EDITORIAL

Diagnosing pulmonary hypertension: is there a revival of the electrocardiogram?

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Even in the most recent and largest series of patients with pulmonary arterial hypertension (PAH), the time interval between the onset of symptoms and eventual diagnosis was a mean of 27 months [1]. This represents an absolutely unacceptable delay, which is tragically even longer than the mean of 2 yrs in the first series of the US National Institutes of Health (NIH) registry about 20 yrs ago [2]. Nowadays, three-quarters of patients are in World Health Organization (WHO) functional classes III or IV, have a 6-min walk distance of ~330 m and a pulmonary vascular resistance of almost $1,000 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ at the time of diagnosis [1]. The mean pulmonary artery pressure ($\bar{P}_{\text{pa}}$) of patients included in large randomised studies remains at values $>50 \text{ mmHg}$, with 60 mmHg in the epoprostenol trial in 1996 [3] and 52 mmHg in the Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY) study in 2008 [4]. Remarkably, the latter intended to include only patients in WHO class II, which implies that even patients with a clinically early form of the disease in fact suffer from an advanced stage of PAH, comparable to those in WHO functional class III–IV. Hence, despite advances in therapeutic options, there is no faint hope of improvement in diagnosing PAH during the past decades. Not unexpectedly, the overall 3-yr survival is still only ~60% [5, 6], a modest 20% better than our ancestors' empirical observations.

Our poor diagnostic performance with respect to the two forms of pre-capillary pulmonary hypertension (PH), *i.e.* PAH and chronic thromboembolic PH, is even more surprising if one considers the obviousness of the clinical presentation. Although PH symptoms are nonspecific, there are hardly any differential diagnoses for the classical triad of 1) dyspnoea or fatigue on exertion, 2) normal lung parenchyma on chest radiography and 3) normal spirometry results. While anaemia and hyperthyroidism can easily be detected by the general practitioner, subclinical left heart disorders will most probably be diagnosed by right heart catheterisation (RHC), and in the presence of the above mentioned triad in patients with arterial hypertension, obesity and depression, a thorough work-up for PH is mandatory anyway.

Hence, our diagnostic incompetence is almost unforgivable. One has to state that there is not only a diagnostic triad but also

a “fatal triad” regarding the early detection of precapillary PH, namely 1) the low specificity of symptoms, 2) the inconspicuous clinical signs and 3) the lack of the physician's awareness. Moreover, the discrepancy between the patients' apparent good health when at rest and the striking discomfort evoked by even mild exertion adds to the fatal triad. Consequently, on the one hand, PH patients are “discriminated against” by the paucity of symptoms in early stage of the disease and, on the other hand, when their physical limitations become apparent, they are also discriminated against from a functional and social point of view.

In this context, the study by BONDERMAN *et al.* [7], in the current issue of the *European Respiratory Journal*, is to be complimented for the authors' tremendous efforts to develop a standard noninvasive diagnostic procedure to correctly identify or exclude pre-capillary PH. They derived a diagnostic classification and regression tree (CART) from a multitude of non-invasive clinical variables. By using their algorithm, that first rules in patients with evidence of right ventricular strain (RVS) on ECG and, secondly, ruling out those with an N-terminal prohormone of brain natriuretic peptide level $\leq 80 \text{ pg}\cdot\text{mL}^{-1}$, they were able to increase the diagnostic specificity of echocardiography with respect to pre-capillary PH by 19.3% and, hence, potentially obviate the need for RHC in 9% of patients. However, aside from the fact that the number of “unnecessary” RHCs is very low and avoiding these few investigations may be helpful only in a very high-volume centre, it has to be emphasised that RHC still remains the crucial diagnostic tool in the evaluation of patients with suspected pre-capillary, as well as post-capillary, PH.

