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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Cognitive impairment after appropriate implantable cardioverter-defibrillator therapy for ventricular fibrillation

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Abstract

Background: Short periods of cerebral ischaemia during ventricular defibrillation testing may be associated with neuropsychological impairment. However, the impact of out-of-hospital ventricular fibrillation (VF) converted by implantable cardioverter-defibrillator (ICD) shock on cognitive functioning is unknown.

Aim: To assess the impact of out-of-hospital VF converted by ICD shock on cognitive functioning.

Methods: The study included 52 primary prevention ICD recipients. Patients with a history of stroke or other neurological impairment, previous head injury and individuals unable to see or speak to complete neuropsychological tests were not included. Initially, a Mini-Mental State Examination was performed in all patients and one patient with a result below 24 points was excluded from the study. The cognitive battery consisted of four tests (six measurements): 1) the Digit Span subtest of Wechsler Adult Intelligence Scale-Revised; 2) the Digit Symbol subtest of Wechsler Adult Intelligence Scale-Revised; 3) the Halstead-Reitan Trail-Making Test A and B; and 4) the Ruff Figural Fluency Test.

Results: The mean time from ICD implantation to cognitive assessment was 26 months. During this period, 15 appropriate shocks for VF were observed in seven (14%) patients. The patients with appropriate ICD therapy were significantly worse in two out of the six neuropsychological measurements and had a significantly lower aggregate result. In multivariate linear regression analysis, defibrillation therapy was an independent factor of poor cognitive functioning, along with age and education.

Conclusions: Short periods of out-of-hospital VF converted by ICD are associated with cognitive impairment in the recipients of primary prevention ICD.

Key words: neuropsychological functioning, appropriate ICD shock

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INTRODUCTION

Implanting a cardioverter-defibrillator is an effective strategy for reducing sudden cardiac deaths in heart failure patients. The device provides high voltage therapy several seconds after the onset of ventricular fibrillation (VF). During this time, the cerebral nervous system is hypoperfused [1–4]. Electroencephalographic changes consistent with cerebral ischaemia have been observed within 7.5–11 s of cardiac arrest [4, 5]. Also a release of neuron-specific enolase and S100 — markers of neuronal injury — has been reported after VF episodes aborted by implantable cardioverter-defibrillator (ICD) [6, 7]. Studies concerning the neuropsychological effects of these short periods of cerebral ischaemia associated with ICD therapy were limited to VF induced artificially during ventricular defibrillation testing (VDT) [5, 7–10]. Although VF provocations during ICD implantation may cause a cognitive impairment after the surgery, the impact of ICD therapy on the neuropsychological functioning in out-of-hospital patients is unknown.

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The purpose of the present study was to investigate the relation between the occurrence of appropriate ICD shocks for VF in everyday life, and cognitive deficits.

METHODS

This study was approved by the Institutional Review Board of the Military Institute of Medicine (IRB followed the Helsinki recommendations, approval number 1/WIM/2011/19012011). All subjects provided informed consent.

Study group

We studied 52 ICD patients who had implants in our centre between December 2003 and March 2011 as primary prevention of sudden cardiac death. Patients were excluded if they had had a history of stroke or other neurological impairment, previous head injury or were unable to see or speak to complete neuropsychological tests. Data regarding education status, the number of years of education and medical data including New York Heart Association functional class, and a history of coronary artery bypass grafting surgery was recorded for each patient. Left ventricular ejection fraction (LVEF) and left ventricular diastolic diameter were determined by echocardiography.

The interrogation of ICD was performed on the day of neuropsychological assessment in every patient. The number of appropriate shocks for VF since implantation of the device was recorded. The appropriateness of the ICD therapy was assessed by two cardiologists. VF was defined as ventricular arrhythmia with a cycle length ≤ 300 ms.

Neuropsychological assessment

A neuropsychological assessment was made once for every patient. The mean time from ICD implantation to administration of the tests was 26 months and ranged from four to 84 months. Initially, a Mini-Mental State Examination (MMSE) was performed in all patients [11]. Only one patient had a result below 24 points and was excluded from the study. The following cognitive battery consisted of: 1) the Digit Span subtest of Wechsler Adult Intelligence Scale-Revised (WAIS-R); 2) the Digit Symbol subtest of WAIS-R; 3) the Halstead-Reitan Trail-Making Test A and B; and 4) the Ruff Figural Fluency Test.

