Metoprolol impairs resistance artery function in mice

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El Beheiry MH, Heximer SP, Voigtlaender-Bolz J, Mazer CD, Connelly KA, Wilson DF, Beattie WS, Tsui AK, Zhang H, Golar K, Hu T, Liu E, Liddington D, Bolz SS, Hare GM. Metoprolol impairs resistance artery function in mice. J Appl Physiol 111: 1125–1133, 2011. First published July 28, 2011; doi:10.1152/japplphysiol.01340.2010.—Acute β-blockade with metoprolol has been associated with increased mortality by undefined mechanisms. Since metoprolol is a relatively high affinity blocker of β2-adrenoceptors, we hypothesized that some of the increased mortality associated with its use may be due to its abrogation of β2-adrenoceptor-mediated vasodilatation of microvessels in different vascular beds. Cardiac output (CO; pressure volume loops), mean arterial pressure (MAP), relative cerebral blood flow (rCBF; laser Doppler), and microvascular brain tissue PO2 (G2 oxyphor) were measured in anesthetized mice before and after acute treatment with metoprolol (3 mg/kg iv). The vasodilatory dose responses to β-adrenergic agonists (isoproterenol and clenbuterol), and the myogenic response, were assessed in isolated mesenteric resistance arteries (MRAs; ~200-µm diameter) and posterior cerebral arteries (PCAs ~150-µm diameter). Data are presented as means ± SE with statistical significance applied at P < 0.05. Metoprolol treatment did not effect MAP but reduced heart rate and stroke volume, CO, rCBF, and brain microvascular PO2 (G2 oxyphor) while concurrently increasing systemic vascular resistance (P < 0.05 for all). In isolated MRAs, metoprolol did not affect basal artery tone or the myogenic response, but it did cause a dose-dependent impairment of isoproterenol- and clenbuterol-induced vasodilation. In isolated PCAs, metoprolol (50 µM) impaired maximal vasodilation in response to isoproterenol. These data support the hypothesis that acute administration of metoprolol can reduce tissue oxygen delivery by impairing the vasodilatory response to β2-adrenergic agonists. This mechanism may contribute to the observed increase in mortality associated with acute administration of metoprolol in perioperative patients.

cerebral hypoxia; β-adrenergic antagonist; isoproterenol; clenbuterol

THE EFFICACY OF β-ADRENERGIC antagonists to reduce mortality and ischemia following an acute myocardial infarction (1, 2) contributed to the subsequent widespread use of this class of medication to treat a broad spectrum of cardiovascular diseases, including hypertension, heart failure, and coronary artery disease (24). In addition, data from two early clinical studies (22, 25) in perioperative medicine suggested that cardioselective β-blockade (atenolol and bisoprolol) reduced the incidence of myocardial infarction and mortality in patients with cardiovascular risk undergoing surgery. As a result of these studies, “cardioselective” β-adrenergic antagonists (metoprolol, atenolol, and bisoprolol) have become one of the most prescribed medications in North America (19).

These apparently favorable trials have lead to the broad application of perioperative β-blocker therapy (metoprolol, atenolol, and bisoprolol) as a strategy to reduce the risk of adverse cardiac events (14, 20). Recently, the enthusiasm toward this approach has been tempered by evidence that acute perioperative β-blockade with metoprolol has been associated with an increased incidence of bradycardia, hypotension, stroke, major adverse cardiac events, and mortality (4–6, 10, 28, 34).

This evidence has prompted a number of clinical studies designed to reassess the efficacy of β-adrenergic antagonism in perioperative medicine. While most studies (26) demonstrated a clear cardioprotective effect, these benefits did not come without significant risk to the patient population. Specifically, the risk for several other adverse cardiovascular events including stroke (4, 10), major adverse cardiac events (6), and mortality (4–6, 10, 28) were increased with perioperative β-blockade in specific patient populations. These data have lead some authors (4) to advocate against the widespread use of β-blockers in the perioperative period. The increased morbidity and mortality have been most strongly associated with 1) acute administration of the β-antagonists (11, 2) use of the relatively poorly β1-selective drug metoprolol (3, 10, 28, 34), and 3) use of β-adrenergic antagonists in the setting of increased cardiovascular demand, including acute blood loss and fluid resuscitation (6, 33). We chose to investigate whether β-blockade alters vascular reactivity, as a potential mechanism underlying the increase in mortality; we focused on metoprolol as it is one of the most frequently prescribed β-blockers in North America (www.imshhealth.com) (5, 6, 19, 34).

