In vitro effects of antihypertensive drugs on thromboxane agonist (U46619)-induced vasoconstriction in human internal mammary artery

K. A. Tanaka, F. Szlam, N. Katori, A. Tsuda and J. H. Levy*

Department of Anesthesiology, Emory University School of Medicine, Division of Cardiothoracic Anesthesiology and Critical Care, Emory Healthcare, Atlanta, Georgia, USA

*Corresponding author. E-mail: jerrold.levy@emoryhealthcare.org

Background. Hypertension is a major problem in the perioperative period of cardiac and non-cardiac surgery. The vascular endothelium plays a crucial role in modulating vascular tone by producing vasodilators as well as vasoconstrictors. Thromboxane A2 (TxA2), a prototypical vasoconstrictor produced by endothelium and platelets, may play an important role in the pathogenesis of hypertension and subsequent ischaemic events. Although multiple drugs are currently available to treat perioperative hypertension, there is a paucity of data comparing these agents. Therefore, we examined the in vitro vascular effects of commonly used antihypertensive drugs on human internal mammary artery (IMA) segments.

Methods. Relaxation responses to adenosine (a nucleoside), enalaprilat (a competitive inhibitor of angiotensin-converting enzyme), fenoldopam (a D1-dopamine receptor agonist), hydralazine, labetalol (an α- and β-adrenergic blocker), nicardipine (a calcium channel blocker), nicorandil (K⁺-ATP channel opener), nitroglycerin (GTN, a nitrosovasodilator), and sodium nitroprusside (SNP, a nitrosovasodilator) were studied in IMA segments pre-contracted with the TxA2 analogue (U46619, 1.0×10⁻⁸ M). Effects of labetalol were also studied in IMA segments pre-contracted with norepinephrine (1.0×10⁻⁶ M). All drugs were added in a cumulative fashion (range 10⁻¹⁰ to 10⁻³ M).

Results. All agents in the current study, with the exception of enalaprilat, dilated the IMA segments pre-contracted with U46619. Only GTN and SNP induced a complete (90–100%) relaxation. The order of efficacy of the in vitro relaxation was as follows: SNP, GTN, nicardipine, nicorandil, fenoldopam, hydralazine, adenosine, and labetalol. The potency was in the order of GTN, SNP, fenoldopam, nicorandil, hydralazine, adenosine, and nicardipine.

Conclusions. Various antihypertensive agents are effective in attenuating U46619-induced IMA vasoconstriction, but the efficacy and potency differ. The in vitro vasodilation may not be simply extrapolated to the clinical efficacy or outcome of each antihypertensive therapy; however, our data provide additional grounds for the choice of antihypertensive medication. Further clinical studies are needed to help to fully elucidate the use of different antihypertensive agents and clinical outcomes.


Keywords: agonists, thromboxane; arterial pressure, antihypertensives; arteries, internal mammary artery; complications, vasoconstriction

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Hypertension is a major problem in the perioperative period, especially in older patients with atherosclerotic disease, presenting for both cardiac and non-cardiac surgery. Controlling arterial pressure is often a challenging task in the perioperative period, and various antihypertensives are often used as vasodilators in order to reduce myocardial stress.

The vascular endothelium plays a crucial role in modulating vascular tone by producing vasodilators (e.g. prostacyclin (PGI2) and endothelium-derived nitric oxide), as well as vasoconstrictors (e.g. thromboxane A2 (TxA2), endothelin, and superoxide anions). Hypertension may be linked to the imbalance in the formation of PG2 and TxA2, and may occur...
in the perioperative period. Elevated levels of TxA₂ may well be a causal factor leading to the arterial constriction and vascular events as reported in aspirin-resistant patients who had a higher risk of myocardial infarction and cardiac death.

