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Research Article:

Nebivolol, but not Propranolol, Induced Relaxation of the Isolated Bovine Coronary Segments: Role of NO and K^+ Channels

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Abstract

Background and objectives: Beta-blockers are the most used antihypertensive agents due to their blood pressure-lowering effect alongside decreasing heart rate. Nebivolol (NB) seems to provide typical antihypertensive alongside vasorelaxant effects. The present study aimed to elucidate the differential impacts of NB on bovine coronary tone with a specific focus on the involvement of nitric oxide and K^+ channels. Using an *in vitro* isolated bovine coronary segments, vascular reactivity was assessed through tension measurement in response to NB. **Methods:** Using isolated tissue baths, the impact of NB on bovine coronary artery segments' contractility was assessed. The contractions were induced by KCl, NB was added to check the vasorelaxant effects, and methylene blue was used to examine the role of NO. In addition, the effect on tone was compared with another β-blocker, propranolol, to determine the role of adrenoceptor. **Results:** NB significantly induced relaxation in the coronary bovine artery segments, 49.7 ± 7.84 VS 4.44 ± 6.87. Incubation with methylene blue (30 µM) inhibited NB relaxation, 46.08 ± 4.37 vs MB 12.16 ± 4.28, KCl depolarization did not affect on the relaxation induced by NB in comparison to U46619 precontraction KCl 39.52 ± 6.19 vs U46619 58.41±28.92. Propranolol had no effect on the coronary tone when compared to NB, 87.05±7.05 VS Propranolol 34.28 ± 5.71. **Conclusions:** Our results show that NO but not K^+ channel activation is involved in the mechanism of NB induced coronary artery relaxation. These results highlight the necessity of taking these pathways into account when extrapolating the effects of NB in clinical settings.

1. Introduction

Nebivolol (NB), a β1-adrenoceptor antagonist, also exhibits endothelium-dependent vasodilation. There is growing evidence that this β1-blocking agent enhances NO bioavailability by one or more of the following mechanisms: increasing the endothelial synthesis of NO by NO synthase; decreasing NO destruction by oxygen radicals (1, 2); and/or increasing the activation of β2 adrenoceptors with β2 agonist-like effects (3). The enhancement of NO bioavailability associated with NB therapy is not only effective in controlling blood pressure but has also been found to have a positive effect on other organs, such as the heart, kidneys, and brain (4, 5). Therefore, it is tempting to speculate that there are better effects of NB than those obtained with classical β-blockers in certain diseases. There is increasing evidence that NB ameliorates endothelial function in various vascular beds, reduces inflammation, and has interesting metabolic properties (6). NB lowers systemic vascular resistance in investigations involving animals and human volunteers while maintaining cardiac output by increasing stroke volume (6). It does not

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appear that this effect on peripheral vascular resistance is caused by effects on β-adrenoceptors, potassium or calcium channel blockage, or peripheral sympathetic nervous system activity (7). According to certain research, nitric oxide mediates the vasodilatory effects. NB causes endothelium-dependent vasorelaxation of the isolated rat mesenteric vascular beds (8), and it increases the effects of ADP-induced endothelium dependent relaxation (9) using the endothelium-dependent relaxant factor (EDRF), which is currently understood to be nitric oxide (10). According to preliminary findings, the drug's vasodilating effects appear to be dependent on processes that are specific to the endothelium. This is supported by the fact that the drug's effects are attenuated in a variety of vascular systems and species, by nitric oxide synthase (NOS) and soluble guanylyl cyclase inhibition. These vasodilatory effects do not appear to be explained by its antagonistic actions on histamine receptors, alpha-adrenoreceptors, or β-adrenoreceptors. NB's effect on adrenoreceptors is debatable, however activation of these receptors usually causes vasodilation that is partially mediated by nitric oxide (NO) (11). Previous data have determined β3-adrenoreceptors have been found in the endothelium of human coronary resistance microarteries (12). In these endothelium-dependent relaxation processes, NO and a hyperpolarizing factor are involved, especially evident when NOS activity or availability is decreased, as is the case in atherosclerotic and ischemic diseases (13, 14). The purpose of this study was to ascertain whether NB, in addition to its antihypertensive qualities associated with β-adrenoceptor blockage, also produces vasorelaxation in tiny arteries through the release of NO. This could lead to protective benefits in the microcirculation.

