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Research Article

Effect of Topically Applied Milrinone or Nitroglycerin on Internal Mammary Artery Free Flow

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Background. Surgical mobilization of the internal mammary artery (IMA) can induce graft vasospasm, which is commonly managed by wrapping the IMA in a vasodilator-soaked swab before grafting. However, the choice of the most effective topical vasodilator remains the subject of continued investigation. We carried out a prospective randomized controlled trial to compare the effect of topically applied milrinone, nitroglycerin, and normal saline on IMA free flow. *Methods*. Forty-six consecutive patients undergoing elective primary coronary artery bypass grafting were enrolled. After the left IMA was harvested, free flow was measured under controlled hemodynamic conditions before any intervention (flow 1) and at a mean of 12.5 minutes after the topical application of one of three agents (milrinone, nitroglycerin, or normal saline) on the IMA (flow 2). *Results*. All agents induced a significant increase in IMA flow, and flow 2 was significantly higher in the nitroglycerin and milrinone groups compared to the normal saline group, even while controlling for flow 1 as a centered continuous variable. Nevertheless, there was no statistically significant difference in flow 2 between the nitroglycerin and milrinone groups. *Conclusions*. Topically applied milrinone and nitroglycerin can increase blood flow of the IMA significantly in the early period after surgical mobilization. IMA blood flow was greater after the topical application of milrinone compared to nitroglycerin, but this has failed to reach statistical significance in the present study setting. This trial is registered with NCT06301880.

1. Introduction

Operative mobilization can induce internal mammary artery (IMA) vasospasm, with reduction in initial IMA blood flow and potential perioperative morbidity and mortality [1–6]. IMA vasospasm is thought to represent a multifactorial phenomenon moderated by various mechanisms, such as surgical manipulation, medications, temperature changes, and endogenous catecholamines. The most commonly adopted approach for dealing with this phenomenon is to wrap the IMA in a vasodilator-soaked swab after harvesting [7, 8], and a variety of single or combinations of vasodilators have been used for this purpose. Selection of the most effective vasodilator remains the focus of continued research.

In the present study, we carried out a prospective randomized controlled trial to compare the effect of topically applied milrinone, nitroglycerin, and normal saline on IMA free flow.

2. Patients and Methods

Fifty consecutive patients undergoing elective primary coronary artery bypass grafting were enrolled in this study. Patients were randomly assigned to receive the topical application of one of the three agents: milrinone (Baxter Pharmaceuticals, Ahmedabad, India) 10 mg in 20 ml of dextrose 5%, nitroglycerin (Caspian Tamin Pharmaceutical, Guilan, Iran) 10 mg in 20 ml of normal saline, or normal saline (0.9% sodium chloride solution) as the control.

All surgical procedures and measurements were carried out by a single surgeon (MBI) who was blinded to the topical agent which was applied. Each patient enrolled in the study gave a written informed consent, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and its later amendments, as reflected in a priori approval by the Damascus University Research Ethics Committee number 1939 dated 12 January 2021. The study protocol was registered at ClinicalTrials.gov (trial identifier: NCT06301880).

2.1. Operative Technique. After sternal incision, the skeletonized left IMA was harvested from the subclavian artery to its bifurcation with low-powered electrocautery, and major collaterals were ligated with hemoclips. Following systemic heparinization (300 units/kg to achieve an activated clotting time target of 480 seconds), the IMA was divided proximal to its bifurcation. The first IMA flow (flow 1) was measured by reading the volume of blood ejected from the tip of the freely bleeding IMA through a one-minute period. Heart rate, mean arterial pressure, and central venous pressure were documented at the same time. The tip of the artery was occluded with a bulldog clamp, and a swab which was soaked with the selected vasodilator at room temperature (18.0–20.0°C) was wrapped around the IMA, and was left undisturbed until the second set of measurements.

