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Reduced lung function is a robust predictor of out-of-hospital sudden cardiac death in middle-aged males <http://ow.ly/A0SjL>

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Autonomic dysregulation: a mechanism of asthma death

To the Editor:

Therapeutic advances in the management of asthma have led to a gradual but sustained reduction in mortality [1, 2]. However, the death of otherwise healthy young individuals remains a tragic and all too frequent occurrence. The unheralded demise of two of our patients with previously minimally troublesome asthma led us to reconsider the mode of death in such patients. Numerous studies and retrospective reports have attributed such mortality to preventable factors such as inadequate severity assessment, discontinuity of medical care, poor concordance to prescribed therapies and poor management of acute asthma exacerbations [3, 4]; others have attributed fatalities to significant behavioural, socioeconomic or psychosocial factors including smoking, denial, depression and alcohol abuse [1, 5, 6].

Whilst these associations are undeniably important they do not adequately explain the observed clinical picture of precipitous deterioration, loss of consciousness, and death. ROBIN *et al.* [7] reported two patients with an abrupt demise, one during a telephone conversation and with no prior asthma-related symptoms. Grubb *et al.* [8] followed a teenage boy with a history of long-standing asthma after repeated near fatal asthma episodes requiring resuscitation. Our similar experience of two unexpected fatalities caused us to

question bronchoconstriction as the primary mode of death. Others have suggested that vasovagally-induced bradycardia results in a potentially lethal syncope in predisposed individuals. We have sought to test this hypothesis in subjects from our asthma clinic who have a history of unconsciousness precipitated by exacerbations using the simulated diving reflex of facial immersion to replicate such events [9].

Participants were recruited through the Academic and Outpatient Respiratory department at Castle Hill Hospital (Cottingham, UK) over a 12-month period. Subjects were excluded if they had significant cardiovascular or neurological comorbidities, a pacemaker, were taking beta-blockers or calcium channel antagonists, or a history of upper airway infection in the past 4 weeks. All participants gave written informed consent and the study was approved by the Hull and East Riding Local Research Ethics committee (LREC 12/YH/0520).

There were three arms to the study: 1) 10 subjects without a history of prior medical problems (control group); 2) 10 subjects with a diagnosis of asthma on treatment step 3 as defined by the British Thoracic Society (BTS) guidelines (asthmatic group) [10]; and 3) five subjects with a prior history of unexplained syncope during an asthma exacerbation on treatment step 3 of the BTS guidelines (syncopal asthmatics). Each participant underwent the same dive reflex protocol outlined below.

Participants were monitored using a Nexfin (Model 1, Bmeye; Amsterdam, the Netherlands) recorder and a 12-lead ECG for a period of 2 min at rest. They were asked to perform a “dive” lasting 30 s. From a sitting position the face was immersed in a bowl of 12°C water, with one preparatory breath and no preceding hyperventilation. In the event that a participant was unable to complete a 30-s dive after three attempts, their longest effort was used for analysis. Recording was continued for 2 min post dive.

The Nexfin derives a beat-to-beat estimation of heart rate, and both systolic and diastolic blood pressures from a finger sensor. These data were transferred in their entirety onto spreadsheets and analysed in 10 s epochs. Mean values for heart rate, systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressures were computed. The 12-lead ECGs were manually measured using CardioSoft (GE Healthcare, Hatfield, UK) software, giving beat-to-beat values for RR and QT. A second value for heart rate was calculated from RR, and QT was corrected using Bazett’s formula to calculate QT interval corrected for heart rate (QT_c). The pulse rate data recorded by the Nexfin were used in the statistical analysis and validated against the CardioSoft heart rate recordings.

From the study by HIEBERT *et al.* [9] we calculated the study sample size to be 25–30 with ten control and asthmatic participants, and 5–10 asthmatics with a history of unexplained collapse. One-way ANOVA would have 80% power to detect at the 0.05 level an effect size of 0.36 (nQuery Advisor, Statistical Solutions Ltd, Cork, Ireland). It was estimated that there would be two dropouts in each group. Change in heart rate induced by the dive was the primary outcome for our study. Data is reported as the mean \pm SD difference from pre-dive baseline in all parameters assessed. Area under the curve (AUC) analysis of the dive was conducted using the trapezoidal rule. Comparison at peak response (+10 s) was by two-tailed t-test and ANOVA (one-way) performed for the overall cohort during the dive. Significance was assumed at the 5% level and all analyses were performed with the SPSS for windows version 18.0 (SPSS Inc., Chicago, IL, USA).

