

# Comparison of the effects on the flow in the left internal thoracic artery using nimodipine and papaverine as vasodilators

*Comparaç o do efeito da nimodipina e da papaverina como vasodilatadores sobre o fluxo na art ria tor cica interna esquerda*

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## *Abstract*

**Objective:** To compare the flow of the left internal thoracic artery under a local pharmacological effect caused by the topical action on the arterial pedicle and the intraluminal effect of a calcium channel blocker with a control group using papaverine.

**Methods:** Over a period from July to November 2004, a prospective study was performed involving 73 patients who were submitted to coronary artery bypass surgery utilizing the left internal thoracic artery as one of a group of grafts. A comparative analysis of the flow was made when using two different pharmacological agents. The patients were randomized to receive either nimodipine or papaverine as vasodilators. Two types of flow were determined: the flow at Time 1 representing the period of topical action of the drug on the arterial pedicle (extraluminal) and the flow at Time 2

representing the intraluminal action of the drug. A comparison of the means of the two types of flow between the two groups of pharmacological agents was carried out using the non-parametric Mann-Whitney test.

**Results:** There is no evidence that the mean flow using the two pharmacological agents is different at Time 1 ( $p = 0.534$ ) or at Time 2 ( $p = 0.063$ ).

**Conclusions:** There is no evidence that the mean flow varies due to the topical action of one or other drug or that the mean flow is different due to the intraluminal action, proving that nimodipine as a locally acting vasodilator is similar to papaverine.

**Descriptors:** Papaverine. Nimodipine. Mammary arteries. Vasodilator agents.

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### Resumo

**Objetivo:** O objetivo do presente estudo é comparar o fluxo da artéria torácica interna esquerda sob o efeito local farmacológico por embebição e o efeito intraluminal de bloqueador do canal de cálcio com um grupo controle com papaverina.

**Método:** Foi realizado estudo prospectivo de 73 pacientes submetidos a revascularização do miocárdio, no período de quatro meses, nos quais se utilizou a artéria torácica interna esquerda como parte do grupo de enxertos, operados no período de julho de 2004 e novembro de 2004, para análise de fluxo comparativo entre dois fármacos. Os pacientes foram aleatorizados para receberem os vasodilatadores nimodipina ou papaverina. Foram determinados dois fluxos: o fluxo no Tempo 1, o qual representou o período de ação farmacológica por embebição (extraluminal), e o fluxo no Tempo 2, este

representou a ação farmacológica intraluminal. A comparação das médias de fluxo entre os dois grupos de fármacos foi realizada através do teste não paramétrico de Mann-Whitney.

**Resultados:** Não há evidências de que os fluxos médios dos dois fármacos sejam diferentes no Tempo 1 ( $p=0,534$ ). Os fluxos médios dos dois fármacos são semelhantes no Tempo 2 ( $p=0,063$ ).

**Conclusões:** Não há evidências de que os fluxos médios dos dois fármacos sejam diferentes sob ação por embebição (extraluminal), assim como os fluxos médios dos dois fármacos são semelhantes quando por ação farmacológica intraluminal, tornando a nimodipina uma opção como vasodilatador de ação local comparável à papaverina.

**Descritores:** Papaverina. Nimodipino. Artéria torácica interna. Vasodilatadores.

## INTRODUCTION

The use of left internal thoracic artery (LITA) grafts to the anterior interventricular artery is associated with greater survival of patients submitted to coronary artery bypass graft surgery (CABG) [1-4] when compared to venous grafts [5-9]. However, perioperative spasms of the LITA, causing an early reduction in flow, have been associated to an increased morbidity rate in the perioperative period [8-16].

The reduction in flow of the LITA in the perioperative period has been attributed to the dissection and preparation of the internal thoracic artery (ITA) graft [10,17,18]. Handling and movement of the graft during dissection cause spasms that may be minimized by the local action of vasodilatory agents [8,19-21].

