A Prospective 1-Year Study of Changes in Neuropsychological Functioning After Implantable Cardioverter-Defibrillator Surgery

Claire N. Hallas, PhD; Julie L. Burke, PhD; David G. White, PhD; Derek T. Connelly, MD

Background—The testing of the implantable cardioverter-defibrillator (ICD), through the induction of repeated episodes of ventricular fibrillation, has been associated with disturbances in cerebral activity and increased levels of cytoplasmic enzymes. However, the neuropsychological outcomes of cerebral changes and their quality-of-life implications are unknown.

Methods and Results—Fifty-two ICD recipients completed standardized validated neuropsychological tests 1 to 3 days before ICD surgery and then 6 weeks, 6 months, and 12 months after surgery. They also completed psychometric tests measuring anxiety, depression, and quality of life. Between 31% and 39% of patients showed a significant neuropsychological impairment from their baseline function 6 weeks, 6 months, and 12 months after surgery. Ten percent of patients had late-onset deficits at 12 months only. Frequent areas of impairment were auditory and visual memory and attention. Neuropsychological impairment was not related to mood or quality of life at follow-up, although anxiety and depression predicted reduced quality of life.

Conclusions—ICD implantation is associated with neuropsychological impairment that dissipates for the majority of recipients after 12 months. Short-term memory function and attention are particularly vulnerable to changes in oxygen during ICD testing. Although anxiety and depression are prevalent, there is little evidence for the direct impact of mood on cognition, and deficits appear not to be associated with reduced quality of life. These results provide evidence for longitudinal outcomes of ICD surgery and have implications for patient rehabilitation and adjustment. (Circ Arrhythm Electrophysiol. 2010;3:170-177.)

Key Words: ICD ■ neuropsychological function ■ quality of life

The implantable cardioverter-defibrillator (ICD) is a valuable device used in the treatment of ventricular arrhythmias and the prevention of sudden cardiac death. However, the ICD has been associated with some negative patient outcomes such as anxiety, depression, and poor quality of life (QoL), which are comparable in prevalence to patients resuscitated from cardiac arrest and cardiopulmonary bypass surgery (see Bostwick and Sola1). In addition, significant evidence has been established for detrimental neuropsychological outcomes related to cardiopulmonary surgery, with cognitive deficits found in 80% of patients during the first 2 weeks after surgery, and 10% to 57% of patients at 3 to 6 months after surgery.2,3,4 Data from studies have led researchers to focus on the cerebral effects of inducing ventricular fibrillation and circulatory arrest during ICD surgery.

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Early EEG tests, PET imaging, and oxygen saturation tests showed increased cerebral ischemia and a reduction in blood pressure occurred during the ventricular defibrillation testing (VDT) procedure.5-9 More recently, Dworshak et al10 measured the cytoplasmic enzymes neuron-specific enolase (NSE) and S100 leaked from brain cells in the early course of cerebral ischemia in 45 ICD recipients. Levels were taken before surgery and 2 hours after surgery. They reported an increase in both enzymes from baseline to 2 hours after surgery with levels similar to bypass surgery. Higher levels were associated with greater time in circulatory arrest during VDT.

The relationship between cerebral ischemia and neuropsychological functioning, however, remains unclear because few studies have assessed ICD recipients.11-13 Murkin et al11 assessed 14 elective ICD patients in whom 12±6 episodes of VF were intraoperatively induced. At postoperative follow-up (5 days), 10 of 14 patients met the criteria for a significant 20% deficit in cognitive function from baseline, in particular, short-term memory and attention. More recently, Karaoguz et al12 assessed 16 ICD patients with 6 standardized cognitive function tests and NSE levels. Tests were administered 24 to 48 hours before implantation, and NSE levels were tested at 2, 24, and 48 hours after surgery. Results showed there were no significant differences in NSE levels and cognitive func-
tion from baseline to 2 days after surgery. Inconsistencies between study results may be due to fewer episodes of VDT being implemented in recent years, therefore giving a shorter duration of circulatory arrest during surgery.