The Digit Span test of WAIS-R was used to assess concentration and immediate memory. The patient was required to repeat a series of digits presented orally — initially in original order and then in reverse order. The scores from both parts were added together [12].

The Digit Symbol test of WAIS-R was selected to measure psychomotor speed. The test consists of digit-symbol pairs followed by a list of digits. The patient was asked to assign a corresponding symbol to each digit within a set period of time. The number of correct pairs was measured [12].

The Trail-Making Test (TMT) was used to assess visual attention and mental flexibility. In part A, the subject was requested to join numbered circles in ascending order. Part B consists of circles containing both numbers and letters. The patient should have joined the circles in ascending alternate numeric and alphabetic order (1-A-2-B-3-C, etc.). The time taken to perform both parts was measured independently [13].

Ruff Figural Fluency Test (RFFT) was selected to assess executive functions. The task was to generate as many unique designs as possible within a specified period of time by connecting the dots in different patterns. The number of unique drawings and the number of perseverations were measured. An error ratio was calculated by dividing the number of perseverative designs by the number of unique designs [14].

Additionally, the level of depression symptoms was assessed using the Beck Depression Inventory [15].

Table 1. First principal component — eigenvectors

Neuropsychological test	Eigenvector
RFFT — unique designs	0.42
RFFT — error ratio	–0.31
Digit Span Test	0.32
Digit Symbol Test	0.46
TMT-A	–0.48
TMT-B	–0.42

RFFT — Ruff Figural Fluency Test; TMT — Trail-Making Test

Statistical analysis

Continuous data is expressed as mean ± standard deviation. Clinical characteristics and the results of the neuropsychological tests were compared between two groups with and without appropriate ICD therapy by the Student's t-test for continuous normally distributed variables or the Mann-Whitney U test in case of non-normally distributed data, and Fisher's exact test for qualitative variables. Principal components analysis was performed to assess an aggregate result of cognitive tests (the eigenvectors of these tests are presented in Table 1). The first principal component was used in further analyses. Multivariate linear regression analysis was employed to identify independent factors of poor cognitive functioning. Statistical differences with a p value < 0.05 were considered significant. All calculations were performed with statistical software (SAS 9.3; SAS Institute Inc.; Cary, NC, USA).

RESULTS

The demographic and clinical data for the 51 patients included in the study is summarised in Table 2. The underlying cardiac disease was ischaemic cardiomyopathy in 82% of cases, dilated cardiomyopathy in 16%, and hypertrophic cardiomyopathy in 2%. Initial defibrillation testing was performed in 43 (84%) patients and a total of 56 shocks were delivered. During the 26-month average (± 22 months) follow-up, appropriate ICD shocks for VF were observed in seven (14%) of 51 patients. The

Table 2. Clinical characteristics of implantable cardioverter-defibrillator recipients

	Appropriate shocks for VF (n = 7)	No or non-appropriate shocks (n = 44)	P
Age [years]	68 ± 7	64 ± 8	0.17*
Male gender	86%	86%	1.00‡
Length of education [years]	11.4 ± 3.8	12.9 ± 2.9	0.25*
Education (primary/secondary/higher)	57%/14%/29%	30%/52%/18%	0.16‡
Coronary artery disease	100%	80%	0.33‡
Coronary artery bypass grafting	14%	32%	0.66‡
Diabetes mellitus	29%	21%	0.64‡
New York Heart Association class	2.4 ± 0.98	2.2 ± 0.6	0.22‡
Left ventricular ejection fraction [%]	35.0 ± 8.3	32.0 ± 7.0	0.35†
Left ventricular diastolic diameter [cm]	6.3 ± 0.9	6.4 ± 0.7	0.95*
Number of shocks during VDT	1.6 ± 1.5	1.0 ± 0.8	0.37†

*Student's t test; †Mann-Whitney U test; ‡Fisher's exact test; VF — ventricular fibrillation; VDT — ventricular defibrillation testing

Table 3. Results of neuropsychological tests

	Appropriate shocks for VF (n = 7)	No or non-appropriate shocks (n = 44)	P
MMSE	27.3 ± 2.6	28.1 ± 1.8	0.54†
Beck Depression Inventory	16.7 ± 7.4	15.1 ± 9.9	0.55†
RFFT — unique designs	34.0 ± 8.6	53.4 ± 23.6	0.021†
RFFT — error ratio	0.20 ± 0.16	0.12 ± 0.11	0.29†
Digit Span Test	8.0 ± 1.6	9.1 ± 2.1	0.22*
Digit Symbol Test	22.4 ± 11.8	31.6 ± 14.2	0.11*
TMT-A	88.0 ± 46.8	54.9 ± 39.7	0.073†
TMT-B	306.7 ± 248.3	154.0 ± 129.0	0.041†
First principal component	–1.66 ± 1.63	0.23 ± 1.66	0.019†

