

# Spirometric findings as predictors of survival

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The basic part of any pulmonary assessment is simple spirometry comprising the measurement of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV<sub>1</sub>). Historically these measurements represent refinements made by Tiffeneau in 1947 of the original concept of vital capacity (VC), introduced by John Hutchinson >100 years earlier.<sup>1</sup> Impressively, Hutchinson not only invented this measurement and described its dependence on age, height and weight, but he also performed the first epidemiological study of >2000 individuals and observed a strong relationship between the measured value and survival. Thus, the actual reason for calling the amount of exhaled air from the fully inflated lungs the 'vital capacity' was the observation made by its inventor indicating that this measurement was strongly related to survival.<sup>1</sup>

Later on, during the first half of the 20th century, although some investigators from time to time reported the usefulness of VC for prediction of health-related outcomes, it seems that the predictive power of VC was to a large degree forgotten.<sup>2</sup> Ironically, in the mid-1970s a series of scientific papers initiated a renewed interest in these measurements in the general population. These studies did not come from respiratory physicians but from cardiologists, and were based on The Framingham Study, the first major cardiovascular epidemiological study.<sup>3,4</sup> The measurement of slow VC was actually included in the Framingham examination panel already in 1956—that is, 8 years after the beginning of the first investigation, whereas spirometry with registration of FEV<sub>1</sub> and FVC was first measured in 1971. Thus, the Framingham investigators rediscovered the astonishing power of lung function measurements, in particular FVC, as predictors of both survival and manifestations of ischaemic heart disease.<sup>3,4</sup> Fortunately, this observation resulted in the inclusion of spirometry in many other large cardiovascular studies all over the world—a situation which has

certainly been very beneficial for subsequent research in the respiratory area as well.

After the first report from the Framingham Study and similar early papers, the interest in the usefulness of spirometry in epidemiology gained momentum and, during the last three decades, >100 publications addressed different aspects of spirometric measurements as predictors of subsequent morbidity and mortality, in the general population, in occupational cohorts and in groups of patients with various pulmonary diseases. In general, both FEV<sub>1</sub> and FVC have been related to mortality from all causes as well as specific causes such as chronic obstructive pulmonary disease (COPD), heart disease, lung cancer, respiratory failure, and non-fatal events including, among others, myocardial infarction, congestive heart failure, atrial fibrillation, diabetes, stroke, pneumonia, osteoporosis and even facial wrinkling. This impressive power of spirometry as a predictor of future health has led to many hypotheses regarding the mechanisms responsible. As always, the explanations were influenced by current ideas and trends in ongoing research. In the late 1970s, at the peak of the smoking epidemic in Western countries, Cohen suggested that impaired pulmonary function should be regarded as a common denominator for the multiple effects of smoking.<sup>5</sup> Although this need not be incorrect in smokers, studies of never-smokers have shown that smoking is not a necessary link between impaired lung function and poor survival.<sup>6</sup>

In a search for further mechanisms, a concept of 'vitality' or general strength, undoubtedly inspired by the nomenclature introduced by Hutchinson, has been introduced as a possible explanation.<sup>7</sup> This concept is actually in line with the findings that individuals who cannot perform satisfactory spirometry due to either physical or mental weakness have a poorer survival in comparison with those who can.<sup>8</sup>

Today, in the era of biomarkers and interest in low-grade systemic inflammation, a suggested notion is that impaired

lung function (a result of pulmonary inflammation), by leading to systemic inflammation, promotes non-pulmonary diseases, such as, for example, ischaemic heart disease.<sup>9</sup> This brings COPD into focus and, after the introduction of widely accepted COPD guidelines, there has been a trend towards including COPD stages (eg, GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages) instead of crude or height- and age-adjusted spirometric values into the regression models focusing on subsequent health events. In a setting of a general population, this approach means that in addition to individuals with COPD and those with normal lung function, there is also a substantial group of individuals with reduced FEV<sub>1</sub> and FVC but no signs of airways obstruction. Among others, Mannino and co-workers have shown that this group with a restrictive spirometric pattern also have a poorer survival than those with normal spirometry.<sup>10</sup> Yet, perhaps because of inclusion of COPD stages in the survival analyses of many of the most recent studies, there has been a misunderstanding that it is the airways obstruction per se (ie, the FEV<sub>1</sub>/FVC ratio) that is the most important predictor of survival.

