EDITORIAL COMMENT

Explaining the Unexplained Causes of Syncope
Are We There Yet?* 

Niraj Mehta, MD, Maria Zildany Pinheiro Tavora, MD, Carlos A. Morillo, MD

Hamilton, Ontario, Canada

When you have eliminated the impossible, whatever remains, however improbable, must be the truth.
—Sherlock Holmes, The Sign of Four (1)

Determining the cause of recurrent unexplained syncope remains a clinical challenge and a permanent quest. Guidelines and multiple studies emphasize that a clear deductive method based on a thorough interrogation and examination can usually disclose the etiology of syncope in the majority of cases (2). Nonetheless, in daily clinical practice, applying a simple comprehensive diagnostic approach to the patient that manifests with syncope remains an unmet goal. From a practical perspective, the main goals when evaluating the patient with recurrent syncope are simple: 1) establish a diagnosis and prognosis; and 2) implement therapy. As simple as this may sound, the reality is that in clinical practice, the strategy for evaluation of the patient with recurrent syncope is inconsistent and usually leads to multiple, low-yield, costly, and unnecessary testing and unwarranted hospital admissions (2).

See page 167

It is of critical importance to initially determine whether the transient loss of consciousness is actually due to syncope and not other causes (i.e., seizures, functional, or other rare causes). By and large, syncope is the most common cause of transient loss of consciousness. Once it has been established that the patient has true syncope, it is useful to further classify the etiology of syncope into 4 categories: 1) reflex neurally mediated; 2) cardiac causes; 3) orthostatic hypotension; and 4) unexplained (2). In the last category are those patients who underwent extensive investigations (including electrophysiological studies and neurological work-up) without revealing the cause of syncope (2). In patients with electrocardiographic (ECG) abnormalities (bundle branch block, fascicular block, prolonged PR interval), particularly those over the age of 65 years, bradycardia is the most plausible cause of unexplained syncope, as several studies using the implantable loop recorder (ILR) have revealed (3). The patient with recurrent unexplained syncope with a pristine ECG, little or no evidence of structural heart disease, and a clinical presentation that is not in keeping with neurally mediated reflex syncope remains part of a challenging group. In this subgroup of patients, the diagnostic strategy usually calls for the early use of the ILR (2).

The ILR, initially developed by the group at the University of Western Ontario in 1992, has provided important insight into the mechanisms of unexplained syncope (4). Similarly, the ISSUE (International Study of Syncope of Uncertain Etiology) studies have provided unique insights into the mechanisms of neurally mediated reflex responses and paroxysmal atrioventricular (AV) block (3,5). In brief, of patients with syncope and no structural heart disease with either a positive or negative tilt test, 34% had recurrent syncope, with the most frequent finding being 1 or more prolonged asystolic pauses, mainly due to sinus arrest (46% of the isolated syncope group and 62% of the tilt-positive patients). Conversely, in patients with bundle branch block and syncope, 42% had recurrence, related almost invariably with AV block (5).

In this issue of the Journal, Brignole et al. (6) further expand our knowledge of unraveling the mysteries of unexplained syncope. In a series of 18 patients (mean age 55 ± 19 years) from 4 centers in Europe who presented with a long-standing history of recurrent unexplained syncope (8 ± 7 years) and an otherwise normal heart, the authors report that idiopathic paroxysmal AV block is the most likely guilty suspect. The patients studied had the following characteristics: 1) normal ECG; 2) absence of structural heart disease; and 3) ECG documentation of paroxysmal third-degree AV block. Prolonged ECG (primarily ILR) documented the presence of third-degree AV block of abrupt onset in all patients. The known mechanisms related with paroxysmal AV block are, namely, intrinsic disease of the AV node conduction system or a neurally mediated vagal reflex response. As discussed by the authors, the former is unlikely as the reported patients did not have evidence of structural heart disease or conduction disorders, as supported by an unremarkable electrophysiological evaluation in the vast majority of these cases. The possibility of a neurally mediated vagal reflex paroxysmal AV block usually requires the presence of sinus arrest or sinus bradycardia preceding the syncopal episodes. Detailed ECG
analysis documented that there was no evidence of a significant P-P cycle or PR-interval prolongations preceding the AV block, probably ruling out a vagally mediated effect. If neither of the described mechanisms was responsible for this paroxysmal AV block, are we then witnessing the discovery of a new cause of unexplained syncope? Holmsian deduction would suggest that, in fact, “When you have eliminated the impossible, whatever remains, however improbable, must be the truth.” So, are we in the midst of the description of a new clinical entity, namely, “idiopathic paroxysmal AV block?” Let us explore with further detail who are these patients reported herein. Are there any clinical features in common that would guide us as clinicians to suspect this new clinical entity as a cause of recurrent unexplained syncope? The population included in this report is heterogeneous with a large age range (13 to 85 years), 5 patients had 3 or fewer syncopal episodes in their lifetime, and most (15 of 18) had no prodromes or clear autonomic triggers at the time of the syncopal episodes. There was no evidence of any ECG abnormalities or structural heart disease. The electrophysiological study was normal in 12 of 15 patients who had the test performed, and tilt-table testing was abnormal in 8 of 17 (47%). Almost one-half of the patients who had a tilt test had a neurally mediated reflex response triggered. It is well known that the specificity and sensitivity to detect both sinus node and AV node conduction disturbances by electrophysiological study is limited even in the presence of documented paroxysmal AV block (7). Additionally, the tilt test also has limited specificity, and the provocation of a neurally mediated reflex does not fully prove or disprove the cause of syncope. So, we are left with no clinical clues that would lead the astute clinician to deduct or suspect the diagnosis of idiopathic paroxysmal AV block.

