Review

The yin and yang of cardiac autonomic control: Vago-sympathetic interactions revisited

J.F.R. Paton[a], P. Boscan[c], A.E. Pickering[b], E. Nalivaiko[d],*

[a]Department of Physiology, School of Medical Sciences, University of Bristol, Bristol BS8 1TD, UK
[b]Department of Anaesthesia, School of Medical Sciences, University of Bristol, Bristol BS8 1TD, UK
[c]Anesthesia and Critical Patient Care, Veterinary Medical Teaching Hospital, University of California, Davis, CA 95616-8747, USA
[d]Department of Medicine and Human Physiology, Flinders Medical Centre, Flinders University, Bedford Park, South Australia 5042, Australia

Abstract

We review the pattern of activity in the parasympathetic and sympathetic nerves innervating the heart. Unlike the conventional textbook picture of reciprocal control of cardiac vagal and sympathetic nervous activity, as seen during a baroreceptor reflex, many other reflexes involve simultaneous co-activation of both autonomic limbs. Indeed, even at 'rest', the heart receives tonic drives from both sympathetic and parasympathetic cardiac nerves. Autonomic co-activation occurs during peripheral chemoreceptor, diving, oculocardiac, somatic nociceptor reflex responses as well as being evoked from structures within the brain. It is suggested that simultaneous co-activation may lead to a more efficient cardiac function giving greater cardiac output than activation of the sympathetic limb alone; this permits both a longer time for ventricular filling and a stronger contraction of the myocardium. This may be important when pumping blood into a constricted vascular tree such as is the case during the diving response. We discuss that in some instances, high drive to the heart from both autonomic limbs may also be arrhythmogenic.
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* Corresponding author. Fax: +61 8 8204 5768.
  E-mail address: eugene.nalivaiko@flinders.edu.au (E. Nalivaiko).

1. Introduction

As with the Chinese philosophy of yin and yang so the vagal and sympathetic drives to the heart can be characterized as polar opposites. However, a more subtle interpretation of the yin–yang principle shows that it is the interrelation of the opposites that is crucial. So with the autonomic control of the heart, the interaction between sympathetic and parasympathetic, which is classically characterized as opposite and reciprocal, can under physiological and pathophysiological circumstances be both synchronous and synergistic. In this review, we outline the circumstances in both health and disease when sympathetic and parasympathetic activation is synergistic.

In an attempt to comprehend the complexities of bodily functions, researchers have often tried to simplify the description of basic physiological mechanisms to facilitate their understanding. The autonomic nervous system is not exempt from such simplification. In fact, today in any basic physiology textbook, the dogma persists that for cardiac regulation, the sympathetic influences oppose the parasympathetic effects. In their 1979 article, Kollai and Koizumi [40] stated "since Langley's time, reciprocal action between sympathetic and parasympathetic outflows to the heart has been taken for granted". Their article provided evidence that a reciprocal antagonistic relationship between the two limbs of the autonomic nervous system is not the only possible pattern observed in cardiac autonomic motor outflow. Indeed such reciprocal regulation may be restricted to the baroreflex. It is this topic that we wish to re-visit.

Kollai and Koizumi [40] were the first to challenge the issue of reciprocal autonomic innervation of the heart, by simultaneously recording cardiac vagal and sympathetic nerves in anesthetized dogs. They found that the efferent cardiac neural pattern varied and depended on the exact experimental intervention. During arterial baroreflex activation, there was an immediate decrease in sympathetic activity and substantial increase in vagal discharge, so that a reciprocal relationship was observed and the faithful dogma upheld (Figs. 1B, C). But just as Kollai and Koizumi [40] reported, we describe here numerous instances in which simultaneous co-activation of the autonomic outputs to the heart can be evoked. We wish to discuss this not only in terms of when co-activation occurs during both experimental situations and real-life scenarios but also how and why it happens.

2. When does sympathetic and parasympathetic co-activation occur?

To address this question, we will consider the autonomic control of the heart during the peripheral chemoreceptor activation, oculocardiac reflexes, the diving response, stimulation of "defence areas" in the brain, and startle and somatic nociceptor-evoked responses.

2.1. Peripheral chemoreceptor reflex response

In contrast to the baroreceptor reflex, activation of peripheral chemoreceptors by direct injection of sodium cyanide into the blood supply of the carotid body resulted in a short-term increase in both vagal and sympathetic outflows to the heart in both anesthetized dogs [40] (Fig. 1A) and unanesthetized decerebrate rats [17] (Fig. 2). The overall heart rate response was profound bradycardia, which was not baroreflex-mediated, indicating that vagally induced chronotropism easily overcame sympathetic influences despite their coincident activation. However, it is acknowledged that the increased cardiac sympathetic discharge may preferentially target ionotropic mechanisms in this instance. Note that following the bradycardia, there is a rebound tachycardia of sympathetic origin, indicating the temporal differences in response profile following activation of cardiac vagal and sympathetic nerves. Mild, prolonged hypercapnia, without concomitant changes in arterial pressure, also produced tonic increase in both vagal and sympathetic cardiac nerve activity that resulted in oscillations of heart rate which could be enhanced by respiratory sinus arrhythmia [40]. Vago-sympathetic co-activation was also elicited by mild hypoxia, while these motor outflows were both inhibited by hypocapnia.