Notwithstanding, the current extensive analysis of a multitude of clinical features in a large cohort of patients with PH has, in my opinion, resulted in a very interesting and important clinical observation: namely, the fact that the ECG finding of a RVS might be a noninvasive clinical tool with a high diagnostic accuracy with respect to pre-capillary PH. So far, the ECG has been discriminated against in its role for the diagnosis of PH. In this context, most authoritative reviews cite the figures published by AHEARN *et al.* [8], who described a sensitivity and specificity of just 55% and 70%, respectively. However, AHEARN *et al.* [8] refer to the presence of right ventricular hypertrophy (RVH) defined by the criteria originally defined by SOKOLOV and LYON [9], which mainly rely on a dominant R-wave of definite voltage in V1. However, it is well known that these criteria may grossly underestimate the frequency of RVH. PADMAVATI and RAIZADA [10], for example, found a

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sensitivity of only 19% using the criteria of SOKOLOW and LYON [9], but a value of 60% if they applied the more liberal definition of PHILLIPS and BURCH [11], who included additional associated features.

Interestingly, in the very first consecutive series of idiopathic PAH (IPAH) patients, FUSTER *et al.* [12] already observed ECG abnormalities, including RVH, right axis deviation or P-pulmonale, in 95% of their patients. In the NIH cohort, the ECG signs of RVH were present in 87% of patients [2]. Admittedly, if compared to the more recent series, these two studies included somewhat more serious cases, as reflected by a $\bar{P}_{pa}$ of 64 and 60 mmHg, respectively. However, there are also later series that found a very high overall sensitivity of the ECG with respect to PH. In the study of BOSSONE *et al.* [13], only six (9%) out of 64 consecutive patients had a normal ECG if interpreted by a cardiologist who was aware of the patients' basic clinic data. This is in contrast to a computer program and a blinded cardiologist, resulting in sensitivities of only ~50%, but most commonly because of a misdiagnosis of an "anterolateral ischaemia". Hence, returning to the study of BONDERMAN *et al.* [7], we should emphasise their reasonably high sensitivity of 77% suspecting pre-capillary PH by ECG. The crucial point of the matter is that the authors used the "RVS pattern", and not only RVH, as their parameter to rule in patients into the pre-capillary PH group.

To date, most of us have taught their fellows and students the importance of the stringent ECG criteria for RVH in a suspected PH patient. Simultaneously, however, most of us had the feeling (or even the knowledge) that there is more hidden wisdom within the ECGs of our PH patients. It is neither a clear-cut RVH, nor a clear-cut right bundle branch block, but rather some kind of nonspecific anterolateral conduction disturbances with corresponding repolarisation abnormalities. With their findings of RVS being the best discriminatory parameter for the selection of patients with precapillary PH, in my opinion, BONDERMAN *et al.* [7] have inadvertently boosted the value of the ECG as an important clinical tool for improving the pre-test probability of pre-capillary PH before RHC. Their findings are consistent with a comprehensive ECG study on 86 patients with IPAH in whom the prevalence of RVS was 95% [14]. Nevertheless, as stated in the most recent international guidelines [15], at present, the ECG cannot be recommended as a screening tool for PH until further studies are available.

But what about specificity? With regard to the normal population, antero-septal repolarisation abnormalities are uncommon. In the largest series, including more than 120,000 ECGs of healthy subjects, only 4.7% showed any abnormality and as few as 0.2% exhibited features of RVS [16]. Of course, the main differential diagnosis of RVS is coronary artery disease. However, as underscored by BOSSONE *et al.* [13], these cases can be sorted out easily using their clinical presentation and the ECG itself. In coronary heart disease, the "strain" pattern is often located at the lateral or inferior leads and, if present in V1–V3, almost always accompanied by a Q wave [17–19]. In addition, there is only very rarely a right axis deviation [20].

In conclusion, though its main finding of a slightly increased specificity by the CART algorithm seems to be of generally

limited benefit for the management of patients with suspected PH, the nicely conducted and laborious study of BONDERMAN *et al.* [7] has shown that, if interpreted on the basis of data available from the literature, the RVS pattern may add substantially to the suspicion of pre-capillary PH in patients with otherwise unexplained fatigue and dyspnoea on exertion. Thus, their study might lead to a revival of an old and discredited tool: the ECG. One just needs to know which parameter to look for.

STATEMENT OF INTEREST

None declared.

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