2. Materials and Methods

2.1. NB (Menarini Farmaceutica Internazionale SRL, UK):

A 5 mg tab was used and was crushed using a pestle and mortar to obtain fine powder. A 4 mg dissolved in 1 ml DMSO to obtain 10 mM, stored in an Eppendorf, adding 20 µl of that stock to a 20 ml bath to reach 10 µM. KCl: KCl 70 mM was used as pre contractile agent. The stock solution was prepared by weighing 2.2 gm of KCl and dissolving in 10 ml of Krebs solution to get stock of 3M. Addition of 400µl of the stock to 20 ml organ bath to get 70 mM required for full depolarization (Table 1). U46691 (Tocris Cookson, Bristol UK): U46619 1 mg dissolved in 1 ml DMSO to obtain 10 mM. By using serial dilution, 10 µl of that stock was added to 90 µl DMSO to get 1 mM. And from that 30 µl is added to 70 µl of DMSO to get 300 µM. Also, 10 µl is taken from 1 mM stock and added to 90 µl DMSO to get 100 µM. By taking 20 µl of those concentrations to the 20 ml organ bath we get the required same concentrations. Methylene blue (Thermo Fisher, UK)

3 mg in 1 ml distilled water to get 10 mM stock from which 20 µl was added to 20 ml bath to get 10 µM. That was required to inhibit NO action without damaging the tissues.

Table 1. Krebs solution components

(compositions in 1 litre of distilled water)	
NaCl	6.9 g
KCl	0.36 g
$MgSO_4$	0.29 g
$NaHCO_3$	2.1 g
KH_2PO_4	0.16 g
Glucose	2.1 g
$CaCl_2$	0.19

2.2. Bovine coronary artery preparation

Small pieces of heart from newly slaughtered cows in the local private butchers were brought to the lab. The coronary artery (**Figure 1**) was removed, cleared of adhering connective tissue and from it, two ring preparations, 2 mm in length, were obtained and kept in Krebs solution.

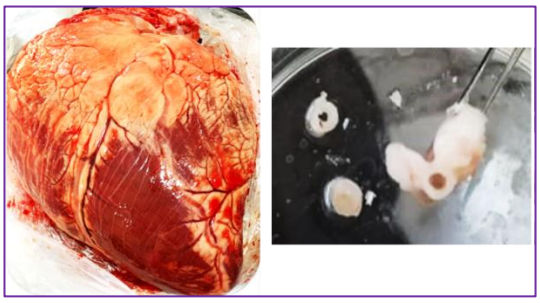


Figure 1. Bovine Coronary artery.

Fresh bovine hearts (Figure 1) were obtained from the butcher's shop in the neighbourhood and instantly placed in a cold Krebs solution. Bovine coronary arteries were used to describe the effects of NB. The coronary arteries anterior proximal descending branch were separated and the artery was removed and cleansed of fat and connective tissues. The artery segments were divided into rings with a length of about 5 mm, and these portions were subsequently prepared for use in the experiment.

General setup: In a 100 ml organ bath (Radnoti company) each coronary was suspended between two stainless steel metal hooks. To record isometric tension, the top hook was attached to a force transducer (iWORX, IWX 404). Each bath was filled with 20 ml of Krebs solution and was connected to a lab companion heated circulatory water bath (Code No.: AAH52325K, Description: Circular Water Bath, Model: CW-20G, Voltage: 230VAC Hz 50Hz A 8.8A, Serial No. P09905) to maintain the temperature at 37oC and constantly gassed with oxygen (96%) using oxygen generator. The whole setup was linked to a laptop to record

the results using Labscribe software 3. The transducers were calibrated with a weight of 20 grams (15-17).