2.2. Diving response

Vagally mediated bradycardia is a major feature of diving response in mammals, including humans [6,7]. Scholander et al. [67] reported that during diving, bradycardia was associated with ventricular ectopic beats in healthy humans. Since enhanced cardiac sympathetic activity is an established cause of ventricular tachyarrhythmias [68], it is possible that diving-related arrhythmic events were elicited by the coincident enhancement of sympathetic and parasympathetic outflows to the heart. Alternatively, profound bradycardia in the presence of high sympathetic tone may produce a tachycardia 'escape' arrhythmias.
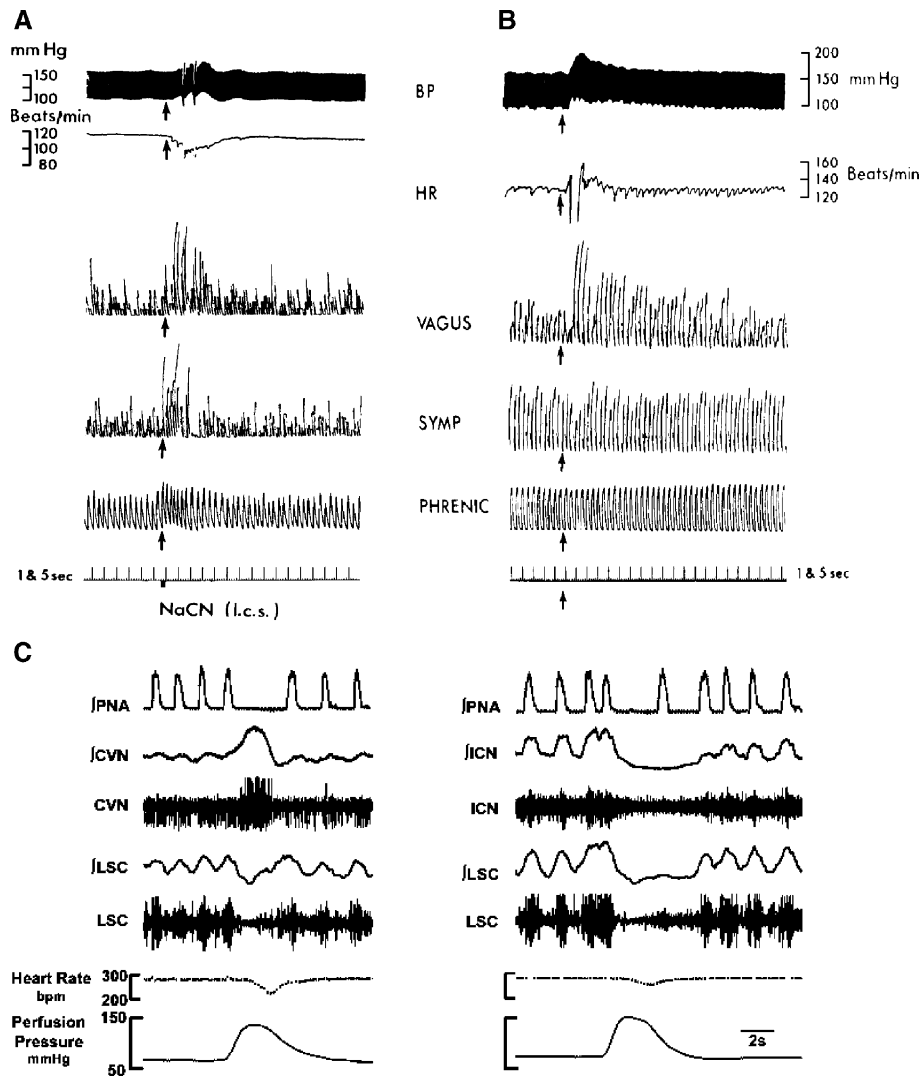
Fig. 1. Non-reciprocal and reciprocal changes in vagal and sympathetic neural outflows to the heart during autonomic reflexes. (A) Non-reciprocal action between the right cardiac vagus and sympathetic nerve activities during chemoreceptor reflex evoked by sodium cyanide injected into the right carotid sinus (r.c.s.). (B) Reciprocal action between the right cardiac vagus and sympathetic nerve activities evoked by a strong pressor response due to iv injection of norepinephrine. From top to bottom: blood pressure, heart rate, integrated nerve activity of cardiac vagal and cardiac sympathetic and phrenic nerve. In both A and B, recordings were made in an anesthetized dog. A and B are modified from [38], with permission. (C) Reciprocal influence on cardiac autonomic outflows during the baroreceptor reflex. Stimulation of arterial baroreceptors by raising pressure produces a reflex fall in heart rate that is accompanied by an inhibition of nerve traffic in the lumbar chain and inferior cardiac sympathetic branch (right panel) but activation of the cardiac vagus nerve (left panel). Note also there is a baroreceptor reflex-mediated depression of central respiratory activity. Recordings were made in an arterially perfused working heart–brainstem preparation. Data presented in right and left panel were obtained from two different animals. Abbreviations: CVN, cardiac vagal nerve; ICN, inferior cardiac sympathetic nerve; LCS, lumbar sympathetic chain; PNA, phrenic nerve activity; $\int$, integrated (100 ms time constant). Data unpublished (Pickering, AE and Paton, JFR).

Cardiac responses during facial or nasopharyngeal stimulation (that can evoke a diving-like response) have been examined in detail in a number of species [24,25, 28,55,56,63,72], including humans [29,31,69]; for review, see Ref. [22]. In conscious rabbits, Nalivaiko et al. [59] reported that during nasopharyngeal reflex, vagally-mediated bradycardia was associated with simultaneous shortening of the electrocardiogram QT-interval, a measure of ventricular repolarization. This QT shortening was prevented by propranolol, and thus was sympathetically

mediated. Blockade of reflex bradycardia by methyl-scopolamine unmasked a small tachycardic component. This latter response was suppressed by subsequent β-adrenergic blockade with propranolol (Fig. 3).