Cannulation for cardiopulmonary bypass was carried out, and the pump was used to transfuse or drain blood from the patient in order to restore the mean arterial pressures as nearly as possible to the previous values. Systemic vasopressors or vasodilators were not used. The IMA was then unwrapped and the second IMA flow (flow 2) was measured in the same way. Time, heart rate, and mean arterial and central venous pressures were also recorded.

2.2. Statistical Analysis. Data used to support the findings of this study have been deposited in the Figshare repository: https://figshare.com/articles/dataset/Effect_of_topically-applied_milrinone_or_nitroglycerin_on_internal_mammary_artery_free_flow/24905154 [9]. The distribution of continuous variables was assessed for normality using the Shapiro–Wilk test. Since some variables had skewed distributions, we elected to report the medians to express central tendency with interquartile ranges, and hypothesis testing was performed using nonparametric tests. Data analysis was carried out using the Wilcoxon/Kruskal–Wallis nonparametric test. A regression model was then built to determine the statistical significance of the relation between differences in flow 2 and the intervention while controlling for flow 1. In this model, flow 1 was entered as a centered covariate to reduce multipolarity due to the linear relationship between flow 1 and flow 2. Continuous variables are presented as the median and interquartile range.

3. Results

Four patients developed acute ischemic events preoperatively and had to undergo emergency surgery and, therefore, were excluded from this study despite having provided the necessary consents, thus this study cohort included forty-six patients. Patients characteristics are presented in Table 1. Continuous variables are shown as the median and interquartile range. Patients in the milrinone group were significantly younger than the normal saline group ($p = 0.011$), while all other pairwise comparisons were not significant. Importantly, using the cardiopulmonary bypass circuit, it was possible to transfuse or drain blood from the patient to maintain equal mean arterial pressures in the two reading points without using systemic vasopressors or vasodilators. There were no significant differences in mean arterial pressures between the three groups (Table 1).

Flow 1 was comparable in the three groups (median flow 22.0 ml/min (17.3–45.3) for the normal saline group, 40.0 ml/min (25.0–75.5) for the nitroglycerin group, and 35.0 ml/min (22.3–50.0) for the milrinone group, $p = 0.458$), and flow 2 was significantly higher than flow 1 in all three intervention groups (median flow 26.0 ml/min (18.5–46.6) for the normal saline group (18.2% increase, $p = 0.003$), 71.0 ml/min (42.0–98.0) for the nitroglycerin group (77.5% increase, $p = 0.095$), and 79.0 ml/min (59.5–103.5) for the milrinone group (125.8% increase, $p = 0.012$)). Moreover, there were significant differences in flow 2 between the three groups (figure 1, $p = 0.0009$).

Pairwise analyses showed that flow 2 was significantly higher in the nitroglycerin and milrinone groups compared to the normal saline group ($p = 0.005$ and $p = 0.0003$, respectively), while there was no significant difference in flow 2 between the nitroglycerin and milrinone groups ($p = 0.369$).

Since flow 2 has a linear relationship with flow 1, an ANCOVA test was performed to determine the statistical significance of the relation between differences in flow 2 and the intervention while controlling for flow 1 as a centered continuous variable. In this regression model, flow 2 continued to be significantly associated with the type of intervention (normal saline, nitroglycerin, and milrinone) even after controlling for flow 1 ($F(2, 42) = 63.1$, $p < 0.0001$).

4. Discussion

Several approaches have been proposed to improve blood flow through the IMA following its surgical mobilization [1–3]. Gentle probing of the IMA with an appropriately-sized probe or hydrostatic dilatation of the artery can be used to induce a significant increase in IMA graft blood flow. However, these mechanical measures can cause endothelial cell loss and impaired release of prostacyclin and endothelium-derived relaxing factor, which are important modulators of vascular tone and inhibitors of platelet adhesion and aggregation. As such, these measures *per se* may predispose to postoperative IMA spasm and potential early graft failure. Papaverine has been used extensively by cardiac surgeons to prevent or treat IMA spasm and can be delivered through injection into endothoracic fascia before IMA surgical mobilization, pedicled perivascular injection, topical spray, and intraluminal administration with or without hydrostatic dilation [10, 11]. However, recent data about the potential damage that can be caused by papaverine to the endothelium and possible induced apoptosis of endothelial

Table 1: Patients' characteristics.

