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REVIEW

Autonomic nervous system control of the cardiovascular and respiratory systems in asthma

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Summary Patients with asthma have exaggerated bronchoconstriction of their airways in response to certain indirect (e.g. cold air, allergens, dust, exercise) or direct (e.g. inhaled methacholine) stimuli. This 'hyper-reactivity' usually co-exists with airway inflammation, although the pathophysiological mechanisms underlying these changes are not fully understood. It is likely that this hyper-reactivity is associated with abnormal autonomic nervous system (ANS) control. In particular, the parasympathetic (vagal) component of the ANS appears to be implicated in the pathogenesis of asthma. In addition, several studies have suggested the existence of differential alteration in ANS function following exercise in asthmatics compared with non-asthmatic individuals.

Several early studies suggested that the altered autonomic control of airway calibre in asthma might be reflected by a parallel change in heart rate. Cardiac vagal reactivity does indeed appear to be increased in asthma, as demonstrated by the cardiac response to various autonomic functions tests. However, other studies have reported a lack of association between bronchial and cardiac vagal tone, and this is in accord with the concept of system-independent ANS control.

This review provides a discussion of cardiovascular–autonomic changes associated with either the pathophysiology of asthma per se or with asthma pharmacotherapy treatment. Previous investigations are summarised suggesting an apparent association between altered autonomic–cardiovascular control and bronchial asthma. The full extent of autonomic dysfunction, and its clinical implications, has yet to be fully determined and should be the subject of future investigation.

Contents

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Introduction

The term 'asthma' encompasses several distinct disease phenotypes leading to differences in diagnostic classification. The most widely accepted definition is 'a chronic inflammatory disorder of the airways … usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli'.[1] About 5.2 million people in the UK have asthma, causing about 69,000 hospital admissions and 1400 deaths in 2003/2004 with an estimated direct cost to the National Health Service of £889 million.[2] Asthma also causes a lot of morbidity with over 70% of sufferers experiencing regular restrictions in their activity.[2]

Patients with asthma undergo episodes of exaggerated bronchoconstriction in response to a wide variety of exogenous and endogenous stimuli (for example cold air, organic/inorganic allergens including dust or exercise). Recent guidelines have emphasised the roles of certain allergens and their avoidance in managing asthma.[3] This 'hyper-reactivity' is generally co-existent with (biopsy proven) airway inflammation and is associated with altered sensory neuronal activity. The pathophysiological mechanism underlying these changes is not fully understood but it is often triggered by allergens and is typified by the presence of eosinophils and T_H2-type immune processes. It is likely that this mechanism is associated with the abnormal autonomic nervous system (ANS) control observed in asthmatic subjects.[4] In particular, the parasympathetic component of the ANS appears to be implicated in the pathogenesis of asthma. The parasympathetic nervous system is involved in the bronchoconstriction that occurs during physical exercise in both asthmatic and non-asthmatic subjects,[5] the bronchoconstriction response to altered airway temperature and/or airway surface osmolarity.[6] In addition, several studies have suggested the existence of differential autonomic function following exercise in asthmatics compared with normal controls.[7–10]

Cardiac vagal activity also appears to be increased in asthma, as demonstrated by the exaggerated cardiac response (bradycardia) to anticholinergic drugs, methacholine and antigen challenge seen in asthmatic subjects.[11,12] It has therefore been suggested that there might be an intrinsic relationship between cardiac and bronchial autonomic control, and that this relationship might be altered in asthmatic individuals.[13] However, vagal regulation of resting bronchomotor tone depends on reflexes initiated in irritant airway receptors,[14,15] whilst vagal activity to the heart occurs in response to arterial baroreceptors.[16,17] This apparent independence of vagal control suggests that bronchial and cardiac vagal activities would be unrelated. In accordance with this concept of system-independent ANS control, some authors have reported a lack of association between changes in ANS control in the cardiac and respiratory systems. For example, Horváth et al.[18] found no correlation between bronchial and cardiac vagal tone (assessed using airway resistance and heart beat period) in non-atopic healthy adults. However, there is also a considerable body of evidence suggesting that numerous cardiovascular parameters are altered as a result of either pathophysiological changes or the administration of therapeutic medication in asthma.

Mechanisms of control in the respiratory and cardiac systems

Mechanisms of airway control

Pre-ganglionic parasympathetic nerve fibres project to the airways via the vagus nerves. They form cholinergic synapses with post-ganglionic neurons via airway parasympathetic ganglia.

Airway parasympathetic ganglia are mainly associated with the larger airways but the subsequent post-ganglionic fibres innervate structures throughout the airway tree.[19] Post-ganglionic parasympathetic cholinergic and non-adrenergic non-cholinergic (NANC) fibres innervate (i) airway smooth muscle, providing the dominant control of smooth muscle tone and thus airway calibre, and (ii) airway glands and microvasculature in the respiratory tract. There is no sympathetic innervation of airway smooth muscle, although the airway vasculature does receive sympathetic innervation. Instead, relaxant innervation of the human airways is provided by the NANC component of the parasympathetic nervous system, and transmission at smooth muscle synapses appears to involve both nitric oxide (NO) and vasoactive intestinal polypeptide (VIP). Figure 1 illustrates the anatomical and functional organisation of the ANS and NANC system in the heart and airways; the influence of asthma on the function of these systems is also shown.

Mechanisms of cardiac control

Neural regulation of heart rate (HR) takes place as a result of the interplay between sympathetic and parasympathetic modulation of the electrical