In conscious rabbits whose myocardium was rendered electrically unstable by dofetilide, an antagonist of I_{Kr} channels, nasopharyngeal stimulation increased cardiac sympathetic outflow to the ventricles as before but this time triggered polymorphic ventricular tachycardia (torsades de points) that developed on the background of
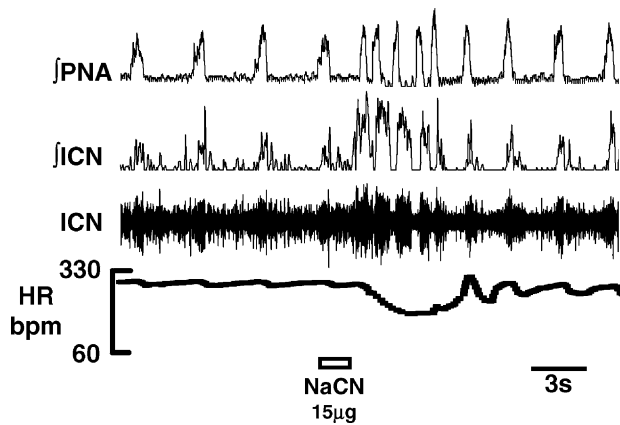
Fig. 2. Peripheral chemoreceptor stimulation co-activates sympathetic and vagal motor supply to the heart. Stimulation of peripheral chemoreceptors with low doses of sodium cyanide (NaCN into the aortic arch) evokes profound bradycardia (sensitive to atropine, not shown). Concurrent with the bradycardia is a dramatic increase in discharge in the inferior cardiac sympathetic nerve. In this scenario, the vagal effect overrides positive chronotropism of the sympathetic activation but this may assist in enhanced contractility to maintain cardiac output. Note the powerful respiratory modulation of heart rate following the bradycardia presumably reflecting a persistence in cardiac vagal motor excitability. Abbreviations: HR, heart rate in beats per minute (bpm); ICN, inferior cardiac nerve activity; PNA, phrenic nerve activity. From Ref. [15], with permission.

profound vagal bradycardia (Fig. 4, [60]). Diving is a recognized trigger of ventricular tachyarrhythmias in patients with some forms of long QT syndrome [3], and,

clearly, activation of only vagal outflow to the heart, as a part of diving response, is an unlikely cause of this potentially fatal cardiac malfunction. The animal data described here provide a plausible explanation of this phenomenon. It may be that simultaneously increased vagal effects on the sino-atrial node coupled with enhanced sympathetic effects on the ventricular myocardium facilitate arrhythmogenesis.

2.3. Oculocardiac reflex

The oculocardiac reflex (OCR) is also elicited from the trigeminal afferent system that produces vagally-mediated slowing of the heart rate. The OCR has been reported mostly from human clinical-based studies in which severe arrhythmias (some being fatal) have been reported during ophthalmic surgeries. The reflex was as well demonstrated in animal experiments [16]. OCR manifests as an atrio-ventricular nodal rhythm or even asystole [35–37,57]; see [23] for review. The OCR may be induced by pressure on the corneal surface of the eye, traction of an extraocular muscle, hematoma, ocular trauma or activation of corneal nociceptors. OCR is commonly seen during eye surgery with a significant incidence (for refs. see those above). Vagally-mediated, transient cardiac arrest may occur as frequently as 1 in 2200 cases during strabismus surgery [13,21]. In patients whose vagal tone is pharmacologically suppressed, the bradycardia is reduced but ventricular
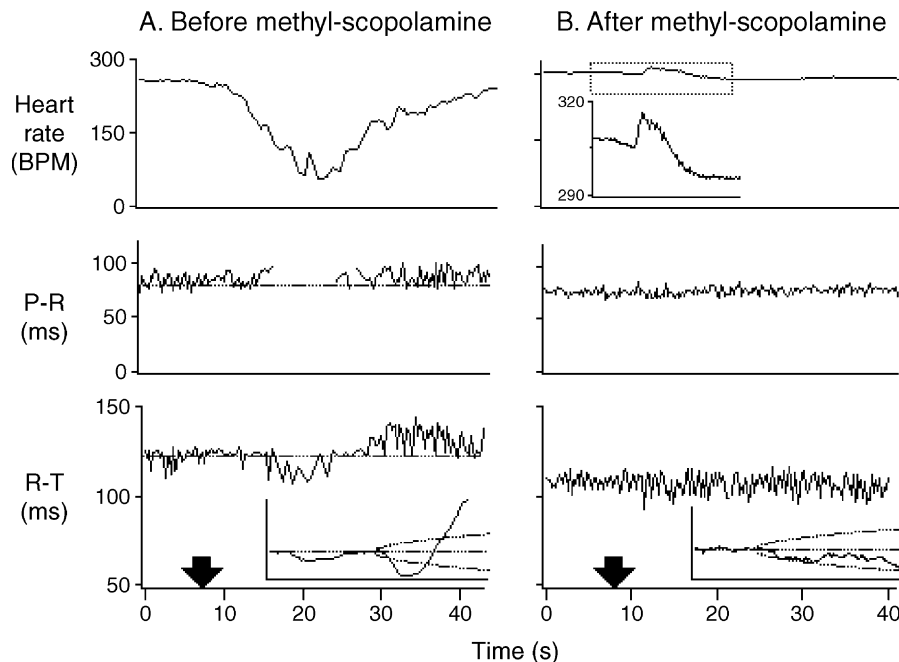