	Normal saline	Nitroglycerin	Milrinone	*P* value
Number of patients	12	18	16	
Gender (male/female)	11/1	17/1	13/3	0.442
Age (years)	68.0 (63.0–72.8)	64.0 (58.0–70.0)	60.5 (50.8–65.0)	0.04
Time between flow 1 and flow 2 readings (minutes)	12.5 (9.1–14.2)	11.9 (9.7–13.9)	12.1 (8.9–15.3)	0.451
Systolic BP (mmHg) at flow 1 and flow 2 readings	116.0 (111.8–129.0)	127.0 (116.5–134.8)	133.5 (110.0–139.3)	0.245
Diastolic BP (mmHg) at flow 1 and flow 2 readings	57.5 (49.6–61.5)	61.5 (53.5–72.3)	66.5 (59.3–74.5)	0.081
Mean BP (mmHg) at flow 1 and flow 2 readings	77.0 (69.8–83.8)	81.5 (73.8–93.3)	87.0 (77.3–100.3)	0.073
Heart rate (bpm)	69.0 (61.3–74.0)	67.5 (61.0–85.0)	80.5 (70.6–89.8)	0.102

Continuous variables are presented as the median and interquartile range. *P* values are expressed for Wilcoxon/Kruskal–Wallis test (BP: blood pressure, bpm: beat per minute).

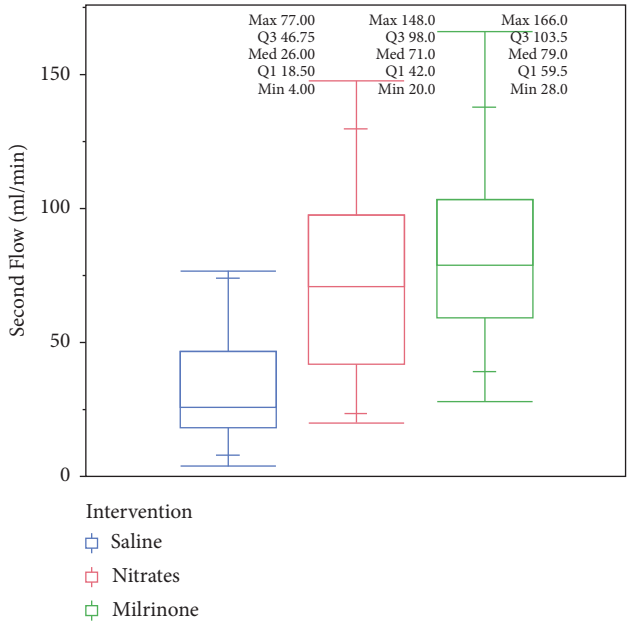

Figure 1: Flow 2 in the three intervention groups.

and smooth muscle cells have discouraged many surgeons from its use [12–14]. Other approaches include intraluminal injection of a mixture of glyceryl trinitrate and verapamil solution [4, 5], use of systemic vasodilators such as enoximone or sodium nitroprusside [4], or preoperative administration of azelnidipine, a third-generation and long-lasting dihydropyridine calcium antagonist [6], which can all be used for the prevention and reversal of IMA graft vasospasm and to produce a significant increase in IMA blood flow.