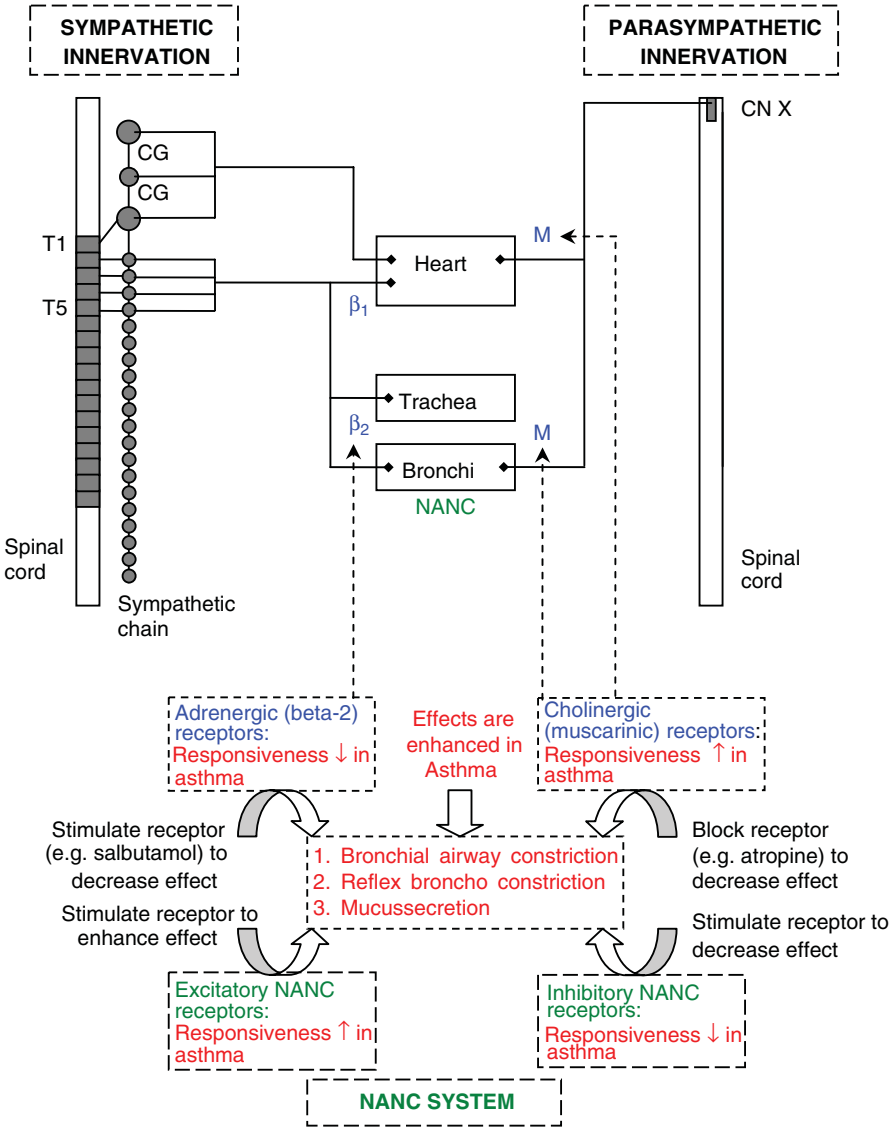

Figure 1 Anatomical and functional organisation of the autonomic nervous system and NANC system in the heart and airways. The influence of asthma on the function of these systems is also shown. (CN X—tenth cranial nerves; CG—cervical ganglia; T1, T5—first, tenth thoracic vertebrae; β_1—beta-1 adrenoceptor; β_2—beta-2 adrenoceptor; M—muscarinic receptor; NANC—non-adrenergic and non-cholinergic system. *Note*: There is no sympathetic innervation of airway smooth muscle but airway vasculature does receive sympathetic innervation.)

activity of the sinoatrial (SA) node. The temporal investigation of HR regulation is commonly referred to as HR variability (HRV) analysis, and this can be achieved using a variety of data processing techniques in both the time and frequency domains. The sympathetic and parasympathetic components of the ANS influence the HRV signal in a frequency-dependant way: the high-frequency (HF) component of the HRV signal (in the range 0.15–0.4 Hz) are mediated via the parasympathetic system; (ii) the low-frequency (LF) component (in the range 0.04–0.15 Hz) are mediated via both sympathetic and parasympathetic systems.[20–22] Of particular interest in the present context, the HF component is associated with HR modulation caused by respiratory influence.[23] These respiratory effects are often described as 'respiratory sinus arrhythmia' (RSA), the phenomenon of HR modulation that occurs at the frequency of respiration. RSA is the pattern of rhythmic variation of HR that occurs at the frequency of respiration, and which is mediated by the vagus nerve.[24] The HF component of HRV is also influenced by respiratory tidal volume, and this effect may be separately distinguished as 'breath amplitude sinus arrhythmia' (BASA).[23]

Relative influence of NO in the bronchial and cardiac systems

Excitatory NANC mechanisms (e.g. the neuropeptides neurokinin A, calcitonin gene-related peptide, substance P, bradykinin, tachykinin, neuropeptide Y) cause bronchoconstriction, microvascular leakage and mucous hyper-secretion.[25–27] Inhibitory NANC mechanisms (NO and VIP) constitute the only known neural bronchodilator pathway in human airways. Both NO and VIP inhibit the release of acetylcholine and relax human isolated bronchial tissue.[25,28] In contrast, NO enhances both the activity of central vagal motorneurons[29] and the cardiac response to vagal stimulation.[30,31] Several authors have also suggested that NO is a sympatholytic agent in animals, i.e. it reduces the activity of sympathoexcitatory brain stem nuclei and central sympathetic outflow[32–34] and it attenuates the cardiac response to sympathetic stimulation.[31] Chowdhary et al.[35] provided the first evidence of a substantive effect of NO on human cardiac autonomic control. In that study systemic inhibition of NO synthase using N^G-monomethyl-L-arginine (L-NMMA) was associated with an increase in HR and a reduction in HRV. The opposite effect was noted following infusion of the NO donor sodium nitroprusside. These authors concluded that NO has a tonic excitatory influence on baroreflex-mediated cardiac vagal activity.

Review of the literature

Methodology

Studies that investigated cardiovascular physiological changes resulting from the pathophysiology of asthma or the pharmacological effects of asthma medication were sought from the published literature. Studies included in the review fulfilled the following criteria: either (i) they described a qualitative or quantitative investigation of cardiovascular physiological parameters in asthmatic and/or atopic individuals, or (ii) they described the effects of pharmaceutical agents used in the management of asthma, in individuals with or without asthma or atopy. Studies that involved either adults or children were included. Articles that only described respiratory or other systemic changes in asthma or asthma therapy, but did not otherwise satisfy the admission criteria, were excluded from the review.

A systematic search of the literature was performed using a selection of electronic literature databases (PubMed, BIDS, CINAHL). The keywords shown in Table 1 were used to filter relevant publications, using keyword combinations constructed as 'Levels 1 and 2'. Citation tracking was performed from the articles obtained via the databases, yielding a second source of references. A total of 23 studies satisfied the eligibility criteria for the review. Table 2 provides a synopsis of the main characteristics of each of the relevant studies.

Results

The role of the autonomic nervous system in asthma

Asthma is associated with abnormal ANS function (dysautonomia) in adults.[4] This is exhibited as: (i) a marked bronchial hyper-sensitivity to cholinergic and NANC constrictors, and (ii) a decreased sensitivity to adrenergic and NANC dilators.[36,37]

Cholinergic responsiveness. The bronchi are tonically constricted at rest[38] owing to inspiratory reflex cholinergic activity.[14,39] There is evidence that tonic parasympathetic (vagal) activity is largely responsible for the maintenance of this resting airway calibre.[10,40,41] The parasympathetic nervous system also has a role in reflex bronchoconstriction[42] and it is generally accepted that this effect is exaggerated in asthmatics, causing a hyper-responsiveness to cold air, rapid breathing, sulphur dioxide, citric acid and histamine. Asthmatic airways are hyper-reactive and respond to

Table 1 Combinations of terms used to search the electronic literature databases (MeSH indicates that the term is a medical subject heading).