Isometric tension recording: Tissues were placed in the organ bath filled with Krebs, solution, initially pre-tensioned to 6 to 7 g, determined from previous studies and then left to relax to baseline for approximately 20- 30 minutes. Once a stable baseline was attained, two successive KCl additions were obtained for standardization. The procedure was then repeated twice to each ring segment to obtain repeatable results. Krebs solution was used to wash out the tissue after each addition and left for 20 min so that the segment tone could return to baseline. In each KCl addition, the contraction was observed and waited until the stable contraction was attained then washed with Krebs, solution. Each treatment experiment followed the general experimental protocol that was previously outlined.

2.3. The role of NB in the induction of relaxation:

In the case of the bovine coronary artery. After about 20 minutes, cumulative addition of U46619 (100 nM to 500 nM) was added to stimulate tissue contraction to about 50-70% of the second KCl response before NB (10 µM bath concentration) addition to one channel and DMSO to the control channel, after about 60 min the effect of NB was observed.

The role of Nitric oxide (NO) on NB action: This method was used for assessing the role of NO by using Methylene blue (Guanylyl Cyclase inhibitor) which inhibits the downstream signal of NO. In this experiment, after preparing the tissue with two successive KCl additions, methylene blue was added to one channel and incubated at least for 20 min and the other channel was MB free, then the same protocol in the experiment of the effect of NB on inhibition of contraction was repeated. The effect of NB in each channel was examined.

2.4. Comparison between the effect of KCl and U46691:

To observe the difference in the contractile effect of KCl and U46619 precontraction on NB relaxation. Two coronary rings were used, and the same general experimental protocol was done as mentioned previously but, in this case, U4 was added in one channel and KCl in the other one and after the contraction of KCl plateaued and U4 was about 70 % of KCl, NB was added and incubated for about 1 hr. – 1.5 hr. The effect of NB in the presence of U4 was compared to that in the presence of KCl.

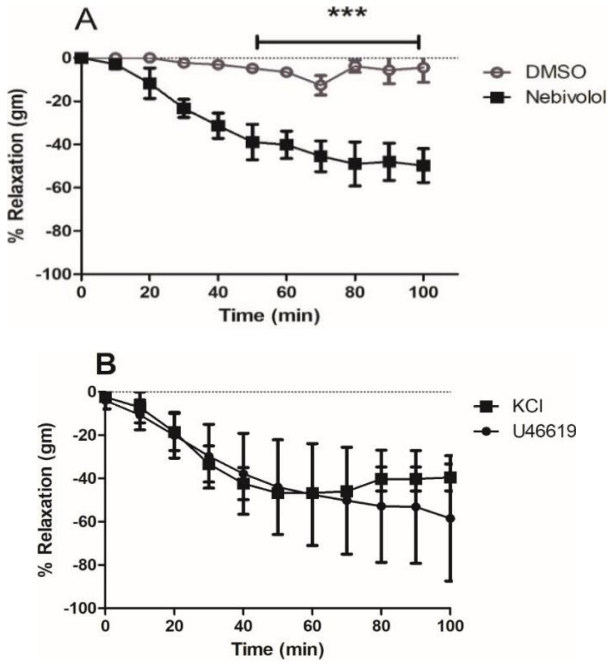
2.5. Data and statistical analysis:

The collected data were analyzed using a two-way ANOVA test. Results are presented as mean±standard error (SE). In cases where the ANOVA was significant, a post-hoc Bonferroni test was performed. The significance level was set at a P value less than 0.05, indicating a statistically significant mean difference. The levels of significance are denoted as follows: *** means p< 0.001, ** means p<0.01, and * means p<0.05. The results of relaxation were compared with values obtained from the DMSO solvent control. Statistical analysis for all experiments was conducted using GraphPad Prism 5 software.

3. Results

Preliminary experiments on isolated bovine aortic rings showed that a 30-minute incubation with NB resulted in the inhibition of KCL-induced contractions. The rate of relaxation was determined by calculating the percentage change from the pre-contraction induced by KCl at a period of approximately 2 hours. Additionally, the rate of contraction was computed as a percentage of the contraction prompted by KCl. The presented values for each repetition represent the mean ± SEM. NB induced significant relaxation 49.7±7.84 in comparison to DMSO 4.44±6.87 as solvent control, the negative values denote relaxation. Comparisons were drawn between the rate of relaxation induced by NB and a control solution containing DMSO (at a concentration of 0.1% v/v) across a 2-hour interval (**Figure 2A**).