Data are limited to determine whether there are acute and/or long-term neuropsychological effects of VDT and ICD implantation. To date, studies have reported on small sample sizes, using unstandardized tests with nonrecommended methods of analyzing cognitive impairment and with only acute postoperative follow-up. In addition, although studies have measured mood after surgery, it is unclear whether this is related to neuropsychological impairment. Therefore, our study objectives were to determine changes in acute and

Table 2. Medical and Neurological Data

<table>
<thead>
<tr>
<th>No. of participants</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>60.63 ± 11.97</td>
</tr>
<tr>
<td>Sex</td>
<td>45 (86.5%) male</td>
</tr>
<tr>
<td>Married or living as married</td>
<td>38 (73.1%)</td>
</tr>
<tr>
<td>Employed</td>
<td>13 (25.0%)</td>
</tr>
<tr>
<td>Cardiac diagnosis</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>40 (76.9%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>38 (73.1%)</td>
</tr>
<tr>
<td>Previous CABG surgery</td>
<td>10 (19.2%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>8 (15.4%)</td>
</tr>
<tr>
<td>Valve disease</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>4 (7.7%)</td>
</tr>
<tr>
<td>Moderate-severe LV dysfunction</td>
<td>40 (76.9%)</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td>Presenting arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>33 (63.5%)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>5 (9.6%)</td>
</tr>
<tr>
<td>Ventricular tachycardia and ventricular fibrillation</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Out-of-hospital sudden cardiac arrest</td>
<td>9 (17.3%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (5.8%)</td>
</tr>
</tbody>
</table>

Table 3. Cognitive Test Score Description

<table>
<thead>
<tr>
<th>Name of Test</th>
<th>Abbreviation</th>
<th>Description of Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
<td>RAVLT1</td>
<td>Sum of word list trials 1–5</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
<td>RAVLT2</td>
<td>Score from distraction list</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
<td>RAVLT3</td>
<td>Immediate recall score of original word list</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
<td>RAVLT4</td>
<td>Delayed recall score of original word list</td>
</tr>
<tr>
<td>Trailmaking Test A</td>
<td>TMA</td>
<td>Time to complete test</td>
</tr>
<tr>
<td>Trailmaking Test B</td>
<td>TMB</td>
<td>Time to complete test</td>
</tr>
<tr>
<td>GPB task</td>
<td>GPB1</td>
<td>Dominant hand time</td>
</tr>
<tr>
<td>GPB task</td>
<td>GPB2</td>
<td>Nondominant hand time</td>
</tr>
<tr>
<td>Logical Memory Story A+B (WMS)</td>
<td>LM1*</td>
<td>Immediate recall story A+B score</td>
</tr>
<tr>
<td>Logical Memory Delayed Recall (WMS)</td>
<td>LM2*</td>
<td>Delayed recall score - immediate recall score</td>
</tr>
<tr>
<td>Visual Reproduction (WMS)</td>
<td>VR1*</td>
<td>Immediate recall total score</td>
</tr>
<tr>
<td>Visual Reproduction Delayed Recall</td>
<td>VR2*</td>
<td>Delayed recall score - immediate recall score</td>
</tr>
</tbody>
</table>

*Denotes test was added to the Statement of Consensus on Assessment for Neurobehavioral Outcomes after Cardiac Surgery tests.

long-term cognitive function after ICD surgery and any subsequent effect of mood on cognition and QoL. We also address previous study limitations with a prospective longitudinal study using standardized tests recommended by the Statement of Consensus and by analyzing cognitive data using their recommended criteria for impairment.14

Methods

Participants

After approval from the regional research ethics committee, 70 patients (see power calculation) who were under the care of a Consultant Cardiologist in a tertiary care UK hospital were approached to participate in our study. All patients were given written information regarding the study, had adequate time to make a decision to participate, and gave written informed consent. Patients were excluded if they had a history of preexisting neurological impairment, were unable to give informed consent, did not speak adequate English to complete tests, or were under 18 years of age. Sixty-seven patients agreed to participate; however, only 52 patients were included in the final analysis as they were required to complete 1 full follow-up assessment (77.6%). This was due an incomplete preimplant assessment as a result of mobility restrictions on ward (n=4), fatigue from late admission (n=2), withdrawing from the study at follow-up (n=5), not receiving the ICD (n=1), death after surgery (n=2), or explantation of the device (n=1). At time 4, the study included 44 patients, with a further 8 patients lost to follow-up due to logistic reasons.