Internal mammary artery (IMA) is widely used as a conduit for coronary artery bypass surgery, can be readily obtained, and serves as a useful model to study the effects of pharmacologic agents on human vasculature. Further, systemic arterial pressure control by i.v. antihypertensive agents administered during bypass surgery is highly likely to affect the vascular tone and blood flow in this conduit artery. Previous in vitro studies have described nitrovasodilators, calcium channel blockers, and phosphodiesterase inhibitors on the IMA, but there is a paucity of information on comparing different pharmacologic class of antihypertensive drugs.

In our in vitro study we investigated the relaxation responses of different classes of antihypertensive agents on human IMA pre-contracted with TxA₂ analogue in order to elucidate differences in potency and efficacy of the different agents routinely used in clinical practice.

## Methods

### Vessel preparation

Following approval by our institutional review board, segments of right and left IMA were collected from 60 patients undergoing CABG. The cardiovascular risk factors and the preoperative drug therapy of these patients are listed in Table 1. The discarded distal end was carefully removed and placed in chilled modified Krebs–HEPES buffer of the following composition (mmol litre⁻¹): NaCl 118, KCl 4.69, CaCl₂ 2.5, MgSO₄ 1.04, NaHCO₃ 25, d-glucose 11.1, and HEPES 21.8, pH 7.40 (0.05). The vessels were transferred to the laboratory and then cleaned of adherent connective tissue. The time delay between vessel harvest and preparation was less than 15 min. The IMA segments were cut into 3-mm rings. Two to four rings were obtained from each vessel. Active endothelial function was confirmed by acetylcholine-induced vasodilation.

### Table 1 The cardiovascular risk factors and preoperative drug therapy of the patients included in the study. All data are numbers of patients (with percentages) unless otherwise stated. ACE=angiotensin converting enzyme

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (no. males)</td>
<td>47 (78.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (70.0)</td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>36 (60.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (38.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>18 (30.0)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>31 (51.7)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25 (41.7)</td>
</tr>
<tr>
<td>β Blocker</td>
<td>30 (50.0)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>15 (25.0)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>Statin</td>
<td>22 (36.0)</td>
</tr>
</tbody>
</table>

### Experiments with isolated vascular rings

The rings were suspended between two wire hooks in organ chambers filled with 25 ml Krebs–Henseleit solution (37°C, pH 7.40) aerated with oxygen 95%/carbon dioxide 5%. The upper hook was connected to a force transducer (Kent-Scientific Corporation, Litchfield, CT), and changes in isometric force were recorded (MacLab® system, ADI Instruments; Milford, MA). A resting tension (4 g) initially defined by preliminary studies was progressively applied, and the rings were allowed to stabilize for 45 min (until a stable baseline was obtained). The IMA segments were then pre-contracted with 60 mM potassium chloride. The contraction was allowed to plateau for 10 min and then acetylcholine was (10⁻⁶ M) added to assess endothelial function. Only rings that exhibited more than 30% relaxation were used in the subsequent experiments. The vascular segments were then washed twice with fresh buffer solution and pre-contracted with the TxA₂ analogue U46619 (10⁻⁸ M). Additionally, when labetalol was used as the relaxing agent, some of the rings were pre-contracted with norepinephrine (10⁻⁶ M). The concentrations of pre-contracting agents (U46619 and norepinephrine) were determined from the cumulative contraction–response curves to achieve 50–80% of the maximum contraction as described previously. After 10–15 min equilibration (time needed for the development of stable contraction), segments of IMA were randomly assigned to one of 10 groups (adenosine, enalaprilat, fenoldopam, hydralazine, labetalol, labetalol/norepinephrine, nicardipine, nicorandil, nitroglycerin (GTN), and sodium nitroprusside (SNP)) and exposed to increasing concentrations (range 10⁻¹⁰ to 10⁻⁷ M) in 0.5 log unit steps of relaxants. Each IMA ring was exposed to only one drug, which was added cumulatively every 5 min. Control, U46619, and norepinephrine contracted rings not challenged with any antihypertensive agent were run in parallel as time controls. No more than 75–80 min was required from the time the relaxing agent was added to the bath until the end of the experiment.