Milrinone has been shown *in vitro* to produce a potent, concentration-dependent, inhibitory effect on IMA contraction. It also exerts a relaxing effect on IMAs contracted with receptor-dependent agents [15, 16]. To our knowledge, only limited work has been done to study the effects of milrinone on IMA blood flow *in vivo* [17], and there have been no formal clinical studies comparing topically applied milrinone with other vasodilators for their ability to overcome IMA spasm. In the present study, both milrinone and nitroglycerin were capable of inducing rapid and significant increase in IMA blood flow when applied topically. Milrinone-induced vasorelaxation of the IMA was more potent than that induced by nitroglycerin even though the difference in the increase in IMA blood flow between the two agents did not reach statistical significance. It is possible that the doses used for these two agents were not equivalent, but these were the maximum concentrations which we believed we could use without experiencing deleterious drop in systemic blood pressure. In contrast, topical application of warm normal saline in the present study did not produce a significant increase in IMA blood flow, which suggests that the vessel does not undergo substantial spontaneous relaxation rapidly following surgical mobilization [18].

Milrinone acts through inhibiting cyclic adenosine monophosphate phosphodiesterase, thereby increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP), which increases calcium uptake in myocardial and smooth muscle cells. The increased cAMP results in increased inotropy and significant systemic vasodilation [19]. None of the patients in this study developed any undesirable drop in systemic blood pressure. This may imply that drug absorption into the circulation through the peri-IMA mediastinal soft tissues was insignificant or that the duration of topical agent application was shorter than the time required for the systemic effects of the agent to manifest. For example, reaching effective plasma concentrations with an associated increase in the cardiac index after a single intravenous bolus of 50 g/kg of milrinone has been shown to take approximately 60 minutes. The relatively short duration of topical milrinone application in this study could have underestimated its full effects, but this duration was thought to have a practical value in treating perioperative IMA spasm since a rapid response is required in this context.

4.1. Study Limitations. Certain limitations of the present study should be highlighted. The number of patients was relatively small, and this might be why the difference in the increase in IMA blood flow between the milrinone and nitroglycerin groups did not reach statistical significance. Another limitation is that hemodynamic monitoring did not include cardiac output measurements for calculations of systemic and pulmonary vascular resistances.

5. Conclusions

This study shows that topically applied milrinone and nitroglycerin can increase blood flow of the IMA significantly in the early period after surgical mobilization. The authors

also found that IMA blood flow was greater after the topical application of milrinone compared to nitroglycerin. Based on our experience, we recommend that careful atraumatic dissection with minimal direct handling of the IMA can be followed by topical application of milrinone. Furthermore, topical milrinone can be used to enhance IMA blood flow in the early phase following separation from cardiopulmonary bypass as this approach is likely to yield IMA grafts with satisfactory blood flows.

Data Availability

The data used to support the findings of this study have been deposited in the Figshare repository: https://figshare.com/articles/dataset/Effect_of_topically-applied_milrinone_or_nitroglycerin_on_internal_mammary_artery_free_flow/24905154.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] M. Masroor, K. Zhou, C. Chen, X. Fu, and Y. Zhao, "All we need to know about internal thoracic artery harvesting and preparation for myocardial revascularization: a systematic review," *Journal of Cardiothoracic Surgery*, vol. 16, no. 1, p. 354, 2021.

[2] M. Gursoy, F. Hokenek, and V. Bakuy, "Therapeutic options against internal thoracic artery spasm," *The Annals of Thoracic Surgery*, vol. 97, no. 3, p. 1121, 2014.

[3] G. W. He, B. F. Buxton, F. L. Rosenfeldt, J. A. Angus, and J. Tatoulis, "Pharmacologic dilatation of the internal mammary artery during coronary bypass grafting," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 107, no. 6, pp. 1440–1444, 1994.

[4] M. B. Izzat, R. R. West, C. Ragoonanan, and G. D. Angelini, "Effect of systemic vasodilators on internal mammary artery flow," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 108, no. 1, pp. 82–85, 1994.

[5] M. B. Izzat, S. Bolsin, A. J. Bryan, and G. D. Angelini, "Enoximone in internal mammary artery hypoperfusion," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 110, no. 3, pp. 868–870, 1995.