*Student's t test; †Mann-Whitney U test; MMSE — Mini-Mental State Examination; RFFT — Ruff Figural Fluency Test; TMT — Trail-Making Test; VF — ventricular fibrillation

total number of appropriate shocks for VF was 15. The mean duration of VF episodes was 17 ± 8 s. The mean cycle length of VF was 263 ± 37 ms. The mean time from ICD shock to the neuropsychological evaluation was 23 ± 12 months.

There were no statistically significant differences between patients with and without appropriate therapy according to age, education and total education time. Patients with appropriate shocks had significantly worse RFFT results (in terms of the number of unique designs) and TMT-B results. They tended to have a lower score in the TMT-A and Digit Symbol test, but this did not reach statistical significance. The aggregate result of all cognitive measurements (the first principal component) was significantly worse in the appropriate shocks group (Table 3).

To identify independent factors of neuropsychological impairment, multiple linear regression analysis was employed. The following explanatory variables were used: age, length of education, gender, history of coronary artery bypass grafting, the presence of diabetes mellitus, LVEF, depression scale, number of out-of-hospital ICD shocks for VF, and the total number of shocks for VF (the sum of out-of-hospital shocks and shocks during VDT). These factors were placed against the result of every cognitive measure separately and against the aggregate result (the first principal component). When analysing each test separately, the only independent factors were age and length of education — the older the patient and the shorter the patient's education, the more severe the cognitive impairment was. However, in the analysis of the aggregate result, the number of out-of-hospital shocks for VF was also independently correlated with cognitive impairment alongside age and length of education — the more ICD shocks, the worse the neuropsychological functioning was (Table 4).

Table 4. Statistically significant independent variables in multivariate linear regression analysis

Neuropsychological tests	Independent variables	Point estimate	95% confidence limits		P
RFFT — unique designs	Age	–1.11	–1.8	–0.4	0.002
	Length of education	2.3	0.4	4.2	0.018
RFFT — error ratio	Length of education	–0.01	–0.02	–0.001	0.028
Digit Span Test	Length of education	0.3	0.09	0.5	0.004
Digit Symbol Test	Age	–0.7	–1.1	0.3	0.001
	Length of education	1.7	0.6	2.8	0.003
TMT-A	Age	1.7	0.4	3.0	0.01
	Length of education	–4.0	–7.5	–0.5	0.03
TMT-B	Age	5.1	0.5	9.8	0.03
	Length of education	–20.3	–32.8	–7.7	0.002
First principal component	Age	–0.09	–0.13	–0.04	0.0003
	Length of education	0.25	0.14	0.37	< 0.0001
	Number of appropriate shocks	–0.56	–1.04	–0.07	0.026

RFFT — Ruff Figural Fluency Test; TMT — Trail-Making Test

DISCUSSION

Our study, to the best of our knowledge, is the first to evaluate the impact of out-of-hospital VF converted by ICD on cognitive functioning. The data regarding the impact of short periods of VF converted by ICD shocks on neuropsychological functioning is limited to studies assessing the outcome of VF induced during VF testing. The results of these studies are inconsistent. In most of them, some degree of cognitive deterioration after ICD implantation (and VDT) was reported [7, 9, 10]. The inconsistencies result mainly from the different number of VF inductions and the different number of ICD shocks per patient across the studies. The mean number of VF inductions ranged from 1.8 to 12 [8, 9]. The greater the amount of VF per patient, the more often cognitive impairment was observed [5, 7–10]. In recent clinical practice, VF inductions have been minimised or even VDT is not performed [16, 17]. In our study, ICD shocks were delivered during VDT on average 1.1 times per patient.

Previous studies included ICD recipients implanted both in primary and secondary prevention of sudden cardiac death. Such study groups are heterogeneous according to neuropsychological functioning. Patients resuscitated from sudden cardiac death are expected to have significant cognitive impairment [18]. In our study, we included only ICD patients implanted in primary prophylaxis.

