Defibrillation Testing and Early Neurologic Outcome

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SUMMARY

During implantable cardioverter-defibrillator (ICD) implantation, ventricular defibrillation testing (DFT) is considered a standard procedure. This procedure often requires multiple ventricular fibrillation (VF) inductions. These repeated short episodes of circulatory arrest with global cerebral ischemia may cause neurological damage. In the present study, patients undergoing initial ICD implantation and limited induction of VF for defibrillation safety margin testing were evaluated for pre- and postoperative cognitive and neurologic functions. In addition, the serum neuron specific enolase (NSE) level, which is a biochemical marker of cerebral injury, was evaluated.

The study was performed on 16 patients undergoing initial elective transvenous insertion of an ICD. A neurologic examination and cognitive assessment tests were performed 24 to 48 hours before and after ICD. NSE was determined before (NSE 1) and at the end of the surgery (NSE 2), as well as 2 hours (NSE 3), 24 hours (NSE 4), and 48 hours (NSE 5) after implantation.

A total of 29 internal shocks (average, 1.8 ± 0.4) with energy ranging from 14 to 41 J (mean, 20 ± 5 ; median, 20 J) were delivered in the ICD group patients. In one patient, 3 external (50, 200 and 360 J) shocks were required for fast VT induced during ICD lead positioning. The mean duration of VF was 10 ± 4 seconds and the mean cumulative time in VF was 16 ± 5 seconds. The mean recovery time between VFs was 5.3 ± 0.6 minutes. NSE levels were not different from the baseline at any time point in the patients of the group that completed the 48-hour observation period ($P > 0.05$). The patients did not report any new neurological symptoms after ICD implantation, and repeat examination after the procedure showed no abnormal findings other than those detected in the previous one. There were no statistically significant differences between the preoperative and postoperative scores obtained in the cognitive assessment.

Single or two VF inductions and the brief arrest of cerebral circulation during ICD implantation are not associated with permanent neurological injury. However, further studies are needed to confirm this finding. (Int Heart J 2008; 49: 553-563)

Key words: Implantable cardioverter defibrillator, Neuron specific enolase, Neuronal injury, Cognitive function

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THE implantable cardioverter defibrillator (ICD) has become standard therapy for a variety of patient groups.¹⁻³⁾ Ventricular defibrillation testing (DFT) at the time of device implantation is considered a standard and required procedure.^{4,5)} Repeated episodes of circulatory arrest due to induced VF can cause cerebral nervous system hypoperfusion.⁶⁾ Intraoperative electroencephalographic (EEG) monitoring during DFT testing has frequently showed EEG wave changes consistent with cerebral ischemia.^{7,8)} Studies on this population by Adams, *et al* and Murkin, *et al* have examined postoperative central nervous system function as determined by neurological and cognitive testing.^{9,10)} Adams and colleagues reported that no significant changes in neurologic functions and neuropsychometric performance were detected in 8 patients undergoing an average of 5.5 ± 5.7 episodes of VF. Murkin, *et al* noted that cognitive dysfunction can occur after insertion of ICD and is related to the duration of reperfusion interval. In this study, the patients underwent an average of 12 ± 6 episodes of VF. In the modern ICD era, the approach to DFT has changed considerably. Many investigators have suggested that an ICD implant could be completed with a single or two VF inductions.¹¹⁻¹³⁾

In recently published studies, significant increases in some biochemical markers of ischemic cerebral injury, such as neuron specific enolase (NSE), have been reported after implantation of ICD.^{14,15)} NSE, a dimeric isoenzyme of the glycolytic enzyme enolase, is mainly found in the cytoplasm of neurons and cells of neuroendocrine origin and has a high predictive value for neurocognitive deficits and neurological outcome after cardiac arrest, stroke, and cardiac surgery.¹⁶⁻¹⁹⁾ However, the literature presents limited data on the relationship between the increase in NSE and neurological outcome after VF during ICD procedures.

