Introduction

Syncope is a clinical condition characterized with transient loss of consciousness due to cerebral hypoperfusion\(^1\). In the younger population, the vast majority of cases are associated with vasovagal syncope (VVS). Although there are still some debates about pathophysiological background of VVS, reflex mechanism consisting of sympathetic nervous system inhibition and subsequent excessive parasympathetic activity seems to be the most plausible mechanism\(^2\).

Demonstration of an increase on sinus rate or atrioventricular conduction properties following various radiofrequency ablation procedures has led to the introduction of several new ideas such that attenuation of parasympathetic innervation might be achieved by endocardial radiofrequency catheter ablation and be used in the treatment of conditions associated with parasympathetic hyperactivity\(^3-4\). The technique is simply named as cardioneuroablation (CNA).

Although effectiveness of the technique was well documented in patients with cardioinhibitory type VVS, there is no clear clinical data about the patients with ongoing syncope after CNA. We aimed to define our approach in a patient with ongoing syncope complaints after CNA.

Case Report

A 30-year-old male had been suffering from recurrent episodes of syncope. On his medical recording, 25 months ago, he was admitted to our center with similar complaints despite of treatment with midodorine hydrochloride (5 mg/day). He had 6 syncope episodes which occurred with upright posture and prodromal symptoms in preceding 6 months accompanied by type 2B response according to the New Vasovagal Syncope International Study (VASIS) classification on Head-up tilt table test (HUT) [Figure 1]\(^5\). The frequency of the syncopal spells was twice a week, but intensity and frequency of episodes considerably increased recently. The patient was offered pacemaker implant in another institution, however, was reluctant to accept and asked for a second opinion at our center. Before performing ablation, conventional treatment modalities consisting of optimal fluid intake and counter-pressure maneuvers were attempted. Within the scope of our previous study, the patient underwent CNA to attenuate the cardio-inhibitory component of VVS 24 months ago [Figure 2]\(^6\). During the procedure, the three-dimensional geometry of both atria was created by using the electro-anatomical mapping system (EnSite Velocity, St Jude Medical, Sylmar, CA, USA). As defined by Pachon et al\(^7\), the compact and the fibrillar atrial myocardium were detected. The potentials showing complex fractionated pattern with ≥ 4 deflections at filter settings of 300-500 Hz were considered as fibrillar atrial myocardium and tagged. Continuous high frequency stimulation (HFS) was then delivered to the presumed ganglionated plexi sites with a frequency of 20 Hz, amplitude of 0.1-1mA, and pulse duration of 1-10 ms for 5 seconds per each site. Subsequently, HFS was started by applying progressive voltage increases until a parasympathetic response was induced. The sites showing a parasympathetic response were assigned as ablation target. RF energy was delivered with power of up to 35 W and a maximum temperature of 43°C with a cooling rate of 18 mL/min until elimination (<0.1 mV) of targeted electrograms and positive parasympathetic responses. As a routine protocol of our previous study, to check the real denervation achievement, atropine response, sinoatrial and atrioventricular nodes functions were evaluated before and after the procedure.

Through out 15 months following the procedure, he had been attending our outpatient clinic, he had no attacks of syncope without any medications. Ten months ago, the patient was admitted again to our center after two syncope episodes within 1 month. After resting
Hemodynamic parameters during head-up tilt table test were obtained before cardioneuroablation procedure.

Heart rate decreased with 6 seconds asystole in the passive phase and the patient lost consciousness transiently (red rectangle, cardioinhibitory type). Although there was a slight decrease in blood pressure, it did not fall below the baseline values. The test was performed under midodrine treatment. BP, blood pressure; CI, cardiac index (The CI was computed as stroke volume divided by body surface area); TPRI, total peripheral resistance index (The TPRI was calculated as mean blood pressure divided by CI).

in a supine position for 20 minutes, the patient was tilted at an angle of 70 degrees for 40 minutes. Neither syncope nor hypotension was induced. A sublingual glyceryl trinitrate was applied with the tilt table at 70 degrees, his systolic blood pressure dropped from 100 to 30 mmHg without bradycardia or asystole [Figure 3]. Within a few seconds, overt syncope occurred and the tilt table was immediately returned to a horizontal position.

