

# Standardization of the sodium heparin dose used in off-pump myocardial revascularization surgery

*Padronização da dose de heparina sódica utilizada na cirurgia de revascularização do miocárdio sem circulação extracorpórea*

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## *Abstract*

**Objective:** To evaluate a methodology of anticoagulation during off-pump coronary artery bypass surgery (CABS) that promotes safe anticoagulation during the procedure (Activated Coagulation Time (ACT)  $\geq$  200 seconds), using an initial dose of 1 mg of sodium heparin/kg weight.

**Method:** 40 patients (30 men and 10 women), with ages ranging from 41 to 85 years, were submitted to off-pump CABS, using an initial sodium heparin dose of 1mg/kg of weight. Ten minutes after the drug was administered, if the ACT was  $\geq$  200 seconds, we initiated the revascularization procedure. If not, we administered an additional dose of 0.5mg/kg heparin. During the surgery, the ACT was measured at 30 minute intervals. After revascularization, heparin reversal was achieved with a dose of protamine chloride equal to the total heparin dose infused during the procedure (1:1).

**Results:** The mean ACT at 10 minutes after heparinization was 372.2 ( $\pm$  104.31) seconds, without significant statistical difference between gender and age groups ( $p > 0.05$ ). The ACT values at 30 and 60 minutes remained greater than 200 seconds in all patients. The ACT at 30 minutes showed a significant statistical difference between age groups and gender ( $p < 0.05$ ). After heparin reversal using protamine, all patients returned to their initial hemostasis level (ACT  $<$  200s).

**Conclusion:** The results show the safety and effectiveness of an initial sodium heparin dose of 1 mg/kg of weight during off-pump CABS maintaining safe ACTs ( $\geq$  200s) even after 60 minutes of heparinization, independently of age and gender.

**Descriptors:** Myocardial Revascularization; Heparin; Whole Blood Coagulation Time

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### Resumo

**Objetivo:** Propor uma metodologia de anticoagulação com heparina sódica monitorizada pelo Tempo de Coagulação Ativada (TCA) nos pacientes submetidos à cirurgia de revascularização miocárdica (RM) sem circulação extracorpórea (CEC), que promova uma anticoagulação segura (TCA  $\geq 200$  segundos), utilizando uma dose inicial de 1mg heparina sódica/kg de peso.

**Método:** Quarenta pacientes (30 homens e 10 mulheres), entre 41 e 85 anos, foram submetidos à cirurgia de RM sem CEC, utilizando uma dose inicial de 1mg heparina sódica/kg de peso. Dez minutos após a administração da droga, quando TCA  $\geq 200$  segundos, iniciava-se a confecção das anastomoses coronarianas. Caso contrário, administrava-se 0,5mg/kg de heparina suplementar. Durante a cirurgia, a cada 30 minutos, novos valores de TCA foram obtidos. Concluídas as anastomoses coronarianas, a heparina foi revertida na proporção de 1:1 utilizando cloridrato de protamina.

**Resultados:** O valor médio de TCA dez minutos pós-heparinização foi de 372,2(+/-104,31) segundos, sem variação estatisticamente significativa entre os sexos ou grupos etários ( $p > 0,05$ ). Os valores de TCA, 30 e 60 minutos pós-heparinização, mantiveram-se acima de 200 segundos. Aos 30 minutos, verificou-se diferença estatisticamente significativa dos valores do TCA entre os sexos e diferentes idades ( $p < 0,05$ ). Após reversão com protamina, todos os pacientes retornaram aos seus níveis basais de hemostasia (TCA  $< 200$ s).

**Conclusões:** Os resultados apresentados demonstram a segurança e eficácia da anticoagulação monitorizada pelo TCA nos pacientes submetidos à RM sem CEC, utilizando doses de 1mg heparina sódica/kg de peso, capaz de manter-se efetiva durante todo o procedimento cirúrgico, independentemente de variáveis como sexo ou idade.