In this issue of *Thorax* (see page 49), Burney and Hooper, using data from a US cardiovascular study of a general population sample, once again explore the relationship between spirometry and mortality.<sup>11</sup> This time the particular focus is on which index (FEV<sub>1</sub>, FVC or FEV<sub>1</sub>/FVC) is most important.<sup>11</sup> Their main message is that it is not the presence of obstruction as such but rather the value of FVC (and also of FEV<sub>1</sub>) that is most important. Their findings are important but should only be extrapolated with great care to the general population, since Burney and Hooper excluded individuals with respiratory symptoms and diseases (presumably excluding quite a few individuals with airways obstruction). These observations unite the findings in different subgroups of individuals including those with normal lung function and those with both obstructive and restrictive patterns. The present observations are also in keeping with the fact that it is beneficial to improve FEV<sub>1</sub> by means of bronchodilation even though this may worsen the level of obstruction as assessed by the FEV<sub>1</sub>/FVC ratio and also with the fact that different prognostic indices such as BODE and ADO include FEV<sub>1</sub> and not the FEV<sub>1</sub>/FVC ratio.<sup>12,13</sup> Thus, Burney and Hooper conclude that size matters more

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than obstruction and, therefore, in search of an explanation, the authors focus on factors affecting lung size. Here they suggest the 'Barker hypothesis' of poor fetal growth as a possible common causal factor responsible for small lungs, cardiovascular disease, diabetes and other chronic conditions.<sup>14</sup> Although this theory cannot be proved in an isolated study of an adult population, their suggestions are in line with studies showing strong 'tracking' characteristics of lung function.<sup>15</sup> However, other explanations are also possible, such as sharing of common genes affecting handling of oxidative stress or genes responsible for detoxification or tissue repair mechanisms.

Poor fetal growth was undoubtedly present at the time of Hutchinson, although the spectrum of pulmonary diseases at that time differed greatly from what we see today in Western countries. While tuberculosis and other lung infections were the main pulmonary killers at that time, diseases such as COPD and lung cancer were rare. Yet, it is amazing that the predictive power of a simple measurement of expired air is still as strong today as it was >150 years ago. Unfortunately, as described by Petty in his brilliant editorial on Hutchinson and his mysterious machine, the spirometer never reached a similar popularity to the sphygmomanometer, which was invented ~50 years later.<sup>16</sup> This is probably the main reason why the patients of today seldom spontaneously ask their doctors

for a measurement of lung capacity, whereas they often wish to have their blood pressure measured. This leads to the typical situation, whereby many patients have their first spirometry performed 10–20 years too late, and also results in the frustrating observation that in many of them, more than half of their lung capacity has already been lost! The fact that we today, >150 years after the invention of the spirometer, still have problems explaining why VC is so vital for future health should, however, not discourage us—studies such as that of Burney and Hooper underline that spirometry should be a part of every standard medical assessment just like the measurement of blood pressure.

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# Echocardiography, troponins and lower extremity ultrasound: the 'Three Musketeers' lead the prognosis of acute pulmonary embolism

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The European guidelines<sup>1</sup> and American guidelines<sup>2</sup> highlight that, in the diagnosis

and management of acute pulmonary embolism (PE), the functional consequences determined by right ventricular (RV) dysfunction and elevation of cardiac biomarkers are more relevant for risk stratification than assessment of the anatomical burden and distribution of the pulmonary artery thrombus. The

mortality rate associated with massive PE may reach 30%, while that associated with so-called submassive PE (defined as the presence of RV dysfunction without systemic hypotension) is between 5% and 10% and that associated with non-massive PE is <5%.<sup>1</sup> While there is consensus that thrombolytic therapy, catheter embolectomy or surgery are indicated in patients with right heart failure and haemodynamic instability, the appropriate treatment of patients with submassive PE remains controversial. In this subset of patients, the 'tricks of the trade'<sup>3</sup> should be identified and clinical-laboratory aspects evaluated to judge the level of severity. RV echocardiographic parameters, cardiac troponins and peripheral ultrasound data are described as poor prognostic factors in the currently available literature.

Each of these tests has its own advantages and limitations. A number of studies have shown that RV dysfunction and

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