Design and Procedure

The study used a prospective, repeated-measures design. ICD recipients underwent neuropsychological assessment 1 to 3 days before ICD surgery (time 1), then at 6 weeks (time 2), 6 months (time 3), and 12 months (time 4) after implant. Preassessment was completed 1 to 3 days before ICD surgery because it was not possible to access patients before they were admitted to the hospital. Follow-up assessments were coordinated with clinic appointments. The deci-
sion to implant an ICD was made according to the UK National Institute for Health and Clinical Excellence guidelines (2001, 2006) and after an electrophysiological study. Recipients were fitted with either a single- or dual-chamber Medtronic or Guidant ICD model. Six patients received combined ICD and biventricular pacemaker devices (see Table 1 for demographics). Data were also collated on surgical outcomes (see Table 2).

**Test Measures**

Neuropsychological tests were selected in accordance with the Statement of Consensus on Assessment for Neurobehavioral Outcomes after Cardiac Surgery. Two additional tests supplemented the battery (marked with an asterisk in Table 3), to increase its sensitivity and specificity. Approximately 1 hour was given for the assessment to reduce fatigue on performance and attrition. All testing was completed by the same postgraduate trained health psychologist, in a quiet room away from the ward or clinic. See Table 3 for test score acronyms.

**Rey Auditory Verbal Learning Test**

A test of auditory memory span, which is a word-list learning task consisting of 15 words, was read one at a time to the participant over a series of 5 trials. After the final trial, a distraction list is read. Participants are asked to recall as many words as they can from the distraction list, and then they are asked to recall the initial list. In the delayed recall condition, participants are asked to recall the original list after 30 minutes.


Part A assesses simple cognitive processing speed and Part B assesses complex cognitive processing speed and mental flexibility.

Part A consists of randomly placed numbered circles, which participants must join in ascending numeric order. Part B consists of circles containing both numbers and letters, which participants must join in ascending alternate numeric and alphabetic order (e.g., 1A, 2B, 3C). Higher error scores indicate poorer performance.

**Grooved Pegboard: A Test of Manual Dexterity and Eye-Hand Coordination**

In the grooved pegboard test (GPB) 25 key-shaped identical pegs are placed in randomly positioned keyholes. Keyholes are arranged in 5 rows with 5 slots per row. Participants are timed to place the pegs into the slots as quickly as possible, first with their dominant hand and then with the nondominant hand. The time taken to insert the pegs and the number of pegs dropped are recorded as test scores. For this study only, the time score was recorded as few participants dropped pegs.

**Logical Memory 1 and 2 From the Wechsler Memory Scale III**

The Logical Memory 1 and 2 tests from the Wechsler Memory Scale III (WMS-III-R) measure immediate and delayed short-term verbal memory. Participants listen to 2 different stories (A and B) and then must immediately recall them from memory. Scoring is based on the accuracy of the retold stories and the ability to recall themes. Thirty minutes later, the participant is asked to recall the stories again for the delayed recall test score.

**Visual Reproduction 1 and 2 From the WMS-III-R**

Participants are shown 5 geometric designs, each for 10 seconds, to assess their spatial memory and asked to redraw them immediately.
after viewing.16 Thirty minutes later participants are asked to redraw the same designs, with the accuracy scored on standard criteria.

**Medical Outcomes Survey, Short Form-36, Version 2**
The Medical Outcomes Survey, Short Form-36, Version 2 (SF-36v2),17 is a generic international version of the original US measure of health status. The scale consists of 36 items, measuring 8 health attributes (physical functioning, physical roles, bodily pain, general health, vitality, social functioning, emotional roles and mental health) and 2 summary scales (physical and mental functioning). The subscales were transformed to norm-based scores using standard scoring algorithms stated in the manual guidelines.

**Hospital Anxiety and Depression Scale**
The Hospital Anxiety and Depression Scale (HADS)18 is a 14-item scale measuring anxiety and depression in medical patients without contamination of scores influenced by physical symptoms. Each item is scored from 0 to 3, with each scale having a range from 0 to 21; scores >11 indicate possible clinical (psychiatric) levels of anxiety and depression.

**Statistical Analysis, Power, and Sample Size Calculation**
Statistical analyses were carried out using the SPSS for Windows (version 15.0). Relationships between normally distributed variables were assessed using the Pearson correlation coefficient and Spearman \( \rho \) correlations (for nonparametric data). Diagnostic group differences in HADS and SF-36 data over time were assessed using mixed-model multiple analyses of variance (MANOVAs). Two multiple linear stepwise regression analyses were conducted to evaluate the relationships between independent and dependent variables (SF-36 physical and mental health outcomes). Variables were selected for the regression after correlational analyses between the HADS, neuropsychological test measures, SF-36, and medical data to determine where significant relationships existed. Only significant relationships were then entered into each separate regression analyses. The significance level was set at 0.05 for all analyses, although where there were multiple correlations or comparisons the probability value was adjusted by the Bonferroni correction test or reduced to 0.01 to reduce the possibility of a Type I error.