**Descritores:** Revascularização miocárdica. Heparina. Tempo de coagulação do sangue total.

## INTRODUCTION

Sodium heparin is the anticoagulant normally used in heart surgery. Pharmacologically, it allows an adequate control of the anticoagulation and the prevention of thromboembolic events, and is responsible for the great development of surgical techniques. However, an adequate and rigorous control of the levels of anticoagulation is necessary, in order to minimize its adverse effects [1,2].

The use of large-dose endovenous sodium heparin in on-pump coronary artery bypass surgery is already well established. Due to the prothrombotic effects induced by the blood circulation in a artificial environment [3], the anticoagulant doses used are high, with levels of up to 3 to 4 mg (300 to 400 IU) of heparin per kg of body weight [1], to reach a safe activated coagulation time (ACT) of over than 480 seconds [2,4].

The technical use of off-Pump coronary artery bypass grafting (OPCABG) surgery reduces the incidence of a series of postoperative complications and the time of hospitalization is comparable to the on-pump procedure [5-7], without damaging the anastomoses [7-8]. Thus, we have seen an increase in the use of off-Pump CABG.

In spite of OPCABG becoming a common technique, there is still no consensus about the ideal dose of heparin to be utilized in this new context [3]. Consequently, the heparinization of patients in this type of surgery has been empirically performed by many surgeons. Some even utilize anticoagulation in doses similar to those employed in on-pump CABG, which may be responsible for the high risk of bleeding in the postoperative period thereby increasing the in-hospital time [9-12]. Additionally, proportionally greater

doses of protamine must be utilized to revert this heparinization, making the dose-dependent deleterious effects of protamine, such as hypotension, myocardial depression and non-cardiogenic pulmonary edema, possible [12,13].

Remembering that in OPCABG surgery the induction of prothrombotic events is less frequent than in on-pump CABG [3], patients submitted to this surgical procedure should, thus, receive differentiated trans-operative anticoagulation, at lower doses.

Based on the fact that OPCABG from the physiological, hemodynamical and functional viewpoints, is similar to peripheral vascular surgery, it has been suggested that the use of heparin doses in OPCABG should be similar to those universally accepted in peripheral vascular surgical techniques. As ACT levels over 200 seconds are considered safe in peripheral vascular procedures, according to current publications [12,14,15], our protocol adopted this ACT level as appropriate for patients undergoing anticoagulation in OPCABG.

Consequently, we present a protocol of a safe method of anticoagulation that can be routinely utilized in this type of intervention. We stress that due to individual variations in the necessities of heparin and the risks involved with small doses, monitoring of the anticoagulant activity of heparin during the surgical procedure is essential [16-19].

## METHOD

Forty patients (30 men and 10 women) with ages between 41 and 85 years (mean: 64.02  $\pm$  11.14 years), participated in the study after signing written informed consent forms. The

patients were consecutively submitted to elective OPCABG surgery from January to June 2005.

This is an observational-type study, with exclusion criteria of previous coagulopathies, patients submitted to reoperations and those that did not accept to participate in the study. The research was approved by the Ethics Committees of the services where the surgical procedures were performed, according to the protocol as follows:

1. All ACT measurements were performed using the 2000® MCA apparatus (Adib Jatene Foundation). In all measurements 3-mL samples of whole blood collected from a peripheral venous vessel was utilized.

2. Before induction of anesthesia, the ACT of the patient (Initial ACT) was determined.

3. After obtaining the initial ACT, EV sodium heparin in bolus at a dose of 1 mg/kg of body weight was infused.

4. Another ACT measurement was made 10 minutes after heparin infusion (ACT<sub>10</sub>). If the determined ACT at this time was 200 seconds or greater, CABG would be initiated. If the ACT was less than 200 seconds, an extra dose of sodium heparin of 0.5 mg/kg of body weight in bolus was administrated EV, aiming at achieving an ACT of more than 200 seconds, defined as safe.