In the current experimental study, we tested the hypothesis that acute administration of metoprolol impairs resistance artery dilation in response to β-adrenergic agonists and thereby worsens vital organ perfusion. We first assessed the impact of acute metoprolol administration in a whole animal model with a focus on cerebral oxygen delivery. Based on evidence of
increased vascular resistance and reduced brain perfusion, we then assessed the effect of metoprolol on ex vivo preparations of isolated mesenteric resistance arteries (MRAs) and posterior cerebral arteries (PCAs).

**MATERIALS AND METHODS**

**Animal model.** All animal protocols were approved by the Animal Care Committee at St. Michael’s Hospital and the University of Toronto (Toronto, Ontario, Canada). Two- to three-month-old C57BL/6J mice were purchased from either The Jackson Laboratory (Bar Harbor, ME) or Charles River Laboratories (Montreal, QC, Canada) and housed under standard conditions with food and water ad libitum. All animals were anesthetized with 2% isoflurane for all in vivo experiments. For the studies utilizing isolated resistance arteries, all mice were euthanized under isoflurane anesthesia by cervical dislocation before vessel isolation.

The following drugs were used for in vitro experiments on isolated MRAs and PCAs: L-phenylephrine hydrochloride (P6126), -metoprolol (+)-tartrate salt (M5391), 1α-iso-proterenol hydrochloride (IS627), and clenbuterol hydrochloride (C5423; Sigma-Aldrich, St. Louis, MO). Metoprolol tartrate solution was used in whole animal studies (Betaloc 1 mg/ml; prod. no. 1352; AstraZeneca Canada, Mississauga, ON, Canada).

**Effect of metoprolol on mean arterial pressure, relative cerebral blood flow, and microvascular brain oxygen tension.** In a separate group of anesthetized mice, femoral artery and vein cannulations were performed to measure mean arterial pressure (MAP) and heart rate (HR) following administration of saline vehicle or metoprolol (3 mg/kg). This dose was chosen based on previous pharmacokinetic studies in rodents (16). HR was measured using EKG electrodes. MAP was measured by direct femoral artery cannulation. In two separate groups of mice, either relative changes in cerebral blood flow (rCBF; laser Doppler, OxyFlo; Oxford Optronix) or quantitative brain microvascular PO2 were measured (phosphorescence quenching) as previously described (27). Briefly, anesthetized (2% isoflurane) spontaneously breathing animals were placed in a stereotactic frame. For rCBF, two bilateral laser-Doppler flow probes were placed directly over the temporal aspect of the skull after exposure via a central skin incision. For brain PO2 measurements, the skull was exposed by a sagittal skin incision and excitation and detection light guides were placed over the parieto-temporal cerebral cortex and positioned such that the light path crossed through the cerebral cortex and deeper brain structures. Mice were injected with Oxyphor G2-phosphorescent dye [0.1 mg in 20 μl, Pd-tetra-(4-carboxyphenyl) tetrabenzoephosphorin dendrimer] allowing measurements of phosphorescence quenching by oxygen through the PMOD 5000 probes (Oxygen Enterprises, Philadelphia, PA). HR, femoral MAP, rCBF, and microvascular brain oxygen tension (PBram-O2) were measured before and within 1 h after saline vehicle or metoprolol 3 mg/kg administration, and data were recorded electronically (PowerLabs).

**Effect of metoprolol on cardiac physiology.** Cardiac catheterization was performed as previously published (37). In brief, animals (n = 6) were placed on a warming pad (37°C), intubated, and ventilated using positive pressure ventilation using 2% isoflurane in 100% O2. Mice were secured in a recumbent position and the right jugular vein was cannulated. Pressure was calibrated after the catheter was warmed in saline solution before vessel isolation.

