Effects of non-depolarizing neuromuscular blocking agents on norepinephrine release from human atrial tissue obtained during cardiac surgery

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We have studied the effect of non-depolarizing neuromuscular blocking agents, at concentrations present in serum during anaesthesia, on release of [³H]-norepinephrine ([³H]NE) from superfused atrial appendage obtained during cardiac surgery from 48 patients. Three of the neuromuscular blocking agents (pancuronium, gallamine and rocuronium), which are known to cause an increase in heart rate during anaesthesia, increased stimulation-evoked release of [³H]NE. In contrast, (+)-tubocurarine and pipecuronium, neuromuscular blocking agents that do not cause tachycardia, did not affect release of N.E. Org 9487 significantly enhanced release while SZ1677 was ineffective, even at concentrations higher than those expected after administration of a 2×ED⁹⁵ dose. Atropine enhanced release. These data suggest that the axon terminals of sympathetic nerves in human heart have muscarinic heteroreceptors whose activation by acetylcholine (ACh) released from the vagal nerve reduces release of NE. This action contributes to lowering of heart rate. Therefore, any neuromuscular blocking agent with antimuscarinic actions and capable of increasing the release of NE may produce tachycardia.

Keywords: neuromuscular block; sympathetic nervous system, norepinephrine; heart, heart rate; surgery, cardiovascular

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The heart is regulated by both divisions of the autonomic nervous system: acetylcholine (ACh) released by the vagal nerve decreases and norepinephrine released by the sympathetic nerves increases heart rate via muscarinic and β₁ adrenoceptors, respectively. Increased vagal–sympathetic antagonism (i.e. augmentation of the vagal action in the presence of prevailing sympathetic activity) is of primary importance for the control of heart rate.¹ This interaction could be manifested either on the sinus node (inhibition of muscarinic receptors on sinus cells) or as was demonstrated recently,²⁻⁵ at the presynaptic terminal of postganglionic sympathetic nerves. Vagal stimulation reduces automaticity, not only by a direct action via muscarinic receptors located on cardiac muscle counteracting the effect of norepinephrine released from the sympathetic nerves, but also by an indirect action, inhibiting the release of norepinephrine via stimulation of M₂ receptors.¹⁻⁶ Similarly, an antimuscarinic, atropine-like effect of pancuronium, leading to increased norepinephrine release, was found⁷ in human ventricular myocardium.

An increase in heart rate during anaesthesia in patients with cardiac disorders is undesirable.⁸⁻¹¹ Therefore, the ideal neuromuscular blocker should have no effect on heart rate. However, as has been shown in animal experiments,⁵ several neuromuscular blockers have antimuscarinic actions, and therefore may cause release of norepinephrine from sympathetic neurones, influencing heart rate.

In this study, we have investigated if those neuromuscular blockers which produce tachycardia in clinical practice influence release of norepinephrine from isolated human atrial tissue obtained during cardiac surgery.

Materials and methods

Human heart atrial appendage was obtained at operation from 48 patients after obtaining informed consent. Tissues (10–20 mg) were selected randomly from patients undergoing valve replacement or coronary bypass surgery performed at the Department of Vascular Cardiovascular Surgery, Semmelweis Medical University Budapest, Hungary. The specimens were placed in oxygenated (95% oxygen–5% carbon dioxide) Krebs solution of the following
composition (mmol litre$^{-1}$): NaCl 113, KCl 4.7, MgSO$_4$ 1.2, CaCl$_2$ 2.5, NaHCO$_3$ 2.5, KH$_2$PO$_4$ 1.2, glucose 11.5, Na$_2$EDTA 0.3 and ascorbic acid 0.03, and maintained during transport (30–40 min) at 4–17°C. Tissues were then cut into small pieces, washed with Krebs 5 ml and loaded for 45 min with $^3$H-norepinephrine (L-7.8-$^3$H- norepinephrine, 37 MBq, 40 Ci mmol$^{-1}$, Amersham) at a concentration of 10 µCi ml$^{-1}$ of Krebs solution. During this time the medium was gassed with a mixture of 95% oxygen–5% carbon dioxide. After incubation, the slices were washed with Krebs solution 5 ml and transferred into a four-channel microvolume perfusion system. Three pieces were placed into each chamber, the preparation was superfused with Krebs solution at 37°C at a rate of 0.6 ml min$^{-1}$ for 60 min (pre-perfusion period) and the effluent discarded. Subsequently, 3-min fractions were collected. Supramaximal (40 V) field stimulation (3 ms, 2 Hz for 2 min; Grass S88 stimulator) was applied during the third (S$_3$) and 13th (S$_{13}$) fractions, delivering 240 shocks in each case. Neuromuscular blocking agents were added from the eighth fraction, 15 min before the second stimulation, until the end of the experiment. At the end of the experiment, the pieces were removed from the chamber and homogenized in 0.5 ml of 10% trichloroacetic acid. A 0.5-ml aliquot of the superfusate and 0.1 ml of the tissue supernatant were added to 2 ml of scintillation cocktail (Ultima GOLD Packard). Tritium was measured with a Packard 1900 TR liquid scintillation counter using an internal standard.