5. At thirty-minute intervals, ACT values were determined (ACT<sub>30</sub> and ACT<sub>60</sub>) and, when they were less than 200 seconds, extra doses of sodium heparin (0.5 mg/kg) were administrated in order to maintain the ACT at over 200 seconds.

6. At the end of CABG, circulating heparin was neutralized by endovenous administration of protamine hydrochloride, controlled using a continuous infusion pump, at a proportion of 1 mg protamine to 1 mg of total heparin administrated. A maximum dose of 50 mg of protamine was administered in each ten minutes.

Ten minutes after the end of protamine infusion, the ACT was measured again (ACT<sub>FINAL</sub>).

## RESULTS

Statistical analysis of the ACT values was made. All the values are in seconds and are reported as arithmetical means, followed by the standard deviation (between parentheses).

To evaluate a possible variation in response between the genders and different age groups to anticoagulation with heparin, we proceeded in the following manner: we obtained mean ACT values of patients from both genders, comparing them and after we utilizing the non-paired t-test. In respect to the analysis of the differences in response according to the age of the patient, we subdivided our sample into three age groups: from 40 to 54 years, from 55 to 69 years and greater than 70 years. For each group the mean

value of ACT was obtained and these values were compared among each other utilizing the one-way analysis of variance test (ANOVA). In both tests, a p-value = 0.05 was considered statistically significant (CI=95%).

The mean of the initial ACT values of studied patients was 127.8 (± 30.57) seconds demonstrating its basal level of hemostatic response. Comparing the mean basal ACT values among the male patients (122.4 ± 29.41) and female patients (143.9 ± 29.66), we obtained a borderline value of p (p= 0.0532), but without significant difference. In the analysis of the basal ACT in the different age groups, we obtained mean values of 134.9 (± 37.47) seconds in the group of 40 to 54 year-olds, 132.4 (± 24.09) seconds in group of 55 to 69 years year-olds and 119.3 (± 30.89) seconds in the group of over 70 year-olds. Comparing the mean values, there is no statistically significant difference among age groups (p= 0.3603).

When the ACT<sub>10</sub> values were analysed, we observed a mean value of 372.2 (± 104.31) seconds. It was verified that there was no statistically significant variation between the ACT<sub>10</sub> of male patients (360.8 ± 106.2) and female patients (406.5 ± 95.13) (p=0.2346) (Figure 1).

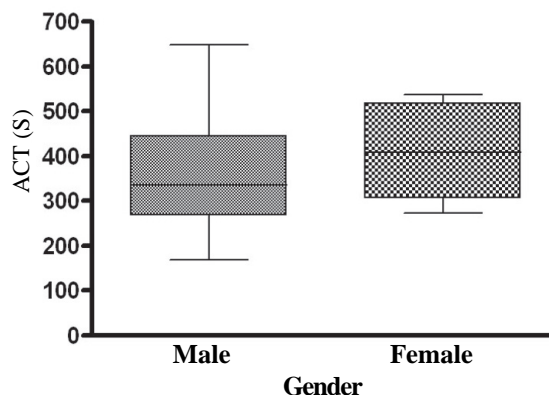


Fig. 1 - ACT<sub>10</sub> versus gender (p=0.2346)

To analyze if the ACT<sub>10</sub> values presented significant variations among the different age groups, we obtained the following values: from 40 to 54 years (371.1 ± 128.3), from 55 to 69 years (395.9 ± 116.1) and over 70 years (352.2 ± 76.1). Comparing these values, we verified that there were no statistically significant variations among the ACT<sub>10</sub> measurements of the different age groups (p= 0.5315) (Figure 2).