In the present study, patients undergoing initial ICD implantation and limited induction of VF for defibrillation safety margin testing were evaluated for pre- and postoperative cognitive and neurological functions. Serum NSE levels were also measured to determine whether this DFT measurement protocol was associated with neuronal injury.

METHODS

The study was approved by the hospital ethics committee, and informed consent from 16 patients undergoing initial elective transvenous insertion of an ICD at our center between May 2005 and March 2006 was obtained. All the ICD patients met the "Class I" criteria according to AHA/ACC/NASPE guidelines published in 2002.¹⁾ The characteristics of the patient population are listed in Table I. The underlying cardiac disease was coronary artery disease in 9 patients, idiopathic dilated cardiomyopathy in 3 patients, hypertrophic cardiomyopathy in

Table I. Clinical Characteristics of the 16 Study Patients

Age (years)*	57.50 ± 12.59
Male/female	13/3
Type of heart disease	
Coronary artery disease	9
Previous myocardial infarction	8
Dilated cardiomyopathy	3
Hypertrophic cardiomyopathy	2
Arrhythmogenic right ventricular dysplasia / cardiomyopathy	1
Congenital heart disease	1
Diabetes mellitus	3
New York Heart Association (NYHA) class	
NYHA class I-II	13
NYHA class III	3
Left ventricular ejection fraction (%) *	35 ± 13
Range	20-55

*Values are given as mean ± SD.

2 patients, congenital heart disease in 1 patient, and arrhythmogenic right ventricular dysplasia/cardiomyopathy in 1 patient.

Preoperatively, the medical history of each patient was obtained, and physical examination, left ventricular ejection fraction measurement, and routine biochemical tests including serum creatinine levels and hemogram were performed.

Devices were implanted in the electrophysiology laboratory. All patients received a dual-coil defibrillation lead and an active pectoral pulse generator under local anesthesia. Transvenous endocardial leads were inserted via either the left cephalic or subclavian vein and positioned in the right ventricular apex under fluoroscopic guidance. In all patients, attempts were made to confirm adequate ventricular sensing (≥ 5 mV) and pacing threshold (≤ 1 V). Dual chamber devices were implanted in 6 patients and single chamber devices were implanted in the others. Monitoring consisted of electrocardiograms, pulse oximetry, noninvasive blood pressure during the procedure time, and intra-arterial blood pressure for DFT testing. Anesthesia was provided during DFT measurement and was performed with intravenous fentanyl, propofol, and midazolam.

Defibrillation testing was performed via the implanted ICD system to establish an adequate safety margin for defibrillation. Ventricular fibrillation was induced by a low-energy shock into the T wave or rapid burst pacing. Defibrillation testing included at least two inductions of VF with successful first shocks terminating VF at a value at least 10 J below the maximum output of the implanted device. Testing was repeated as long as the patient remained hemodynamically

stable. If the first defibrillation could not terminate VF, a second endocardial direct current shock at maximum energy was applied. If that was not successful, an external shock at ≥ 300 J was also applied. Recovery time was defined as the time from defibrillation to the induction of a new test. Usually, 5-minute intervals were allowed between each induction. Intraoperatively, VF time, mean recovery time, defibrillation energy, number of shocks, and duration of surgery were recorded.

Clinical outcome was assessed by comparing preoperative with postoperative neurologic examinations and neurocognitive test scores. The same neurologist examined the patients within 24 to 48 hours before and after ICD implantation. Neurologic examination comprised a review of specific symptoms (changes in consciousness, headache, vertigo, dizziness, speech abnormalities, failing memory, visual disturbances, weakness and/or numbness in the limbs or face, unsteadiness and gait disorders) and assessment of the mental status (level of consciousness, speech, orientation, memory, knowledge of current events, judgment, object recognition, praxis), cranial nerves, motor functions (muscle tone and strength), reflexes (deep tendon reflexes, plantar reflex and abnormal reflexes), sensation (light touch, pain and position sense), and cerebellar functions (finger-to-nose test, heel-to-knee test, rapid alternating movements, the Romberg test, and gait).