**Calculation of resting and evoked release of radioactivity**

Data were expressed as absolute amount of radioactivity in Bq g$^{-1}$ (disintegration per second per gram of tissue) or as fractional release. Fractional release is expressed as a percentage of the total stored radioactivity in the tissue.

Radioactivity released in response to field stimulation was calculated (either from the amount of radioactivity expressed in Bq g$^{-1}$ or from fractional release values) by subtracting the means of the basal release values determined during two collection periods, before (FRR$$_1$$) and after stimulation (FRR$$_2$$). The amount of norepinephrine released is proportional to the amount of radioactivity released above resting release (i.e. area under the curve) calculated from the stimulus-evoked increase in tritium efflux and calculated basal efflux.$^3$ These values were calculated for each stimulation (S$_1$, S$_2$).

The effects of the drugs on electrical stimulation-induced outflow were expressed as the ratio of fractional release in the second (S$_2$) compared with the first (S$_1$) stimulation (FRS$$_2$/FRS$$_1$$). The effect of the drugs on resting release was expressed as FRR$$_2$/FRR$$_1$$ ratio: drugs were present in the superfusion fluid from the ninth collection period and maintained throughout the experiment.

**Analysis of catecholamines**

$^3$H]Catecholamines were identified in heart tissue and superfusate fluid by high pressure liquid chromatography (HPLC) using electrochemical and radiochemical detection. The HPLC system consisted of a Gilson 305 solvent delivery pump and a Gilson 805 manometric module, connected to a Nucleosil 3 C-18 analytical column (100×4.0 mm) through a Rheodyne 7125 injector valve (loop sizes 20 and 100 µl). A guard column Nucleosil 3 C-18 (20×4.0 mm) was inserted between the injector valve and the analytical column. The outlet of the analytical column was connected to a BAS 400 electrochemical cell which contained a glassy carbon electrode vs Ag−AgCl reference electrode, and oxidizing potential was maintained at 0.75 V by an Eltron potentiostat. The detector signal was monitored with a Shimadzu integrator. The mobile phase was sodium phosphate 50 mmol litre$^{-1}$, citric acid 25 mmol litre$^{-1}$, pH 3.6, EDTA 0.25 mmol litre$^{-1}$, octane sulphonic acid sodium salt 0.75 mmol litre$^{-1}$ and 5% acetonitrile:methanol (3.5:1.0). Flow rate was 1.0 ml min$^{-1}$.

Norepinephrine and its metabolites in human heart tissue were extracted by mixing 100 mg of freeze-dried, powered sample with 1 ml of HCl 0.1 mol litre$^{-1}$ which contained dihydroxybenzyl amine 72 µmol litre$^{-1}$ as internal standard. Homogenates were centrifuged at 3000 rpm for 20 min. Excess acid of the supernatant was removed with potassium citrate (9:1 v/v). After repeated centrifugation, a 20-µl aliquot of the sample was injected onto the column.

