Syncope in acute pulmonary embolism

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In his pioneering work, published in 1880 and devoted to pulmonary embolism (PE), Beniamino Luzzatto[1] wrote about syncope: "The most important initial nervous manifestation is undoubtedly the loss of consciousness, which is far from uncommon ...".

However, even though loss of consciousness is still considered one of the possible presentations of PE, recent contributions usually deal with it as an anecdote, and its epidemiological, pathogenetic and prognostic aspects are seldom extensively discussed. Koutkia and Wachtel's definition of "forgotten sign" of life-threatening PE is therefore appropriate[2].

Epidemiological data are far from being univocal. This is not surprising since PE is not a single morbid entity, but rather a complication of various illnesses and its clinical manifestations are not always those classically described (i.e. acute cor pulmonale, pulmonary infarction, sudden and unexplained dyspnea).

In 1957, Israel and Goldstein[3] recorded syncope in only 2.2% of PE cases, whereas 20 years later Thames et al.[4], among 132 cases of angiographically documented PE, found syncope to be the initial or chief complaint in 13% of patients. In PE patients without underlying cardiorespiratory pathology, Stein et al.[5] observed syncope in 9% of cases. This figure is almost identical to that reported later by the same group in a prospective study in which PE with syncope and PE with shock were unified[6]. In a multicenter survey including nearly 400 patients carried out in France, Ferrari et al.[7] found a 14% prevalence of syncope. This figure is identical to that reported in the ICOPER registry[8] grouping over 2000 individuals with PE. The incidence of syncope was remarkably higher (35%) in the German registry MAPPET where 1001 patients with major PE have been enrolled[9]. In a series of 160 patients with acute cor pulmonale – 22% of whom with overt heart disease – Casazza et al.[10] identified 44% of subjects with "vigilance disorders", including both fainting and true syncope (defined as a transient, self-limited loss of consciousness, usually leading to loss of postural tone)[11,12]. Sometimes the clinical history does not enable us to distinguish true syncopal cases form other states of altered consciousness (i.e. dizziness, vertigo, seizure, etc.) and it may be reasonable to doubt whether all syncopal cases in the setting of PE are actually genuine.

The differential diagnosis between syncope caused by PE and that due to other pathological conditions (e.g. stroke, transient ischemic attack, postural syncope) may be difficult, particularly in individuals > 70 years, not only because of the frequent coexistence of peripheral venous disease and cerebrovascular disease, but also on account of the prevalence of orthostatic hypotension in the later decades of life[2,12-14].

Natangelo et al.[15] considered the problem from a different viewpoint. During an average follow-up of 20 months, they evaluated 152 patients admitted for a transient loss of consciousness, and found that only one case could be attributed to PE. In a recent prospective study, Sarasin et al.[12] recorded an 8.1% prevalence of PE among 650 syncopal patients admitted to an emergency department. The incidence of unexplained syncopal events ranged from 14% in a prospective study[12] to 36.6 and 39% respectively in two retrospective studies[13,14].

A detailed description of the pathogenetic mechanisms of syncope due to acute, massive PE is beyond the scope of this review. We shall merely mention three

of them, i.e. hemodynamic, metabolic and reflex mechanisms. Hemodynamic disorders including acute right ventricular failure, a drop in stroke volume and cardiac output, systemic hypotension, myocardial ischemia and a reduced cerebral perfusion are sometimes secondary to tachy- or bradyarrhythmias, but are more often themselves responsible for cardiac arrhythmias. As for systemic hypotension, only 13% of PE patients with syncope enrolled in the ICOPER registry were hypotensive[8]. Often underestimated are the metabolic mechanisms, such as hypocapnia caused by hyperventilation and hypoxemia due to several factors (ventilation/perfusion mismatch, intrapulmonary or intracardiac shunts, impaired alveolar-capillary diffusion, mixed venous blood desaturation).

A vasovagal mechanism has been postulated by Simpson et al.[16] and by Akinboboye et al.[17]. The former described two fatal cases of recurrent PE in which syncope was associated with severe bradycardia, high degree atrioventricular block and junctional escape rhythm. The latter observed a similar case, showing a transient second degree atrioventricular block, attributed by the authors to a "near syncope"[17]. It should be stressed, however, that more than a single mechanism may be operating in the individual case.

As for the course and prognosis of syncopal patients with acute PE, the aforementioned Luzzatto[1] stated that "... in about a quarter of cases the patient dies almost immediately: in such cases thromboemboli may be found at the level of the pulmonary artery trunk or in a large number of peripheral branches. Usually, however, loss of consciousness starts the attack, but is short-lasting; and even when the patient dies quickly, he recovers consciousness spontaneously before it happens ...".

The ICOPER registry[8] showed that the 3-month mortality of syncopal patients with PE was 26.8%, the overall mortality being 17%. Thames et al.[4] found significant differences in terms of hemodynamic changes and pulmonary angiographic obstructions between PE with and without syncope. Similarly, Stein et al.[5] observed syncope in 4% of submassive and in 13% of massive PE ($p < 0.01$) classified on the basis of Walsh's angiographic score. Incidentally, according to Thames et al.[4] pulmonary infarction is uncommon in patients with PE who had a syncopal event, but much more common in PE patients with syncope.

Underestimating or misinterpreting a PE-induced syncope can lead to a misdiagnosis and to inappropriate treatment. Even in this field malpractice leads with an ever increasing frequency to medico-legal implications and subsequent judicial proceedings.

In a recent editorial Maisel and Stevenson[18] rightly state: "Syncope is a common and challenging problem. It occurs in the old and in the young; it can be infrequent and recurrent, and it may have a benign or fatal prognosis". Wolfe and Allen's warning should be carefully considered as well: "... the following findings in combination with a history of syncope should lead to further investigation of PE as a possible cause: hypotension, tachycardia, transient bradydysrhythmia, dyspnea, chest pain, evidence of acute cor pulmonale (suggested by distended neck veins, a loud second heart sound, S3 gallop, S1Q3T3 or incomplete right bundle branch block) or risk factors for venous thromboembolism"[19]. A prompt diagnostic approach is therefore recommended even in syncopal patients who rapidly recover and are in apparently stable hemodynamic conditions. Since the outcome of these patients is often unfavorable, an aggressive treatment is required, as suggested – for instance – by the ANMCO-SIC Working Group on Pulmonary Embolism[20].

In conclusion, the prevalence of syncope in PE patients ranges from 2.2 to 40% (average 15%) in the various patient populations, being higher in cases of massive PE. The clinical presentation is similar to the usual pattern of acute cor pulmonale: as a matter of fact, single anecdotal cases are described by a few authors[12,19]. Syncope most likely represents an intermediate condition between hypotension and cardiac arrest, as the failure to regain consciousness results in cardiac arrest, and those who recover consciousness have a high incidence of hypotension[4]. The prognosis is conditioned by the underlying pathology, the patient's age and the possibility of prompt and adequate treatment aiming to prevent a fatal recurrence.

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