Anesthesiology 2002; 96:336–41

Effects of the Selective H_1 and H_2 Histamine Receptor Antagonists Loratadine and Ranitidine on Autonomic Control of the Heart

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Background: **H_1 and H_2 histamine receptor subtypes are present throughout the heart and may be involved in disturbances of cardiac rhythm that occur during anaphylaxis. Although H_1 and H_2 receptor antagonists are used in the treatment of anaphylaxis, there have been reports implicating these drugs in the genesis of dysrhythmias. This study was designed to investigate the effects of the selective H_1 and H_2 receptor antagonists loratadine and ranitidine on physiologic autonomic control of the healthy cardiovascular system.**

Methods: **Using a double-blind, crossover design, 14 healthy volunteers completed the protocol and were randomized to receive one dose of loratadine (20 mg), ranitidine (300 mg), or placebo on each of three separate testing sessions. Continuous electrocardiogram and BP recordings were obtained before and 3 h after administration of study drug. Effects on cardiac autonomic control were quantified using power spectral analysis of heart rate variability and calculation of spontaneous baroreflex sensitivity.**

Results: **Neither placebo nor loratadine significantly altered indices of autonomic cardiovascular control. Conversely, H_2 antagonism with ranitidine resulted in a 23.3% decrease in baroreflex sensitivity ($P < 0.05$) and a corresponding 25.0% decrease in the ratio of high frequency to total power of heart rate variability, both indices of parasympathetic modulation ($P < 0.01$). Furthermore, ranitidine evoked a concomitant 103.8% increase in the ratio of low to high frequency power of heart rate variability, an index of sympathetic control ($P < 0.01$).**

Conclusions: **H_1 receptor antagonism with loratadine does not influence physiologic cardiovascular control in young healthy subjects. However, the altered cardiac sympathovagal balance after oral administration of the H_2 receptor antagonist ranitidine indicates a shift toward sympathetic predominance in heart rate control. The authors postulate that this could have implications regarding susceptibility to arrhythmias in conditions of heightened sympathetic stimulation.**

HISTAMINE is a hydrophilic autocoid, synthesized by mast cells and basophils, that exerts widespread cardiorespiratory effects through interactions with G-protein–coupled membrane receptors.[1] At least three histamine receptor subtypes have been characterized, all of which are found, to varying degrees, in the heart. Histamine subtype 1 (H_1) receptors are found in conductive tissue of the atrioventricular node and slow heart rate by decreasing atrioventricular nodal conduction.[1] Cardiac H_1 receptors are also found in epicardial coronary vessels,[2] where they mediate vasoconstriction.[2,3] Histamine subtype 2 (H_2) receptors are also found in the coronary vasculature, where their vasodilating action opposes that of the H_1 receptor.[2] Moreover, H_2 receptors are widely distributed throughout the myocardium and nodal tissue, where they exert positive inotropic and chronotropic effects, respectively.[1,2,4] The third histamine receptor subtype (H_3) found in the heart is localized to presynaptic postganglionic sympathetic fibers and is autoinhibitory to presynaptic norepinephrine release.[5,6]

The rich distribution of histamine receptors throughout the myocardium and coronary vasculature predisposes the heart to potential cardioregulatory insult in the face of the massive histamine release that characterizes the type I immediate hypersensitivity (anaphylactic) immune response.[3,7] Use of antihistamines in the acute treatment of anaphylactic shock is directed at blocking further histamine-mediated vasodilation and resulting hemodynamic instability, as well as at reducing respiratory and other systemic complications.[8] As such, the administration of H_1 receptor blockers remains a cornerstone in the acute treatment of anaphylaxis. The addition of H_2 receptor antagonists to H_1 antagonists during acute allergic reactions has been shown to speed resolution of symptoms.[9] However, concerns have been raised about the possible attenuation of H_2-mediated increases in inotropy and chronotropy, thereby limiting potential cardioexcitatory compensatory mechanisms.[8] Clinically, this does not appear to be the case, as anaphylactic shock refractory to fluids, vasopressors, and H_1 antagonists has been reversed with high-dose intravenous H_2 blockers.[10] However, a dysrhythmogenic effect of ranitidine treatment before anesthesia has also been suggested.[11]