Fig. 3. Nasopharyngeal stimulation evokes vagally-mediated bradycardia associated with sympathetically-mediated tachycardic component and sympatheti-cally-mediated QT shortening. Recordings show changes in heart rate, PQ and QT intervals in conscious rabbit before (A) and after (B) parasympathetic blockade with methyl-scopolamine. Inset in the top right panel shows a segment of heart rate trace at the extended time scale. This tachycardia, as well as QT shortening, were subsequently eliminated by sympathetic blockade with propranolol. Insets on the lower panels represent results of cumulative sum analysis, with shaded area indicating confidential intervals. From Ref. [57], with permission.
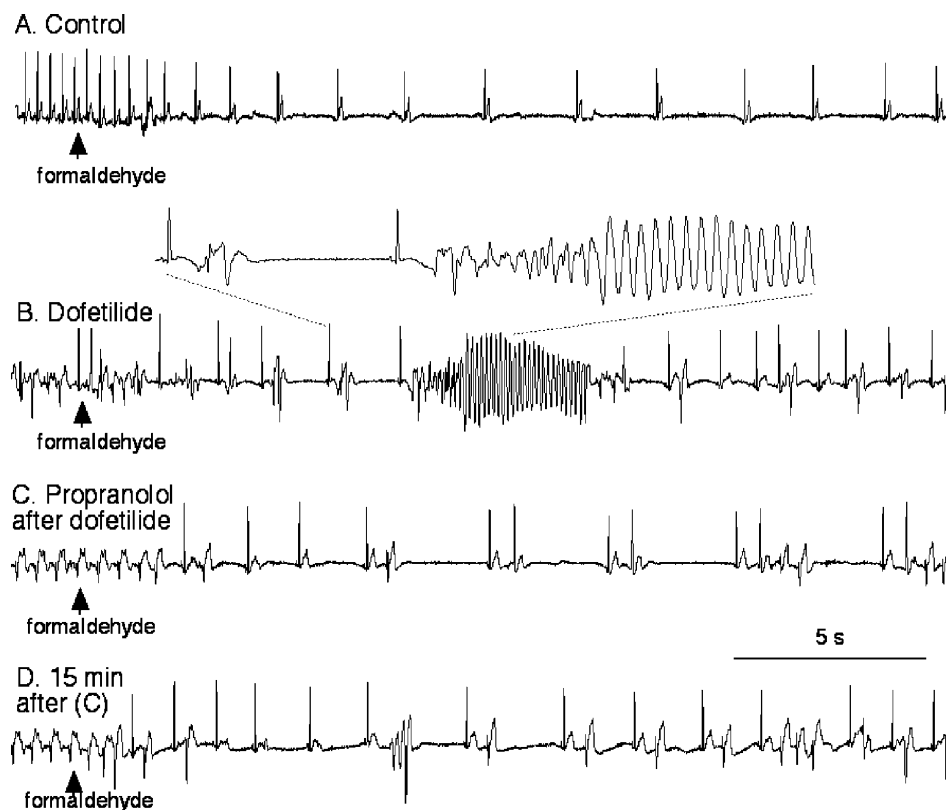
Fig. 4. Sympathetically-mediated cardiac arrhythmia triggered on the background of vagally-mediated bradycardia. ECG records during nasopharyngeal stimulation by formaldehyde vapor in conscious rabbit. A—stimulus delivered during control period; B—after termination of dofetilide infusion; C—during subsequent ß-blockade with propranolol (10 min after propranolol injection); D—after termination of propranolol action (25 min after propranolol injection). Formaldehyde stimulation was delivered when indicated by arrowheads. Note a period of the polymorphic ventricular tachycardia (torsades de points) shown at the extended time scale in B and a short 4-beat run of the same arrhythmia in D. From Ref. [58], with permission.

ectopic beats can occur [58]. This suggests that the OCR may also have a sympathetic component, with increased outflow to the ventricles. Unpublished data by Boscan and Paton support this notion since both mechanical and electrical stimulation of the cornea co-activates both vagal and sympathetic outflow to the heart in decerebrate rats (Fig. 5). This co-activation could lead to a risk of arrhythmias.

2.4. Centrally evoked "defence responses"

Koizumi and Kollai [38] demonstrated that stimulation of discrete hypothalamic areas may result in all possible combinations of changes in vagal and sympathetic nerve activities destined for the heart. Depending on the site of stimulation, they observed both reciprocal (sympathetic activation/vagal inhibition or vice versa) and non-reciprocal (co-activation or co-inhibition) patterns. The initial parts of these centrally mediated neural responses were baroreflex-independent as they began prior to alterations in arterial pressure. In the cases of co-activation, heart rate followed vagal changes, again suggesting that the early activation of parasympathetic influences on the sino-atrial node dominate. Selective autonomic blockade was not performed in

these studies, and it is unclear as to the functional role of the described changes in cardiac efferent neural activity on cardiac function.