Similarly, NB inhibits U46619-induced contraction of bovine coronary rings, with no significant difference between relaxation obtained from U46619 58.41±28.92 versus isolated bovine coronary rings precontracted with KCl 39.52±6.19 (**Figure 2B**), The presented values for each repetition represent the mean ± SEM where NB and the number of repeats for this experiment and all other organ bath experiments was 5 (n=5). To examine the role of NO in NB induced relaxation. methylene blue (30µM) incubation was able to significantly inhibit NB relaxation, providing evidence for NO dependent relaxation (**Figure 2C**).



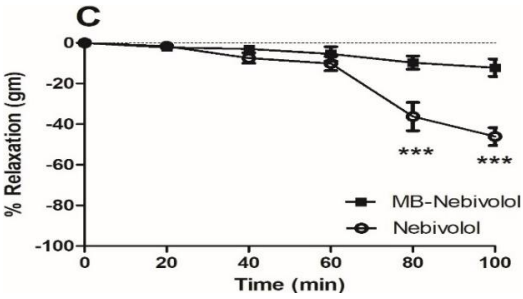


Figure 2. (A) Effect of NB incubation for 30 minutes on the contractile response of the isolated bovine coronary segments to U46619-induced contraction (n=5). (B) The effect of depolarization with 70mM-KCl on NB relaxation in isolated bovine coronary segments (n=5). The presence of 70mM-KCl significantly attenuated the relaxation caused by NB when compared to pre-contraction induced by U46619. (C) Effect of MB incubation for 30 minutes on the relaxant response of the isolated bovine coronary segments to U46619-induced contraction (n=5). Data expressed as mean±SD. *** indicates significant differences at p<0.0001 in the two-way analysis of the variance (ANOVA) followed by using the Bonferroni post-hoc test.

As depicted in **Figure 3**, the acute addition of propranolol (control) has no effect on the coronary tone in comparison to NB induced a time-dependent relaxation in isolated bovine coronary artery segments pre-contracted submaximally with KCl. The effect reaches a significant value after about 1hr incubation with NB 87.05±7.05 VS Propranolol 34.28±5.71. Data are represented as the percentage of relaxation of the KCl-induced contraction and are mean ± SEM from 5 different samples of bovine coronary artery.

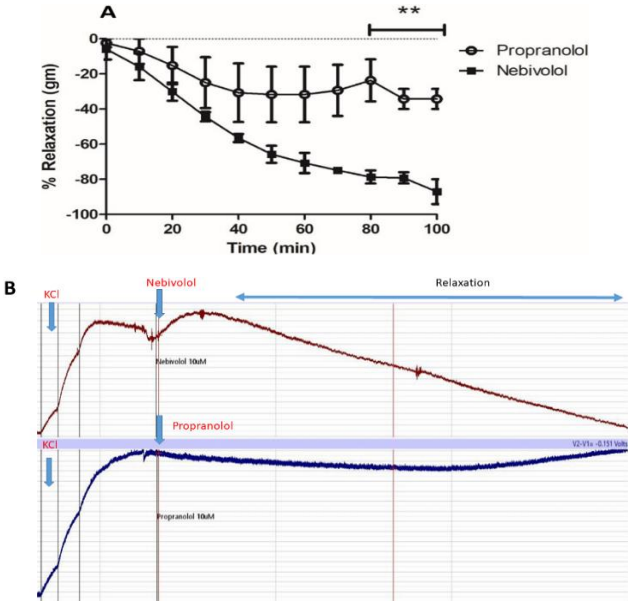


Figure 3. (A) Effect of NB versus propranolol incubation for 30 minutes on the contractile response of the isolated bovine coronary segments to U46619-induced contraction (n=6). (B) A representative sample providing the action of tested drugs. Data expressed as mean±SD. ** indicates significant differences at p<0.001 in the two-way analysis of the variance (ANOVA) followed by using the Bonferroni post-hoc test.