Nevertheless, we know that the beneficial effect of this is temporary and may not prevent LITA spasms in the postoperative period [22], so our investigation focused on the perioperative period assessing the capacity of a calcium channel blocker, nimodipine, to maintain an adequate blood flow in recently dissected anterior interventricular artery grafts compared to the use of papaverine.

Few clinical trials have studied the utilization of vasodilators applied to the LITA in an attempt to minimize the spasms [14,23,24] and promote a greater blood flow during the perioperative period. Among the groups of pharmacological agents studied are papaverine [25], calcium channel blockers [26,27], sodium nitroprusside [28], nitroglycerine [26,29], milrinone [29,30] and phenoxybenzamine [27,31], which were used either topically

or in a intraluminal manner with the aim of treating vasospasms of arterial grafts. Papaverine is a phosphodiesterases inhibitor with a half-life of 100 minutes [9] which is very commonly utilized in ITA grafts after dissection. The pharmacological group of calcium channel blockers is empirically recommended for the control of vasospasms [32-40]. Among calcium channel blockers, the one that has the most intense vasodilation action promoting a high coronary blood flow is nimodipine [41]. This agent does not require a minimum effective concentration nor does it have a toxic concentration [41] however it should be used with caution to avoid systemic arterial hypertension.

## METHOD

This study enrolled hemodynamically stable patients electively submitted to CABG. The patients were randomized into two groups using the method of sealed envelopes which were opened at the time of surgery; the first group of patients, denominated Group A, was a control group in which papaverine at a concentration of 1 mg/mL was used as a vasodilator for the ITA graft; for the second group of patients, Group B, nimodipine at a concentration of 0.0012 mg/mL was used as the vasodilator. Two one-minute periods were determined to measure the blood flow.

To compare the two groups, a protocol of these measurements was established:

- The length of the LITA was considered from its origin to its end at the bifurcation or trifurcation;
- The graft was not skeletalized;

- c) The mean arterial pressure (PAM) at the time of blood flow measurement was 70 mmHg ( $\pm 5$  mmHg);
- d) The heart rate at blood flow measurement was 80 beats per minute ( $\pm 5$  beats per minute);
- e) The temperature of the topic vasodilation solution was heated to 37°C to prevent vasoconstriction due to hypothermia.

After total dissection of the LITA, it was soaked using gauzes drenched in the vasodilator solution. To perform the quantitative analysis of the blood flow, we chose the internationally accepted method described in publications [9,42]. After heparinization of the patient, the graft was sectioned at its end as mentioned in item 'a' above and its flow determined with the blood collected in a surgical flask over a 60-second period for future measurement and return to the blood system of the patient by the cardiopulmonary bypass. The time of pharmacological action from soaking to sectioning of the graft was denominated Time 1.

The one-minute blood flow measurement was denominated Flow 1. Subsequently, the lumen of the graft was inspected using a 1.5-mm Garrett vascular dilator followed by intraluminal infusion of the pharmacological agent with occlusion of the distal end using a metallic clip. After a determined period of intraluminal action, the distal portion was sectioned and the blood flow was again measured (denominated Flow 2) with this period denominated Time 2. The time of soaking (Time 1) and the time of intraluminal action (Time 2) were identical.

Comparison of the measurements between the two groups was made using the Mann-Whitney non-parametric test.

## RESULTS

Over a period of four months, a total of 73 patients were included in the study the grafts of whom were randomly treated with either nimodipine or papaverine satisfying the conditions of the study protocol independently of gender, age, body mass index and co-morbidities.

Two flow rates were determined: flow at Time 1 (extraluminal action) and at Time 2 (intraluminal action).

Other variables included absolute differences and percentages between flows at Times 2 and 1 denominated "T2 - T1" and "T2/T1" respectively.

Table 1 shows the sample sizes for both groups.

Tables 2 and 3 describe the means and standard deviations of flows at Times 1 and 2 as well as the absolute differences and percentages.

Figure 1 illustrates the mean flows and standard errors obtained at Times 1 and 2 for the two groups.

