ORIGINAL ARTICLE

# Cognitive assessments in patients with implantable cardiac pacemaker

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**Abstract: Background/aim –** Bradyarrhythmias cause low cerebral blood flow and imbalance of the cerebral autoregulation, favoring neuronal ischemia and cognitive dysfunction. The main treatment in bradyarrhythmia is pacemaker (PM) implantation, which keeps the heart rate in normal range and increase cardiac output. The present study proposed the cognitive evaluation of PM group patients and a control group (CG), but with similar cardiovascular risk factors. Cognitive assessment has been achieved by applying the Mini-Mental State Examination (MMSE), Clock-Drawing Test (CDT) and Mini-Clock for both groups. **Materials and methods –** Observational study, performed on 40 patients divided into 2 groups (PM group and control group). Patients were investigated for the presence of cardiovascular risk factors, and echocardiographic assessment. Cognitive evaluation was performed in all patients by applying the MMSE and Clock-Drawing Test for better accuracy in detecting cognitive impairments related to visual-spatial skills. CDT was scored based on Rolueau scoring system. Also we calculated the Mini-Clock Score defined as sum of MMSE and CDT. **Results –** Patients with cardiac pacemaker presented lower cognitive scores. Median MMSE score was 27.3 for PM group vs. 29.3, p value <0.0005, CDT scores was 7.35 vs. 8.65, p value 0.045, and for Mini-Clock score was 35.4 vs. 38.2, p value 0.0019, compared to the control group. MMSE score was reduced especially in terms of short-term memory function (p<0.0004), attention and calculation (p<0.004) in comparison with the control group. Also, we noticed the presence of moderate positive correlation between the MMSE score and CDT score. **Conclusion –** The results of the study reveal that pacemaker patients presented statistically significant lower MMSE scores, CDT scores and Mini-Clock compared to the control group. MMSE combined with CDT proves to be fast and easy screening examination which can be helpful in detecting mild cognitive impairments in patients with implantable pacemaker.
**Keywords:** MMSE, Clock-drawing Test, Mini-Clock, pacemaker, bradyarrhythmia.

**Rezumat:** Bradiaritmiile reprezintă un factor de risc în dezvoltarea disfuncției cognitive și ulterior apariția demenței. Abordarea terapeutică a bradiaritmiilor simptomatice constă în terapia prin pacemaker. Prezentul studiu și-a propus evaluarea cognitivă a pacienților purtători de pacemaker și a unui grup de subiecți fără istoric de bradiaritmii dar cu factori de risc cardiovasculari similari. Testările cognitive utilizate au fost Mini-Mental State Examination, Testul ceasului, respectiv evaluarea Mini-Clock. În urma evaluărilor cognitive și a analizei statistice s-au observat performanțe cognitive mai scăzute la pacienții purtători de pacemaker comparativ cu grupul control. Scorurile obținute sugerează prezența disfuncției cogntive la această categorie de pacienți, în special disfuncții legate de capacitatea de calcul și memoria de scurtă durată.
**Cuvinte cheie:** MMSE, Testul Ceasului, Mini-Clock, pacemaker, bradiaritmii.

## 1. INTRODUCTION

Cognition is the superior cortical function that generates mental processes involved in knowledge (attention, perception, memory, reasoning) and the outcome of these processes (associations, images, knowledge, conceptions).

Cognition includes several functions including short / long-term memory, attention, working memory, executive function, psychomotor speed, speech, visual and spatial ability, functions that can be measured by various neuropsychological tests. Deterioration of any of these functions is defined as cognitive dysfunction or cognitive impairment[1].

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Cognitive decline is often a disregarded subject in clinical activity, very often the patient remain undiagnosed and untreated. This status is seen like a predementia stage where one or more cognitive domains are affected like memory, executive function, language, visuospatial skills, but without affecting the functional abilities. The most common cognitive impairment encountered is memory loss[2].

Factors like hypertension, dyslipidemia, stroke, atrial fibrillation, diabetes, heart failure as well as bradyarrythmias are considered to be independent risk factors in development of cognitive decline and dementia. Thus, association of 3 or more cardiovascular risk factors increases the risk of dementia by 3.4 times compared to those without risk factors[3,4].