**Pressure myography in isolated resistance arteries.** Pressure myography experiments were conducted as previously described (7, 21). For MRA and PCA isolation, the mesentery or brain was removed following cervical dislocation under anesthesia (2% isoflurane) and placed in a dish containing ice-cold MOPS-buffered saline solution (MOPS pH 7.4: (in mmol/l) 145 NaCl, 4.7 KCl, 1.5 CaCl2·2H2O, 1.17 MgSO4·7H2O, 1.2 NaH2PO4·2H2O, 2.0 pyruvate, 0.02 EDTA, 3.0 MOPS, and 5.0 glucose). Second order MRAs (~200 μm in diameter) were dissected under ice-cold conditions and mounted onto a pressure myography system (Living Systems Instrumentation; Burlington, VT, USA). For PCAs, the brain was rapidly removed from the cranium and placed in ice-cold MOPS. First order PCA segments (~150-μm diameter) were isolated and mounted onto a pressure myography system (Living Systems Instrumentation). Both artery types were warmed to 37°C at a transmural pressure (TMP) of 45 mmHg for 30 min. After warming, MRA TMP was raised to 60 mmHg. All vasomotor responses were assessed at 60 mmHg in MRAs and at 45 mmHg in PCAs (in both cases, from no flow through the vessel lumen).

Vessel viability was assessed at the start of the experiment by stimulating vasodilation with 1 μM (MRAs) or 10 μM (PCAs) phenylephrine (α1-adrenergic agonist); viable vessels maintained ≥30–50% constriction from baseline. All data are presented as tone, which represents normalized acute diameter measurements. Tone is normally stable. Paired comparisons were made before and following the pressure step, when the constriction turned off for 5–10 s with the animal apneic. With the use of the pressure conductance data, a range of real-time functional parameters were then calculated using the ADVantage system (Scisence). These included end diastolic pressure, end systolic pressure, end diastolic volume, end systolic volume (SV), cardiac output (CO), and systemic vascular resistance (SVR).

**Statistical analyses and calculations of vascular tone and dilation.** All data are presented as means ± SE; n values indicated number of animals or number of vessels tested. For in vivo experiments, analysis of differences in HR, MAP, rCBF, PBram-O2 was performed by two-way repeated measures ANOVA. For rCBF experiments, all data (HR, MAP, and rCBF) were normalized to baseline for each animal as the rCBF values are reported in relative, nonquantitative, units. Analysis of cardiac responsiveness and left ventricular function were performed by paired t-test. Statistical analyses were done in SigmaPlot 11 (Systat Software, Chicago, IL).

An increase in percent dilation is indicative of increased vasodilation. Dose-response curves of agonist before and after incubation with 0, 5, 10, or 50 μM metoprolol were tested by two-way repeated measures ANOVA. The concentration of agonist that elicited half the maximal response of a dose-response curve is expressed as the EC50 (mol/l) value and is represented here as the logEC50, which is unitless. Mean logEC50 values are tested by paired t-test when both curves were generated in the same artery otherwise they were tested by...
unpaired student’s t-test. Dose-response curves were also compared by the percent response at the top of the curve (E_max), which corresponds to maximal response of the vessel to the agonist. Vasocostrictr (tone) and vasodilator (%dilation) responses to any one dose of agonist before and after metoprolol (or MOPS buffer) incubation were tested by paired t-tests. Statistical analyses were performed in Prism 5 (GraphPad Software, La Jolla, CA). Differences were significant at alpha P value <0.05.

RESULTS

Effect of acute metoprolol treatment on cardiovascular physiology in mice. In isoflurane anesthetized mice, metoprolol caused a reduction in HR, SV, and CO, while SVR increased (Fig. 1; P < 0.05 for all). On average, changes in stroke volume (26 ± 4 vs. 20 ± 4 μl) and ejection fraction (39 ± 9 vs. 26 ± 4%) achieved statistical significance (n = 6; P < 0.05). No differences in end systolic or diastolic pressures or volumes were observed. An example of a pressure volume loops, before and after metoprolol, is demonstrated in Fig. 2. In a second group of anesthetized mice, metoprolol caused a decrease in HR and rCBF by ~20% after 60 min (P < 0.05; Fig. 3), while femoral MAP remained unchanged. In a third group of anesthetized mice, metoprolol caused a comparable reduction in HR while femoral MAP was maintained (Fig. 4). In these mice, PBrmvO2 was decreased by ~15% relative to baseline and control saline-treated mice (Fig. 4; PBrmvO2, 60.8 ± 2.5 vs. 69.7 ± 2.1 mmHg; P < 0.05).