The mean extraluminal (soaked in gauze) and intraluminal times of action of the nimodipine were both 10.24 minutes

and the mean extraluminal and intraluminal times of action of the papaverine were both 10.60 minutes. There were no significant differences in respect to the times of action for the two groups.

The supposition of a normal distribution for student t-test was rejected for the four variables by the Kolmogorov-Smirnov test. Thus, comparison between the two groups was made using the Mann-Whitney non-parametric test.

There was no evidence of significant differences in flow rates at Time 1 between the two groups (p-value = 0.534). The flow rates of the two groups were also similar at Time 2 (p-value = 0.063). The absolute and relative differences between Time 2 and Time 1 were greater for papaverine than for nimodipine (p-value = 0.006 and p-value = 0.034, respectively).

A level of significance of 5% was adopted for statistical conclusions.

Table 1. Number of patients who received each type of vasodilator

Vasodilator	Nº patients
Nimodipine	33
Papaverine	40

Table 2. Mean flows at Times 1 and 2, absolute differences and percentages

Vasodilator	Time 1 (T1)	Mean Flow (ml/min)		
		Time 2 (T2)	T2 - T1	T2/T1 - 1
Nimodipine	52.7	69.2	16.5	35%
Papaverine	55.2	79.0	23.9	48%

Table 3. Standard deviations of the Flows at Time 1 and Time 2, absolute differences and percentages

Vasodilator	Time 1 (T1)	Time 2 (T2)	Standard deviation of flow (ml/min)	
			T2 - T1	T2/T1 - 1
Nimodipine	22.7	27.2	9.4	23%
Papaverine	24.5	34.4	21.5	31%

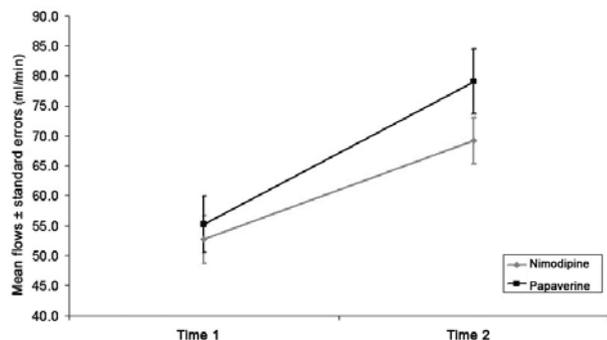


Fig. 1 - Graph of the mean flows and standard errors (mL/min) at Times 1 and 2 for the vasodilators nimodipine and papaverine demonstrating the similarities in the flow rates

## DISCUSSION

Dilation of the LITA, not only for anastomosis to the native coronary artery, but also for the blood flow of the graft, is a basic necessity during surgery in order to significantly reduce the morbidity in the perioperative period [10-15].

As papaverine is a well-known internationally accepted arterial vasodilator used by soaking the post-dissection graft, we chose to utilize it in the Control Group and analyze whether on soaking there is a significant difference between the two groups. There is no evidence that the flow rates are significantly different at Time 1 between the two groups (p-value = 0.534).

In this investigation, using identical periods of extraluminal and intraluminal action, the flow rates after intraluminal action of the vasodilators were also compared giving a more objective and reliable evaluation of the flow.

The mean flows in the two groups were also similar at Time 2 (p-value = 0.063) with a greater vasodilator action of the papaverine.

Similar results were obtained in a comparative study of flows between papaverine and a selective voltage-dependent calcium channel antagonist, analyzing the flows after soaking and intraluminal action [9]. These authors believe that the advantage of verapamil over papaverine is related to the greater lesions caused by the acidic pH of the papaverine (pH between 4.4 and 4.8) compared to verapamil (pH 7.4).

## CONCLUSION

Based on this study, there were no significant differences in mean flow rates using the two pharmacological agents

after soaking or after intraluminal action. Hence, nimodipine can be considered an option as a locally acting vasodilator similar to papaverine. The study opens the possibility of further studies with the aim of utilizing the drugs during the operation and also in the postoperative period as an endovenous infusion to prevent vasospasms of arterial grafts.

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