From the physiological point of view, cerebral blood flow and blood-brain barrier play a leading role in preserving cognitive function. Most patients with bradyarrhythmias develop intermittent cerebral hypoperfusion which causes local ischemia and injury. There is also the hypothesis of low clearance of amyloid beta precursor protein due to low cerebral flow, that causes it to accumulate in the neuronal cell and favours apoptosis and the occurrence of cognitive dysfunction[5].

There are some studies which suggest that patients with bradyarrhythmias may develop intellectual decline and that pacemaker therapy may have some benefits in prevention. However, the results are not conclusive, and sometimes in contradiction[1,6,7].

First observations regarding development of chronic encephalopathy in subjects with bradyarrhythmias were formulated in 1965, observing an improvement in neurological symptoms after pacemaker implantation[8]. Since then, there have been few studies that proposed cognitive assessment in this category of patients. We found only 2 studies that assess cognitive function using the MMSE scale, and no study using CDT evaluation[6,9].

Based on the literature findings, our study goal was evaluation of cognitive function in pacemaker patients using the MMSE, CDT, and mini-Clock, in comparison with a control group with similar cardiovascular risk factors other than history of bradyarrhythmias.

## 2. MATERIAL AND METHODS

This is an observational study performed on a group of 40 patients divided in 2 equal groups, the pacemaker group and control group, admitted to the Cardiology Department of the Rehabilitation Hospital, Cluj-Napoca, Romania. For the pacemaker group we enrolled all the subjects which were admitted to our department with indication for pacemaker implantation in a limited period of time, between January 9 and March 11 2019. The control group was selected randomly from the same department hospitalized for other cardiovascular diseases other than bradyarrhythmias.

Cognitive evaluation was performed by a single blinded investigator without knowing whether or not the patient is wearing a pacemaker. The cognitive scales applied to all patients were Mini Mental State Examination (MMSE) and Clock-Drawing Test. Finally we calculated the Mini-Clock score based on the results of the other two scores.

The MMSE examination is composed by several sections aimed for assessing cognitive function related to temporo-spatial orientation, naming / identifying objects, short-term memory, attention and calculation, language, giving a total score of 30 points, of which 10 points for temporo-spatial orientation, 3 points for short-term memory, attention and calculation 5 points, language 4 points, executive function and writing 5 points, identification 3 points.

Clock Drawing Test is the second neuropsychometric instrument which was applied to population studied. The subject must draw a clock face with numbers, and also must draw the hands of the clock face which should indicate a specific time. In our study we asked patient to indicate eleven o'clock and ten minutes. For quantitative evaluation of the test in the literature, there are no less than 15 scoring models. We used for scoring a revised scale used by Rouleau et al. The scale has a total score of 10 points, of which up to 2 points are awarded for integrity of the clock, 4 points for number sequence of the clock, 4 points for correct placement of the hands on the clock face.

After we gathered the score from MMSE and CDT, we calculated the mini-Clock resulting from the amount of MMSE and CDT score, with a maximum points of 40. The advantage of calculating this score was in increasing the specificity and sensitivity in detection of mild cognitive impairment or dementia.

Cognitive tests were performed in all patients placed in an appropriate and comfortable environment, with the purpose of achieving objective evaluation.

Also all patients underwent echocardiography and were assessed for cardiovascular risk factors (presence of diabetes, hypertension, atrial fibrillation, dyslipidemia, heart failure). Regarding LVEF there were 4 categories: subjects with preserved EF (≥50%), mild im-

pairment FE (45-50%), moderate impairment (30-45%) and severe impairment (≤30%). The lipid profile evaluation consisted in: hypercholesterolemia being defined as total cholesterol >190 mg/dl, hypertriglyceridemia >150 mg/dl, low levels of HDL-cholesterol <40 mg/dl, elevated levels of LDL-cholesterol >115 mg/dL.

Exclusion criteria were patients diagnosed with neurological or psychiatric disorders (mental retardation, depression, psychotic disorders, documented dementia) as well as subjects using benzodiazepines, barbiturates, antipsychotics or anticholinesterases, as they may have an impact on cognitive function. Another exclusion criterion was level of education below 8 years, respectively patients who achieved an MMSE score <20 points.