Cognitive tests were performed within 48 hours prior to implantation and 24 to 48 hours after the implantation by the same investigator. The patients were fully awake and none had received any psychotropic medication before the assessment. The cognitive battery included the Stroop Color Word Test, Digit Span Forwards and Backwards subscores of the Wechsler Memory Scale-Revised (WMS-R), as well as the Block Design, Object Assembly and Arithmetic subscores of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test.²⁰⁻²²⁾

The Digit Span subtest of the Wechsler Memory Scale-Revised (WMS-R) was used to assess attention and immediate memory. In the forward test, the patients were required to repeat a series of digits. In order to achieve that, the digits were orally presented to the patient. In a second independent test, the patients were required to repeat the digits in reverse order (backward).

The Block Design from the WAIS-R was selected to assess the visuoconstructional abilities of the patients. A set of 4 blocks was presented to the patient in the first 6 tasks and 9 blocks were given in the next 4 tasks. The faces of the blocks were painted red or white. The patient was then asked to form a copy of the figure shown to him/her using the blocks. Then, increasingly complex figures were shown. The time taken by the patient to complete each design was recorded.

The Arithmetic subtest of the WAIS-R was selected to assess the ability to conceptualize verbally and express numerical concepts, and the ability to concen-

trate and resist distraction, for the problem-solving process demands concentration and application. This subtest consists of 14 timed items. For items 1 through 4, the patient was allowed 15 seconds to reply verbally after the problem had been read by the examiner. Through item 10 the time limit was increased to 30 seconds; from items 11 through 13 to 60 seconds; and for item 14 to 120 seconds. A bonus could be obtained for speedy performance on the last 4 items.

The Object Assembly subtest of the WAIS-R was selected to determine visual analysis and its coordination with simple assembly skills as well as the patient's understanding of the relationship of parts to one another and to the whole. The subtest consists of 4 cut-up figures, presented in the same manner and sequence. All items are scored for both time and accuracy. The time limits were 120 to 180 seconds. A bonus could be obtained for speedy performance.

The Stroop Color Word Test assesses selective and focused attention, and evaluates the ability of the subject to suppress, actively, irrelevant information and to enhance, selectively, relevant information stored in his/her memory. Several versions of this test are available; in the present study, it consisted of 4 separate tasks given in a fixed sequence. In the first task (word reading), the patient was asked to read aloud the names of colors written in black ink, whereas in the second task the patient was asked to read colored words whose meanings corresponded to the color in which they were printed. In the third task (color naming), the patient was shown colored rectangles and was asked to name the colors aloud. In the last task (color word naming), the names of colors were printed in colors that do not correspond to the meaning of the written word, and the patient was asked to state the colors in which the words were printed. The time, in seconds, taken to complete each task, was recorded. The Interference Score was obtained by subtracting the time to completion of the second task from that of the fourth task in order to give a measure of attention controlling for psychomotor speed.

Blood for NSE was collected via venipuncture, allowed to clot for 20-30 minutes at room temperature, and then centrifuged at 800-1000 rpm for 10 minutes. The serum was stored at -80°C and assayed after all the samples were completed. NSE was determined before (NSE 1), and at the end of surgery (NSE 2), and 2 hours (NSE 3), 24 hours (NSE 4) and 48 hours (NSE 5) after implantation. NSE was measured using a NSE two-site immunoluminometric assay test kit (LIAISON® NSE, DiaSorin S.p.A., Vercelli, Italy). The manufacturer reported that the LIAISON® NSE measured concentrations between 0.04 and 200 µg /L and the 95th percentile of normal serum concentrations was below 12.5 µg /L. The detection limit of the LIAISON® NSE was < 0.04 µg /L (mean value + 2 standard deviations). Visibly hemolytic samples were not used for analysis.