For measurement of released $^3$H]norepinephrine and its metabolites, 1.5-ml aliquots of the perfusion fluid (from 2×3 min samples) were collected, frozen and evaporated to dryness. The dried samples were redissolved in 150 µl of eluent which contained norepinephrine 0.3 µmol litre$^{-1}$ (not labelled), epinephrine and normetanephrine as internal standards. The aliquot (100 µl) was injected and radioactivity was measured by liquid scintillation counting, as described above, in each 1-min sample of the effluent. Recovery of radiolabelled activity averaged 73.8±6.4% (n=12). Standards were dissolved in HCl 0.1 mol litre$^{-1}$; the stock solutions were stored at −20°C. Working solutions were prepared by appropriate dilution of the 1.0 mg ml$^{-1}$ stock solutions before use.

**Drugs**

The following drugs were used: (+)-tubocurarine, obtained from Research Biochemical International (Natrick, MA, USA); gallamine triethiodide and atropine sulphate, obtained from Sigma Chemical Co. (St Louis, MO, USA); pancuronium, pipercuronium, rocuronium, and Org 9487, obtained from Organon Inc. (West Orange, NJ, USA); and SZ1677 {1-(3α-hydroxy-17β-acetyloxy)-2β-(1.4 dioxa-8-azaspiro [4,5] dec-8-yl)-5α-androstane-16β-yl)-1-(2-propenyl) pyrrolidinium bromide}, obtained from Gedeon Richter (Budapest, Hungary) and Maruishi Pharmaceutical Co Ltd (Osaka, Japan).

In the present in vitro study, equipotent concentrations of 2×ED$_{95}$ ((+)-tubocurarine 1.0 mg kg$^{-1}$, pancuronium 0.1 mg kg$^{-1}$, gallamine 2.0 mg kg$^{-1}$, pipercuronium 0.1 mg kg$^{-1}$ and rocuronium 0.6 mg kg$^{-1}$)$^{12-14}$ used in
clinical practice were calculated and at least two concentrations in this range were applied. Therefore, ED_{95} concentrations, generally determined on a mg kg^{-1} basis, were converted to mol litre^{-1}. For Org 9487 and SZ1677, there were no clinical data available. Therefore, because the relative potencies of steroid-type neuromuscular blockers in clinical use are relatively similar in guineapigs and humans, we estimated ED_{95} values (Org 9487 2.3 mg kg^{-1} and SZ167 0.06 mg kg^{-1}) from data obtained in guineapigs.

The corresponding concentration of 2HED_{95} in plasma was calculated by dividing 2HED_{95} by plasma volume, which was estimated as approximately 5% of body weight. Because this is a rough estimation, not taking into account differences in protein binding, we used two or three different concentrations in the same range.

Statistical analysis
All data are expressed as mean (SEM). Statistical significance was determined using analysis of variance (ANOVA) followed by Dunn’s test. P<0.05 was considered significant.

Results

Content of endogenous and tritiated norepinephrine in atrial tissue
Norepinephrine content of atrial tissue, measured by HPLC with electrochemical detection, was 0.65 (0.14) µg g^{-1} (n=8).

After loading the tissue with [3H]norepinephrine, total tissue [3H] content was 313 3659 (238 418) Bq g^{-1} (n=48). Of the total radioactivity, 98.0 (0.6)% (n=4) was found to be [3H]norepinephrine. This indicates that [3H]norepinephrine taken up by the tissue may be stored in such a way that it is protected from degradation, as only a small amount (2.0%) can be accounted for by metabolites.

Fractional release of [3H]norepinephrine at rest and during stimulation
Because at the end of each experiment the [3H] content of the right appendage was determined and the efflux of radioactivity was measured throughout the experiment, it was possible to calculate the fractional release that occurred during each 3-min period. Efflux of radioactivity expressed as fractional release was moderate during successive collection periods. Under resting conditions, 8200 (266) Bq g^{-1} (n=48) (i.e. 0.26 (0.09)% of the radioactivity present in the tissue at the onset of stimulation. The ratio FRS_{2}/FRS_{1} measured in those experiments in which neuromuscular blockers were present did not differ from controls.