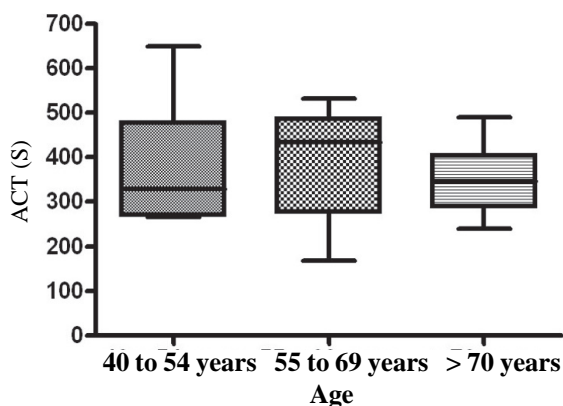


Fig. 2 - ACT<sub>10</sub> versus age (p= 0.5315)

In respect to the mean ACT<sub>30</sub> value, we calculated it to be 342.27 (± 87.14) seconds. It was thus demonstrated that the heparin dose utilized maintained the patients safely anticoagulated in the thirtieth minute after its administration. Comparing the mean values among male patients (319.2 ± 75.15) and female patients (403.9 ± 90.28), we verified that there was a statistically significant variation, with levels of response to the anticoagulation greater in the female group than those obtained in male group (p-value = 0.0067) (Figure 3).

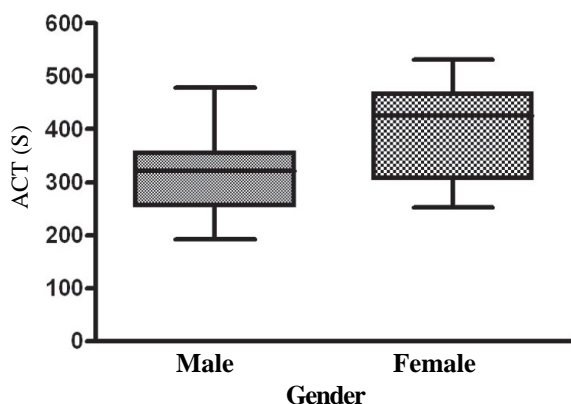


Fig. 3 - ACT<sub>30</sub> versus gender (p= 0.0067)

Comparing the ACT<sub>30</sub> among the three aforementioned age groups, we obtained the following values: from 40 to 54 years – 287.3 (± 67.99), from 55 to 69 years – 396.8, (± 87.79) and over 70 years – 314.7 (± 73.7). Statistically significant differences were identified with the levels of anticoagulation among the different age groups (p-value = 0.0047) (Figure 4). Using the Newman-Keuls test for multiple comparisons,

we observed that this difference occurs only between the 55- to 69-year-old Group and the other two groups. Between the 40- to 54-year-old Group and over 70-year-old Group, there was no statistically significant difference.

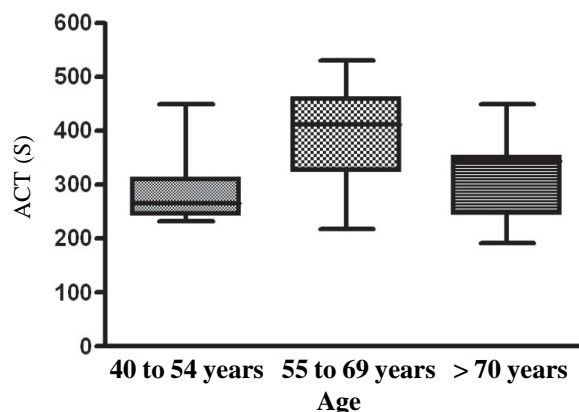


Fig. 4 - ACT<sub>30</sub> versus age (p= 0.0047)

For those patients who were still in surgery for coronary anastomoses at 60 minutes after the initial heparinization (13 patients), a new measurement of the ACT was performed. In these patients the mean ACT value was 324.61 (± 98.80) seconds, thus still within safe levels. Again, there was no statistically significant variations between the ACT<sub>60</sub> of male patients (321.1 ± 78.3) and female patients (330.3 ± 150.5) (p-value = 0.8979). In respect to an analysis among the different age groups, from 40 to 54 years, from 55 to 69 years and more than 70 years, we obtained the following means, 259.0 (± 78.39), 427.7 (± 123.1) and 316.8 (± 61.6) respectively. There was also no statistically significant difference between these values (p= 0.0645).