Level 1	Level 2
Asthma (MeSH) or asthmatic Hypersensitivity (MeSH) or atopy or atopic	1. Autonomic or autonomic nervous system (MeSH) or ANS 2. Sympathetic nervous system (MeSH) 3. Parasympathetic nervous system (MeSH) 4. Heart (MeSH) or cardiac or cardiovascular system (MeSH) 5. Blood pressure (MeSH) 6. Pressoreceptors (MeSH) or baroreceptor or BRS 7. Heart rate (MeSH) or heart rate variability or HRV 8. Autonomic pathways (MeSH) or nerves or nervous system (MeSH) 9. (Cholinergic or muscarinic or adrenergic) and (agents or agonists or antagonists) (MeSH) 10. Sympathomimetics (MeSH) or sympathomimetic or anticholinergic 11. Adrenal cortex hormones (MeSH) or corticosteroid or glucocorticosteroid

doses of inhaled methacholine or carbachol (cholinergic agonists) that do not affect normal subjects.[4] Specific antigen challenge also causes immediate bronchoconstriction followed by hyper-reactivity.[43–45] Animal experiments have abolished both bronchoconstriction and hyper-reactivity by vagotomy or vagal blockade.[46] Cholinergic (parasympathetic) hyper-sensitivity can occur in different body systems, being exhibited as exaggerations in smooth muscle tone, pulmonary blood flow, endothelial permeability, airway secretions[47] or sweating (eccrine gland response).[48] Enhanced cholinergic airway responsiveness has even been suggested as a contributing factor to the development of bronchial asthma.[13,49] The abnormally increased airway tone and hyper-reactivity in asthma[49,50] might be caused by either (i) an increased release of acetylcholine from nerves, or (ii) increased sensitivity of the post-junctional muscarinic receptors. Anticholinergic drugs such as atropine and ipratropium diminish both the increased constrictive tone and the airway hyper-reactivity in asthmatic individuals,[36,51,52] thereby confirming the cholinergic nature of the hypersensitivity. Ipratopium bromide has been used in the management of acute asthma.[3]

Adrenergic responsiveness. In addition to exaggerated cholinergic reactivity, changes in adrenergic activity have also been documented in asthmatic subjects. Kaliner et al.[4] compared the response of allergic asthmatic, allergic rhinitic, allergen-sensitive and normal control subjects to alpha (α) adrenergic, beta (β) adrenergic and cholinergic stimuli. These authors observed that asthmatic subjects had hyper-reactive α-adrenergic responsiveness and hypo-reactive β-adrenergic responsiveness. Furthermore, there are four types of β receptor[53]; of these both β_1 and β_2 adrenoceptors are found in the lung but β_2 is the most important and most widely expressed, as demonstrated by autoradiographic imaging.[54] Indeed one of the cornerstones of contemporary asthma therapy is the β_2-adrenoceptor agonist (e.g. salbutamol), the function of which is to stimulate β_2-adrenergic receptors in the lung and thus produce bronchodilation. β_1 receptors in the lung are confined to glands and alveoli and therefore β_1-adrenoceptor agonists do not relax airway smooth muscle.

NANC responsiveness. Although the evidence for clinically significant NANC dysfunction in asthma is not yet conclusive, there is reason to believe that inhibitory NANC mechanisms might be reduced and excitatory NANC mechanisms might be increased in asthma.[25,55] Several possible mechanisms have been proposed in support of an altered NANC responsiveness in asthma, and this dysfunction might be expected to exaggerate bronchoconstriction in asthmatic individuals.

NO (one of the inhibitory NANC mediators) is widely distributed in the body, functioning as a messenger in a variety of biological processes. NO is broken down by oxygen free radicals associated with inflammatory cells,[56] thereby degrading its bronchodilatory effect. There is evidence that exhaled NO levels correlate with markers of asthma disease control such as eosinophil concentration determined from bronchial biopsy and bronchial lavage.[57] Notably, the distinction between atopic, asthmatic and atopic-asthmatic individuals seems to be important in this regard. It is also possible that dysregulation of NO production alters the control of blood flow in the lungs and airways, and thus contributes to the pathogenesis of asthma.[58] Similarly, the enzymatic degradation of VIP might be enhanced in severe asthma, for example as a result of the release of tryptase from mast cells.[25]

Table 2 Studies fulfilling the inclusion criteria for the review.

Author	Investigation	Study drug	Sample size (M/F)	Age range (mean) (years)	Sample characteristics	Variables measured
Leitch et al.[111]	Cardiovascular and biochemical response to β_2-agonist	Salbutamol (IV 10 μg min^{-1} for one hour)	7 (M)	25–35	Non-asthmatic healthy subjects	Ventilation, HR, plasma potassium, plasma glucose, serum insulin
Kaliner et al.[4]	Cardiovascular, respiratory and biochemical response to α and β adrenergic and cholinergic stimuli	Allergen (skin test)	1: 9 (M), 13 (F) 2: 12 (M), 12 (F) 3:2 (M), 6 (F) 4:20 (M), 37 (F)	1: (32.0) 2: (26.9) 3: (20.3) 4: (23.0)	1: Mild allergic asthma (positive skin test to allergen) 2: Allergic rhinitis (no asthma) 3: Pre-allergic (positive skin test to allergen) 4: Normal controls (no asthma, negative skin test to allergen)	Mydriasis (pupillary dilation), cutaneous blood flow (radioactive xenon), BP (IV catheter), cAMP (radioimmunoassay), FEV_1
Scheinin et al.[79]	Cardiovascular and biochemical response to β_2-agonist	Fenoterol, salbutamol (inhaled). Three doses for each drug (1200, 1800 and 2400 μg), more than 1 week apart.	6 (M)	22–26	Non-asthmatic healthy subjects	ECG (QRS duration, T wave amplitude), HR, BP (automated oscillometric device, Nippon Colin). Blood samples: plasma potassium, plasma sodium, cAMP, endogenous adrenaline, noradrenaline
Morrison et al.[69]	Cardiovascular and respiratory response to anticholinergic drug	Atropine (IV 30 μg kg^{-1})	10	26–54	Asthma, 6 subjects also atopic. Diurnal variation in PEF $>$ 20% for preceding two weeks	PEFR and HR at 4 am and 4 pm
Shah et al.[61]	Cardiovascular response to anticholinergic drug	Atropine (IV)	Asthmatic: 33 (M), 17 (F), 9 atopic, 41 non-atopic Controls: 13(M), 7(F)	(33) (asthma) (32) (control)	Bronchial asthma. No medication affecting ANS or HR for preceding two weeks. No cardiac, pulmonary CNS, PNS or ANS disease	Spirometry, FEV_1, FVC, PEFR, HR. Sympathetic tests: postural BP response; sustained handgrip test. Parasympathetic tests: respiratory sinus arrhythmia (deep breathing); Valsalva HR response; carotid massage response; atropine test; postural HR response
Garrard et al.[62]	Cardiovascular response to β_2-agonist	None	29 (10 healthy, 9 asymptomatic asthmatics, 10 asthmatics)	19–46 (29.7)	Asthmatic	FEV_1, FVC, ECG (HR), HRV, respiratory impedance (plethysmography)
Bremner et al.[100]	Cardiovascular response to β_2-agonist	Hexoprenaline and Salbutamol (inhaled, 5 $\times$ 200 μg doses administered at 15 min intervals)	4 (M), 8 (F)	20–38 (29)	Non-asthmatic healthy subjects	Electromechanical systole, BP (automatic cuff), ECG and QTc, plasma potassium