2.5. Startle reflex

The issue of sympathetic/parasympathetic interaction in the control of heart rate during stress was specifically addressed in a number of studies by Printz et al.. They found that in conscious rats, air-jet stress caused a biphasic cardiac response, consisting of an initial bradycardia and subsequent tachycardia that were shown to be baroreflex-independent. The bradycardia was vagally-mediated [18], while the tachycardia was partially sensitive to beta-blockers with the remaining attributable to vagal with-drawal [1]. It was noted that these chronotropic responses may substantially overlap, and in some instances tachy-cardia masked the bradycardia and vice versa [1,18,19]. Interestingly, with repetitive air-puffs, bradycardia elicited during initial trials rapidly habituated to extinction. In contrast, the tachycardic component did not habituate. This observation led to a suggestion that alerting stimuli initially elicit an "orienting reflex" that manifests as a motor reaction, bradycardia and transient vasoconstriction.
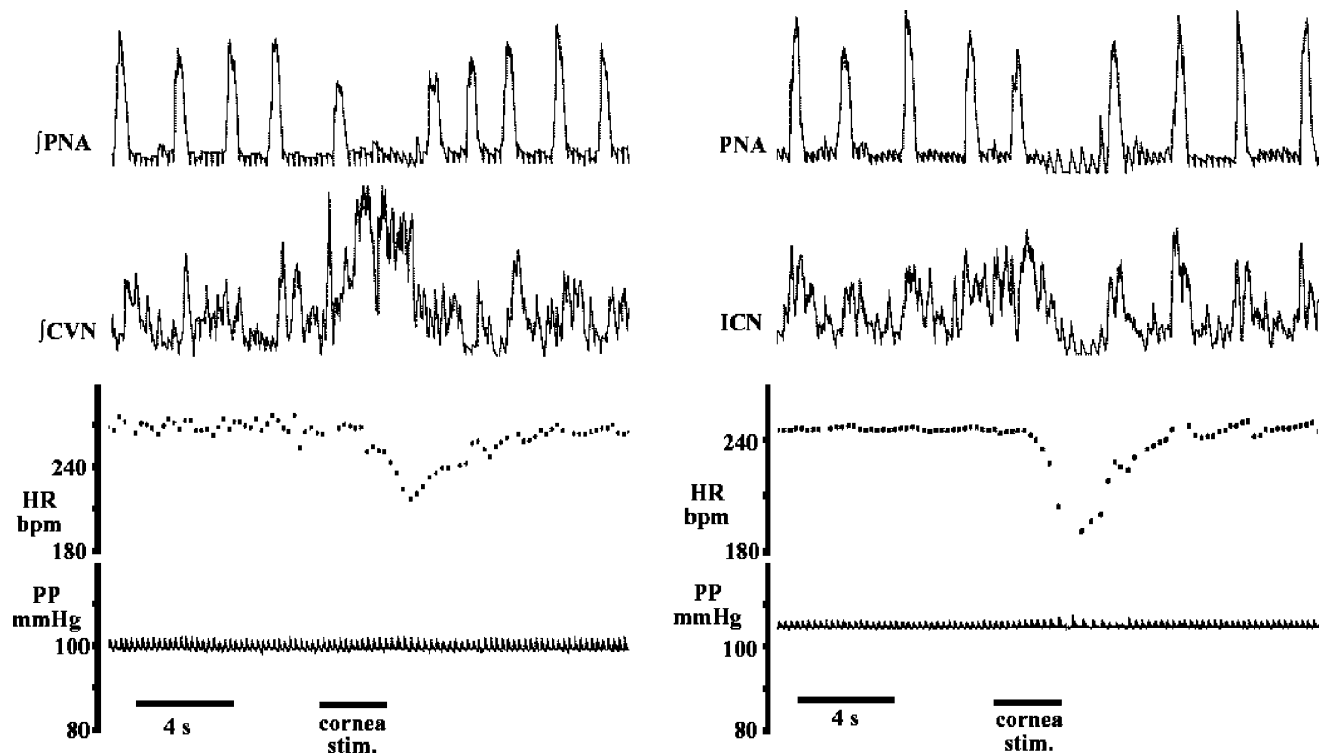
Fig. 5. Cornea afferent evoked bradycardia is associated with activation of cardiac sympathetic motor activity. Mechanical stimulation of corneal afferents ('cornea stim') evokes a bradycardia that is accompanied by activation of both the cardiac vagal and inferior cardiac sympathetic motor supply to the heart. The functional role of sympathetic activation to the heart may be to increase contractility. Recordings of CVN and ICN were made from the same rat at different times. Abbreviations: CVN, cardiac vagal nerve; HR, heart rate in beats per minute, ICN, inferior cardiac nerve; PNA, phrenic nerve activity; PP, perfusion pressure. Data unpublished (Boscan, P and Paton, JFR).

During repetitive trials, the stimulus probably loses its novelty such that the "orienting reflex" gives way to a "defence"-like reaction, with the increase in heart rate predominating [19]. It should also be recognized that the intensity of the vagal component during alerting-elicited cardiac vago-sympathetic co-activation substantially varies
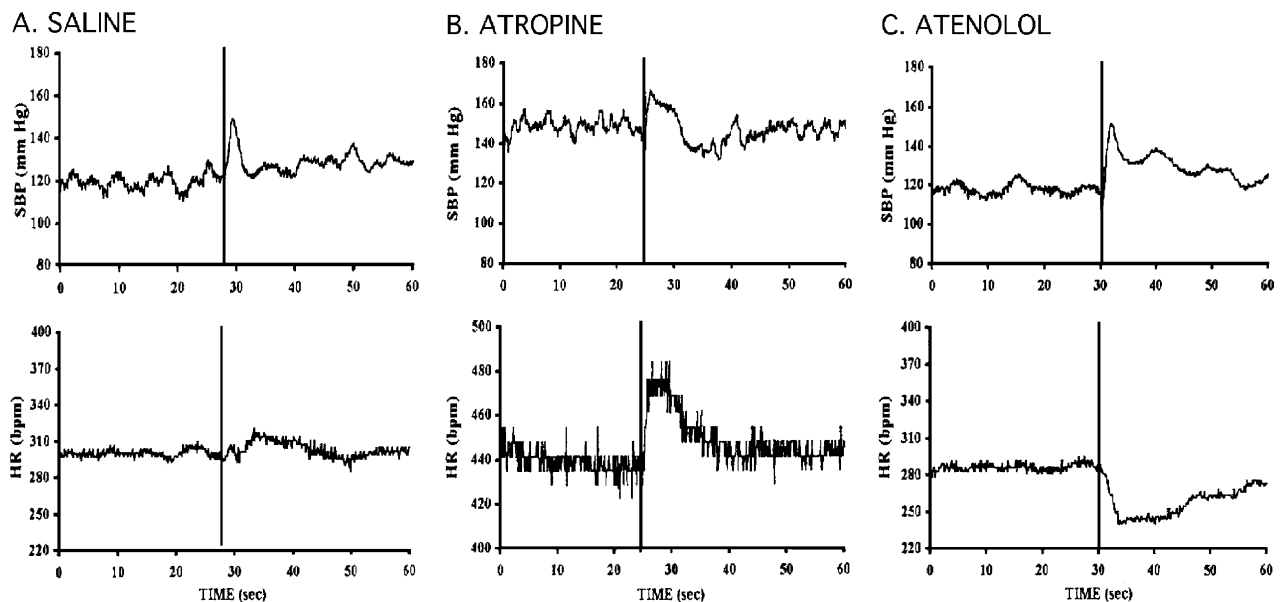

Fig. 6. Combined vagal and sympathetic effects on changes in heart rate elicited by acoustic stimulation in conscious rat. An example of a 60-s stretch of recording of heart rate (HR, in beats per minute or bpm) illustrating the responses to an acoustic startle stimulus (vertical line) in three separate treatment conditions (either saline or atropine or atenolol). Based on the cardiac drug interventions, it is clear that both the cardiac sympathetic and vagal motor outflows were activated concurrently during the startle stimulus. Modified from Ref. [10], with permission.

between rat strains [1]. This suggests that genetic differences may affect the susceptibility for simultaneous cardiac autonomic nerve activation.

