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**The ventriculophasic response in  
pacemaker-dependent patients with  
advanced heart block**

**Doctoral Thesis Abstract**

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**Key Words:** Ventriculophasic Response, Complete heart block, Autonomic Nervous Sytem, Left Ventricular Ejection Fraction, Sinus Arrhythmia.

Ventriculophasic sinus arrhythmia, which is also known as the ventriculophasic response (VR), refers to brief acceleration of the sinus node (SN) that sometimes occurs when a ventricular systole is interposed between two P-waves in patients with advanced heart block (AHB). This phenomenon was observed approximately 100 years ago. Many researchers attempted to explain it based on their observations in isolated cases. In 2008, a small study performed by Drs. Blendea and McPherson showed that VR was correlated with echocardiographic measurements in a group of AHB patients who had pacemakers or implanted defibrillators. These findings were presented at CHEST 2008: the American College of Chest Physicians 74th Annual Scientific Assembly in Philadelphia, PA, USA. After this pilot study, it was felt that further study of VR required a semiquantitative definition of this phenomenon.

In this project 51 AHB patients who were treated with either a pacemaker or an implanted defibrillator were analyzed. The devices allowed more accurate measurement of the P-P intervals and they also afforded the opportunity to study VR on demand. Pacer function was temporarily programmed to VVI mode at 30 ppm as electrocardiogram lead II and intracardiac atrial and ventricular electrograms were recorded at 50 mm/second paper speed. The P-P interval shortening was calculated as the percent of shortening of the QRS-containing P-P interval compared with the preceding P-P interval without a QRS.

The first phase of this project was focused on developing a semiquantitative definition of VR and to assess its clinical correlations. The relationship of the timing of the QRS within the P-P interval to the amount of P-P interval shortening was assessed. It was observed that P-P interval shortening of <3% appeared to be random, whereas a shortening of >3% was not. Also, a shortening of >3% was more likely to occur when the QRS fell in the first 60% of the anticipated P-P interval. Based on these observations, the following definition of VR was proposed: VR is present during heart block when an interposed QRS, occurring in the first 60% of the anticipated P-P interval, results in a >3% shortening of the P-P interval surrounding the QRS compared with the preceding P-P interval. When the new definition of VR was used to reassess the clinical correlations of VR, it was found that VR was seen most often in women and in patients with good left-ventricular ejection fraction (LVEF>40%).

Over more than 100 years since it was first observed in 1910, three theories have been postulated to explain why VR occurs. The theories include 1) changes in the blood supply to the sinus node that alter its impulse generation; 2) a direct mechanical effect of the contracting ventricle on sinus node automaticity, perhaps related to more efficient ventricular emptying; and 3) modulation of sinus node rate via the autonomic nervous system through vagal-mediated reflexes such as the baroreceptor reflex, or the Bainbridge reflex. These theories may not be mutually exclusive.

In a second phase of the study, the potential physiology mediating VR was explored. For this purpose, the relationship between VR and respiratory sinus arrhythmia (RSA) was studied. The behavior of VR during deep breathing was observed and compared with the VR before and after deep breathing. It was noted that deep breathing enhances VR and that VR correlates with RSA, suggesting that the two phenomena may share common physiologic pathways. It was also observed that VR was less prominent when 2 P-waves surrounded wide paced QRS complexes than when they surrounded narrower escape or conducted complexes. This is an observation that previous investigators could not have made due to lack of pacemaker technology. This suggests that ventricular synchrony may play an important role in VR.

Based on previous observations and our results, it was proposed that VR to be considered as the result of a very complex interaction between ventricular mechanics and the autonomic nervous

system. After performing an extensive literature search on the autonomic nervous system and autonomic cardiovascular reflexes, several physiological pathways, involving both mechanical and autonomic components that may modulate VR were proposed.

The study cohort composed of patients with AHB treated with devices allowed obtaining more accurate measurement of the P-P intervals. This study is also the first study that elaborates a semiquantitative definition for VR and investigates its clinical correlations. This study represents the largest study of VR in the literature and many of our findings are novel.