25 subjects fulfilled the inclusion criteria and simulated dive protocol; 10 controls, 10 asthmatics and five syncopal asthmatics. It should be noted that, despite scrutiny of the inclusion/exclusion criteria, one of the subjects recruited into the syncopal asthmatic group was subsequently found to have Holmes–Adie syndrome and was excluded from the analyses.

There were consistent and reproducible responses to the dive protocol in all three groups. Significant differences in change in heart rate between the syncopal asthmatic and control groups were noted in both the AUC over the 30-s period of water immersion ($p=0.04$) and the peak tachycardia and immediate bradycardia induced by immersion ($p=0.03$). No significant difference was observed between the responses of the two asthmatic groups (fig. 1a). Similar statistical differences were noted in the QT_c; however, no subject exhibited a pathological prolongation (fig. 1b).

All groups showed the typical change in blood pressure in response to a dive and there were no significant differences noted between any of the groups. There were no adverse events reported in the study.

The use of high-dose or potent β_2 -agonists, inappropriate patient management, and significant behavioural, socioeconomic or psychosocial factors have been implicated in unexpected asthma deaths by various groups [1, 4–6]. To invoke “lifestyle” as an explanation does not aid in our understanding of the pathophysiology of these events. Necroptic studies and case series’ have identified that sudden demise of asthmatics is not always related to the severity of asthma or to having the typical pathophysiological changes seen in prolonged status asthmaticus [7, 8, 11, 12]. This raises doubt over the suggestion that severe bronchospasm

