Shortness of breath, prescription of bronchodilators and the risk of myocardial infarction
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Symptoms, then are in reality nothing but the cry from suffering organs.

Jean Martin Charcot

Among the most common symptoms reported by patients and encountered by physicians, and indeed all other healthcare professionals, are those related to disturbances of breathing. As the practising physician knows well, patients report such symptoms in a myriad of ways: ‘difficulty in breathing’, ‘shortness of breath’, ‘wheeze’, ‘tight chest’, and many others, which we can describe collectively as dyspnoea. As would be expected, the origin of these symptoms commonly lies in respiratory, or alternatively cardiac, pathology. However, delineating the precise cause of an individual patient’s dyspnoea, and making a diagnosis, is often challenging. The diagnostic process is aided by the physician taking, and having sufficient time and resources to take, a detailed history. In the primary care setting in particular, this is seldom straightforward; for instance, in the UK, the time available for a consultation in primary care is less than 10 min.

Physicians quite reasonably consider as part of the diagnostic process the therapeutic response to prescription of an individual therapy. For the patient presenting with dyspnoea, the initial ‘working’ diagnosis is often asthma, and the therapeutic trial is in the form of inhaled therapy. In the UK, and in many other countries, such therapy is initially with inhaled short acting (SABA), and later with long-acting, β2-adrenoreceptor agonists (LABA). The β2-adrenoreceptor plays important, and to a large extent opposite, roles in modulation of respiratory and cardiovascular function: receptor stimulation in the lung mediates bronchodilatation, and is the target of therapy in asthma. In comparison, in cardiac tissue, the β-adrenoreceptor mediates increased heart rate, leading to increased myocardial oxygen demand and a greater propensity to ischaemia.

Thus, in patients with ischaemic heart disease, β-adrenoreceptor stimulation is theoretically, and often clinically, undesirable; indeed β-adrenoreceptor blockade is one of the mainstays of pharmacological therapy in this setting [1]. It is also recognised that, in patients with ischaemic heart disease, acute withdrawal of β-blockade may lead to rebound exacerbation of symptomatic myocardial ischaemia, indicating that rapid changes in receptor/ligand interaction may in some circumstances be detrimental. On this background, a number of observational studies have suggested an association between the initiation of inhaled β2-agonist therapy with increased heart rate [2], and potentially more importantly, with increased risk of acute myocardial infarction (AMI) [3,4]. In contrast, inhaled corticosteroids (ICS), via a (theoretical) favourable influence on coronary plaque stability and other mechanisms, have been associated with reduced risk of ischaemic myocardial events [5,6]. As noted above, assertions to date regarding associations between initiation of asthma therapy and increased/decreased risk of AMI have been considered on the basis of observational studies, which have important inherent weaknesses. Most important among these is confounding by indication, an even more relevant issue in asthma where the severity of the conditions determines drug exposure.

In the current issue of the journal, Zhang et al. [7] describe the association between prescription of asthma medications and the occurrence of acute myocardial infarction, in a large, representative, UK population of over 500 000 patients and 5.5 million inhaled SABA, 4.0 million inhaled ICS and 1.3 million LABA prescriptions. This study considers not only the nature and strength of the relationship between risk of AMI and prescription of asthma medication, but also the temporal pattern of such interactions. In contrast to standard statistical approaches, which utilise regression analysis, Zhang et al. [7] have utilized sophisticated pattern analysis. This considers temporal patterns in hazard rates of AMI associated with prescription of asthma therapy; should initiation of inhaled β-agonist be associated with increased AMI risk, and inhaled ICS associated with reduced AMI risk, patterns of relative risk will differ initially and later converge. Should there be no difference between alternative therapies, temporal patterns of hazard rates for these treatments will be similar.

The study by Zhang et al. [7] has a number of important observations. Firstly, patterns of risks of MI were similar between inhaled SABA, LABA and ICS. Secondly, for each of these therapies, hazard rates for AMI were increased
soon after the initiation of treatment, and reduced thereafter. Thirdly, hazard rates were also increased in heavy, long-term users (≥13 prescriptions of the same asthma therapy in the year prior). Fourthly, in patients prescribed asthma medication, the risk of AMI was powerfully associated with the Framingham MI risk score.

What do these observations tell us? Firstly, in terms of risk of AMI, there are no major differences among inhaled SABA, LABA and ICS. The observations suggest that, if these agents have any effect, the influence on risk is similar for ICS compared with β-agonists; mechanistically, this seems unlikely. Secondly, for patients receiving a first-ever prescription of SABA, rates are low with respect to the subsequent prescription of asthma medication; less than 50% of the patients who recently started treatment received a prescription for any other asthma medication in the subsequent 6 months. Although there are several possible reasons for this pattern, one likely explanation is that these patients did not show a therapeutic response to SABA, leading to a review of the diagnosis of asthma. If we consider this together with the pattern of AMI risk, which, for all asthma medications, was increased in the first few months after the initiation of therapy, it seems likely that the initial presentation with symptoms suggesting asthma (dyspnoea presumably) was, in a large proportion of cases, the presentation of ischaemic heart disease.

In the words of Charcot, ‘Symptoms, then are in reality nothing but the cry from suffering organs’. The art of medicine lies in defining which organ is in distress. From my personal experience in secondary care, a significant proportion of patients admitted to coronary care with AMI have recently been prescribed inhaled asthma therapy, for various symptoms which can be described broadly as ‘dyspnoea’; very few are proven to have asthma. The study by Zhang et al. [7] suggests, without showing directly, that, in many primary care patients presenting with dyspnoea, ischaemic heart disease is likely to be the culprit and that the well established Framingham risk score can identify these patients in routine practice. Adult-onset asthma is relatively rare with a suggested incidence of two cases per 1000 person-years. UK guidelines [8] indicate associated features (e.g. family history, symptoms in response to exercise, allergen exposure, and cold air), which make a diagnosis of asthma more likely in adults.

Zhang et al. [7] are to be congratulated for taking a novel, and informative approach to what has been perceived as a possible concern regarding the initiation of asthma therapy in adults. The results should serve as a timely reminder of the utility of considering reasonable differential diagnoses in patients presenting with nonspecific symptoms, and of the art history-taking in the practise of medicine.

References