Different electrocardiographic manifestations of the cardioinhibitory vasovagal reflex

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This editorial refers to ‘Electrocardiographic characteristics of atrioventricular block induced by tilt testing’ by Dorota Zyśko et al., on page 225

Syncope is a transient symptom. Typically patients affected by vasovagal syncope (VVS) are asymptomatic at the time of evaluation, and the opportunity to capture a spontaneous event is rare. The increasing use, during the last two decades, of tilt testing and prolonged electrocardiographic (ECG) monitoring in the clinical practice, especially implantable loop recorder (ILR), has made easier the ECG documentation of an attack, thus increasing our knowledge on the mechanism of the cardioinhibitory vasovagal reflex.

Very little has been reported in the literature on the ECG characteristics of vagally induced atrioventricular (AV) block. Atrioventricular block during tilt testing is a rare finding. The majority of previous reports described only few cases.1–4 Zyśko et al.5 report a systematic evaluation in a consecutive series of 31 patients who had an AV block induced during tilt testing. Since a positive hypotension/bradycardia response during tilt testing is considered highly specific of VVS, the authors correctly argue that a comprehensive description of the different patterns of reflex AV block could help to distinguish reflex from intrinsic cardiac AV block due to a degenerative disease of the conduction system. Nevertheless, arrhythmias induced in laboratory remain somewhat artificial and how these correlate with the spontaneous event remains uncertain. Some recent evidences show a weak correlation with the ECG characteristic of the spontaneous VVS documented by ILR.6,7 However, also this latter method has pitfalls. Indeed, while with ILR the true ECG pattern responsible for syncope is obtained, its nature cannot be proven with certainty because the present technology does not allow the simultaneous recording of blood pressure and other signals, and the aetiology of VVS still remains uncertain. The results of the study of Zyśko et al.5 are helpful for a better understanding of the mechanism of spontaneous syncope.

Table 1 shows comparative results of the findings observed during tilt testing in the study of Zyśko et al.5 and during spontaneous syncope diagnosed as likely neurally mediated and documented by ILR in the ISSUE 2 study.7 The spontaneous cardioinhibitory reflex was twice as frequent as that of the induced one. Lone sinus arrest was about four times more frequent than AV block + sinus bradycardia/arrest in both situations. Lone AV block was present only during spontaneous events. How to interpret these findings?

Established patterns of reflex atrioventricular block

Also thanks to the study of Zyśko et al.5 we can definitely conclude that a reflex AV block has two major characteristics:

(i) to be associated with sinus rhythm slowing before and during AV block;
(ii) to have a very heterogeneous presentation characterized by:
(a) Mobitz I second-degree AV block; or (b) 2:1 AV block;
or (c) Mobitz II second-degree AV block; or (d) advanced AV block (or third-degree AV block); or (e) the frequent association of two or more of the above features.

In these circumstances, the diagnosis of reflex AV block can be considered certain.

Atrioventricular block during tilt testing is a rare finding. It was found in 5.2% of positive responses in the study of Zyśko et al.5 and in 5% of the study of Brignole et al.4 Sinus dysfunction is four-fold more frequent and was found in 23.3 and 23%, respectively, in the above studies. There are two possible explanations. The first is that sinoatrial node is more sensitive than AV node to extrinsic vagal output. The second is that vagal stimulation on sinoatrial node masks the effect on the AV node, i.e. the sinus arrest does not allow to recognize AV conduction disturbances because of the lack of any atrial electrical activity.

Pattern under investigation

Lone AV block, i.e. without any sinus slowing, was never observed in the study of Zyśko et al.,5 whereas it was documented in 15% of
spontaneous syncopal episodes in the ISSUE 2 study,\(^7\) the so-called ‘type 1C’ pattern. In this latter study, the diagnosis of neurally mediated syncope was considered likely based on clinical presentation and the absence of structural heart disease, and AV conduction abnormalities.