4. Discussion

NB is a third generation β-blocker which has an additional vasodilating effect. Despite the reports regarding the positive effects of NB on endothelial dysfunction, there is no direct study in the literature showing the acute effect of NB on both pressure and flow-mediated relaxation of resistance arteries. The purpose of the current study was to investigate whether the acute addition of NB causes vasodilation on vascular tone and whether the dilation was regulated by nitric oxide. To achieve this, we looked at how isolated coronary arteries were affected by NB in comparison to propranolol, a known β1-selective adrenoceptor antagonist. The role of NO was examined by incubation with MB, an inhibitor of NO, to investigate the role of the L-arginine/NO pathway in mediating the vasorelaxing effect of NB (18, 19). The findings demonstrated that the addition of NB diminished the relaxation of the coronary vascular in the KCl pre-constricted preparation (20). Additionally, the effect of NB was compared with the same concentrations of a β1 receptor antagonist, propranolol, To explain the participation of the β1 receptors in the mechanism of vasodilation. The results showed that in vitro single applications of NB, but not propranolol, induced coronary vasorelaxation (21-23).

Endothelial cell dysfunctions are the leading cause of hypertension, heart disease, and many other circulatory problems (24). Therefore, endothelial cell functions have gained significantly in importance. It is well known that flow-mediated dilation takes place in the endothelium by the release of endothelial-derived relaxing factors such as nitric oxide (NO) that may be involved in the molecular mechanism coupling factors toward relaxation. Similarly, the ACh-dependent control of arterial pressure is regulated by endothelium-derived nitric oxide (NO) and pharmacological antagonism of ACh-dependent control of arterial pressure reduces flow shear stress-mediated vasodilation (25, 26).

In the clinical setting, NB treatment is associated with a significant decrease in global and central blood pressure (1) and a significant improvement in the radial artery endothelial function of hypertensive patients and patients with metabolic syndrome (27). NB's effects beyond b-blockade could be significant in terms of improving peripheral and coronary blood flow, reversing endothelial dysfunction, and having antioxidant and anti-inflammatory properties (28). When compared to conventional b-blockers, these pharmacological characteristics seem to be more tolerable and may provide further protection against cardiovascular events. NB's overall antihypertensive efficacy is comparable to that of other β-blockers, calcium channel antagonists, and renin-angiotensin antagonists; however, it has a less adverse side effect profile than conventional β-blockers (29). Four weeks of NB treatment

has improved coronary flow in hypertensive patients and idiopathic dilated cardiomyopathy (12). Similarly, It is well accepted that NB induced relaxation of human and rat urinary bladder via activation of β3 adrenergic receptors (15,16), NB also induce smooth muscle relaxation via nitric oxide-dependent pathway in different vascular Beds like thoracic and abdominal aortic vessels (11). In vitro studies with experimental β3 agonists, a suggested target for NB, provide further evidence for β3 induced endothelium-dependent relaxation (18)(30). While propranolol did not affect nitric oxide (NO) bioactivity for the same level of blood pressure control (2,3)(4), NB boosted both baseline and stimulated endothelial NO release (5). NB, but not propranolol greatly enhanced the vasodilatory response to acetylcholine (6). Moreover, there was a notable decrease in the endothelium-dependent vasoconstrictive response to N(G)-monomethyl-L-arginine (L-NMMA), which was not seen with propranolol (7).

Systemic vascular resistance originates from small arterioles, and relaxation of these arterioles efficiently changes blood pressure, in hypertensive patients, these arterioles are constricted, and dilation of these blood vessels leads to reduced blood pressure, dilation of these vessels mainly focuses on endothelial-derived NO (4). Accumulation of endothelin and reactive oxygen species has been associated with reduced NO production, hence vasoconstriction ensues an action that has been reversed with NB (9). This action explained the results obtained in the present study through significant vasodilation of bovine coronary artery rings induced by NB compared to propranolol, In fact, the mechanism exact is still obscure, nonetheless, the involvement of NO was central (4).

Since propranolol (β1-adrenoceptor antagonism) has no vasorelaxant activity, therefore, it's uncommon to be due to β1-adrenoceptor antagonism. Hence, NB has induced these effects via a different mechanism i.e. NO generation (20).

