [25].

Conclusions

It is very difficult to explain why the issue of heparin resistance was not previously addressed in the literature in the context of perioperative complications and mortality. Our research shows that the typical, mild forms of "heparin resistance" are relatively frequent and are not associated with increased morbidity and mortality. The isolation of severe heparin resistance as an independent predictor of death in our large cohort of coronary patients suggests that this phenomenon should be given more attention in future studies.

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