Similar results were obtained by Baudrie et al. [10] who examined the contribution of sympathetic and parasympathetic influences on the cardiovascular response to acoustic stimuli in conscious rats (Fig. 6). The stimulus provoked a small transient tachycardia of variable amplitude. This response was substantially augmented following vagal blockade, whereas marked bradycardic response was observed after sympathetic blockade.

In another study, aversive acoustic stimulation evokes tachycardia that persisted after β-adrenoreceptor blockade with atenolol, propranolol or chemical sympathectomy using guanethidine. The remaining evoked tachycardia after sympathetic blockade was abolished during either bilateral vagotomy, atropine or methyl scopolamine administration [30,41]. Thus, the mechanism for this is either vagal withdrawal or a paradoxical vagally mediated tachycardia (see below for discussion).

2.6. Somatic nociception

In humans, stimulation of somatic nociceptors typically evokes tachycardia, an increase in blood pressure and hyperpnoea [5,62,66]. This pattern of response was also observed in animals [2,4,8,9,15,54,61]. In rats, the tachycardic response was concomitant with simultaneous increases in both inferior cardiac and vagal nerve discharge (Fig. 7). The reflex-evoked increase in cardiac vagal activity was powerfully modulated by central respiratory activity whereas the increase in the inferior cardiac nerve also comprised a tonic discharge component. Atropine *attenuated* the reflex tachycardia in a dose-dependent manner (Fig. 8A). In all cases, the remaining tachycardia was completely abolished by subsequent administration of atenolol (Fig. 8A). The atropine effect might suggest a positive synergistic interaction between these effectors possibly at the level of the target organ as described by Levy [43,45], but we cannot rule out additional effects within the cardiac ganglia. A caveat of this study, which has hindered interpretation, was that each blocking drug affected baseline heart rate. The fact that the heart rate response was relatively small to start with, compounded this problem. For example, an increase in baseline heart rate with atropine may mask the amplitude of the tachycardia as ceiling limits of heart rate may have been reached. However, atenolol-induced blockade of β_1-adrenoreceptors or reserpine-induced depletion of catecholamine storage attenuated the nociceptive-evoked tachycardia by only ~35%. The remaining tachycardia was abolished completely by atropine (Fig. 8B). Thus, somatic nociception evokes a tachycardia part of which is atropine-sensitive but unlikely to be due to cardiac vagal withdrawal because the activity in this nerve is reflexly increased. However, this assumes that the activity recorded is destined to controlling heart rate and not coronary blood flow or electrical
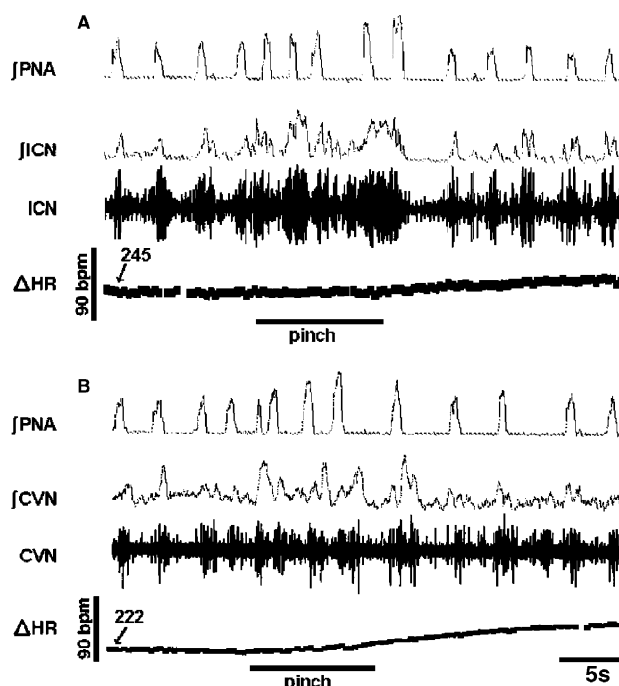

Fig. 7. Tachycardia evoked by somatic nociceptors involves heightened activity in the vagal motor supply to the heart. Stimulation of somatic nociceptors of a forepaw by mechanical pinching resulted in tachyapnoea and tachycardia. The cardiac effect was associated with co-activation of both inferior cardia (A) and cardiac vagal (B) motor nerves, which were recorded from the same rat at different times. Abbreviations: CVN, cardiac vagal nerve activity; HR, heart rate in beats per minute (bpm); ICN, inferior cardia nerve activity; PNA, phrenic nerve activity. Data unpublished (Boscan, P and Paton, JFR).

conduction. We do submit that the increase in cardiac vagal discharge is back to control before the peak heart rate response is achieved. This may imply its importance in the initiation of tachycardia and not its maintenance. The latter may be a consequence of release of neuropeptides either from post-ganglionic vagal endings or cells intrinsic to the cardiac ganglia. Nevertheless, the possibility remains that cardiac vagal fibre activation by nociceptor stimulation cause a paradoxical tachycardia as described previously [43,45].