Effect of non-depolarizing neuromuscular blockers on resting and stimulation-evoked release
In six experiments, gallamine, pancuronium, rocuronium, Org 9487, (+)tubocurarine, pipecuronium and SZ1677 were added to the organ bath 15 min before the second (S_{2}) stimulation. Concentrations of neuromuscular blockers were selected on the basis of their approximate concentrations in humans. None of the neuromuscular blockers had a significant effect on resting release (Table 1). The ratios FRR_{2}/FRR_{1} measured in those experiments in which neuromuscular blockers were present did not differ from controls.
Pancuronium, gallamine, rocuronium and Org 9487 significantly increased release of norepinephrine. Pancuronium 3 \( \mu \text{mol litre}^{-1} \) and gallamine 150 and 300 \( \mu \text{mol litre}^{-1} \) increased release of norepinephrine from sympathetic nerve terminals (Table 1). FRS2/FRS1 ratios were 1.08 (0.04), 1.19 (0.05) and 1.97 (0.21), respectively. Rocuronium 100 \( \mu \text{mol litre}^{-1} \) significantly increased norepinephrine release: FRS2/FRS1 ratio was 1.33 (0.16). The effect of Org 9487 on norepinephrine release is shown in Figure 1B. Org 9487 had no effect on release of \( ^{[3]H} \)norepinephrine at rest, but enhanced stimulation-evoked release of \( ^{[3]H} \)norepinephrine (Fig. 1B). In contrast, (+)-tubocurarine, pipecuronium and SZ1677 had no effect on norepinephrine release, even at concentrations much higher than those required to produce neuromuscular block in humans.

(+)-Tubocurarine 5 and 30 \( \mu \text{mol litre}^{-1} \) had no effect on norepinephrine release from sympathetic nerve terminals. FRS2/FRS1 ratios were 0.82 (0.06) and 0.93 (0.08), respectively. In our study, SZ1677 30 \( \mu \text{mol litre}^{-1} \) (which is a relatively high concentration compared with its ED95 in guineapigs) did not increase the release of norepinephrine from sympathetic nerve terminals in human atrial tissue. FRS2/FRS1 ratio was 0.91 (0.04).

Atropine 0.1 \( \mu \text{mol litre}^{-1} \) significantly enhanced release of norepinephrine: FRS2/FRS1 ratio was 1.58 (0.09) \((n = 6, P<0.01)\). Resting release was not affected.

### Discussion

The aim of this study was to investigate the effects of different neuromuscular blockers on norepinephrine release from human atrial tissue at clinically relevant concentrations. We have reported, for the first time, neurochemical and pharmacological evidence obtained in human atrial tissue that neuromuscular blockers (pancuronium, gallamine, rocuronium and Orgon 9487) increase release of norepinephrine at concentrations near those used in clinical practice. (+)-Tubocurarine, pipecuronium and SZ1677 did not affect release of norepinephrine. Several studies have shown that autonomic modulation of heart rate is determined by interaction of sympathetic and vagal innervation at the effector level (sinus node) and at the presynaptic level, influencing release of norepinephrine. Muscarinic receptors located both on the atrial pacemaker and papillary muscle15 16 and on axon terminals1–7 of noradrenergic neurones may be involved in setting sympathetic inflow, heart rate and heart muscle force (Fig. 2). Pharmacological and clinical studies have shown that with the exception of vecuronium and pipecuronium, all other neuromuscular blockers can inhibit muscarinic receptors and in some cases produce tachycardia, which is not desirable during anaesthesia in patients with cardiac disorders.

Recent animal studies have provided evidence in isolated right atrium that neuromuscular blockers with anti-muscarinic (atropine-like) activity may increase sympathetic activity in the heart in two ways: (i) by a direct effect on heart muscle cells by preventing the negative chronotropic and inotropic effect of ACh released from the vagus15 16 and (ii) by blocking neuronal uptake of norepinephrine and preventing the inhibitory effect of ACh released from the vagus nerve on norepinephrine release from sympathetic nerve endings.1–7 17 19

Heart rate is regulated by both divisions of the autonomic nervous system: ACh decreases and norepinephrine increases heart rate via muscarinic and \( \beta_{1} \) receptors. As convincing evidence is available that release of norepinephrine is under the tonic muscarinic control of ACh released from the vagus nerve1 ensuring vagal dominance, the effect of neuromuscular blockers on muscarinic receptor-mediated control of norepinephrine release may be clinically important (Fig. 2).