Table 2 (*continued*)

Author	Investigation	Study drug	Sample size (M/F)	Age range (mean) (years)	Sample characteristics	Variables measured
Lehrer et al.[118]	Cardiovascular and respiratory response to anticholinergic drug	Ipratropium bromide (inhaled), Saline (placebo)	13 (M), 18 (F)	18–40	Asthmatic. No other respiratory, cardiovascular or neurological disease and no psychoactive medication	Spirometry (flow volume curves, FEV_1, FVC), ECG, HRV
Horváth et al.[18]	Cardiovascular and respiratory response to complete pharmacological cholinergic blockade. Relationship between bronchial and cardiac vagal tone	Atropine	7(M), 5(F)	18–52 (27)	Non-asthmatic and non-atopic healthy subjects	Airway resistance, lung volume, thoracic gas volume (whole body plethysmography). HR and BP (automated sphygmomanometer)
Jartti et al.[99]	Cardiovascular response to β_2-agonist	Salbutamol, Terbutaline, Salmeterol	Asthmatic: 7 (M), 3 (F) Asthmatic (no medication): 4(M), 5(F) Non-asthmatic: 4(M), 6(F)	9–11	Asthmatic and non-asthmatic	ECG (RR), continuous BP (Ohmeda), HRV, BPV, BRS, flow-volume spirometry
Jartti et al.[75]	Cardiovascular and respiratory response to β_2-agonist	Salbutamol (600 μg inhaled)	5(M), 3(F)	(10.5)	Asthmatic and non-asthmatic	HRV, beat-to-beat BPV, BRS, flow spirometry
Parlow et al.[116]	Cardiovascular response to anticholinergic drug	IV atropine (20 $\mu g\,kg^{-1}$) or Glycopyrrolate (8 $\mu g\,kg^{-1}$)	14	Not specified	Non-asthmatic healthy subjects. No cardiovascular, respiratory, endocrine or neurological disease. No medication affecting the cardiovascular system	ECG, HR, HRV, BRS, continuous BP (Finapres), respiratory rate
Jartti et al.[78]	Cardiovascular response to β_2-agonist (LABA) administered over four weeks and to β_2-agonist (SABA)	Salmeterol (50 μg twice-daily), Salbutamol (single 600 μg dose)	7(M), 4(F)	8.8–12.1 (10.5)	Stable asthma	HR, HRV, PEFR
Jartti et al.[97]	Cardiovascular response to β_2-agonist	Terbutaline	6 (M)	(24)	Non-asthmatic healthy subjects	HRV, BRS

Rossinen et al.[105]	Cardiovascular response to β_2-agonist in co-existing coronary artery disease and asthma	Salbutamol (inhaled)	19 (M), 5 (F)	47–73 (62)	Patients with coronary artery disease and asthma, taking a variety of medication	Ambulatory ECG, BP, HRV. Cycle ergometry, spirometry, PEFR, chest radiograph,
Hanratty et al.[98]	Cardiovascular response to β_2-agonist and β_2-antagonist	Salbutamol (8 mg), ICI 118,551 (25 mg), salbutamol (8 mg) plus ICI 118,551 (25 mg)	17 (M)	(30)	Non-asthmatic healthy subjects	Ambulatory ECG, HR, HRV
Scheinin et al.[129]	Cardiovascular response to anticholinergic drugs	IV Atropine Sulphate (10 $\mu g\,kg^{-1}$), Glycopyrronium bromide (5 $\mu g\,kg^{-1}$), Scopolamine hydrobromide (5 $\mu g\,kg^{-1}$), physiological saline (placebo). Glucose infusions	8(M)	21–26	Non-asthmatic healthy subjects	ECG, HRV, BP (periodic automated sphygmomanometer), flow spirometry. PK-PD modelling of plasma drug concentrations
Fujii et al.[10]	Investigated autonomic regulation of the heart following exercise	None	Asthmatic: 11 (M), 4 (F) Controls: 5 (M), 2 (F)	6–15 (11)	Asthmatic group free from other significant medical conditions	FEV_1, HR, BP (intermittent cuff), SaO_2
Guhan et al.[102]	Cardiovascular and respiratory response to β_2-agonist	Formoterol (MDI, 24, 48 or 96 μg) and Salmeterol (MDI, 100, 200 or 400 μg)	11 (M), 5 (F)	19–56	Non-asthmatic healthy subjects	ECG, HR, QTc, systolic and diastolic BP (automated sphygmomanometer), venous plasma potassium and glucose concentrations, pulse oximetry
Eryonucu et al.[87]	Cardiovascular response to β_2-agonist	Salbutamol (200 μg inhaled) and Terbutaline (500 μg inhaled)	9 (M), 11 (F)	28–47 (37)	Asthmatic	HR, HRV
Burggraaf et al.[109]	Cardiovascular response to β_2-agonist during hypoxia	Inhaled Salbutamol (800 μg)	8 (M)	21–26	Mild asthma	Forearm blood flow (computerised venous occlusion plethysmography). ECG, QTc, SpO_2, oscillometric mean arterial BP, serum potassium
Penttila et al.[130]	Cardiovascular response to anticholinergic drug	Glycopyrrolate (IV)	8 (M)	19–29	Non-asthmatic healthy subjects	ECG, HR, HRV, respiratory rate
Kuusela et al.[103]	Cardiovascular response to β_2-agonist	Terbutaline	6 (M)	(24)	Non-asthmatic healthy subjects	ECG, continuous BP (Ohmeda), air flow

Abbreviations: ANS, autonomic nervous system; BP, blood pressure; BPV, blood pressure variability; BRS, baroreceptor reflex sensitivity; CNS, central nervous system; cAMP, adenosine 3c,5c-cyclic monophosphate; FEV_1, forced expiratory volume in 1 s; FVC, force vital capacity; HR, heart rate; HRV, heart rate variability; IV, intravenous; MDI, metered dose inhaler; PEFR, peak expiratory flow rate; PK–PD, pharmacokinetic–pharmacodynamic; PNS, peripheral nervous system; QT_c, heart rate-corrected QT interval (period of ventricular depolarisation-repolarisation); SaO_2, arterial oxygen saturation; SpO_2, an estimate of SaO_2 obtained using pulse oximetry.