In respect to the additional heparinization, only one patient presented with an ACT<sub>10</sub> less than the minimum of 200 seconds. An extra dose of 0.5 mg/kg of weight of sodium heparin was administrated to this patient. After this dose, the patient's ACT increased from 168 seconds (ACT<sub>10</sub>) to 403 seconds.

Completing the surgical time corresponding to coronary anastomoses and the protamine infusion the ACT<sub>FINAL</sub> was checked. At this moment, the mean time was from 120.47 (± 22.83) seconds, demonstrating adequate neutralization of the circulating heparin and an efficient return to the initial levels of hemostasis for the patients. Comparing male and female patients, the mean values were 116.4 (± 22.65) and 132.7 (± 19.6) seconds respectively, giving a statistically significant difference between genders (p-value = 0.0492) (Figure 5). When comparing the values among the three age

groups, the mean ACTs were 123.8 ( $\pm$  29.71), 124.9 ( $\pm$  22.5) and 114.6 ( $\pm$  18.01), respectively. No statistically significant differences between the ACT<sub>FINAL</sub> values and the different age groups were identified ( $p$ -value = 0.417) (Figure 6).

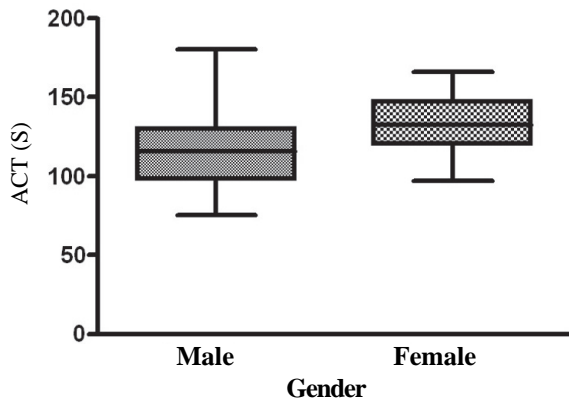


Fig. 5 - ACT<sub>FINAL</sub> versus gender ( $p=0.0492$ )

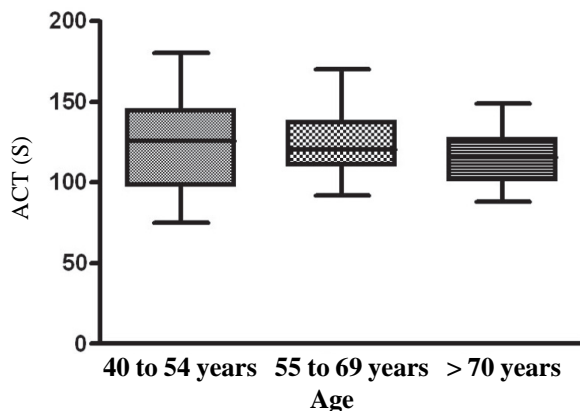


Fig. 6 - ACT<sub>FINAL</sub> versus age ( $p=0.417$ )

## DISCUSSION

With the growing use of the OPCABG, the number of scientific publications, both national and international, related to the use of this surgical technique has increased considerably. However, there are the several gaps in the

scientific literature about the most adequate heparin doses to be employed in this procedure. Through this study, our group aimed at maintaining the levels of anticoagulation of patients submitted to OPCABG to reduced doses of heparin of 1 mg/kg of body weight, similar to the doses utilized in the peripheral vascular surgery.

A concern at the start of the study was about individual variations among patients who could respond heterogeneously to the standard heparin dose, as has already been reported in published studies [16-19]. To try to get around this problem, we adopted the practice of intraoperative monitoring of the ACT, attempting to continuously measure the response of each patient to the heparinization and to immediately increase the dose if patients did not present adequate anticoagulation for the procedure [20,21]. Accordingly, we determined a safety level to perform the surgery with an ACT of at least 200 seconds.

Only one patient presented an unsatisfactory ACT of less than 200 seconds at 10 minutes after heparinization, but the ACT increased immediately to a safe level with an additional dose of 0.5 mg heparin/kg of body weight.

