Is Syncope Always a Predictor of Unfavorable Outcome?

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The history of syncope is as long as human history. The classical Hebrew literature describes the first meeting of Queen Esther with King Ahasuerous: Esther fainted when the king stood up [1]. Many Medieval and Renaissance painters adopted this event in their masterpieces. The first discussion of syncope belongs to Hippocrates in the 4th century BC [2]. The Greeks also contributed by naming the fainting spell syncope (in Greek syncoptein means cessation or pause) [3]. During the period 1719–1827 several authors described the cardiac cause of syncope and the condition was named Stokes-Adams disease [4]. This disease is mainly related to bradyarrhythmic syncope, but occasionally also to tachyarrhythmic syncope. Although the condition was well known for thousands of years, the scientific workup of syncope began about 100 years ago with the first scientific publications on this subject [5]. A vast number of publications have accumulated since then, yet even today the unknown outweighs the known.

Hippocrates was the first to link recurrent syncope with sudden cardiac death ( Aphorism, Chapter II, paragraph 41) [2]. During the last 50 years it has become evident that syncope is an unfavorable prognostic indicator for patients with structural heart disease and, more specifically, in patients with impaired ventricular function. Before the wide clinical implication of implantable defibrillators, Middlekauff and colleagues [6] demonstrated that syncope, regardless of the underlying cause, is strongly associated with sudden cardiac death in patients with advanced heart failure. Soteriades et al. [7] studied the incidence and prognosis of syncope among participants of the Framingham Heart Study. They showed that cardiac syncope predicts increased total mortality from any cause and cardiovascular events.

Cardiac syncope can be caused by arrhythmia or obstruction. Attempts to prevent death with medication were inferior compared to defibrillator implantation. For this reason defibrillator implantation has become routine procedure for both secondary and primary prevention of death in patients at high risk. How is the outcome of patients with syncope affected by this procedure?

In the SCD-HeFT study, 162 patients had syncope before randomization, 256 after randomization, and 46 before and after randomization [8]. The presumptive cause for all cases with syncope was both cardiac and non-cardiac. Only QRS duration and absence of beta-blocker treatment predicted syncope post-randomization. Syncope before the randomization was not associated with death. Syncope after the randomization was associated with increased risk. Patients with syncope had a higher risk of all-cause mortality and a greater risk of cardiac death but not sudden cardiac death. As patients with syncope used the defibrillator to terminate ventricular arrhythmia more frequently, syncope may suggest that these patients had a more advanced cardiac condition, and if so a higher rate of mortality may be expected [8].

The effect of syncope in patients with reduced heart function was the subject also of another large study. The MADIT-RIT study evaluated conventional defibrillator therapy with delayed therapy and with therapy only at a high cutoff rate [9]. The cumulative probability for the first occurrence of syncope was similar in the three treatment groups. However, all-cause syncope, arrhythmogenic syncope and non-arrhythmogenic syncope were associated with increased risk of death, regardless of the treatment group.

In this issue of IMAJ, Goldenberg and co-authors [10] evaluated the outcome of patients with syncope before implantation of a defibrillator for primary prevention. Patients with syncope had non-ischemic cardiomyopathy more frequently, a higher ejection fraction, more renal failure and less atrial fibrillation compared to patients without a history of prior syncope. Moreover, patients with syncope were more frequently treated with class I anti-arrhythmic drugs. Finally, these patients had a higher rate of ventricular arrhythmia occurrence but there was no difference in mortality, neither cardiovascular nor total death. The difference between this study’s population and the population of the other large studies is the unusual association of higher ejection fraction and less atrial fibrillation compared to the control group. The less advanced cardiac condition (ejection fraction and atrial fibrillation) counterbalanced the effect of syncope on survival. This study suggests that although syncope predicts higher mortality in patients with reduced left ventricular (LV) function, the degree of LV function preservation is also important and may counterbalance the unfavorable effect of syncope.

In conclusion, syncope is only one of the predictors for increased mortality in patients with reduced LV function, and it affects the survival in concert with other predictors. The final outcome of these patients is determined by the relative effect of all the predictors.
The epigenetics of exhaustion

During cancer or chronic infection, T cells become dysfunctional, eventually acquiring an “exhausted” phenotype. Immunotherapies aim to reverse this state. Using a mouse model of chronic infection, two studies now show that the epigenetic profile of exhausted T cells differs substantially from those of effector and memory T cells, suggesting that exhausted T cells are a distinct lineage. Sen and group (Science 2016; 354:1104) defined specific functional modules of enhancers that are also conserved in exhausted human T cells. Pauken et al. (Science 2016; 354:1165) examined the epigenetic profile of exhausted T cells after immunotherapy. Although there was transcriptional rewiring, the cells never acquired a memory T cell phenotype. Thus, epigenetic regulation may limit the success of immunotherapies.

Eitan Israeli

Gene signatures associated with adaptive humoral immunity following seasonal influenza A/H1N1 vaccination

Aiming to identify gene expression markers shared between both influenza hemagglutination inhibition (HAI) and virus-neutralization antibody (VNA) responses, Ovsyannikova et al. enrolled 158 older subjects who received the 2010–2011 trivalent inactivated influenza vaccine. Influenza-specific HAI and VNA titers and mRNA sequencing were performed using blood samples obtained on days 0, 3 and 28 post-vaccination. For antibody response at day 28 versus day 0, several gene sets were identified as significant in predictive models for HAI (n=7) and VNA (n=35) responses. Five gene sets (comprising the genes MAZ, TTF, GSTM, RABGGTA, SMS, CA, IFNG and DOPEY) were in common for both HAI and VNA. For response at day 28 versus day 3, many gene sets were identified in predictive models for HAI (n=13) and VNA (n=41). Ten gene sets (comprising biologically related genes, such as MAN1B1, POLL, CEBPG, FOXP3, IL12A, TLR3, TLR7 and others) were shared between HAI and VNA. These identified gene sets demonstrated a high degree of network interactions and likelihood for functional relationships. Influenza-specific HAI and VNA responses demonstrated a remarkable degree of similarity. Although unique gene set signatures were identified for each humoral outcome, several gene sets were determined to be in common with both HAI and VNA response to influenza vaccine.

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“"The wisest man is he who does not fancy that he is so at all"”

Nicolas Boileau-Despraux (1636-1711), French poet and critic

“One of the oldest human needs is having someone to wonder where you are when you don't come home at night”

Margaret Mead (1901-1978), American cultural anthropologist and often controversial academic who popularized the insights of anthropology in modern American and Western culture. Her reports detailing the attitudes towards sex in South Pacific and Southeast Asian traditional cultures influenced the 1960s sexual revolution. She was a proponent of broadening sexual mores within a context of traditional Western religious life.