Although questions remain regarding the use of histamine receptor antagonist therapy during anaphylaxis,[8–11] it is also unclear whether histamine contributes to normal physiologic regulation of cardiac function. Widespread and diverse distribution of histamine receptors throughout the myocardium, nodal tissue, and coronary vasculature suggests that these receptors may play a role in the physiologic regulation of the normal healthy heart. Where previous studies have documented no gross hemodynamic effects of antihistamine administration,[12,13] such aggregate measures of cardiovascular function have been shown to be insufficient to detect more subtle effects of some drugs on control of cardiovascular function.[14] This study was designed to determine the effects

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Received from the Department of Anesthesiology, Queen's University, Kingston, Ontario, Canada. Submitted for publication March 12, 2001. Accepted for publication September 18, 2001. Supported by the Heart & Stroke Foundation of Ontario, Toronto, Ontario, Canada (M.A. Nault). Presented in part at the 7th International Congress of Cardiothoracic and Vascular Anesthesia, Quebec City, Canada, June 3, 2000.

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of the widely used selective H_1 and H_2 receptor antagonists loratadine and ranitidine on physiologic autonomic heart rate control in healthy volunteers.

Materials and Methods

Subjects

After obtaining approval from the Queen's University Research Ethics Board and written informed consent, 16 healthy male and female volunteers, aged 21–27 yr, were studied in a randomized, double-blinded, placebo-controlled, crossover protocol. Subjects were excluded on the basis of history or presence of symptoms or physical signs of cardiovascular disease, diabetes, pregnancy and lactation, history of allergy or atopy, current or previous use of tobacco products, documented history of intolerance to either test drug, and intake of any compound affecting cardiovascular or autonomic nervous system function, or gastrointestinal motility.

Experimental Protocol

Continuous, noninvasive blood pressure (BP) was monitored using the volume clamp method (Finapres® 2300; Ohmeda; Englewood, CO), and electrocardiogram using lead II (Tektronix 400; Tektronix, Beaverton, OR) for calculation of R-R intervals. Data were acquired during low-light conditions with subjects seated in a semireclined position. A metronome was used to pace respiratory frequency at each subject's resting level, with a minimum frequency of 12 breaths per minute. After a period of quiet rest, 12 min of stable baseline BP and electrocardiogram data were acquired, after which subjects ingested either 20 mg of the H_1 receptor antagonist loratadine (Claritin®; Schering Canada, Point-Claire, Quebec, Canada), 300 mg of the H_2 receptor antagonist ranitidine hydrochloride (Gen-Rantidine, Genpharm, Etobicoke, Ontario, Canada), or an inactive placebo. The three treatments were prepared by the hospital research pharmacist in identical gelatin capsules packed with lactose powder. Three hours after drug administration, 12 min of repeat BP and electrocardiogram data were obtained.

Subjects were randomized to receive each of the study drugs on 1 of 3 separate testing days. Testing days were separated by a minimum of 48 h to minimize drug carryover effects. Study drugs were identically packaged, and dosing schedules were determined using computer-generated tables. Dosing codes were prepared and sealed by the hospital research pharmacist until completion of the protocol. Subjects abstained from caffeine, alcohol, tobacco, and heavy physical activity for 12 h before each study session.

Data Acquisition and Analysis

Analog electrocardiogram and BP signals were acquired on-line and digitized using a 12-bit analog–digital converter at a sampling rate of 1,000 Hz (DAS-16®; Metrabyte, Taunton, MA). During digitization, systolic and diastolic BP, as well as the R-R interval, were measured on a beat-by-beat basis. Electrocardiogram data were analyzed using customized software (Richard Hughson, Ph.D., Department of Kinesiology, University of Waterloo, Ontario, Canada). Power spectral analysis of heart rate variability was used to determine indices of the relative sympathetic and parasympathetic influences on the heart.[15] Briefly, a fast Fourier transformation was applied to a string of 512 consecutive R-R intervals (obtained from stationary data) to generate a power spectral curve (in units of milliseconds squared per hertz). By integrating the power in the low-frequency (0–0.15 Hz), high-frequency (0.15–0.50 Hz), and total frequency (0–0.50 Hz) ranges of the spectral curve, indices of parasympathetic (high frequency/total frequency ratio) and sympathetic (low frequency/high frequency ratio) modulation of cardiovascular control were calculated.[15]

Cardiac baroreflex sensitivity was calculated using the spontaneous baroreflex (sequence) method.[16–18] During each recording period, sequences of spontaneously occurring increases or decreases in BP that were accompanied by concordant (*i.e.*, baroreflex-mediated) changes in R-R interval were identified. The paired R-R interval and BP sequences were plotted on an x–y curve, and a regression slope was determined for each. The mean regression slope for all sequences represents the spontaneous baroreflex sensitivity, an index of parasympathetically mediated beat-by-beat heart rate control. These values have been shown to reflect those obtained using pharmacologic baroreflex stimulation during resting conditions.[18]

After each data collection session during drug treatment, subjects were questioned regarding the presence of side effects, including sedation, dry mouth, headache, or rash.