### Drugs

All drugs were obtained from commercial sources as follows: adenosine diphosphate (Fujisawa USA, Inc., Deerfield, IL), enalaprilat (Merck, Rahway, NJ), fenoldopam (Neurex Corporation, Menlo Park, CA), hydralazine (American Regent Laboratories, Shirley, NY), labetalol (Glaxo-Wellcome, Inc., Research Triangle Park, NC), nicardipine (Wyeth Laboratories, Inc., Philadelphia, PA), nitroglycerin (Solvay-Laboratories, Elk Grove Village, IL), nicorandil (Chugai Pharmaceutical Co. Ltd, Japan), norepinephrine (Abbott Laboratories, Chicago, IL), TxA₂ analogue (U46619) (Upjohn Company, Kalamazoo, MI), SNP and KCl (Sigma Chemical Company, St Louis, MO). An aliquot of TxA₂ analogue (U46619) was evaporated to dryness under nitrogen and re-dissolved in absolute ethanol to 10⁻³ M and then serially diluted in distilled water. All other drugs were...
seriously diluted in distilled water. Drugs were prepared before each experiment and stored on ice. Drug concentrations are expressed as final molar concentrations in the bath solution.

**Data and statistical analysis**

Contraction responses to norepinephrine, and the TxA2 analogue (U46619) were expressed in gain of tension (in grams). Relaxation responses were calculated as percentage of norepinephrine or U46619 induced contraction. Data were averaged for each patient in all experiments. For curves that saturated, the effective concentration of vasodilator agent that caused 50% relaxation (EC50) was determined for each IMA (responses from vascular segments were averaged for one IMA) by the logistic curve fitting the equation:

\[ E = \frac{E_{\text{max}} \times C^\gamma}{C^\gamma + E_{\text{max}}^\gamma} \]

where \( E \) is the response, \( E_{\text{max}} \) is the maximal relaxation, \( C \) is the concentration, and \( \gamma \) is the slope parameter (Sigma Plot®, SPSS, Inc., San Rafael, CA). Results are expressed as mean (SD). Statistical analysis (STATVIEW (Macintosh OS9)) was performed with Kruskal–Wallis \( H \)-test followed by Bonferroni correction. A probability value <0.05 was considered significant.

**Results**

**Concentration–response curves**

There were no differences in baseline pre-contraction and maximum contraction levels between the groups (Table 2), and the maximum contraction achieved by U46619 and norepinephrine in control IMA rings was stable for the duration of the relaxation experiments. The \( E_{\text{max}} \) and EC50 Values for nicorandil, nicardipine, and adenosine were not calculated as the respective concentration–response curves had not saturated at the highest concentration achieved during the study (Figs 1–3). GTN and SNP were the only two agents, which allowed maximum relaxation (\( E_{\text{max}} \)) of 90–100% of IMA segments pre-contracted with U46619 (Fig. 1). The EC50 for relaxation was higher for nitroglycerin (4.51 (3.4) \( \times 10^{-8} \) mol litre\(^{-1} \)) than for SNP (3.90 (1.6) \( \times 10^{-8} \) mol litre\(^{-1} \)), but the difference was not significant.

Nicardipine, a calcium channel blocker, caused a concentration-dependent relaxation of IMA, but its efficacy and potency were lower than GTN or SNP (Fig. 1, Table 2). Nicorandil also caused a concentration-dependent relaxation of IMA, however, it was as efficacious but less potent than nicardipine (Fig. 2, Table 2). Fenoldopam caused slightly, but not statistically significant less relaxation of IMA when compared with nicorandil (54.3 vs 70.7%, respectively; \( P=0.231 \)) (Fig. 2, Table 1). \( E_{\text{max}} \) value for fenoldopam was lower that those of SNP and GTN (\( P<0.01 \) vs SNP and GTN). EC50 value for fenoldopam was higher than those of GTN and SNP (Table 2). Adenosine and hydralazine caused only a small concentration-dependent