Data collection and statistical analysis were performed using Excel 2007 and SPSS 22. Tests used for analytical statistics were *F*-Test Two Sample for Variances, *T*-Test Two-Sample Assuming Equal/Unequal Variances, Chi_Square, Pearson correlation. $p<0.05$ was considered as statistically significant.

## 3. RESULTS

General characteristics of patients are summarized in Table 1. Regarding pacemaker implantation, 70% of the patients received a pacemaker one year ago, 20% in the last 12 months not less than 3 months ago, and 10% received 24 months ago. Pacing mode was VVI for 55% of subjects, respectively DDD mode for 45%. 50% of the patients were treated by pacemaker implantation for sinus node disease, 15% for complete AV block, and 35% for AV block grade 2 type 2. Left ventricular ejection fraction (LVEF) was normal for 65% of the patients, 15% presented mild impairment, 10% moderate impairment, and 10% were with severe impairment. LVEF in the control group was in 70% of cases normal, 15% of cases presented mild impairment, 5% moderate impairment and 10% severe impairment.

Using statistical analysis (Chi-Square Test) we found no statistical differences related to sex, presence of diabetes, hypertension, atrial fibrillation, between pacemaker group and control group. Applying *T*-Test we found no statistical differences regarding age, level of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and no statistical differences related to ejection fraction of left ventricle between the two groups.

There was also no statistical differences related to years of education between groups.

MMSE score in the pacemaker group was significantly lower compared to the control group, with a mean difference of 2 points between the studied groups. The score related to short-term memory, was significantly lower in the pacemaker group compared to the control group ($p = 0.00044$) with a mean score of 1.95 vs. 2.68 points. Also the score for attention and calculation was more reduced in the pacemaker group ($p=0.004$) with a mean score of 3.67 vs. 4.63 points in comparison with patients from control group.

Regarding Clock-Drawing Test, we noticed that the score in the pacemaker group was significantly lower, compared to control group (7.35 vs. 8.65 points).

The differences between groups studied were even higher after calculating the mini-Clock score (35.4 vs. 38.2 points) (Table 2).

**Table 1. Baseline characteristics**

| Characteristics | Control Group (n=20) | Pacemaker Group (n=20) | p-value |
|---|---|---|---|
| Mean Age ± SD (years) | 68 ±7.49 | 66±7.18 | 0.34 |
| Female sex (%) | 45 | 55 | 0.75 |
| Male sex (%) | 55 | 45 | 0.75 |
| Hypertension (%) | 65 | 85 | 0.16 |
| Diabetes mellitus (%) | 35 | 35 | 1 |
| Atrial fibrillation (%) | 15 | 25 | 0.42 |
| Hypercholesterolemia (%) | 90 | 95 | 0.54 |
| Hypertriglyceridemia (%) | 45 | 60 | 0.34 |
| Total cholesterol± SD (mg/dl) | 187±49.6 | 168±50.5 | 0.21 |
| LDL-cholesterol± SD (mg/dl) | 109±40 | 97±42.9 | 0.31 |
| HDL-cholesterol± SD (mg/dl) | 42±7.55 | 38±8.6 | 0.14 |
| Triglycerides± SD (mg/dl) | 163±55 | 158±87 | 0.77 |
| LVEF (%) | 45 | 45.5 | 0.84 |
| Years of education (years) | 10.31 | 10.35 | 0.96 |

Baseline characteristics of patients with pacemaker and control group. LVEF = Left Ventricular Ejection Fraction. $p<0.05$ is considered statistically significant.

**Table 2. Cognitive assessments**

| Cognitive Assessment | Control Group (n=20) | Pacemaker Group (n=20) | p-value |
|---|---|---|---|
| Clock-drawing test | 8.65 | 7.35 | 0.045156 |
| MMSE total Score | 29.3 | 27.3 | 0.00055 |
| Mini-Clock | 38.2 | 35.4 | 0.0019 |
| Attention and calculation | 4.63 | 3.67 | 0.0045 |
| Language | 4 | 3.94 | 0.33 |
| Orientation | 10 | 9.89 | 0.33 |
| Short term memory | 2.68 | 1.95 | 0.00044 |
| Executive function and writing | 5 | 4.94 | 0.33 |
| Identification | 3 | 2.94 | 0.33 |

Cognitive assessments of patients with pacemaker and control group. $p<0.05$ is considered statistically significant.