In the other patients, the proposed heparinization gave an effective ACT level, with mean values of 372.2 ( $\pm$  104.31) seconds after administration, well over the pre-established minimum of 200 seconds, a level at which there is surely no intravascular coagulation [16]. We also demonstrated that, independently of gender or age the ACT<sub>10</sub> level was always greater than the acceptable minimum. That is, even taking into account individual variations, differences in gender and age, the utilization of this heparin dose is capable of inducing a safe anticoagulation level, well above the minimum of 200 seconds stipulated by previous studies [12,14,15].

This level of heparinization was even adequate 30 minutes after heparin infusion, as the mean ACT<sub>30</sub> was 342.27 ( $\pm$  87.14) seconds. At this time interval, variables such as gender and age influenced the degree of response to heparinization. However, even responding differently, all patients remained above the safety level.

In those patients in which anastomoses were still being performed 60 minutes after the initiation of heparinization, the ACT was, on average, 324.61 ( $\pm$  98.80) seconds, still considered an adequate level. At this point we can affirm that patients submitted to OPCABG using doses of 1 mg of sodium heparin per kilogram of body weight are safely maintained anticoagulated during all the period necessary to perform the coronary anastomosis procedure.

At the end of the anastomoses, reversal of the heparin was initiated using protamine hydrochloride at a proportion of 1:1. This total reversal at the end of OPCABG, is known to avoid complications such as excessive postoperative bleeding, and the consequent need of blood derivatives and their inherent risks [8,18]. Ten minutes after the end of



the infusion of the protamine, the  $TCA_{FINAL}$  had a mean value of  $120.47 (\pm 22.83)$  seconds. At this moment, there was a slight difference between the genders, again with women having higher ACTs. However, differences among age groups were not identified.

Nevertheless, even with possible individual variations, the heparin reversal protocol brought all patients back to safe hemostasis states – practically similar states to those obtained before the start of the surgical procedure, where the mean ACT was  $127.8 (\pm 30.57)$  seconds (p-values = 0.2284).

The results presented in this study demonstrate the safety and efficacy of anticoagulation of patients who will be submitted to OPCABG utilizing low doses of sodium heparin – 1 mg/kg of body weight. In all patients the response was satisfactory with safe ACTs, adequate to complete the procedure. We also demonstrated that this response lasts for at least 30 minutes or even 60 minutes after initiation of heparinization, maintaining the patient safely anticoagulated throughout.

The efficiency of heparin reversal with protamine at a proportion of 1:1 (total reversion), is also evident, returning the hemostasis of the patients at the end of the surgical procedure to levels similar to the basal level (Figure 7).

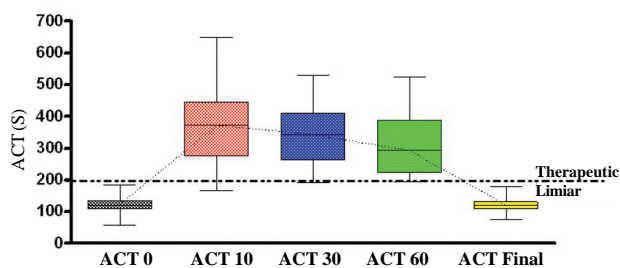


Fig. 7 - Evolution of the ACT (Activated Coagulation Time) over the off-pump CABG procedure

It was also clear that, independently of variables such as gender and age, heparinization at the proposed dose allows adequate levels of anticoagulation to be achieved. Even when the response was statistically different between the genders or age groups, as seen with the  $ACT_{30}$  and the  $ACT_{FINAL}$ , this does not put the patient at risk, because the ACTs remain at adequate levels.

Finally, we believe that according to the results presented in this study, the efficiency of the anticoagulation using 1 mg of sodium heparin/kg of body weight for patients submitted to OPCABG was proven, maintaining the ACTs at safe levels (200 seconds), minimizing the adverse effects resulting from heparinization.

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