Statistical data was evaluated with the nonparametric test using SPSS (Statistical Package for Social Sciences, version 10.0) for Windows. The results are

reported as the mean and standard deviation for baseline characteristics of the patient group. The Friedman and Wilcoxon tests were used for the comparisons within the groups. A *P* value < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the 16 study patients are listed in Table I. Most of the patients were male, and the mean left ventricular ejection fraction was $35 \pm 13\%$. Nine of the patients (56%) were reported to have coronary artery disease, 8 of whom had at least one documented myocardial infarction. At the time of implantation, 13 patients were classified as New York Heart Association (NYHA) functional Class I-II and 3 as Class III.

The mean duration of ICD implantation was 84.6 ± 18.2 minutes (median, 90; range 50-120). A total of 29 internal shocks (two shocks per patient in 13, and one shock per patient in 3, average, 1.8 ± 0.4) with energy ranging from 14 to 41 J (mean, 20 ± 5 ; median, 20 J) were delivered. In one patient, 3 external (50, 200

Table II. Neurological Abnormalities in the Patients Before and After ICD Implantation

No	Age	Gender	Neurological diagnosis	Abnormal findings in neurological examination before ICD implantation	Abnormal findings in neurological examination after ICD implantation
1	45	Male	-	Asymmetry of the nasolabial folds	Asymmetry of the nasolabial folds
2	42	Female	-	-	-
3	45	Female	-	-	-
4	83	Male	Distal symmetric sensorial polyneuropathy	Position sense was decreased in the legs, Achilles and plantar reflexes were absent bilaterally	Position sense was decreased in the legs, Achilles and plantar reflexes were absent bilaterally
5	58	Male	Lumbar radiculopathy	Achilles reflex was absent on the left	Achilles reflex was absent on the left
6	67	Male	-	Asymmetry of the nasolabial folds	Asymmetry of the nasolabial folds
7	49	Male	-	-	-
8	55	Female	-	-	-
9	43	Male	-	-	-
10	46	Male	Lumbar radiculopathy	Achilles reflex was decreased on the left	Achilles reflex was decreased on the left
11	60	Male	-	Short-term memory was defective	Short-term memory was defective
12	71	Male	Lance-Adams syndrome (Postanoxic action myoclonus)	Action myoclonus in the upper limbs and head	Action myoclonus in the upper limbs and head
13	50	Male	-	-	-
14	67	Male	Ischemic stroke	Facial paresis, spastic hemiparesis (4/5) and Babinski reflex on the right	Facial paresis, spastic hemiparesis (4/5) and Babinski reflex on the right
15	65	Male	-	-	-
16	74	Male	Essential tremor	Postural tremor in the upper limbs	Postural tremor in the upper limbs

and 360 J) shocks were required for fast VT induced during lead positioning. The mean duration of VF was 10 ± 4 seconds (median, 9 seconds; range, 6 to 25 seconds), and the mean cumulative time in VF was 16 ± 5 seconds (median, 14 seconds; range, 10 to 25 seconds). The mean recovery time between VFs was 5.3 ± 0.6 minutes (median, 5 minutes; range, 4.5 to 7 minutes).

The results of neurological examination and cognitive tests: Abnormal findings in the neurological examination prior to ICD implantation and relevant diagnoses are shown in Table II. There was distal symmetric sensorial polyneuropathy in one patient, lumbar radiculopathy in two patients, Lance-Adams syndrome in one patient, ischemic stroke in one patient, and essential tremor in one patient. Postoperatively, neurologic abnormalities were unchanged in these patients, and no patient had a new neurologic deficit.

There were no statistically significant differences between the preoperative and postoperative scores obtained in the cognitive assessment (Table III).