[6] F. Formica, O. Ferro, M. Brustia et al., "Effects of papaverine and glycerilnitrate-verapamil solution as topical and intraluminal vasodilators for internal thoracic artery," *The Annals of Thoracic Surgery*, vol. 81, no. 1, pp. 120–124, 2006.

[7] G. W. He and D. P. Taggart, "Antispastic management in arterial grafts in coronary artery bypass grafting surgery," *The Annals of Thoracic Surgery*, vol. 102, no. 2, pp. 659–668, 2016.

[8] G. Gao, X. C. Liu, W. B. Jing, Q. Yang, and G. W. He, "Vasorelaxation induced by new third-generation dihydropyridine calcium antagonist azelnidipine in human internal mammary artery," *The Annals of Thoracic Surgery*, vol. 96, no. 4, pp. 1316–1321, 2013.

[9] M. B. Izzat: https://figshare.com/articles/dataset/Effect_of_topically-applied_milrinone_or_nitroglycerin_on_internal_mammary_artery_free_flow/24905154.

[10] G. S. L. Gowda, J. H. V. Kumar, S. V. G, A. K. Mathew, and M. C. Nanjappa, "Effect of papaverine on left internal mammary artery flow: topical spraying versus perivascular injection method," *Brazilian Journal of Cardiovascular Surgery*, vol. 35, no. 2, pp. 181–184, 2020.

[11] E. Dregelid, K. Heldal, F. Resch, L. Stangeland, K. Breivik, and E. Svendsen, "Dilation of the internal mammary artery by external and intraluminal papaverine application," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 110, no. 3, pp. 697–703, 1995.

[12] M. Mayranpaa, J. Simpanen, M. W. Hess, K. Werkkala, and P. T. Kovanen, "Arterial endothelial denudation by intraluminal use of papaverine-NaCl solution in coronary bypass surgery," *European Journal of Cardio-Thoracic Surgery*, vol. 25, no. 4, pp. 560–566, 2004.

[13] Y. J. Gao, S. Stead, and R. M. K. W. Lee, "Papaverine induces apoptosis in vascular endothelial and smooth muscle cells," *Life Sciences*, vol. 70, no. 22, pp. 2675–2685, 2002.

[14] O. Unal, M. O. Ulukan, V. Bakuy et al., "Comparison of the apoptotic effects of topically applied papaverine, diltiazem, and nitroprusside to internal thoracic artery," *Brazilian Journal of Cardiovascular Surgery*, vol. 35, no. 5, pp. 626–633, 2020.

[15] J. J. Liu, L. A. Doolan, B. Xie, J. R. Chen, and B. F. Buxton, "Direct vasodilator effect of milrinone, an inotropic drug, on arterial coronary bypass grafts," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 113, no. 1, pp. 108–113, 1997.

[16] M. Onomoto, I. Tsuneyoshi, A. Yonetani et al., "Differential pharmacologic sensitivities of phosphodiesterase-3 inhibitors among human isolated gastroepiploic, internal mammary, and radial arteries," *Anesthesia and Analgesia*, vol. 101, no. 4, pp. 950–956, 2005.

[17] R. Gitter, J. M. Jr Anderson, and G. Kimble Jett, "Influence of milrinone and norepinephrine on blood flow in canine internal mammary artery grafts," *The Annals of Thoracic Surgery*, vol. 61, no. 5, pp. 1367–1371, 1996.

[18] G. J. Cooper, G. A. Wilkinson, and G. D. Angelini, "Overcoming perioperative spasm of the internal mammary artery: which is the best vasodilator?" *The Journal of Thoracic and Cardiovascular Surgery*, vol. 104, no. 2, pp. 465–468, 1992.

[19] A. A. Alousi, J. M. Canter, M. J. Montenaro, D. J. Fort, and R. A. Ferrari, "Cardiotonic activity of milrinone, a new and potent cardiac bipyridine, on the normal and failing heart of experimental animals," *Journal of Cardiovascular Pharmacology*, vol. 5, pp. 792–803, 1983.