(+)-Tubocurarine has been used clinically for approximately 50 yr. This drug does not produce tachycardia but because of its histamine-releasing properties and hypertensive effect, (+)-tubocurarine was superseded by other non-depolarizing neuromuscular blockers, for example pancuronium and vecuronium. It has been suggested that gallamine has vagolytic10 11 and sympathomimetic effects8 20 and occasionally produces significant tachycardia. For this reason, few anaesthetists use this drug. Nevertheless, clinical concentrations of gallamine (90 \( \mu \text{mol litre}^{-1} \)) failed to increase release of norepinephrine, but it had atropine-like activity and enhanced release of norepinephrine at higher concentrations (Table 1).

Pancuronium has vagolytic and sympathomimetic effects21–23 and some workers have demonstrated that it blocks norepinephrine uptake into sympathetic nerve endings. In our study, pancuronium 3 and 100 \( \mu \text{mol litre}^{-1} \) increased release of norepinephrine associated with axonal activity. FRS2/FRS1 ratios were 1.08 (0.04) and 1.73 (0.22), respectively. Tachycardia, which is sometimes observed

### Table 1 Effects of non-depolarizing neuromuscular blocking agents on stimulation-evolved release of \( ^{[3]H} \)norepinephrine from human atrial tissue. The effect of the drugs on electrical stimulation-induced outflow is expressed as the ratio of fractional release in the second (S2) compared with the first (S1) stimulation (FRS2/FRS1). The effect of the drugs on resting release is expressed as FRR2/FRR1 ratio.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conc (( \mu \text{mol litre}^{-1} ))</th>
<th>n</th>
<th>FRS2/FRS1</th>
<th>P</th>
<th>FRR2/FRR1</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>6</td>
<td>0.93 (0.04)</td>
<td>0.95 (0.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)-Tubocurarine</td>
<td>5</td>
<td>4</td>
<td>1.08 (0.04)</td>
<td>1.08 (0.05)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>3</td>
<td>100</td>
<td>6.13 (0.05)</td>
<td>6.13 (0.06)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Gallamine</td>
<td>200</td>
<td>20</td>
<td>6.19 (0.05)</td>
<td>6.19 (0.06)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>5</td>
<td>100</td>
<td>6.19 (0.05)</td>
<td>6.19 (0.06)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>100</td>
<td>10</td>
<td>6.19 (0.05)</td>
<td>6.19 (0.06)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Organon 9487</td>
<td>100</td>
<td>5</td>
<td>6.19 (0.05)</td>
<td>6.19 (0.06)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>SZ1677</td>
<td>100</td>
<td>5</td>
<td>6.19 (0.05)</td>
<td>6.19 (0.06)</td>
<td>&lt;0.01</td>
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during anaesthesia with gallamine or pancuronium, has been explained by vagolytic and sympathomimetic effects. Recently, our group provided direct neurochemical evidence, by measuring release of \[^{3}H\]norepinephrine and \[^{3}H\]acetylcholine from isolated right atrium of guineapigs, that gallamine and pancuronium prevent the inhibitory effect of muscarinic receptor stimulation on norepinephrine release from sympathetic nerve endings. We also reported that AF-DX 116, a selective M\(_2\) muscarinic antagonist, was effective in blocking the presynaptic muscarinic receptor and concluded that ACh controls release of norepinephrine via M\(_2\) muscarinic receptors located on adrenergic axon terminals.

Pipercuronium, a long-acting neuromuscular blocker, does not produce tachycardia and this is its main advantage in clinical practice. In our study, pipercuronium 2.8 and 10 \(\mu\)mol litre\(^{-1}\) did not increase release of norepinephrine, as expected from clinical experience. Rocuronium, an aminosteroid neuromuscular blocker, which in humans has a fast onset of action and minimal cardiovascular and vagal side effects, only slightly increased release of norepinephrine.