Our results showed the negative effect of out-of-hospital ICD shocks on cognitive functioning. Patients with appropriate ICD therapy had worse results in two out of the six neuropsychological measurements used in our study. The analysis of the aggregate result of our cognitive battery confirmed the negative effect of ICD therapy. However, the patients with appropriate shocks were insignificantly older and less well-educated. After adjusting the results of the tests for other factors, the number of appropriate shocks was not significantly associated with cognitive impairment when multivariate linear analysis was performed separately for each test. But when the aggregate cognitive assessment was analysed, the number of appropriate shocks was an independent negative factor along with age and length of education. The cognitive impairment is so imperceptible that it is only when considering the summation index, which is the first principal component ICD shocks appear to adversely affect cognitive functions.

Limitations of the study

The main limitation of our study is a very broad range of time within cognitive tests and ICD implantation, as ICD shock may have affected neuropsychological functioning in different degrees depending on the time from the shock to the cognitive assessment. Another limitation is that the study groups differed slightly according to variables such as age, education, number of ICD shocks during VDT, or other unknown factors that may influence neuropsychological functioning.

However, our finding that ICD therapy may harm cognitive functions was confirmed in multivariate linear regression, where the results of the tests were adjusted for possible factors affecting neuropsychological status. Moreover, we excluded from the study patients with a history of stroke or other neurological disease, including significant dementia assessed by MMSE, to obtain a more homogenous study group. Another method to assess the impact of ICD therapy on neuropsychological functions is to examine every patient before implantation and then after a set period of time. Then the demographic and clinical differences between patients do not affect the analysis. The disadvantages of such a method are the effect of practice that may decrease sensitivity and ageing that may decrease specificity.

CONCLUSIONS

Short periods of out-of-hospital VF converted by ICD are associated with cognitive impairment in the recipients of primary prevention ICD. However, the level of neuropsychological functioning depends mostly on age and education.

Conflict of interest: *Krystian Krzyżanowski has received consultant honoraries from Biotronik.*

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Wpływ adekwatnych wyładowań kardiowertera-defibrylatora na zaburzenia poznawcze

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Streszczenie

Wstęp: Krótkie okresy niedokrwienia ośrodkowego układu nerwowego w czasie oznaczania progu defibrylacji mogą się wiązać z następczymi zaburzeniami poznawczymi. Jednak wpływ pozaszpitalnych epizodów migotania komór (VF) przerywanych przez wyładowania wszczepialnego kardiowertera-defibrylatora (ICD) jest dotąd nieznany.

Cel: Celem pracy była ocena wpływu pozaszpitalnych epizodów VF przerywanych przez ICD na zaburzenia poznawcze.

Metody: Do badania włączono 52 pacjentów z ICD wszczepionym w ramach prewencji pierwotnej. Kryteria wyłączenia z badania były następujące: przebyty udar mózgu, uraz głowy, zaburzenia widzenia lub mówienia uniemożliwiające wykonanie testów neuropsychologicznych. U wszystkich pacjentów przeprowadzono test Mini Mental — 1 pacjent z wynikiem < 24 punktów był wyłączony z badania. Zestaw testów neuropsychologicznych składał się z 4 testów (6 zmiennych): 1) Test Powtarzania Cyfr — podtest Skali Inteligencji Wechslera, 2) Test Symboli — podtest Skali Inteligencji Wechslera, 3) Test Łączenia Punktów A i B, oraz 4) Test Płynności Figuralnej Ruffa.

Wyniki: Średni czas od wszczepienia urządzenia do oceny neuropsychologicznej wynosił 26 miesięcy. W tym okresie stwierdzono 15 wyładowań ICD w odpowiedzi na VF u 7 (14%) pacjentów. Chorzy z adekwatnymi wyładowaniami charakteryzowali się istotnie gorszymi wynikami 2 z 6 ocenianych parametrów neuropsychologicznych oraz osiągnęli istotnie gorszy wynik sumaryczny zastosowanych testów. W analizie wieloczynnikowej adekwatne wyładowania ICD stanowiły niezależny czynniki gorszego funkcjonowania poznawczego — obok wieku i wykształcenia.

Wnioski: Krótkie epizody pozaszpitalnego VF przerywanego przez ICD wiążą się z zaburzeniami poznawczymi u pacjentów z wszczepionym urządzeniem w ramach prewencji pierwotnej.

Słowa kluczowe: funkcje neurofizjologiczne, adekwatne wyładowania ICD

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