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**Results**

**Analyzing Neuropsychological Data**
Several alternative criteria have been used by researchers to assess cognitive impairment. Our study analyzed cognitive change data using the method of detecting a 20% decline from baseline scores on 20% of the overall test scores (12 scores derived from 5 tests/2.4 tests; a conservative approach was agreed to set at 3 tests), as it been shown to be a robust and valid method of detecting subtle changes in neuropsychological functioning.11

**Deficits in Neuropsychological Function**
The incidence of cognitive impairment was significant (see Table 2 and Figure 1), and appeared consistent at >30% for each follow-up period. However, it was not consistent be-
tween participants over time; of 17 participants who were impaired at 12 months (time 4), only 5 of these (10% of the sample) had impairments at 6 weeks (time 2). Seven participants showed temporary impairment only at 6 weeks (time 2), whereas 12 participants showed delayed impairment at 6 months (at time 3). The greatest number of participants (n = 9) with a single time deficit was at 6 months (time 3). However, for 12 participants, impairments developed at 6 months (19%) and 12 months (7%). Auditory memory (RAVLT tests), delayed visual recall (VR2), and attention (TM) test scores were most impaired (see Figure 2).

Neuropsychological Impairment and Medical Variables

There were no significant correlations or differences found between medical variables (cardiac diagnosis, β-blocker versus ACE inhibitor medications, VDT frequency, postoperative shock status) and neuropsychological scores or a 20:20 deficit (see Table 2 for VDT/deficit frequency).

Comparing ICD Cognition With Norm Data

Raw scores on the LM and VR, RAVLT, and GPB (no norms for TM) were converted into scale scores and compared by z-tests with healthy population norms from test guidelines (by age group) for each time point (see Tables 4 and 5). Participants compared poorly with norms over time on WMS-VR1 and WMS-LM2, with the oldest group (70 to 74 years) scoring significantly lower on all tests before ICD placement (P < 0.05). On the RAVLT, the youngest and oldest group scored significantly lower than the norms and at all time points (P < 0.05). ICD patients performed significantly worse on the GPB test than the norms and at all time points (P < 0.0001).

Mood and QoL

Participants with postsurgery clinical levels of anxiety (11+ scores) were those who experienced presurgery anxiety. At
time 4, 11 of the 13 participants classified as clinically anxious reported presurgery anxiety (see Table 6). A 1-way mixed-methods MANOVA (Wilks Lambda accessed through repeated-measures SPSS design model) was conducted to test the significance of the group differences in HADS anxiety, depression, and the SF-36 summary mental and physical health subscales (the dependent variables). Time since implant was entered as the independent variable. The univariate ANOVA showed that the mental health subscale was the only scale that improved significantly from baseline to time 4 (F(3, 43) = 2.230, P = 0.01) in the model, and the univariate ANOVA showed that the mental health subscale was the only scale that improved significantly from baseline to time 4 (F(3, 43) = 2.230, P = 0.01) in the model. Significant improvement from preimplant score, P < 0.005.

### QoL, Mood, and Neuropsychological Functioning

Two stepwise forward multiple linear regression analyses were conducted for the summary SF-36 mental and physical functioning subscales (P < 0.01 was shown between depression, anxiety, and QoL). Neuropsychological impairment and individual cognitive tests did not predict QoL at any time (see Table 8). Depression, however, significantly predicted SF-36 physical and mental health at all postoperative time points, and anxiety significantly predicted SF-36 mental health at all time points.

#### Discussion

Our study aimed to identify whether neuropsychological impairments were measurable over 12 months after elective ICD surgery and if mood state and impairments significantly affected postoperative QoL. Results confirmed that a significant proportion of patients were impaired after surgery at all time points, with 31% at 6 weeks, 35% at 6 months, and 39% at 12 months; 10% of patients had late-onset deficits only 12 months after surgery. Most impaired domains of functioning were immediate and delayed auditory and visual memory and attention/executive functions.