More recently there has been discussion of the link between exercise-induced bronchoconstriction and NO in patients with asthma. Kanazawa et al.[59] found that episodes of bronchoconstriction in susceptible patients were associated with increased sputum concentrations of NO derivatives, and excess NO production was associated with prolonged airway narrowing. Moreover, inhibition of NO synthesis reduces airway constriction following exercise.[60] These results suggest that NO has an important role in the pathogenesis of exercise-induced asthma.

Interaction between the cardiac and respiratory systems in asthma

Heart rate and its variability. Kallenbach et al.[13] suggested that altered autonomic control of airway calibre in asthma might be reflected by a parallel change in HR. Several authors later reported tendencies towards higher resting HRs in asthmatic subjects compared with non-asthmatic controls.[61,62] Garrard et al.[62] found that resting HR was significantly higher in acute asthmatics compared with both non-asthmatics and asymptomatic asthmatics. The observed increase in HR suggested an increased sympathetic tone and higher levels of circulating catecholamines in the asthmatic individuals.[63] Shah et al.[61] tested sympathetic response by observing the systemic (HR and blood pressure (BP)) responses to a sustained hand grip test and to a change of posture. These authors found that there was a tendency for asthmatic subjects to display an exaggerated fall in systolic BP on standing and an exaggerated rise in diastolic BP in response to a sustained hand grip test.

Tokuyama et al.[64] observed that both asthma and allergy are associated with increased parasympathetic activity and that asthma causes increased total HRV. Later, Shah et al.[61] assessed basal parasympathetic tone via the rise in HR induced by postural change and atropine administration tests. These authors observed a tendency towards a greater HR response to atropine in asthmatic subjects compared with non-asthmatic controls. Although basal parasympathetic (vagal) *tone* was not found to differ significantly between these two groups, cardiac vagal *reactivity* was significantly greater in asthma. In fact the authors associated the severity of asthma with the magnitude of vagal reactivity. This was demonstrated by the significantly greater cardiac responses to deep breathing (RSA), Valsalva manoeuvre and carotid massage in asthmatic subjects compared with controls. Vagal reactivity results were similar when subjects were analysed in atopic asthmatic and non-atopic asthmatic subgroups, but vagal tone was significantly greater in the atopic group.

Circadian patterns of autonomic control. The nocturnal worsening of asthma manifests as a reduction in lung function, an increase in bronchial hyper-reactivity and increased wheezing. These changes have been related to diurnal changes in both hormone concentration and ANS control.[65] Several authors have also documented a circadian pattern in the components of HRV, the LF component having minimal power and the HF component having maximal power during the nocturnal period.[66–68] Morrison et al.[69] investigated the effects of vagal blockade with atropine on both nocturnal peak expiratory flow rate (PEFR) and HR in asthmatic subjects. Atropine administration during the day and night (at 4 am and 4 pm) caused significant bronchodilatation (PEFR increased from 260 to 390 l min^{-1} at 4 am and from 400 to 440 l min^{-1} at 4 pm). There was a significant concomitant increase in HR from 60 to 121 beats min^{-1} at 4 am and from 76 to 122 beats min^{-1} at 4 pm. The authors noted that nocturnal asthma effects were almost totally reversed by atropine, implying that vagal mechanisms are fundamental in its pathophysiology. Morrison and Pearson[70] subsequently demonstrated a circadian variation in vagal activity on bronchomotor tone and HR, with higher vagal activity during the night (4 pm) compared with during the day (4 am). It has since been confirmed that cardiac vagal tone is enhanced at a time corresponding to the usual sleep period, with an acrophase between 4 am and 5 am.[71] This corresponds closely with the documented period of maximal bronchoconstriction in nocturnal asthma, suggesting that there might be a common vagal influence in the bronchial and cardiac systems.

Impact of pharmacological agents on the cardiovascular system in asthma

The aims of pharmacological management are the control of symptoms, prevention of exacerbations and the achievement of best possible pulmonary function with minimal side effects.[3] Short-acting beta-agonists (SABAs) are prescribed at all levels of severity of asthma as well as in high dose inhaled, nebulised and intravenous routes during acute attacks. In chronic management, about 30% of asthmatics are prescribed SABAs alone, as required (Step 1, BTS Guidelines); about 12% of asthmatics are prescribed a long-acting beta-agonist (LABA) as add on therapy when moderate doses of inhaled corticosteroids (200–800 mcg beclomethasone equivalent) do not control their disease (Step 3). A further 6% of asthmatics are prescribed LABAs in conjunction with regular

aminophylline/leukotriene antagonists (Step 4) or in addition to regular oral steroids (Step 5).[3]

Influence of β-adrenoceptor agonists and antagonists in healthy individuals. β-adrenergic stimulation of the human respiratory tract produces several responses of benefit to the asthmatic patient: bronchodilation,[72] increased water and chloride flux (which might reduce the viscosity of tracheobronchial secretions),[73] and impairment of the immunological release of the mediators of allergy.[74] However, several relatively mild adverse effects of β_2-adrenoceptor agonists have also been reported, including tremor, palpitations and headache after taking salbutamol.[75] The main adverse effects of oral and inhaled β_2 agonists relate to their systemic activity following drug absorption into the blood, with subsequent cardiovascular, metabolic and neuronal changes.[76]

Specific potential adverse cardiovascular effects of β_2-adrenoceptor agonists include: circulatory disturbances via (i) hypokalemia (including electrocardiographic anomalies such as a reduction in amplitude of the T-wave); (ii) prolongation of the cardiac depolarisation–repolarisation (QT) interval and sinus tachycardia[77]; (iii) interference with cardiovascular and respiratory autonomic control.[78] The cardiovascular actions of β adrenergic agonists result from (i) direct chronotropic and inotropic myocardial influences, and (ii) indirect rate effects resulting from baroreceptor reflex responses to β_2-mediated dilation of peripheral arterioles.[79–81] The chronotropic and inotropic effects are mediated via both β_1 and β_2 receptors of the heart.[82–84] However, it is more likely that contractile changes are β_1 effects, whilst HR changes can be either β_2 or both β_1- and β_2-mediated.[85] These potential side effects are clinically relevant with many patients unable to tolerate SABAs and especially LABAs because of palpitations (KEL–pers. comm.).