3. Functional significance of co-activating cardiac sympathetic and parasympathetic nerves

A general interpretation as to the role of reciprocal versus simultaneous co-activation of autonomic control is made by Berntson et al. [12]. Simultaneous co-activation allows precise control of the response direction, which is determined by the dominating limb of the autonomic nerve, and hence allows the fine tuning of target organ function. Since the dynamic range and the gain of the response is restricted in this situation, the tendency here is towards stabilization of the functional state of the target organ. In terms of reflex control of the heart this is important (e.g., during a dive) where the operating range needs to be confined but precisely controlled.
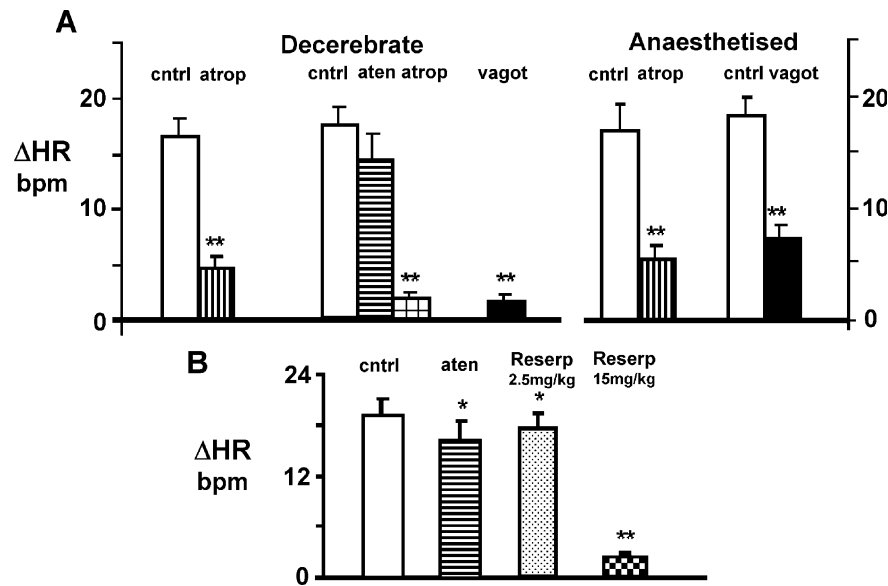
Fig. 8. Cardiac vagal innervation augments reflex tachycardia. The heart rate response to somatic noxious stimulation following numerous pharmacological treatments. In A, atropine (atrop; 15 μg/kg) reduced the reflex tachycardia which was further reduced with additions of both atenolol (aten; 45 mg/kg) and atropine (15 μg/kg). Bilateral vagotomy (vagot) also reduced the reflex tachycardia. Since cardiac vagal efferents are activated with this stimulus (see Fig. 7), this suggests the necessity of vagal activity for this tachycardic response. In B, both atenolol treatment (45 mg/kg) and low dose of reserpine (to block catecholamine release) both marginally attenuated the reflex tachycardia to mechanical noxious stimulation. High dose of reserpine, to block release of peptides, virtually abolished the reflex tachycardia. Data unpublished (Boscan, P and Paton, JFR).

In contrast, during reciprocal control, such as with baroreflex control of the heart, both the range and gain are massively increased in one direction or in the other due to the synergism of both limbs. This pattern is advantageous for guaranteeing response direction as well as high speed and large magnitude, but may be less efficient for precise adjustments.

Kollai and Koizumi [40] made a suggestion that the functional significance of vago-sympathetic co-activation may be to coordinate the relationship between ventricular contractility and heart rate so as to maximize cardiac output. As described above, they found that during simultaneous cardiac vago-sympathetic co-activation, vagal activity is mainly responsible for chronotropic effects, and suggested that the concomitant increase in sympathetic outflow targets the ventricular myocardium. In an attempt to prove this interpretation, in a follow-up paper, these authors demonstrated that direct simultaneous electrical stimulation of vagal and sympathetic cardiac nerves (using spike trains to mimic endogenous activity) resulted in a greater increase in cardiac output than did sympathetic stimulation alone [39]. However, it is unknown whether the artificially applied electrical stimuli activated the same neural fibers that were activated reflexly during physiological stimulation, and thus the issue requires further investigation. We fully acknowledge that fibers recorded from cardiac nerve bundles may also target coronary blood vessels or cells releasing atrial naturetic peptide, and that future work needs to address the responses of these target organs. This will not be an easy task providing that some sympathetic and parasympathetic fibers affect cardiac functions indirectly, via the intracardiac neuronal network.

Regarding the diving response, the elicited bradycardia is an adaptive physiological reaction that protects the heart from hypoxia by dramatically reducing oxygen consumption (the heart is an organ with major demand for oxygen due to both its inherently high metabolic rate and inability to respire anaerobically). Since bradycardia causes substantial fall in ventricular contractility via non-neural mechanisms (Bowdich effect; see [53]), it may be that the increase in sympathetic outflow to the ventricular myocardium may serve the purpose to counteract rate-dependent fall in contractility, thereby optimizing stroke volume, similar to the situation during the chemoreflex. An additional possibility is that the increased sympathetic outflow, via activation of beta-adrenoreceptors in coronary arterioles, decreases coronary vascular resistance to maintain blood flow and maintain oxygen delivery to the heart. Since the destination of sympathetic fibers was not determined, this remains an open question.