Laboratory results: In two patients, the 3rd sample; in one patient, the 1st sample, and in one patient, the 5th sample of NSE were not studied. Twelve patients in the group completed the 48-hour observation period. The NSE median and range values of these patients increased from 12.34 (6.29-30.13) $\mu\text{g/L}$ to 13.23 (9.04-30.27) $\mu\text{g/L}$ at the end of surgery, to 13.51 (7.75-34.96) $\mu\text{g/L}$ 2 hours after surgery (NSE 3), to 12.71 (8.46-23.49) $\mu\text{g/L}$ at 24 hours (NSE 4) and 13.00 (7.11-

Table III. Cognitive Assessment Before and After the Implantation

	Before	After	<i>P</i>
WMS-R Digit Span Forward			
Mean (SD)	5.93 (2.54)	6.43 (2.22)	0.09
Median (R)	5.50 (2-11)	6.00 (3-11)	
WMS-R Digit Span Backward			
Mean (SD)	4.56 (1.78)	4.06 (1.43)	0.25
Median (R)	5.00 (2-9)	4.00 (2-7)	
WAIS-R Arithmetic			
Mean (SD)	9.25 (3.25)	9.31 (3.51)	0.97
Median (R)	9.50 (5-15)	9.50 (4-15)	
WAIS-R Block Design			
Mean (SD)	19.12 (7.55)	20.75 (10.01)	0.27
Median (R)	20.00 (4-34)	24.00 (0-38)	
WAIS-R Object Assembly			
Mean (SD)	21.87 (7.83)	24.93 (7.46)	0.07
Median (R)	21.00 (7-36)	24.00 (7-36)	
Stroop Interference Score			
Mean (SD)	97.93 (51.44)	85.93 (50.63)	0.30
Median (R)	95.00 (35-220)	72.00 (20-230)	

R indicates range; WMS-R, Wechsler Memory Scale-Revised; and WAIS-R, Wechsler Adult Intelligence Scale-Revised.

Figure. Changes in median and range of serum neuron-specific enolase (NSE) levels of 12 patients who completed the 48-hour observation period from baseline to end of surgery. NSE 1 indicates baseline serum NSE concentration; NSE 2, serum NSE concentration at end of surgery; NSE 3, serum NSE concentration 2 hours after surgery; NSE 4, serum NSE concentration 24 hours after surgery; and NSE 5, serum NSE concentration 48 hours after surgery. NSE was not different from baseline at any time point in ICD patients ($P = 0.77$).

21.91) $\mu\text{g/L}$ at 48 hours (NSE 5) (Figure). NSE was not different from baseline at any time point ($P = 0.77$, Friedman test).

DISCUSSION

The cerebral effects of repeated short episodes of circulatory arrest during DFT have been assessed with various monitoring techniques.^{7,8)} The monitoring technique most often used to assess cerebral ischemia is the EEG. In addition to the laboratory tests, in a few studies, patients undergoing ICD implantation were examined for clinical evidence of cerebral dysfunction as determined by neurological examination and neuropsychometric tests. Murkin, *et al* reported cognitive dysfunction and minor neurological deficits after ICD implantation.¹⁰⁾ In their study, an average of 12 ± 6 episodes of VF were induced intraoperatively. Ten of 14 patients demonstrated postoperative cognitive dysfunction according to the individual change in performance from baseline after the operation. Adams, *et al*, in contrast to this report, noted that brief arrest of cerebral circulation induced during implantation of an ICD was not associated with permanent neurological injury.⁹⁾ They performed preoperative and postoperative neurological and cognitive assessments in 8 patients undergoing an average of 5.5 ± 5.7 episodes

of VF intraoperatively after ICD implantation. The mean duration of arrest was 13.6 seconds. While showing transient electroencephalographic abnormalities, no significant deterioration in postoperative neuropsychometric function was detected by either group rate or even rate analysis of the neuropsychometric scores. None of the patients exhibited a new neurological deficit. In the present study, 16 patients undergoing initial ICD implantation were evaluated for preoperative and postoperative cognitive and neurological functions. The patients did not report any neurological symptoms after ICD implantation and the findings were similar to those found in pre-ICD examination. In addition, the lack of a significant difference between the preoperative and postoperative scores for attention, immediate memory, working memory, and visuospatial abilities suggests that the procedure is not associated with a significant cognitive dysfunction in these domains. In our study, an average of 1.81 ± 0.40 episodes of VF were induced intraoperatively, and the mean duration of VF was 10 seconds and cumulative time in VF was 16 seconds. These results demonstrate fewer episodes of VF and shorter duration of circulatory arrest per patient. The different results reported by earlier studies may be due to methodological differences and duration of hypotension during defibrillation testing.²³⁾