Most investigations using HRV analysis suggest a shift of the ANS's sympathovagal balance towards sympathetic dominance following administration of β_2 agonist medication.[78,86,87] Relative sympathetic hyper-activity in the cardiovascular system is in itself associated with increased mortality and morbidity and with an increased risk of sudden coronary death.[88,89] Consequently it is possible that these drugs might be implicated in the pathogenesis of a number of cardiovascular risk factors, including insulin resistance, hyper-tension and cardiovascular hyper-trophy,[90] and in the evolution of conditions such as coronary artery disease (CAD) and sudden coronary death. Salpeter et al.[91] have performed a meta analysis of studies evaluating the cardiovascular safety of β_2 agonists in patients with obstructive airway disease, concluding that their use increases the risk for adverse cardiovascular events. There is also some evidence that the systemic effects of inhaled β_2 agonists might be greater in healthy individuals compared with asthmatic patients.[92]

It is instructive here to also briefly consider the cardiovascular effects of β-adrenoceptor antagonists, and specifically their possible effects in asthmatic individuals. The majority of studies into the effects on cardiac autonomic control of β-adrenoceptor antagonism in cardiovascular disease states have involved β_1 receptor antagonists. The results of these studies suggest a shift in autonomic balance towards enhanced parasympathetic and reduced sympathetic activity, generally acknowledged to be a 'cardioprotective' effect.[93,94] However, it has been shown that the administration of β-adrenergic receptor antagonists in asthmatics can induce asthmatic attacks[95] and increases the bronchoconstrictive response to histamine and methacholine[96] and clinical guidelines specify that β-adrenergic receptor antagonists are contraindicated in asthma, even in the form of topical eye-drops.[3]

Cardiovascular influence of β-adrenoceptor agonists in asthmatic patients

Garrard et al.[62] noted that HR was significantly higher for acute asthmatics than for either non-asthmatic controls or asymptomatic asthmatics. Several authors have since investigated the influence of β_2-adrenoceptor agonists on HR and HRV parameters in both the time and frequency domains. Each of the main studies has reported an increase in HR in medicated asthmatic subjects compared with non-asthmatic and non-medicated asthmatic controls following administration of these drugs. Mean HR in non-asthmatics is significantly increased following both salbutamol and terbutaline.[87,97,98] Interestingly, the relative increase in HR following salbutamol in asthmatic children is greater in the supine compared with the standing posture.[75] Furthermore, Hanratty et al.[98] found that the time-domain parameters SDANN (an LF analogue), RMSSD and PNN50 (HF analogues) and SDNN (an index of Total HRV) were all significantly reduced in healthy adults following the administration of salbutamol compared with placebo.

Garrard et al.[62] evaluated HR and frequency-domain HRV parameters (LF, HF, LF/HF powers) in asthmatic adults and normal controls. Subjects were classified as either asymptomatic asthmatic or treated asthmatic, the latter receiving a β_2-adrenoceptor

agonist for acute asthma attacks. Control subjects had significantly greater values of normalised LF power than both asthmatic groups, the latter showing no relative difference in this parameter. The control group also displayed significantly higher values for the LF/HF ratio than asymptomatic asthmatics, with no significant differences between the other groups. In contrast, Jartti et al. found that the LF/HF ratio was significantly greater for both medicated asthmatic children[99] and adults[97] compared with controls and non-medicated asthmatics. In addition, Jartti et al.[97] observed an increase in the LF component of adult asthmatics following medication. A later study by Eryonucu et al.[87] investigated the specific effects of salbutamol and terbutaline on HRV in adult asthmatic patients. Changes in frequency-domain HRV parameters were similar following administration of the two drugs and confirmed the data of Jartti et al.[99] in demonstrating a shift to sympathetic dominance: LF and LF/HF ratio were significantly increased after taking each drug. Jartti et al.[75] also reported a significant post-drug increase in the LF/HF ratio in children, but observed a reduction in the LF component in the standing posture. Only Jartti et al. found any significant changes (reductions) in the HF component of HRV after taking β_2 agonist medication in adults[97] and children in the supine posture.[75] Garrard et al.,[62] Jartti et al.[75,97] and Eryonucu et al.[87] all observed significantly diminished total HRV in asthmatics after taking these drugs.

Bremner et al.[100] observed a tendency for both hexoprenaline and salbutamol to increase systolic BP and to reduce diastolic BP. However, Scheinin et al.[101] found no change in BP following salbutamol and fenoterol, whilst Guhan et al.[102] noted a reduction in diastolic BP only following formoterol and salmeterol. In addition to their work on HRV, Jartti et al.[99] also studied BP variability and BRS in asthmatic and non-asthmatic children. Subjects were assessed in both supine and standing postures and during fixed and spontaneous breathing patterns. It was found that HF (BP) was significantly greater for non-medicated asthmatics compared with non-asthmatics during all posture and breathing conditions. The authors noted that this probably indicated a mechanical respiratory (rather than a vagal control) effect since there was no difference in either HF (RR) or BRS between these groups. LF (BP) during supine spontaneous breathing was significantly greater in the medicated asthmatics than in the other groups. The same researchers[75] later found a tendency for a dose-dependant post-drug reduction in BRS for children the standing posture. In a subsequent study, Jartti et al.[97] observed dose-dependant increases in LF (BP) power, LF/HF (BP) ratio, and dose-dependant reductions in BRS following terbutaline administration in healthy adults. The clinical importance of these specific changes is unknown. All variability and BRS changes started to occur only after a threshold terbutaline dose had been reached.

Jartti et al.[78] investigated the influence on cardiovascular autonomic regulation of a single (acute) dose of a short-acting β_2 agonist (salbutamol) in asthmatic children who had taken a long-acting β_2 agonist (salmeterol) twice-daily for the previous 4-week period. In agreement with their previous work, these authors observed a shift to sympathetic dominance in HRV and BPV following regular salmeterol administration. Autonomic function tests performed pre- and 20 min post-administration of the acute salbutamol dose showed that 4 weeks of salmeterol therapy diminished the acute post-salbutamol changes in HR and HRV (shift to sympathetic dominance) but did not affect the bronchial dilation (PEFR) response. This indicated that subjects had developed a slight tolerance to the cardiovascular effects of salmeterol, whilst its therapeutic effect was maintained.

Jartti et al.[97] also examined the dose–response effects of terbutaline on the complexity (approximate entropy (ApEn) and fractal dimension (FD)) of HR (RR interval) and systolic arterial BP (SAP) signals in healthy adults. Dose-dependant reductions were observed in ApEn (RR), ApEn (SAP) and FD (RR); reductions in FD (SAP) were not dose dependant. Subsequently, Kuusela et al.[103] used a variety of non-linear data analysis techniques to assess the effects of terbutaline on SAP and RR signals in healthy adults. High doses of terbutaline drastically reduced cardiac parasympathetic modulation and dampened arterial baroreceptor function. The mutual interaction of the BP and RR systems was also weakened following terbutaline administration, so that BP did not modulate HR (i.e. there was no baroreceptor control) in this condition. In fact it was determined that the complexity (ApEn) of the RR signal was maintained post-terbutaline but the BP signal became less complex. Reduced cross-entropy showed that the pattern architecture of the BP and RR signals became more similar after terbutaline, the suggested explanation for which was that, in this state, respiration (an 'external' factor) modulates both RR and BP signals.