Since it was not observed during tilt testing, the diagnosis of reflex AV block should be ruled-out. However, even if very rarely, this pattern was also observed during tilt-induced VVS by others. Sra \textit{et al.}\(^6\) reported the case of two young female patients (18 and 16 years old) with recurrent syncpe suspected to be of vasovagal origin and documentation of sinus tachycardia along with high-grade AV block at the time of one episode of spontaneous syncope; the same pattern could be reproduced during tilt testing. Paravolidakis \textit{et al.}\(^8\) observed a 42-year-old man who had had five syncopal episodes during the previous month. During tilt testing, initially there was an acceleration of the heart rate; thereafter, when syncope occurred, the ventricular response was attributed to an increased susceptibility of the AV node to adenosine. In fact, an adenosine-mediated mechanism has been held responsible for some clinical cases of AV block, which was resistant to atropine, but reversed by theophylline, an adenosine antagonist. Donateo \textit{et al.}\(^12\) described three middle aged women with adenosine sensitive AV block (AV block without sinus slowing induced by a bolus of 20 mg adenosine intravenous) who had the same pattern documented by ILR during a spontaneous syncopal episode (\textit{Figure 1}). Atrioventricular block with normal sinus rhythm was also observed by Deharo \textit{et al.}\(^6\) in a 69-year-old woman with a clinical history of VVS who experienced a third-degree AV block documented 7 months after ILR implant. She had positive responses to both tilt testing and adenosine test and negative response to electrophysiological study. Finally, one of the patients of the above-mentioned study of Mendoza \textit{et al.}\(^10\) had an AV block induced by either adenosine and by tilt testing. Although the specificity of adenosine test is low, the authors\(^6,12\) speculated on some pathophysiological relationship between endogenous adenosine release and AV block. Adenosine test is frequently positive in patients with tilt-positive VVS; a clinical overlap exists too. Adenosine is released from myocardial cells under physiological and pathological conditions (for example, in the case of myocardial oxygen supply–demand imbalance) and have similar effects. Although the receptors are different, the cardiac actions of adenosine are remarkably similar to those of the neurotransmitter acetylcholine. Both acetylcholine and adenosine produce the same effects and share similar receptor–effector coupling systems. Moreover, a major role of acetylcholine and adenosine, in addition to their direct effect, is to function in parallel to oppose the cardiac stimulatory action of the

\begin{table}
\centering
\caption{Different electrocardiographic manifestation of the cardioinhibitory reflex during tilt-induced and spontaneous (implantable loop recorder documented) vasovagal syncope}
\begin{tabular}{|l|c|c|c|}
\hline
ECG pattern & Tilt testing & Spontaneous (ILR documented) & \(\chi^2\) value \\
& (% of positive responses) & (% of total diagnosis) & \\
\hline
Total CI reflex & 28.5 & 53.8 & 0.001 \\
Sinus arrest alone & 23.3 & 30.2 & 0.3 \\
AV block + sinus bradycardia/ arrest & 5.2 & 8.5 & 0.5 \\
AV block alone & 0 & 15 & 0.001 \\
Non-CI reflex & 71.5 & 46.2 & 0.001 \\
\hline
\end{tabular}
\end{table}

\textbf{Figure 1} Implantable loop recorder documentation of a spontaneous syncope in a patient with positive adenosine test. The onset of atrioventricular block is sudden, with a long ventricular asystole of 7 s. The sinus rate increases during the spontaneous event. The increase in sinus rate during the episode argues against the presence of a vagal reflex. The noise recorded probably reflects jerking movements of the patient during syncope. In this patient, the bolus of adenosine caused an abrupt third-degree atrioventricular block with long ventricular asystoles of 5.2, 6.0, and 4.5 s. The sinus rate also increases during adenosine-induced block.
sympathetic neurotransmitters, norepinephrine and epinephrine, on adenilcyclase. Thus, adrenergic, cholinergic, and purinergic outflows are integrated at the level of the receptor–effector coupling system, and the final cardiac effect results from the sum of these excitatory and inhibitory effects. In a study, endogenous adenosine plasma levels were higher in patients with a positive tilt test than those with a negative test and they increased during tilt-induced syncope. These observations suggest that adenosine release may be involved in the triggering mechanism of syncope induced during tilt testing. Thus, PAVNB without sinus slowing could be a form of extrinsic (functional block), different from the typical vasovagal patterns. The possible mediator could be the adenosine system.

In conclusion, some hypothesis can be generated, but at present the meaning of AV block in patients without structural heart disease and negative electrophysiological study remains unknown.

Conflict of interest: none declared.

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