Statistical Analysis

Using variance data from previous studies utilizing the same methodology,[14] sample size analysis indicated a need to study at least 12 subjects to detect a 30% change in spontaneous baroreflex sensitivity with a power of 80% and $P < 0.05$. Between-drug comparisons, using percent change from baseline for each treatment, were conducted using one-way repeated-measures analysis of variance for normally distributed data (heart rate, BP) and repeated measures on ranks for nonnormally distributed data (heart rate variability data). Where significant differences were found ($P < 0.05$), *post hoc* analyses were performed using the Tukey method.

Results

Two subjects were withdrawn after enrollment: one on the basis of frequent premature contractions at base-

Table 1. R-R Interval and Blood Pressure Data

	Placebo		Loratadine		Ranitidine	
	Pre	Post	Pre	Post	Pre	Post
RRI (ms)	912 ± 29	930 ± 30	965 ± 41	904 ± 33	973.1 ± 34.8	925.6 ± 41.3
SBP (mmHg)	105.6 ± 2.4	104.3 ± 3.9	102.1 ± 2.7	103.5 ± 3.32	107.6 ± 2.45	104.5 ± 4.16

Values are mean ± SEM for R-R interval (RRI) of the electrocardiogram and systolic blood pressure (SBP).

line, making analysis of heart rate variability impossible; the other experienced a pronounced vasovagal episode during a baseline measurement and withdrew. All subjects tolerated the study drugs well, and none reported any adverse drug effects.

Baseline heart rate and BP were similar on all test days and remained unchanged after drug administration (table 1). Baseline measures of autonomic control were also consistent between subjects and within subjects across testing days.

Figure 1 depicts a complete set of experiments on a representative subject, showing a reduction in high-frequency power (> 0.15 Hz) only after administration of ranitidine. Overall, neither placebo nor loratadine significantly altered sympathetic or parasympathetic indices of heart rate variability (figs. 2A and B, respectively) or