It has been suggested that the positive chronotropic, positive inotropic and systolic hyper-tensive effects of β_2-agonists leads to increased myocardial oxygen consumption,[104] and this might provoke silent myocardial ischaemia or infarction. However, no resultant myocardial ischaemia was observed by Rossinen et al.[105] in their study of the effects of

salbutamol in patients with clinically stable asthma co-existent with CAD. It should be noted that, in disagreement with most other studies, these authors also reported a lack of arrhythmias or changes in HRV parameters for the same group of subjects. Gaspardone et al.[106] noted that intravenous administration of salbutamol to patients with CAD who were taking β-blocker medication diminished the time to onset of ischaemia and reduced maximum exercise duration. Inhaled β_2 agonist (salbutamol) treatment has also been associated with myocardial infarction[107] and the β_2 agonist has occasionally caused myocardial injury when administered by infusion during late pregnancy to prevent preterm labour.[108]

Burggraaf et al.[109] showed that patients with asthma who were hypoxic and inhaled salbutamol at a relatively low dose experienced significant and potentially detrimental cardiovascular effects. In that study salbutamol was administered 30 min into a 1-h period of mask breathing of ambient air or a N_2/O_2 (hypoxic) mixture. Inhalation of salbutamol during hypoxia resulted in a significant increase in HR and peripheral blood flow (inversely proportional to peripheral vascular resistance) at the end of the assessment period, compared with salbutamol inhalation during normoxia. The reported positive chronotropic effect was in agreement with previous reports of the effects of salbutamol during hypoxaemia[110] and during combined hypoxia and hyper-capnia.[111] In three of the 26 subjects observed by Burggraaf et al.[109] a rapid decline in SpO_2 (arterial oxyhemoglobin saturation measured non-invasively by pulse oximetry) occurred following salbutamol inhalation in the hypoxic state. This was interpreted as an indication of pulmonary shunting, the induction of which had previously been associated with β_2 agonists.[112] Burggraaf et al.[109] thereby provided a possible explanation for the association between β_2 agonist use and sudden death in asthma: in the hypoxic state, reduced peripheral resistance might decrease venous return (especially when standing), eliciting the Bezold–Jarisch reflex (hypoxic syncope) with possible subsequent cardiac arrest.[113]

Salbutamol has been associated with hypokalaemia (an abnormally low concentration of potassium ions in the blood) following intravenous, oral and inhaled administration.[79,111,114] Similar changes have been observed after taking fenoterol,[79] formoterol[101] and salmeterol.[101] Furthermore, Jartti et al.[97] suggested that the hypokalaemia observed following terbutaline administration is related to both arrhythmia and decreased HRV. Scheinin et al.[79] reported a reduction in the ECG T-wave amplitude following salbutamol and fenoterol administration in healthy subjects, but observed no change in QRS duration despite an increase in HR after taking these drugs. Bremner et al.[100] found that HR-corrected QT interval (QTc) tended to increase following salbutamol. However, Burggraaf et al.[109] and Crane et al.[77] found that salbutamol had only a minor effect on QTc ($<7\%$ prolongation) and serum potassium level ($<5\%$ decrease) during both normoxia and hypoxia. It is therefore possible that inhaled β_2 agonist overdose might have adverse clinical consequences in asthmatic patients with pre-existing hypokalaemia. The risk of hypokalaemia is higher when asthmatics take other drugs e.g. steroids, thiazide or loop diuretics (for hyper-tension) or if there are high circulating levels of endogenous catecholamines (as might be caused by the stress of a serious asthma attack). Patients with concomitant heart disease or those using drugs such as digitalis (which can sensitise the heart to hypokalaemia) might also be at risk. Clinical guidelines recommend monitoring serum potassium, especially during emergency treatment.[3] Formoterol is a full LABA and has an onset of action within 6 min with sustained action over 12–24 h; it has now been licensed for top-up or as-required inhalations, as part of a flexible dosing regime is asthma. Any cardiovascular side effects may be more problematical with repeated doses and a long drug half-life.

Influence of anticholinergic drugs

Cholinergic receptors in the airways and sinus node are of the muscarinic type and can be blocked by the anticholinergic drugs atropine[115] and glycopyrrolate.[116] Ipratropium bromide is an antimuscarinic that can be used to provide short-term relief (bronchodilation) in chronic asthma (although short-acting β_2 agonists work more quickly). When taken in aerosol form, ipratropium bromide is generally considered to act locally on the airways of the lung without systemic effect[117] and with no significant effect on either cardiac vagal tone or HR.[118] Each of these cholinergic and muscarinic receptor antagonists can substantially inhibit or abolish the hyper-reactive response to inhaled stimulants in asthmatics.[19] Administration of atropine or glycopyrrolate is the method of choice for the assessment of tonic vagal activity.[119,120] Akselrod et al.[121] first demonstrated pharmacological parasympathetic blockade using power spectral analysis of HR data following a single dose of glycopyrrolate in dogs. This dose almost totally abolished the HF peak of HRV, and the effect was later confirmed in adults.[122] Low doses of atropine

can paradoxically have parasympathomimetic effects on the heart, causing a decrease in HR[18,123] and an increase in beat-to-beat HRV.[124] Higher doses of atropine cause an increase in HR and a decrease in HRV.[18,125] The HR reduction at low doses of atropine is believed to be associated with blockade of peripheral muscarinic M_1 receptors at sympathetic ganglia or inhibitory M_1 receptors that modulate acetylcholine release.[126–128] The increased HR at higher doses is likely to be caused by the blocking of pre-synaptic M_2 muscarinic receptors.[25] Parlow et al.[116] have since detailed the time course of parasympathetic blockade following the administration of clinical doses of common anticholinergic drugs, whilst Scheinin et al.[129] have developed a pharmacokinetic pharmacodynamic (PK–PD) model for atropine and glycopyrrolate using radioreceptor array (RRA) and HRV methods.