![Fig 1](https://academic.oup.com/bja/article-abstract/93/2/257/260098/1)

**Table 2** Summary of resting and contracted tensions along with potency and efficacy estimates. Vessel tensions in grams and effects of different vasodilator agents in IMAs pre-contracted with the TxA2 analogue U46619 (1.0\( \times 10^{-3} \) mol litre\(^{-1} \)) or norepinephrine (1.0\( \times 10^{-8} \) mol litre\(^{-1} \)). Data are expressed as mean (SD), \( n \) = number of vessel segments. \( M \) = concentration of drug in mol litre\(^{-1} \). Maximum relaxation (\%) is that observed in the experiment at the maximum concentration added (see Figs 1–4). EC50 denotes the effective concentration of vasodilator agent that caused 50% of relaxation. \( E_{\text{max}} \) is the maximal relaxation calculated from regression analysis. NC = not calculated. *Different from SNP and GTN groups (\( P<0.05 \)).

<table>
<thead>
<tr>
<th>Drug</th>
<th>( n )</th>
<th>Resting tension (g)</th>
<th>Tension after U46619 (g)</th>
<th>Tension after norepinephrine (g)</th>
<th>Maximum relaxation (%)</th>
<th>EC50 (M)</th>
<th>( E_{\text{max}} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalaprilat</td>
<td>6</td>
<td>3.75 (0.39)</td>
<td>12.31 (2.1)</td>
<td>–</td>
<td>6.02 (14.6)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Adenosine</td>
<td>6</td>
<td>3.92 (0.50)</td>
<td>11.80 (2.5)</td>
<td>–</td>
<td>33.9 (12.5)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>6</td>
<td>3.88 (0.51)</td>
<td>11.25 (2.3)</td>
<td>–</td>
<td>54.3 (12.3)</td>
<td>1.73 (2.5) ( \times 10^{-7} )</td>
<td>56.4 (11.1)*</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>6</td>
<td>4.08 (0.45)</td>
<td>11.95 (2.8)</td>
<td>–</td>
<td>36.9 (14.5)</td>
<td>2.27 (3.3) ( \times 10^{-6} )</td>
<td>40.6 (13.8)*</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>7</td>
<td>3.95 (0.40)</td>
<td>11.50 (2.0)</td>
<td>–</td>
<td>74.0 (14.6)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>6</td>
<td>4.12 (0.38)</td>
<td>12.22 (2.0)</td>
<td>–</td>
<td>70.7 (11.3)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>6</td>
<td>3.95 (0.44)</td>
<td>11.56 (1.6)</td>
<td>–</td>
<td>88.0 (7.0)</td>
<td>4.51 (3.4) ( \times 10^{-8} )</td>
<td>90.2 (6.9)</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>6</td>
<td>3.92 (0.41)</td>
<td>11.87 (2.3)</td>
<td>–</td>
<td>102.1 (3.5)</td>
<td>3.90 (1.7) ( \times 10^{-7} )</td>
<td>98.3 (2.3)</td>
</tr>
<tr>
<td>Labetalol</td>
<td>6</td>
<td>3.98 (0.45)</td>
<td>11.51 (2.0)</td>
<td>–</td>
<td>27.5 (14.2)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Labetalol</td>
<td>5</td>
<td>4.03 (0.35)</td>
<td>–</td>
<td>8.53 (2.0)</td>
<td>88.2 (14.3)</td>
<td>2.37 (1.7) ( \times 10^{-7} )</td>
<td>91.08 (3.9)</td>
</tr>
</tbody>
</table>
relaxation of IMA segments (37.7 (14.5) and 39.0 (14.8)%), respectively, which were significantly less than the responses to GTN, SNP, nicardipine, and nicorandil (Fig. 3 and Table 2). Labetalol minimally relaxed U46619 constricted IMA at the highest concentration used; therefore, its EC50 was not calculated (Fig. 4). However, it caused an almost 90% relaxation when the vessel was pre-contracted with norepinephrine (Fig. 4). Enalaprilat was ineffective in reversing TxA2 analogue induced contraction, even at the highest concentration used (10–3 M); therefore, its Emax and EC50 were not calculated (Fig. 4). The overall efficacy of the antihypertensive drugs used in the current in vitro evaluation, based on U46619 pre-constriction was as follows:

SPN>NTG>nicardipine>nicorandil>fenoldopam>hydralazine>adenosine>labetalol.