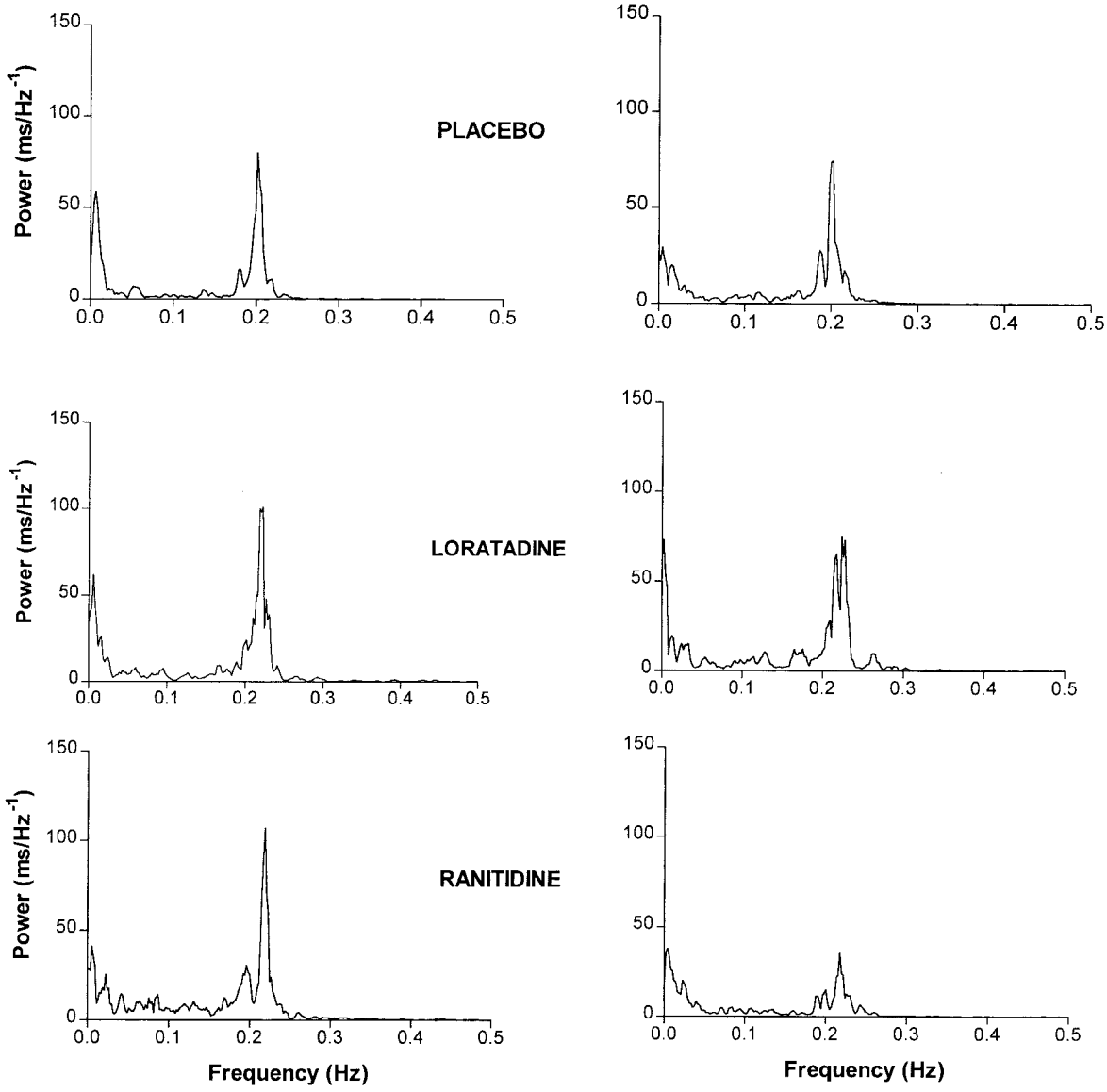

Fig. 1. Complete set of power spectral curves from one subject on 3 study days. The left column represents baseline measures, and the right column represents data collected 3 h after ingestion of the study drug.