![Fig. 1. Changes in cardiovascular function after metoprolol administration in mice. Heart rate (A), stroke volume (B), and cardiac output (C) are significantly reduced while systemic vascular resistance (SVR; D) is increased following metoprolol injection (3 mg/kg). Average end-systolic and diastolic pressures and volumes (E–H) were not affected by metoprolol treatment (n = 6; *P < 0.05). bpm, Beats/min.](http://jap.physiology.org/cgi/content/full/111/5/1127/DC1)
Metoprolol impairs \( H_9252 \)-adrenergic-mediated dilation in MRAs. Metoprolol did not cause a change in vessel diameter after drug administration (Table 1). Metoprolol (50 \( M \)) did not alter the magnitude of the myogenic response or kinetics (assessed as the time to half-maximal response, control: 163 ± 18 s, metoprolol: 153 ± 24 s; \( n = 5; P > 0.05 \)) of the myogenic response in isolated MRAs (Fig. 5).

The nonselective \( \beta \)-adrenergic agonist isoproterenol was used to generate dose-response curves before and after incubation with metoprolol. Data for each metoprolol-treated vessel were compared with its own isoproterenol control response. A typical experiment (vessel diameter) is depicted in Fig. 6A. There was no effect of time on the isoproterenol dose-response curve as shown before and after incubation with 0 \( M \) metoprolol (Fig. 6B). Similarly, there was no effect with 5 or 10 \( M \) metoprolol (Fig. 6, C and D). A significant right shift in the isoproterenol dose-response curve was observed at a metoprolol concentration of 50 \( M \) (Fig. 6E). The log\( EC_{50} \) of isoproterenol at 50 \( M \) metoprolol was significantly higher than at 0 \( M \) metoprolol (\( 4.1 \pm 0.082 \) vs. \( 4.6 \pm 0.084; n = 6–7; P < 0.05 \)). In addition, the percent dilation at the control \( EC_{50} \) dose of isoproterenol was significantly attenuated by metoprolol at 50 \( M \) (17 ± 2.3 vs. 34 ± 2.0%; \( n = 6; P < 0.05 \)). At all concentrations of metoprolol, dose-response curves reached equivalent \( E_{max} \) plateau values. The relative \( \beta_2 \)-specific agonist clenbuterol dose-response curve was significantly right shifted by 50 \( M \) metoprolol, relative to its control curve (Fig. 6F; \( P < 0.05 \)). The percent dilation at the control \( EC_{50} \) dose (10 \( M \) or log\( EC_{50} = -5 \)) was significantly attenuated at 50 \( M \) metoprolol (25 ± 1.6 vs. 34 ± 1.0; \( n = 5; P < 0.05 \)). Comparable \( E_{max} \) plateaus were achieved in both groups (Fig. 6).

Metoprolol impairs PCA dilation in vitro. Preliminary experiments demonstrated that 3 \( M \) of phenylephrine was optimal for preconstriction in PCAs. At this dose, there were no significant changes in tone or dilation over time before or after
administration of 50 μM metoprolol. Isoproterenol dose-response curves were generated before and after metoprolol incubation (0 μM metoprolol), which represented a time control (Fig. 7, A and B). In the control experiment, 0 μM metoprolol had no significant treatment or interaction effect on the isoproterenol curve. However, there was a significant treatment and interaction effect before and after incubation with 50 μM metoprolol (Fig. 7B; n = 7; P < 0.05). There was no effect of metoprolol on the logEC50 but the Emax of isoproterenol was significantly reduced at 50 μM metoprolol (61 ± 5.5 vs. 79 ± 4.0%; n = 7; P < 0.05).

**DISCUSSION**

These experimental results support the hypothesis that metoprolol may impair vital organ perfusion by attenuating β2-adrenergic-mediated vasodilation at the level of the small resistance artery. When metoprolol was administered to anesthetized mice in vivo, MAP was maintained while HR, SV, CO, rCBF, and PBrmvO2 were all reduced. This occurred in the context of increased SVR. Thus metoprolol exerted the expected negative chronotropic effect by inhibiting β1-adrenoreceptors at the level of the cardiac myocyte (9). The concurrent reduction in stroke volume suggested that, in addition to its negative chronotropic effect, metoprolol may have also exerted a negative lusitropic effect. The combined impact on HR and stroke volume led to a 40% reduction in CO with acute metoprolol treatment. However, mean femoral arterial pressure and end-systolic and end-diastolic left ventricular pressures were maintained by an increase in SVR. This increase in SVR may have been due to a reflex increase in efferent sympathetic output to maintain microvascular tone and/or due to a direct effect of metoprolol at the level of the β2-adrenoreceptor on the vascular smooth muscle of resistance arteries. If the increase in SVR was mediated by an increase in sympathetic tone, then cerebral perfusion would have been expected to be maintained by endogenous mechanisms including cerebral blood flow autoregulation. The observed reduction in microvascular rCBF and brain tissue PO2 provide evidence for a direct effect of metoprolol on brain perfusion. This effect was not likely influenced by changes in the cerebral metabolic rate for oxygen, as this parameter was not acutely affected by metoprolol in anesthetized humans (12). Subsequent experiments were performed in isolated arteries to demonstrate a direct effect of metoprolol on the vasculature.