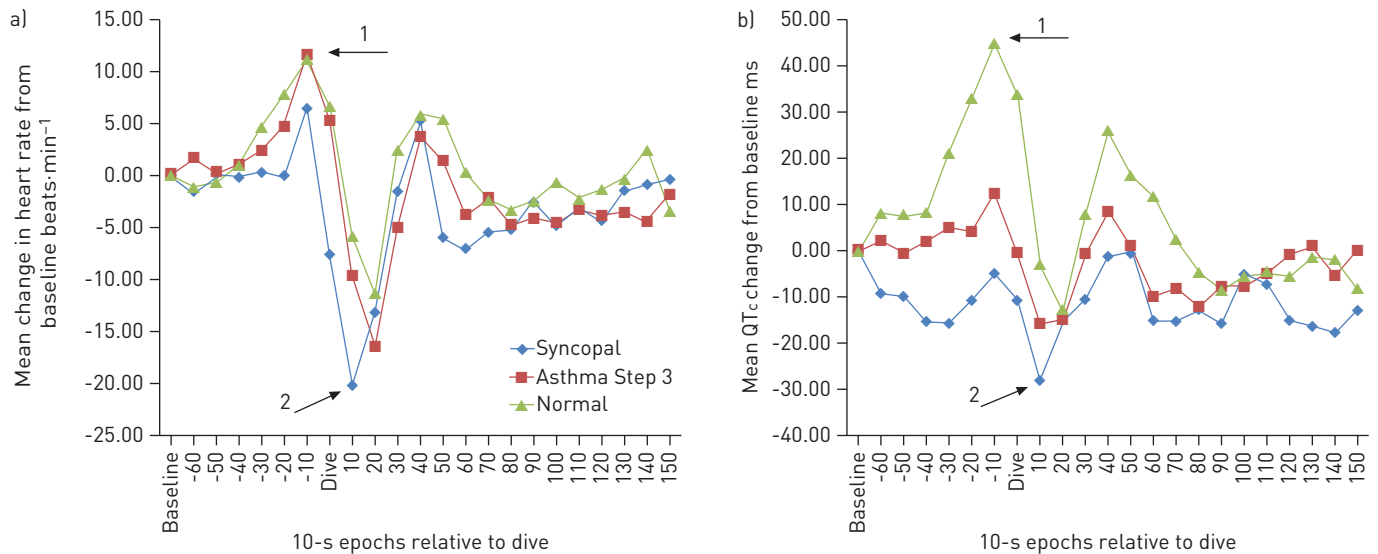


FIGURE 1 a) Mean change in heart rate from baseline throughout the dive protocol. Each point represents mean group value over a 10-s period. The arrows highlight time-points where 1) there is a variation in pre-immersion tachycardia (dive -10 s) and 2) immediate post-immersion bradycardia (dive +10 s) between the subjects. b) Mean change in QT interval corrected for heart rate (QTc) from baseline throughout the dive protocol. Each point represents mean group value over a 10-s period. The arrows highlight time points where 1) there is a variation in pre-immersion QTc (dive -10 s) and 2) immediate post-immersion QTc (dive +10 s) between the syncopal asthma subjects and normal subjects.

is the sole mechanism of these fatalities. It is possible that sudden death in asthma may be a manifestation of cardiovascular rather than respiratory pathophysiology.

In our study we have attempted to test the hypothesis that bradycardia may be a relevant autonomic dysregulatory mechanism to describe collapse or fatalities some patients with asthma. Clearly, such a hypothesis is impossible to test in the *post mortem* situation and we have used as a surrogate patients under our care who have a history of syncope during acute episodes. To our knowledge this subset of patients has not previously been studied, possibly because unconsciousness may simply be assumed to be due to asphyxia. Alternatively cough syncope may be invoked. Cough syncope has been described for over a century. The traditional mechanism, loss of consciousness due to an increase in intrathoracic and/or cerebrospinal fluid pressure, is now regarded as inadequate [13]. A neural-mediated reflex, distinct from carotid sinus syndrome or vasovagal syncope, resulting in a vasodepressor-bradycardia and ensuing syncope has been implicated [14]. The findings of our study suggest that a similar syndrome may occur in asthma.

The major observation of our study, that asthmatics with a preceding history of syncope, have a blunted tachycardia on initiation of a dive and that this relative bradycardia continues throughout the 30-s stimulation of the diving reflex suggests autonomic dysregulation either through increased vagal tone or a failure of sympathetic drive. This was a preliminary examination and not designed to definitively test the mechanisms underlying any observed change. More invasive and detailed studies will be required to determine pathophysiological mechanisms. Interestingly, we did observe that there was no change QTc prolongation, which is thought to be protective of arrhythmias during bradycardia. However, other diving reflex assessments have reported no alteration in the QTc on cold water facial immersions [15]. Thus, although the autonomic system has a clear influence on QT interval, it remains unclear as to whether the sympathetic or parasympathetic autonomic activity induced by the diving reflex exerts its own effects on QT interval in addition to heart rate [16].

Tests of autonomic function are notoriously difficult to evaluate. Although a number of methods exist to assess autonomic function [17], in our study we used the validated, reliable and practical test of the dynamic cardiovascular response to an abrupt stimulus, the diving reflex. Its limitations include: 1) the involvement of multiple receptors and afferent pathways during these manoeuvres; and 2) that repeated manoeuvres may result in habituation or short-term training and hence may result in a more profound bradycardia [18, 19].

There are a number of limitations in our study. Recruitment was slower than expected in both asthmatic groups because of a perception that facial immersion could lead to worsening of asthma symptoms. All the subjects were aware of the study hypothesis and we cannot exclude some functional or autonomic influence on the results seen. That the observations in both the control asthmatics and healthy volunteers had similar trends in the parameters assessed makes this less likely. The major criticism of this study is the small number

of subjects and while we have shown statistical (and we believe clinically) significant effects studies with larger numbers of subjects would be needed to confirm and extend these observations.

In this study we report the first experimental data showing that in patients with a history of asthma and collapse there may be an inherent autonomic dysregulation. Although our numbers of subjects were small and larger evaluations are needed, it may be postulated that neutrally-induced cardiovascular dysfunction may result in some of these tragic and precipitate events.



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Initial data show in patients with a history of asthma and collapse there may be an inherent autonomic dysregulation <http://ow.ly/zj3JW>

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