A great effort has been made to develop non-depolarizing neuromuscular blocking agents with rapid onset, short duration of action and without cardiovascular effects. In our study, we also investigated the effects of the new non-depolarizing neuromuscular blockers, SZ1677 and Org 9487, on release of norepinephrine from sympathetic nerve terminals in the human atrium. SZ1677 is a 3-OH derivative of 1-(3a,17\(\beta\)-bis(acetyloxy)-2\(\beta\)-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)-5\(\alpha\)-androstan-16\(\beta\)-yl)-1-(2-propenyl)-pyrrolidinium bromide. SZ1677 does not inhibit vagal-induced depression of heart rate in cats, and does not have antimuscarinic effects in in vitro experiments. Therefore, it was concluded that SZ1677 is unlikely to produce tachycardia in human atrium. From neurochemical evidence, indicating that SZ1677 does not have antimuscarinic activity in human isolated atrial preparation, it seems unlikely that it will produce tachycardia during anaesthesia.

Org 9487 is an aminosteroid and the 16-N-allyl-17-\(\beta\)-propionate analogue of vecuronium. The main advantage of Org 9487 is its rapid onset and rapid reversibility. Its effect on heart rate has not been investigated. In our study, Org 9487, at concentrations of 50 \(\mu\)mol litre\(^{-1}\), less than those expected in plasma after administration of 2 \(\times\) \(\text{ED}_{95}\), increased release of norepinephrine from sympathetic nerve terminals.

Significant changes in the modulation of sympathetic nervous system activity after anoxic or ischaemic periods contribute to generation of malignant arrhythmias in the intensive care unit. It has been shown that in human cardiac tissue during anoxia, the inhibitory effects produced via stimulation of \(\alpha_2\) adrenoceptors on norepinephrine release are lost (i.e. negative feedback modulation of norepinephrine release) and \(\beta_2\)-adrenoceptor-mediated facilitation of norepinephrine release becomes dominant. Therefore, under anoxic or hypoxic conditions, the norepinephrine releasing effect of neuromuscular blockers with antimuscarinic action is much more dominant, and therefore these agents should not be selected for neuromuscular block.

In summary, our observations in human atrial tissue that some non-depolarizing neuromuscular blockers have atropine-like antimuscarinic properties and at higher concen-

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**Fig 2** Schematic representation of how non-depolarizing neuromuscular blocking agents with antimuscarinic actions increase norepinephrine (NE) release from sympathetic nerve endings in the heart. A: Vagal dominance. Acetylcholine (ACh) released from the vagal nerve ending reduces release of norepinephrine from the sympathetic nerve terminals via stimulation of M\(_4\) muscarinic receptors. Note that vagal nerve endings are not equipped with inhibitory \(\alpha_2\)-receptors, but there is a feedback modulation; ACh reduces its own release via M\(_2\) muscarinic receptors. The release of norepinephrine is under negative feedback modulation via \(\alpha_2\)-adrenoceptors. Norepinephrine released from sympathetic nerve endings acts on the sinus node (\(\beta_1\)-adrenoceptor) increasing heart rate. B: Non-depolarizing neuromuscular blockers with antimuscarinic action (atropine-like effect on M\(_2\)-receptors) prevent the inhibitory effect of ACh on norepinephrine release, thereby increasing release of norepinephrine. It is suggested therefore, that neuromuscular blockers with antimuscarinic activity may produce tachycardia during anaesthesia in two ways: (i) by inhibiting muscarinic receptors (M\(_2\) subtype) expressed on the sinus node and preventing the negative chronotropic and inotropic effects and (ii) by increasing release of norepinephrine. Under hypoxic conditions, the situation is worsened because there is no \(\alpha_2\)-adrenoceptor-mediated negative feedback modulation of norepinephrine release.
trations block the effect of ACh in reducing release of norepinephrine, thereby enhancing norepinephrine release, suggests that these drugs may have unwanted effects (tachycardia, arrhythmia). This is important under conditions in which the fast elimination of norepinephrine is reduced (e.g. in patients chronically treated with imipramine or during hypoxia). In clinical practice, this has already been reported by Edwards and colleagues.10

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