As should be expected by a deductive group, Brignole et al. (6) had an ace up their sleeves. It is unclear whether the investigators consciously or serendipitously drew adenosine plasmatic levels in these patients. Notwithstanding, the observation of consistently and significantly reduced levels of adenosine is the only common thread in this population of patients and may provide some hypothetic insight into the mechanism of this disorder. Furthermore, the administration of adenosine in a bolus injection disclosed significant abnormalities in 16 of 18 (88%) patients, primarily due to AV block with long pauses ranging between 3.3 and 25 s. The authors are not very enthusiastic about this finding and rightly suggest that further studies are needed to determine the role of plasmatic adenosine and the adenosine test to aid in the diagnosis of idiopathic paroxysmal AV block. In light of the current recommendations from the European Society of Cardiology syncope guidelines regarding the adenosine test (Class III), it may well be that this entity may resurrect this simple but difficult to interpret diagnostic test (2). Speculation that chronic low adenosine plasma levels, may lead to up-regulation of high-affinity adenosine A1 receptors and thereby lead to a hypersensitive AV node response to adenosine is attractive but awaits further proof. These observations pose the question of whether this entity is part of the spectrum of neurally mediated reflex responses modulated by chronic purinergic receptor down-regulation cannot be fully eliminated; however, using the Holmesian deductive methodology, this appears rather improbable.

As initially discussed, the main goals of the assessment of the patient with recurrent unexplained syncope are to establish a diagnosis and prognosis, and implement therapy. In this particular case, the only obvious method of establishing the diagnosis is the direct correlation of paroxysmal AV block with syncope. This objective is clearly achieved by prolonged ECG monitoring, preferably by means of an ILR. Therefore, it is clear and supported by evidence that the early use of prolonged ECG monitoring in patients with the characteristics described by Brignole et al. (6) may be the best diagnostic strategy. The role of adenosine plasmatic levels and the potential that the adenosine test may in fact be useful in this population is an attractive possibility, but remains to be explored in future cases of idiopathic paroxysmal AV block. The prognosis of this entity appears to be quite benign as none of these patients had complete AV block during the relatively prolonged follow-up period (mean 4 years). This benign course raises the question whether some of these patients had some unusual form of reflex-mediated paroxysmal AV block, particularly in the 4 patients <45 years of age.

Finally, the ultimate goal of describing a new clinical entity is to provide a treatment that reduces or eliminates the symptoms. In the series reported by Brignole et al. (6), 17 of 18 patients received a dual-chamber pacemaker, with complete resolution of symptoms in all patients and no recurrence of syncope or presyncope. Is a permanent dual-chamber pacemaker then, the treatment of choice for this new entity? Analyzing in detail, the population reported that 8 of 17 patients paced had a burden of syncope of 4 or fewer syncopal episodes in their lifetime. Furthermore, 4 of these patients had only 2, and some had a single episode of syncope during their lifetime. Of note, a 13-year-old patient with a single episode of syncope and a pause of 3.5 s was committed to permanent pacing. The only patient who declined pacing therapy was, interestingly, the patient with the highest burden of syncope (very frequent) and a pause of 4.5 s, remaining completely asymptomatic during 1.7 years of follow-up. The authors provide no information on the potential complications of pacing (i.e., lead dislodgement, infection, and so forth), pacing programmability, and percent time of pacing. It is interesting that all patients became completely asymptomatic after pacing, particularly for paroxysmal AV block that was not preceded by bradycardia but instead was of abrupt onset. In this setting, one would expect that in some instances, depending on the lower rate programmed, some of these patients may have aborted syncope but still have some episodes of presyncope. On that basis, it is possible that permanent pacing is the therapy of choice, but further studies are certainly needed to prove their efficacy in patients with idiopathic paroxysmal AV block.
As expected, the description of a new clinical entity awakens mixed responses that vary from immediate adoption to overt skepticism. Many questions arise from descriptions of new clinical entities; how frequent is this entity, how do we identify these patients, and how do we treat them? Brignole et al. (6) should be congratulated for describing this new entity in detail, and they raise important issues that should alert clinicians to think of the diagnostic possibility of idiopathic paroxysmal AV block in patients with recurrent unexplained syncope, with no evidence of structural heart disease, and a normal ECG. Early adoption of a prolonged ECG strategy, possibly with an ILR, is recommended, and the role of adenosine levels and the role of the adenosine test as a diagnostic tool in this population remain to be determined. Permanent pacemaker therapy may be the treatment of choice, but certainly more studies need to be performed to establish the true efficacy of this therapy given the benign prognosis from the patients described by Brignole et al. (6). In true Holmesian deductive reasoning, it appears “elementary” that we are presented with new evidence for idiopathic paroxysmal AV block as a potential cause of unexplained syncope, thereby unraveling another mystery in the syncope saga.

Reprint requests and correspondence: Dr. Carlos A. Morillo, Arrhythmia and Pacing Service, David Braley CVSRI, PHRI Room 3C-120, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: morillo@hhsc.ca.

REFERENCES

Key Words: adenosine • atrioventricular block • ECG monitoring • electrocardiography • syncope.