NB, in contrast to the majority of conventional b-blockers, causes an initial drop in peripheral vascular resistance in vivo that is quickly accompanied by a drop in blood pressure (31). This theory is based on research demonstrating that the removal of endothelium and the injection of NO synthase inhibitors impair the vasodilator response to the medication. NB had a similar effect on the dorsal hand vein and forearm vasculature of humans in vivo (32, 33), as well as isolated canine coronary arteries in vitro. Additional preparations utilized include venous preparations and conduit arteries, like the rat's aorta and caudal artery and the dog's saphenous vein (34, 35). Nevertheless, there are no investigations on resistance vascular beds, which are distinguished by a high level of neurogenic control over vascular tone and whose role may be more significant for hemodynamic regulation. Consequently, we have described the vascular effects of NB in this investigation using an isolated resistance vascular bed.

5. Conclusion

NB, but not propranolol, had induced vasorelaxant activity in the bovine coronary artery. The relaxation was NO-dependent, however K^+ channel block did not affect NB relaxation in the isolated bovine coronary segments.

6. Conflict of interest:

All authors declare that there is no conflict of interests.

7. Acknowledgments:

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النبيفيلول وليس البروبرانولول يسبب استرخاء عضلات الاوعية القلبية البقرية المعزولة : دور نايترك اوكسايد وبوابات البوتاسيوم

الخلفية والأهداف :حاصرات بيتا هي أكثر العوامل الخافضة للضغط استخداما بسبب تأثيرها في خفض ضغط الدم إلى جانب انخفاض معدل ضربات القلب . نيبيفولول يميل لتخفيض الضغط بصورة نموذجية بالإضافة الى استرخاءالاوعية .تهدف الدراسة الحالية إلى توضيح التأثيرات التفاضلية للنبيفولول على تقلص الشريان التاجي البقري مع التركيز بشكل خاص على دور أكسيد النيتريك وقنوات البوتاسيوم باستخدام قطع من الشريان التاجي البقري المعزولة في المختبر، تم تقييم تقلص الأوعية الدموية المعزولة من خلال قياس التوتر **الطرق** :باستخدام حمامات الأنسجة المعزولة، تم تقييم تأثير النبيفولول على انقباض قطع الشريان التاجي البقري .وقد تسببت الانقباضات التي بواسطة KCL، تمت إضافة النبيفولول للتحقق من آثار الاسترخاء للاوعية، واستخدمت الميثيلين الأزرق لدراسة دور ناترك اوكسايد. بالإضافة إلى ذلك، تمت مقارنة التأثير على التقلص مع مانع آخر، بروبرانولول ، لتحديد دور المستقبلات الأدرينية **.النتائج :**النبيفولول : الاسترخاء الناجم بشكل كبير في شرائح الشريان التاجي البقري، 49.7 ± 7.84 مقابل 4.44 ± 6.87 .الحضانة مع الميثيلين الأزرق 30µ) م (تحول دون الاسترخاء النبيفولول ، 46.08 ± 4.37 VS مقابل مثلين بلو 12.16 ± 4.28، لم يؤثر التقلص بواسطة ملح البوتاسيوم على الاسترخاء الناجم عن النبيفولول بالمقارنة مع يوفور 46619 عن ملح البوتاسيوم 39.52 ± 6.19 مقابل يوفور 46619 58.41 ± 28.92 .كان بروبرانولول أي تأثير على تقلص الاوعية التاجية بالمقارنة مع النبيفولول ، 87.05 ± 7.05 مقابل بروبرانولول 34.28 ± 5.71 .**الاستنتاج :**تظهر نتائجنا أنه ناترك اوكسايد له دور ولكن ليس قناة البوتاسيوم دورفي آلية استرخاء النبيفولول للشريان التاجي . تسلط هذه النتائج الضوء على ضرورة أخذ هذه المسارات في الاعتبار عند استقراء تأثيرات ملحوظة في البيئات السريرية.

الكلمات المفتاحية : نيبيفولول، أكسيد النيتريك ، قناة البوتاسيوم، أجزاء الشريان التاجي، استرخاء الأوعية الدموية .