Scheinin et al.[129] examined the parasympatholytic effects of atropine and glycopyrrolate with regard to HRV in healthy non-asthmatics subjects. These authors observed the following changes (average values) in comparison with placebo (physiological saline): 22% and 18% increases in HR, respectively; 99% and 94% reductions in HF power, respectively; decreased total and LF power of HRV; 11- and 7-fold increases in the LF/HF ratio of HRV; 87% and 73% reductions in the Hayano index. Parlow et al.[116] also compared the effects of atropine and glycopyrrolate on HRV and BP in non-asthmatic individuals. Mean cardiac (RR) interval decreased significantly after both atropine and glycopyrrolate, but systolic BP increased after glycopyrrolate only. Atropine and glycopyrrolate caused similar reductions in baroreceptor sensitivity (BRS), HF power and the HF/total power ratio. The authors noted that atropine caused a significantly greater duration of impaired cardiac parasympathetic control (of several hours duration, measured using BRS and HRV) compared with glycopyrrolate. Penttila et al.[130] later demonstrated that HF power and its time-domain analogues (pNN50 and RMSSD) were almost completely abolished in non-asthmatics following intravenous glycopyrrolate infusion.

Horváth et al.[18] investigated the relationship between bronchial and cardiac vagal tone in non-atopic healthy adults. They examined the correlation between changes in airway resistance and changes in heart period in response to complete pharmacologically induced cholinergic blockade using atropine. The study assumed that the effects of atropine on airway resistance (R_{aw}) and RR interval was entirely due to vagal blockade, thereby allowing an assessment of vagal tone in each system. The authors found that R_{aw} (used as a marker of bronchial vagal activity) and RR interval (used as a marker of cardiac vagal activity) decreased after full doses of atropine. However, there was no correlation between the magnitude of R_{aw} and RR interval, suggesting a lack of association between cardiac and bronchial vagal activity (different central control). Morrison and Pearson[70] found a strong correlation between the initial responses of airway calibre and HR to vagal blockade, although the bronchodilation effect persisted longer than the cardioacceleration. The authors suggested that this might be the result of differing sensitivities of pulmonary and cardiac muscarinic receptors to anticholinergic antagonists. The newer, long-acting anticholinergic—tiotropium bromide is currently not licensed for use in asthma.

Discussion

There is an apparent association between altered autonomic cardiovascular control and asthma. This relationship is twofold: a consequence of both the pathophysiology of asthma per se and the effects of asthma pharmacotherapy. The full extent of these changes, and their implications, have yet to be fully quantified and their clinical significance may have been overlooked. This autonomic and resultant cardiac dysfunction may even contribute t some sudden and often unexpected deaths in patients with asthma.

Altered autonomic balance in the heart is clearly associated with unfavourable prognosis in established cardiovascular disease.[131] Drugs that oppose cardiac sympathetic stimulation (β-adrenoceptor antagonists or 'β-blockers') improve patient survival following myocardial infarction.[132] β_1 receptor blockade in cardiovascular disease has been associated with enhanced parasympathetic activity and reduced sympathetic activity (assessed via HRV), and this is generally accepted to confer a 'cardioprotective effect'.[133] For example, the increased LF/HF ratio in HRV that accompanies passive orthostatic tilt is diminished after β-receptor blockade.[134] Conversely, several authors have described a shift of HRV control towards sympathetic dominance and reduced total HRV following β_2 agonist medication in asthma. A shift towards sympathetic dominance in HRV has been associated with mortality and morbidity, and specifically with hyper-tension[135] and an elevated risk of sudden coronary death.[136,137] It is therefore possible that bronchodilator therapy might be associated with a detrimental change in the balance of

cardiovascular autonomic function. It must be borne in mind, however, that the relative importance of β_1 and β_2 adrenoceptors in the modulation of autonomic control of the heart (HRV) is not known at present,[98] and this is certainly an area worthy of further study. (It should be noted that the administration of some β-adrenergic receptor antagonists to asthmatics can induce asthma attacks.[138])

It would be useful to determine a reliable set of baseline autonomic–cardiovascular indices for the asthmatic condition. The rapid systemic changes observed by Guhan et al.[102] following inhalation of both formoterol and salmeterol suggests that a sizeable amount of drug is absorbed rapidly into the blood. Peak plasma levels of formoterol, for example, apparently occur within five minutes of dose ventilation in normal subjects.[139] Jartti et al.[75] noted that the main effects of salbutamol on cardiovascular regulation had almost disappeared 2 h post-inhalation of the drug, although a significant disturbance of sympathovagal balance could still be identified at this time. Baseline autonomic indices should therefore be defined with regard to specified drug administration regimes. Moreover, a physiological model should be developed that incorporates both acute and chronic dynamic changes in these indices (that is, perturbations owing to the effects of chronobiology, antigen challenge or physical exercise). When addressing these issues, future studies will need to separately assess the pathophysiological and pharmacological contributions to altered physiological function in the asthmatic individual.

The early study of Kaliner et al.[4] demonstrated that both asthmatic and allergic (atopic) individuals are hypo-reactive to β-adrenergic stimuli and hyper-reactive to cholinergic stimuli. In order to determine the origin of these altered sensitivities, investigations should include a comparison of atopic and non-atopic individuals (asthmatics and non-asthmatics). In particular it would be of great clinical value to quantify the autonomic-cardiovascular indices for each of these subject groups.

β agonists are classified by adrenoceptor selectivity, potency and pharmacological efficiency. All currently available synthetic β_2 agonist bronchodilators are 'good' to 'highly selective' agonists at the β_2 receptor (the exception is isoproterenol (isoprenaline) which is approximately equally active on β_1 and β_2 receptors). The majority of these are also 'partial agonists' in that they activate signal transduction at the receptor less efficiently and to a lesser extent than the natural catecholamine adrenaline. (For further details on β adrenoceptor agonist drugs see Lipworth and Grove.[140]) Despite their apparently similar properties, it would be useful to compare the specific autonomic-cardiovascular influences of each of the main bronchodilators and combination therapies. Bennett et al.[141] observed that the majority (of the order two-thirds) of systemic effects of salmeterol inhaled via a metered dose inhaler were the result of drug absorption from the lung, with the remaining one-third from gastrointestinal absorption. Comparison of the relative autonomic-cardiovascular influence of primary routes of absorption for different drugs would be another interesting challenge.

An appropriate standard methodology for the assessment of cardiovascular and respiratory autonomic function now needs to be developed. This is likely to involve the non-invasive, synchronised quantification of HR and BP variabilities, BRS and other beat-to-beat haemodynamic parameters. A patient assessment protocol that involves paced and spontaneous breathing (when clinically stable), standardised static and dynamic exercise, or multiple postural-shift phases, will facilitate provocation of state changes in the autonomic, cardiovascular and haemodynamic systems. This will facilitate computational modelling of both normal cardiovascular–respiratory ANS activity in asthma and it's treatment. The development of advanced power spectral and non-linear analysis techniques, as described by Jartti et al.[97] and Kuusela et al.[103] are likely to be instrumental in this goal.

It is now timely and technologically feasible to elucidate specific ANS changes in asthma and, importantly, to determine the clinical implications of these changes. Autonomic-cardiovascular investigation should be a priority focus in future asthma research.

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