Discussion
In the current in vitro study of antihypertensive drugs on the reversal of U46619-induced vascular contraction, we observed three broad patterns of responses: (i) clear dose–response relationship in the therapeutic range (SNP and GTN); (ii) obtunded response requiring concentration greater than therapeutic range (adenosine, fenoldopam, hydralazine, nicardipine, and nicorandil); (iii) no response (labetalol and enalaprilat).

Perioperative stress along with vascular injury and platelet activation cause vasoconstriction presenting as systemic hypertension. Understanding the efficacy and potency of antihypertensive drugs on IMA should be useful because it is widely used as a conduit for coronary artery bypass surgery, and antihypertensive therapy may be potentially useful in preventing vasospasm-related myocardial ischaemia after surgery. TxA2 agonist, U46619, and other vasopressors (e.g. phenylephrine) cause vasoconstriction by increasing intracellular inositol phosphate turnover via G-protein (Gq/11) coupled TP receptors. We tested whether antihypertensive drugs could reverse U46619-induced vasoconstriction in vitro. All of the agents used are important clinically and represent the major classes of i.v. drugs with antihypertensive properties.

Both nitrodilators cause nitric oxide-mediated vasodilation of systemic artery in a dose-dependent manner (Fig. 1). Their clear potency and efficacy are a result of a nitric oxide-mediated mechanism of action. SNP and GTN were the most potent and efficacious agents from all the antihypertensive drugs that we evaluated in the current study. Nicardipine, a dihydropyridine calcium channel inhibitor, exerted moderate vasodilatory effect (79.2%) at 10–4 M,
but this was only achieved at much higher than the therapeutic plasma concentrations (0.5–1.0 \( 10^{-7} \text{M} \)) (Fig. 1).\(^{11}\) We have reported previously a similar difference between GTN and a short-acting calcium channel blocker, clevidipine.\(^{12}\) Nicorandil, an ATP sensitive \( \text{K}^+ \) channel opener, also exerted vasodilation (71.7%) of human IMA, which is in agreement with others,\(^{13}\) and its potency was similar to nicardipine. Increased \( \text{K}^+ \) efflux by ATP channel opening causes hyperpolarization of the vascular smooth muscle and subsequent relaxation, and nicorandil is also presumed to increase cGMP.

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Dopamine receptor stimulation leads to increased intracellular cAMP, resulting in vasodilation. Our results suggest the existence of D1-dopamine receptors in IMA (Fig. 2). EC\(_{50}\) value for the relaxant effect of fenoldopam (1.73\( \times 10^{-7} \text{M} \)) (Table 1) was higher than the therapeutic concentrations reported in plasma (0.20–6.7\( \times 10^{-7} \text{M} \)).\(^{11}\) D1-Dopamine receptors are located at various systemic sites, such as renal, mesenteric, coronary, and cerebral arteries. We have reported previously that fenoldopam could induce \( \alpha \)-adrenergic stimulation and cause vasoconstriction of human umbilical artery.\(^{11}\) In the current study, however, we did not observe vasoconstriction at comparable concentrations. In the study by Hughes and colleagues, fenoldopam effectively reversed norepinephrine-induced IMA contraction (71.7%) of human IMA, which is in agreement with others,\(^{13}\) and its potency was similar to nicardipine. Increased \( \text{K}^+ \) efflux by ATP channel opening causes hyperpolarization of the vascular smooth muscle and subsequent relaxation, and nicorandil is also presumed to increase cGMP.

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