Given the vasodepressor response during HUT, we speculated that the episodes were partially due to vasodilatation and that CNA was not strong enough to prevent his syncope. Therefore, we attempted administration midodrine hydrochloride. The tilt table test was performed again with the patient taking midodrine hydrochloride 5 mg/day and syncope was not induced even by the administration of sublingual nitroglycerin [Figure 4]. He was discharged with this medication. At the end of 9 months follow-up period, he has had no attacks of syncope.

Discussion

We have described a case of resolution of recurrent syncope after sequential interventional and medical treatments for VVS. Pathophysiological nature of VVS was detected by well interpreted HUTs. The present case demonstrated that the major component of syncope or the response to HUT might change according to applied treatments. A similar phenomenon may be one of the reasons of ongoing syncope episodes despite normal functioning pacemaker. Thus, we considered that a well interpreted HUT may provide valuable clinical information in following patients who undergo CNA and change our approach.

Previous reports demonstrated that CNA might be an alternative to permanent pacemaker in well selected patients with VVS⁸. Although short-term results after CNA are promising, ratio of positive response may be up to 23% of patients at post-procedural HUTs⁹. Since the type of positive response is not clearly indicated in the studies, there is no clinical data on what to do next. As it demonstrated in the present case, syncope or prodromal symptoms may recur after CNA with a different mechanism. To explain the different types of VVS, different degrees of activation or depression of the autonomous nervous system are be used: (1) cardioinhibitory VVS is associated with an activation of the parasympathetic nervous system which provokes bradycardia; (2) vasodepressor VVS primarily originates from the acute loss of sympathetic stimulation which causes a drop of blood pressure; (3) Nevertheless in most cases a combined mechanism is seen and called as mixed VVS. In the present case, pre-procedural HUT demonstrated a decline in blood pressure was accompanied by a fall in heart rate would suggest a mixed type VVS. Despite this suggestion, the nature of the spontaneous syncope could not be fully explained. It is well known that a HUT solely based diagnose might be deceivable. For evaluation of the syncope mechanism, Holter or Loop recordings could add valuable clinical
In our case, the passive phase of HUT lasted longer than 30 minutes. Protocols with shorter passive phases, followed by sensitization with nitrate or isoproterenol, are linked with greater specificity than protocols with a more prolonged passive phase. That may be why vasodepressor syncope in our case was not observed in some mixed cases. Although our study excluded patients with vasodepressor syncope, we performed the technique as described in the HUT protocol of the patient who underwent the procedure.

In our case, the contribution of the vasodepressor component was probably not detected in the pre-procedural HUT due to the fact that we did not perform the technique as described in the HUT protocol of the patient who underwent the procedure. However, after successful vagal denervation, the vasodepressor response became obvious. Kim et al. recently assessed the vasodepressor response and demonstrated glyceryl trinitrate-stimulated vasodepressor response in different components of VVS. The concept of CNA may offer an alternative way to treat recurrent cardioinhibitory VVS cases.

**Conclusion**

When performing protocols with a more prolonged passive phase, followed by sensitization with nitrate or isoproterenol, vasodepressor syncope may be seen in some cases. Although our study excluded patients with vasodepressor syncope, we performed the technique as described in the HUT protocol of the patient who underwent the procedure. However, after successful vagal denervation, the vasodepressor response became obvious. Kim et al. recently assessed the vasodepressor response and demonstrated glyceryl trinitrate-stimulated vasodepressor response in different components of VVS. The concept of CNA may offer an alternative way to treat recurrent cardioinhibitory VVS cases.