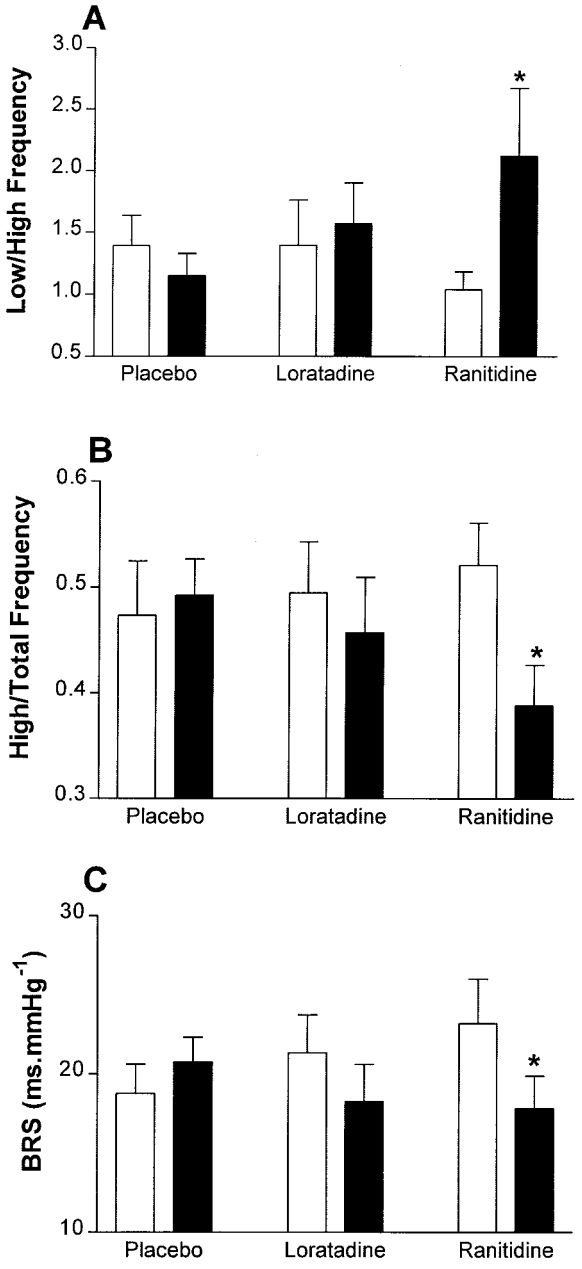

Fig. 2. (*A*) Low/high frequency ratio of heart rate variability (sympathetic indicator); (*B*) High/total frequency ratio of heart rate variability (parasympathetic indicator); and (*C*) spontaneous baroreflex sensitivity (BRS); at baseline (white columns) and 3 h after oral administration of placebo, loratadine, or ranitidine (black columns). Columns represent mean ± SEM. *Significant change from baseline ($P < 0.05$).

baroreflex sensitivity (fig. 2C). By contrast, ranitidine decreased the parasympathetic indicator, high frequency/total frequency ratio, by 25% (0.52 ± 0.04 to 0.39 ± 0.04; $P < 0.01$; fig. 2B). Likewise, ranitidine reduced baroreflex sensitivity by 23.3% (23.3 ± 2.8 to 17.8 ± 2.1 ms/mmHg; $P < 0.05$; fig. 2C). The reduction in parasympathetic indices was accompanied by a concordant increase of 103.8% in the low frequency/high frequency ratio (1.04 ± 0.15 to 2.12 ± 0.55; $P < 0.01$; fig. 2A), indicating a strong shift toward sympathetic predominance during conditions of H_2 receptor blockade with ranitidine.

Discussion

Physiologic regulation of cardiac and hemodynamic function depends on intact neurohumoral and autonomic mechanisms. Accordingly, diverse receptor types, including those for catecholamines, acetylcholine, and autocoids such as histamine and bradykinin, are present throughout cardiac structures.[1–4,6] It is well recognized that the heart is a target organ in anaphylaxis,[7] yet localization of histamine receptors to the myocardium, coronary vessels, and nodal tissue suggests that modulation of physiologic cardiac control, possibly by resting concentrations of circulating histamine, may also be a function of cardiac histamine receptors.

Results of this study, indicating significant changes in cardiac autonomic balance after administration of ranitidine in the absence of gross hemodynamic changes, underscores the insight that indices of autonomic control can contribute to a comprehensive understanding of cardiovascular regulation. To our knowledge, this study represents the first investigation of the role of histamine receptor subtypes in resting autonomic control of the cardiovascular system. The contribution of histamine to autonomic heart rate control was investigated by selective pharmacologic antagonism of H_1 and H_2 receptors. To minimize the side effects common to first-generation H_1 blockers, we investigated potential H_1-mediated effects with the second-generation H_1 antagonist loratadine. Loratadine is a tricyclic antihistamine that displays selective peripheral H_1 antagonism and lacks anticholinergic and central nervous system side effects characteristic of the first-generation H_1 blockers.[19] Potential H_2 receptor–mediated contributions to autonomic cardiovascular control were characterized using the specific H_2 receptor antagonist ranitidine. Clinically, H_2 receptor antagonists are used to inhibit H_2-mediated gastric acid secretion in the treatment of peptic ulcers and dyspepsia; however, these antagonists have also been shown to bind H_2 receptors in the myocardium and coronary vasculature.[20–23] H_2 receptors are also found in the central nervous system. Although ranitidine does cross the blood–brain barrier, central side effects are rare and generally confined to the elderly and patients with impaired hepatic or renal function.[24] However, a central, rather than end-organ, effect of ranitidine on brainstem cardiovascular integration cannot be ruled out.

Both loratadine and ranitidine are available in an oral preparation, facilitating their comparison in a double-blinded protocol. Drugs were administered at twice the usual therapeutic dose to achieve near-complete receptor antagonism. The time between drug administration

and repeat electrocardiogram and BP sampling was based on a time-to-peak plasma concentration of 1.0–1.5 h for loratadine[25] and 2–3 h for ranitidine.[26] Percent maximal plasma concentrations are therefore similar at 3 h, given half lives of 7.8–14.4 and 4.8 ± 0.3 h for loratadine and ranitidine, respectively.[25,26]

In addition to the presence of cardiac H_1 and H_2 receptor subtypes, a cardiac H_3 histamine receptor subtype is also recognized.[5,6] Although a number of H_3-specific antagonists have been developed [thioperamide, clobenpropit, (R)-α-methylhistamine], these agents are used exclusively in basic research and have not yet been made available for clinical use. This study was therefore limited to investigation of potential H_1- and H_2-mediated effects.