In our study, the prevalence of cognitive deficits were comparable with the Murkin et al study, showing a high level of deficits found in the acute period at 6 weeks. Our results also showed that the prevalence of deficits were consistent over 12 months, although this did not reflect individual patient patterns of change, as the majority of acute postsurgery deficits did not remain across the year. This variable pattern cannot be substantiated with other ICD studies; however, it can be compared with other cardiac populations. Thornton et al assessed 52 cardiopulmonary bypass patients with a comprehensive cognitive test battery at baseline and 6 weeks after surgery. The 20:20 categorization of deficit showed that 42% of patients at 6 weeks after surgery had significant impairments with this, reducing to 22% at 6 months. In our study, 32% of patients at 6 weeks were impaired, with 39% at 6 months. In addition, 4 patterns of cognitive deficit were shown in the Thornton et al study, which are comparable to our study: sustained impairment (SI), no impairment (NI), early impairment at 6 weeks (EI), and late impairment at 6 months (LI). The percentage of bypass patients with cognitive deficits were SI = 17%; NI = 54%; EI = 19%; and LI = 10%. In our study, fluctuations in deficit patterns were different, however, with SI = 11%; NI = 61%; EI = 10%; and LI = 18%. For our 12-month follow-up, the deficit incidence was 7%.

From these data, we can see that our ICD population had a higher incidence of later-onset deficits at 6 months than bypass patients, although ICD patients had a lower overall incidence of sustained impairment and a higher nondeficit population than the bypass patients. Both populations did, however, show evidence of deficits dissipating over time. Overall, the data suggest that bypass patients recover their cognitive function from 6 weeks after surgery, whereas a
A recent study of CABG surgery patients has also shown that 6 weeks after surgery, newly detected diffuse ischemic lesions in the parieto-occipital cortex (using MRI scanning) were found in 51% of patients. Lesions were significantly related to early cognitive auditory and visual memory impairments and were subsequently found to be the only significant predictor of late-onset cognitive decline 3 years later. Cerebral lesions in specific “watershed” areas of the brain appear more vulnerable to changes in cerebral oxygen, in particular those that lay along the boundaries of the major arteries (the anterior, middle, and posterior cerebral arteries) and the parieto-occipital cortex, and these maybe associated with later-onset deficits.

**Neuropsychological Function and QoL**

Neuropsychological impairment was not significantly associated with postoperative QoL or anxiety and depression. Anxiety and depression were prevalent, however, and depression was a significant predictor of physical and mental QoL, whereas anxiety predicted mental QoL. Previous studies have found inconsistent evidence for the relationship between mood and cognitive decline, indicating that depression may be associated with subjective perceptions of impairment rather than objective test outcomes. This may be due to patients’ being unable to recall with accuracy their past experiences and having negative interpretations of events from depressed thinking, which results in them being unable to make valid comparative judgments about their present QoL. This hypothesis could find endorsement from our data, as our depressed patients did report lower physical and mental QoL; however, it remains that depression did not have a direct relationship with cognitive function.

**Limitations**

It is possible that although the 20:20 criterion is a rigorous scoring method, some of our scores may have overinflated the impairment prevalence. For example, the RAVLT subtests are scored from 0 to 15; however, this limited range means that a participant can be scored as impaired by having only a small decline in performance. A decrease from 10 words at time 1 to 8 words at time 2 constitutes a 20% drop in performance on this test. In contrast, the GPB, which is scored by time and can produce scores in excess of 300, can show a relatively large decline in performance yet not identify an impairment (see Lewis et al for a review of statistical limitations in analysis of cognitive data).

**Conclusion**

The prevalence of neuropsychological impairment after ICD implantation has confirmed that brief VDT does significantly affect acute and long-term cognitive function. Transient changes in auditory and visual memory recall, attention, and executive function occur on a varied pattern of onset, making it unclear which patients are at risk from late-onset deficits. Deficits were not related to cardiac diagnoses, shock frequency, mood, and QoL, although older and younger patients were most impaired. Depression and anxiety, which have also been associated with these age groups did affect QoL. Follow-up care should reflect the impact of cognition on the recovery of patients and consider that basic deficits could reduce the efficacy of clinical care and have a possible impact on adherence to lifestyle changes and patient psychological adjustment.

**Sources of Funding**

This study was supported by a Doctoral Research Studentship Grant by Staffordshire University, United Kingdom.

**Disclosures**

None.
Neuropsychological Deficits After ICD Surgery


12. Hallas et al. Neuropsychological Deficits After ICD Surgery


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Circ Arrhythm Electrophysiol. 2010;3:170-177; originally published online March 2, 2010;
doi: 10.1161/CIRCEP.109.909580
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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