In our study, the interval between two cognitive assessments was shorter than 4 days for all patients. Lack of a significant difference in the test scores could also have resulted from a practice effect, especially for the visuospatial abilities, tasks that would be expected to improve with practice. In other words, practice might have masked a possible negative influence of the procedure on these cognitive abilities. The results of cognitive assessment should be interpreted cautiously since comparison with a control group is not available, rendering it difficult to rule out differences originating from the sensitivity of these tasks to change in the population we studied. On the other hand, attention, immediate memory and working memory, by definition, are less likely to improve with practice; therefore, the lack of a significant effect on these domains suggests that the ICD implantation and DFT measurements do not have a deleterious effect on these cognitive domains in the short-term.

In more recent studies, neuron specific enolase, which is a known marker of ischemic brain damage, was used to determine cerebral injury after brief periods of global cerebral ischemia during ICD implantation.^{14,15)} Dworshcak, *et al* determined the NSE serum level preoperatively, immediately postoperatively, and 2 hours postoperatively in 45 patients undergoing ICD implantation.¹⁴⁾ The serum NSE level of all the ICD patients increased significantly from baseline to 2 hours after surgery. In the subgroup of ICD patients with an extended observation period, NSE reached its maximum level between 6 hours after surgery and the end of the 24-hour observation period, after which evaluation was terminated.

Similar results have been reported by Weigl, *et al.*¹⁵⁾ They studied 42 patients undergoing ICD ($n = 21$) or PM insertion ($n = 21$) and serum NSE levels were determined at the same time period mentioned in the previous study. Serum NSE levels increased over time in the ICD group. Values immediately after surgery and at the 6th and 24th hours after surgery were significantly higher in ICD patients as compared with baseline. In contrast to these reports, in the present study, we were not able to demonstrate a significant increase in serum NSE after ICD implantation. We measured the marker before and after the early period of ICD implantation and at the 24th and 48th hours after surgery. Postoperatively, the highest median NSE level was obtained at the 2nd hour after the procedure. This increase, however, did not reach statistical significance. In the present and previously published two studies, similar patient groups were included and various factors which could alter NSE results, such as hemolysis and tumor secretion, were excluded. Thus, this discrepancy can be explained by the differences in the number of induced VF and the duration of cerebral hypoperfusion. It was shown that the increase in NSE values after ICD implantation were significantly associated with the number of shocks and the cumulative time in circulatory arrest.¹⁴⁾ In our study, the average shocks per patient were 1.8 and the mean cumulative time in VF was 16 seconds. Dworscak, *et al* reported that in their study, an average of 3 shocks per patient were delivered and the mean cumulative time in cardiac arrest was 33 seconds. In the study of Weigl, *et al*, on average, 3 arrests were induced, which resulted in an average cumulative duration of cardiac arrest of 25 seconds.

Study limitations: Clearly, the relatively small number of patients seen in this study limits the power of calculation. Furthermore, this study has no control group, and the patients could only be evaluated in the early postoperative period. Long-term follow-up is required to determine whether cognitive deficits exist in the late period after implantation.

In conclusion, no significant increase in serum NSE levels or a new neurological deficit, exacerbation of a preexisting neurological condition or significant deterioration in cognitive tests after ICD implantation and DFT testing were found. This finding suggests that single or two VF inductions and the brief arrest of cerebral circulation during ICD implantation is not associated with permanent neurological injury. However, further research is needed to confirm this hypothesis.

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