Evidence in favor of a direct effect of metoprolol on β2-adrenoreceptor-mediated vasodilation was obtained in ex vivo MRAs and PCAs. We first performed studies in the most widely used model of resistance artery function: the MRA. Results demonstrated that metoprolol inhibited both isoproterenol (1/2-nonspecific agonist)- and clenbuterol (2-specific agonist)-mediated vasodilation. A similar effect for isoproterenol was observed in isolated PCAs demonstrating that the impact of metoprolol was conserved across different vascular beds. The similar effect of metoprolol on two different vascular beds suggests that β2-adrenergic-mediated vasodilation may be generally impaired by metoprolol.

**Table 1. Baseline vessel diameters**

<table>
<thead>
<tr>
<th>Artery Type</th>
<th>Control, μM</th>
<th>Metoprolol, μM</th>
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<tbody>
<tr>
<td>Mesenteric arteries</td>
<td>Isoproterenol ± 5 μM metoprolol (n = 7)</td>
<td>199 ± 27</td>
</tr>
<tr>
<td></td>
<td>Isoproterenol ± 10 μM metoprolol (n = 7)</td>
<td>217 ± 36</td>
</tr>
<tr>
<td></td>
<td>Isoproterenol ± 50 μM metoprolol (n = 6)</td>
<td>224 ± 14</td>
</tr>
<tr>
<td>Posterior cerebral arteries</td>
<td>Isoproterenol ± 50 μM metoprolol (n = 7)</td>
<td>148 ± 7.6</td>
</tr>
</tbody>
</table>

Values are means ± SE.
By contrast, incubation with metoprolol did not have a direct effect on resting tone in either mesenteric or brain vessels in vitro. This may reflect the lack of neural inputs and/or the lack of endogenous adrenergic agonist activity relative to vessels in vivo. In addition, metoprolol did not affect the myogenic response in mesenteric arteries in vitro. This suggests that the impact of metoprolol was limited to adrenergic-mediated vasodilation, as supported by the ability of metoprolol to inhibit isoproterenol- and clenbuterol-mediated vasodilation. This may occur at the level of the $\beta_1$- and $\beta_2$-adrenoreceptor since both receptor types have been identified on vascular smooth muscle on mesenteric arteries in the rat (8). Metoprolol has a relatively high affinity for the $\beta_2$-adrenoreceptor, which may explain its effect on inhibition of clenbuterol-mediated vasodilation.

$\beta$-Blockers are one of the most frequently prescribed medications in North America, with prescriptions for metoprolol exceeding 70 million in 2010 (www.imshealth.com). We chose to study metoprolol because it remains one of the predominant $\beta$-blockers in current clinical use in North America with published concerns regarding increased morbidity and mortality (5, 10, 28, 34). An increasing number of clinical reports have suggested that metoprolol is associated with increased ischemic organ injury (brain and heart; Refs. 6, 10) and mortality (6, 10, 28, 34), relative to placebo or other more $\beta_1$-selective drugs (atenolol and bisoprolol; Refs. 5, 28, 34). Our experimental data support the clinical hypothesis that metoprolol may impair adrenergic-mediated resistance artery dilation by a direct inhibitory effect at the $\beta_2$-receptor.