As expected we also found a positive moderate correlation between CDT score and MMSE score (Pearson Correlation Coefficient $R^2= 0.3604$).

## 4. DISCUSSION

Main findings in the present study were that patients with implantable cardiac pacemaker had lower scores for the MMSE, CDT, Mini-Clock assessments, compared to control group. The cut-off values for cognitive assessments which we used in our study depends on a number of several factors such as level of education and age.

Some studies define a cut-off score for MMSE of 24 for the diagnosis of dementia. The cut-off is arbitrarily chosen, with a sensitivity of 86% and a specificity of 87%, a 55% positive predictive value and 97% negative predictive value, mentioning that the majority of cut-offs have the sensitivity higher than the specificity because MMSE remain a mental screening instrument. Even so, normal scoring, does not rule out the absence of dementia, that's way at least two cognitive tests should be used for evaluation[10,11].

Mild cognitive impairment (MCI) is defined below a cut-off point of 27 or 28, having a a sensitivity of 45 to 60% and specificity of 65 to 90%. However these cut-offs are more indicative and should not represent fixed cut-offs in diagnosis of MCI. In our study the median MMSE score was 27.3 points, above the cut-off for dementia diagnosis, but reaching the cut-off for MCI[2,12,13].

Cut-off values for Clock Drawing Test is 8 points according to Aprahaian et al., with a sensitivity 76.2% and a specificity 69.7%. In our study the median score for pacemaker group was 7.35 points, again below the normal values.

Combination of CDT with MMSE (Mini-Clock Test) is a valid tool with a better sensitivity and specificity in comparison with MMSE or CDT used alone. The sensitivity is 76.2% and specificity is 77.3% using a cut-off of 36 points. It is a useful test in discriminating patients with MCI versus controls and rule out mild cognitive impairment. The mean score for Mini-Clock in our study was 35.4 points for the pacemaker group, and 38.2 points in the control group which again indicate that MCI may be more common in the patients with implantable pacemaker[14,15].

The current guidelines do not recommend routine use of neuroimaging test for positive diagnosis of mild cognitive impairment, often is necessary only the signs of impairments in different cognitive domains. Once the MCI is present, the annual rate conversion to dementia is very high, ranging from 6 to 25% depending on the population studied[2,16].

Another study worth of mentioning is a cohort study conducted on 16245 participants which conclude that patients with dementia and mild cognitive impairment carrying a 1.8 greater risk of having a pacemaker, compared to general population. These findings indicate that subjects with a history of bradyarrhytmia are more prone to develop over time cognitive dysfunction, due to neuronal injury[17,18].

Our study limitation is the absence of cognitive assessment before pacemaker implantation, and reduced number of subjects. Based on this limitation we cannot establish the influence of pacemaker therapy in the population studied.

In light of these data, we draw attention to the fact that there is a close connection between the presence of cognitive impairments and pacemaker patients. Furthermore, we suggest that brain injury in this category of patients occurs long before pacemaker implantation, and at the time of implanting, patients are in an advanced stage of bradyarrhythmia often associated with multiple syncope episodes.

Unfortunately therapeutic and primary prevention strategies for dementia subjects are limited, and need further investigation. Prevention of dementia begins with early control of cardiovascular risk factors and early treatment of associated cardiovascular diseases such as bradyarrhythmias.

## 5. CONCLUSIONS

Pacemaker patients have lower MMSE, CDT, Mini-Clock scores, when compared to control group, primarily with reduced scores in short-term memory, attention and calculation. Mini Mental State Examination scale combined with Clock-Drawing test is a fast and easy screening examination which might be helpful in detecting cognitive dysfunctions even in pacemaker patients.

**Conflict of interest:** none declared.

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