4. Vagally mediated tachycardia

The co-activation of vagal and sympathetic neural outflow to the heart may have a physiological advantage if the evoked effects are synergetic. As mentioned above for acoustic startle responses and those evoked by somatic nociceptors, vagal activity may enhance sympathetically mediated tachycardia, or can by itself produce a paradoxical vagally mediated tachycardia. Fig. 9 illustrates this phenomenon by showing that bilateral vagotomy attenuates the reflex tachycardia to somatic nociceptor activation, but this can be restored, in
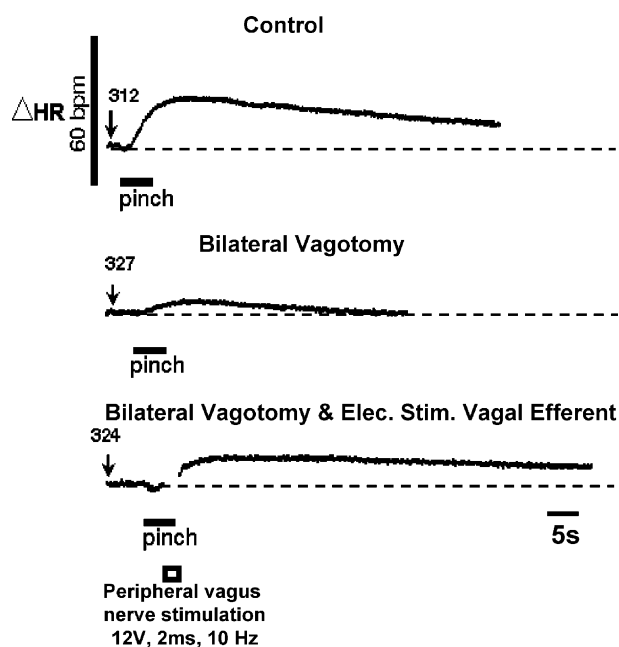
Fig. 9. Reflex tachycardia depends on activity within the vagus nerve. The reflex tachycardia to noxious pinch stimulation of a forepaw was reduced by sectioning both vagi. However, the response was partly reinstated by concomitant vagal efferent stimulation suggesting that vagal activity can potentiate sympathetically mediated positive chronotropic responses during nociception. Data unpublished (Boscan, P and Paton, JFR).

most part, by electrical stimulation of vagal efferents. A plausible mechanism for this synergistic interaction includes possible activation of chromaffin or small intensely fluorescent cells (SIF) in the cardiac ganglia. For example, acetylcholine released in the sympathetic pelvic ganglia acts via muscarinic receptors to release cathecolamines from chromaffin cells [64]. In the cardiac ganglia, the chromaffin or SIF cells have abundant vagal innervation and their fluorescence is confined to vesicles containing catecholamines [18,34,42,46,52,70]. Thus, the paradoxical vagally mediated tachycardia (see Ref. [45]) could be due to release of catecholamines from these vesicles contained within the intrinsic cardiac neurones. However, these chromaffin or SIF cells also contain other neuropeptides which could play a role in a tachycardic responses [32,33,44]. It must also be recognized that the cardiac vagal nerve may also contain some sympathetic efferent axons that could participate in this effect. However, since number of sympathetic fibers is small relative to the number of cardiac vagal efferents, it is quite unlikely that their contribution was substantial.

An alternative possibility to explain cardiac mediated tachycardia is that the vagal endings release a co-transmitter under different conditions, perhaps related to a specific pattern of firing. Several neuropeptides are present within vagal nerve fibers including vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), phenyl-histidin-isoleucine, substance P (SP) and enkephalines [20,47,49–51,71]. These neuropeptides can be co-localized with acetylcholine in cardiac vagal fibers (see Ref. [33]). While the role of some of

these neuropeptides remains unknown, others (VIP and phenyl-histidin-isoleucine) have the same effect as noradrenaline to increase heart rate [11,27,44,48,65]. The presence of peptides within neuronal elements of the cardiac ganglia could explain the observation that activation of somatic nociceptors evoked an atropine-sensitive tachycardia that appears not to be due to vagal withdrawal. Moreover, the reflex tachycardia to noxious stimulation persisted in rats pre-treated with reserpine (Boscan and Paton, unpublished data), which is known to deplete only catecholamines [14,26,52,70]. In contrast, rats treated with high doses of reserpine, used to deplete both catecholamines and neuropeptides [52], failed to exhibit the tachycardia evoked by following noxious pinch stimulation (Fig. 8B). If vagally mediated tachycardia is indeed a physiological phenomena, it may be that in some instances vago-sympathetic co-activation may result in a true synergic effect on heart rate.

5. Summary

Many reflexes that are apparently protective (peripheral chemoreceptor, startle, noxious, ocular, defensive), but not regulatory or homeostatic (e.g., the baroreceptor), appear to excite both autonomic outflows to the heart simultaneously. As we have discussed, the view of the sympathetic and parasympathetic inputs to the heart as being polar antagonists is no longer tenable, rather they should be viewed as the yin and yang, different but often complimentary. In the same way that co-activation of both autonomic limbs regulates penile erection, micturition and secretory gland function, we can see that the control of cardiac function is often regulated by the sympathetic and parasympathetic systems in tandem. Co-activation of cardiac vagal and sympathetic fibers can produce bradycardia (e.g., peripheral chemoreceptor), tachycardia (somatic nociceptors) or biphasic responses in heart rate (e.g., startle). The possible physiological relevance of co-activation has been discussed, but it is clear that this may also have pathophysiological significance as it is potentially pro-arrhythmic. Interpretation of results obtained by recordings from cardiac nerves are not as straighforward as it seemed, as many details of interaction of vagal and sympathetic postganglionic neurons with the intrinsic cardiac nervous system are still unknown. Further investigation of the mechanisms of sympathetic and parasympathetic cardiac interaction will require recordings from functionally identified motor fibers to determine their destination: sino-atrial node, ventricular muscle, conduction tissue, coronary arteries and control of atrial naturetic peptide release. Until such measurements are made, we will struggle to provide definitive conclusions about the relevance of autonomic activity to the heart and indeed to determine whether the vagus nerve can, under certain circumstances, really cause tachycardia. From a clinical point of view, it is important to recognize that in some

instances, high drive to the heart from both autonomic limbs may be arrhythmogenic.

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