The clinical settings in which metoprolol administration has been implicated as a risk for increased morbidity and mortality include patients undergoing surgery. Maintenance of vital organ perfusion is required at all times but is of particular importance during times of increased oxygen demand (surgery and exercise; Ref. 13) and/or reduced oxygen supply (blood loss and anemia; Ref. 23). The additional stress of acute blood loss and fluid resuscitation is known to elicit a strong adrenergic response (27). Under these conditions of increased adrenergic stress and reduced blood oxygen content (acute hemodilutional anemia), $\beta$-adrenergic mechanisms have been demonstrated to maintain microvascular perfusion in experimental models (15, 27). Adrenergic mechanisms are also required to increase cardiac output and maintain optimal oxygen delivery to vital organs under these conditions (13, 27, 30, 31), in part by diverting an increased proportion of cardiac output toward vital organs with high oxygen demand such as the heart and brain (13, 15, 32). Thus the heart and brain receive increased blood flow by mechanisms that tightly couple oxygen supply and demand. Inhibition of these mechanisms by $\beta$-blockers may contribute to the pathophysiology of organ injury and increased mortality in perioperative patients treated with this class of drug (5, 33). These findings are supported by clinical studies that demonstrate an increased incidence of stroke (10), myocardial infarction (6, 33), and mortality (5) in acutely anemic patients treated with metoprolol. The current study supports the hypothesis that metoprolol may impair organ perfusion by limiting active cerebral vasodilation.

In a recent meta-analysis (3), hypotheses were explored to determine why metoprolol was associated with worse clinical outcomes. The authors propose that metoprolol’s relatively poor $\beta_1$-selectivity, compared with the other clinically available $\beta$-blockers (bisoprolol and atenolol), may result in direct vascular cross-reactivity and impairment of $\beta$-adrenergic-mediated vasodilation. Our data provide direct evidence for this hypothesis. Indeed, recent clinical trials with bisoprolol did not report an increased incidence of stroke (25, 26), suggesting that more cardioselective $\beta$-blockers may be preferential when used to reduced the risk of myocardial ischemia in the perioperative setting (3, 33).

Fig. 5. Effect of metoprolol on the myogenic response in isolated mesenteric arteries. There is no effect of metoprolol (50 $\mu$M) on the myogenic response kinetic (A), reversal of distension (B), or vessel diameter (C).
There are several limitations to our study: 1) we assessed the impact of metoprolol in a mouse model that has a much higher intrinsic HR than humans. Attempts were made to use a clinically relevant dose of metoprolol that reduced HR by ∼10–20%. 2) In addition, the dose of metoprolol was assessed as pharmacologically comparable to appropriate clinical doses in humans (16, 17). The isolated arteries studied are denervated and therefore lack the input from autonomic and other perivas-
cular nerves. Although this shortcoming cannot be overcome by this model, our in vivo data are in agreement with the isolated vascular data and provide a closer tie to data obtained from clinical studies. 3) We did not study the effect of metoprolol in a stroke model, although such experimental models may provide further important insight into the impact of metoprolol on ischemic stroke. Our data remain relevant since many patients who are reported to have a stroke after metoprolol treatment did not have a past history of cerebral-vascular disease. 4) The dose of metoprolol required to produce similar pharmacodynamic responses in rats is higher that required in humans (17, 29, 35, 36). In human studies, oral doses of metoprolol (25–100 mg po) result in peak plasma levels near 136 ng/ml. After intravenous administration of metoprolol in rats, a corresponding dose of 3 mg/kg results in similar HR responses but at a higher plasma concentration (~1,200 ng/ml). However, pharmacokinetic and pharmacodynamic studies (16, 17) have demonstrated that an intravenous dose of 3 mg/kg is the lowest dose that provided a clinically relevant reduction in HR ~20%. The concentration of metoprolol, which impaired adrenergic-mediated vasodilation in vitro (50 uM), corresponded to an ~10-fold higher drug concentration. This higher dose may be required in vitro as the isolated vessels lack extrinsic innervation and the drug was applied by superfusion to the adventitial side of the vessel. 5) We have not measured the effect of metoprolol on other vasodilatory mechanism (i.e., nitric oxide).

In conclusion, we have provided new evidence that metoprolol can limit cardiac output and increase systemic vascular resistance in a mouse model in vivo. This was associated with a reduction in CBF and microvascular brain tissue PO2 in anesthetized mice suggesting that brain perfusion can be impaired by metoprolol. Isolated mesenteric and cerebral arteries were utilized to demonstrate a direct effect of metoprolol to inhibit β-adrenergic-mediated vasodilatation. These data support a vascular mechanism for the observed reduction in brain perfusion in vivo and may help to understand the observed increase in stroke and mortality in patients treated with metoprolol. These data could be utilized to develop treatment strategies with newer β-adrenergic antagonists that may have less impact on the systemic and cerebral vasculature.

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GRANTS

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DISCLOSURES

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