The results of this study suggest that basal autonomic control of the normal healthy heart is not influenced by cardiac H_1 receptor stimulation, as H_1 antagonism with loratadine did not alter indices of autonomic heart rate regulation. By contrast, the reduction in parasympathetic measures and shift toward sympathetic predominance after ranitidine suggests a basal level of H_2 receptor activation in the normal healthy heart that enhances parasympathetic cardiac activity, possibly by suppressing tonic sympathetic drive.[27] The finding of a relative increase in cardiac sympathetic influence on heart rate after H_2 blockade supplements previous work that demonstrated a prolongation of norepinephrine-mediated cardiac stimulation during H_2 receptor blockade.[28] In addition, a ranitidine-mediated positive inotropic effect has been shown in the absence of gross changes in heart rate or BP in young healthy males.[29]

Although we have demonstrated a shift toward cardiac sympathetic predominance after H_2 blockade with ranitidine, conflicting case report data allude to an enhancement of parasympathetic cardiac input, including bradydysrhythmias,[30] atrioventricular block,[31] or asystole[32] after administration of ranitidine. The additional finding that these hemodynamic responses were reversed with the muscarinic antagonist atropine[30,31] emphasizes their likely parasympathomimetic origin. These effects are in keeping with experimental evidence showing an inhibitory effect of H_2 blockers on the cholinesterase enzyme.[33,34] However, such effects are not evident clinically in healthy people, and the majority of the aforementioned cases involved elderly patients presenting with concomitant cardiovascular, renal, or gastrointestinal disease and variably receiving multiple medications.

Two further explanations for the observed shift toward sympathetic predominance after administration of ranitidine have been considered. First, certain H_2 blockers (*i.e.*, burimamide) show partial agonist effects, yet these findings are not uniformly attributable to all H_2 antagonists.[35] Moreover, partial agonist activity has not been reported for ranitidine, making this explanation for the cardiac sympathetic prevalence after administration of ranitidine unlikely. Second, H_2 antagonists demonstrate cross-reactivity at histamine H_3 receptors.[36] Because H_3 receptors are inhibitory to presynaptic norepinephrine release from sympathetic fibers in the heart,[5,6,36] blockade of these receptors by ranitidine could result in uninhibited sympathetic outflow.[28] It has been speculated that basal H_3-mediated contributions to cardiovascular control are minimal, increasing only during episodes of cardiac stress such as myocardial ischemia.[5,37] Thus, H_3 receptor inhibition may become particularly relevant in patients at risk for myocardial ischemia, where cardiac norepinephrine concentrations are increased and the threshold for dysrhythmias is reduced.[37] Additional work is required to fully elucidate the clinical implications of these findings.

Although the current study documented effects in healthy resting volunteers, the clinical implications of this work are particularly relevant in situations of heightened histamine release, either related to drug administration during anesthesia or, in the extreme, during anaphylactic reactions. The common practice of treatment with H_2 antagonists before anesthesia to increase gastric pH could potentially increase the risk of disrupted autonomic cardiac control and resultant cardiac dysrhythmias in the event of an allergic response[11] or myocardial ischemia.[37] On the other hand, combined H_1 and H_2 receptor blockade have been shown to be more effective that H_1 receptor antagonism alone in reducing histamine-related cardiorespiratory disturbances during anesthesia.[38,39] Future studies are needed to extend the findings of this investigation to conditions of heightened plasma histamine concentrations, including documenting the effects of combined H_1 and H_2 blockade on autonomic balance, in the absence of and during conditions of heightened histamine release.

In summary, our findings suggest that cardiac H_1 receptor stimulation by circulating histamine does not alter autonomic control of heart rate in healthy resting subjects. By contrast, H_2 receptor antagonism with ranitidine led to a decrease in indices of parasympathetic modulation of heart rate, suggesting a possible role of histamine receptors in resting autonomic balance. The implications of these findings to the perioperative setting or during conditions of histamine release merit further study.

The authors thank Nicole Avery, M.Sc. (Queen's University, Kingston, Ontario, Canada), for assistance with data acquisition and analysis.

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