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Aritmia ventriculofazica la pacientii cu  
bloc atrioventricular tratati cu pacemaker

Rezumatul Tezei de Doctorat

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**Cuvinte cheie:** Aritmia ventriculofazica, Bloc Atrioventricular, Sistem Autonomic Cardiac, Fractie de ejectie a ventriculului stang, Aritmie Sinusala

Aritmia ventriculofazica (AV) se refera la accelerarea de scurta durata a nodulului sinusal care are loc cand o sistola este interpusa intre doua unde P la pacienti cu bloc atrio-ventricular avansat (BAV). Acest fenomen a fost observat aproximativ acum 100 de ani. Multi cercetatori au incercat sa explice acest fenomen bazat pe observatii pe cazuri izolate. In 2008 un studiu pe cativa pacienti realizat de catre Dr Blendea si McPherson a aratat ca AV este corelata cu masuratori ecocardiografice intr-un grup restrans de pacienti cu BAV care au fost tratati cu defibrilatoare. Aceste rezultate au fost prezentate la CHEST 2008 in Philadelphia, USA. Dupa acest studiu pilot, a fost simtita nevoia unei definitii cantitative pentru AV.

In studiul de fata, au fost analizati 51 pacienti cu BAV care au fost tratati cu defibrilatoare sau pacemakere. Aparatele au permis o masuratoare mult mai precisa a AV. Aparatele au fost programate la 30 batai pe minut in timp ce derivatia II de EKG de suprafata cat si electrogramele intra-atriale si intra-ventriculare au fost inregistrate pe o hartie de EKG la 50 mm/sec. Scurtarea intervalului P-P a fost calculata ca si scurtarea intervalului P-P care contine complexul QRS relative cu intervalul P-P precedent care nu contine un complex QRS.

Prima faza a studiului a fost directionata spre dezvoltarea unei noi definitii cantitative pentru a putea sa analizam corelatiile clinice ale AV. Pentru aceasta a fost analizata relatia dintre momentul cand complexul QRS apare in intervalul P-P si procentul cu cat s-a scurtat intervalul P-P. S-a observat ca intervalul P-P se scurteaza cu mai mult de 3% in predominanta cand complexul QRS apare in prima 60% din lungimea anticipata a intervalului P-P. Bazat pe aceste informatii urmatoarea definitie a fost propusa pentru AV: AV se considera a fi prezenta in blocul atrioventricular atunci cand un complex QRS care apare in prima 60% din intervalul P-P produce o scurtare a acest interval cu mai mult de 3% in comparatie cu intervalul P-P precedent. Cand aceasta definitie a fost folosita pentru a analiza corelatiile clinice ale lui AV, s-a observat ca AV apare predominant la femei si la pacientii cu o fractie de ejectie buna (>40%).

In cei 100 de ani de cand a fost decoperit acest fenomen, 3 teorii au fost postulate pentru a explica substratul sau fiziologic. Aceste teorii includ: 1) schimbari in fluxul de sange la nodulul sinusal care rezulta in alterarea ritmului sau normal; 2) efectul mecanic direct al ventriculului care se contract asupra automaticitatii nodulului sinusal, cel mai probabil declansat de o golire mai eficienta a ventriculului; si 3) mediarea frecventei nodulului sinusal prin schimbairile tonului sistemului nervos autonom prin reflexe mediate vagal ca de exemplu reflexul baroreceptor si reflexul Bainbridge. Aceste teorii nu sunt neaparat exclusive.

In partea a doua a acestui studiu au fost explorate potentialele mecanisme care ar putea contribui la AV. In acest scop a fost analizata relatia dintre AV si aritmia sinusala. Comportamentul AV in timpul respiratiei profunde a fost observat si comparat cu AV in timpul respiratiei normale si dupa respiratie profunda. S-a observat ca respiratia profunda accentuaza AV si aritmia sinusala coreleaza cu AV, ceea ce sugereaza ca cele doua fenomene pot avea ca fiziopatologice comune. A mai fost observat ca AV este mai pronuntata cand complexul QRS este generat de un impuls condus prin nodulul atrioventricular decat cand complexul QRS este stimulat de pacemaker. Aceasta observatie nu ar fi putut fi facuta de catre investigatorii precedenti datorita lipsei pacemakerelor. Aceasta observatie sugereaza ca sincronia ventriculara are un rol important in AV.

Bazat pe observatiile noastre cat si cele precedente a fost sugerat ca AV este un rezultat al interactiunii complexe intre procese mecanice si autonome. Dupa o revizuire atenta a literaturii au fost propuse cateva cauze fiziologice prin care AV ar putea avea loc.

Originalitate acestei lucrari constituie in faptul ca populatia noastra de pacienti cu BAV tratat cu pacemaker sau defibrilatoare a permis studierea in detaliu a AV. Acest studiu este primul care a elabarat o definitie a AV precum si corelatii cu parametrii clinici. Analizele din acest stuidiu au permis elaboararea unor ipoteze legate de mecanismele fiziologice care contribuie la AV.