Clinical Paper

Survivors of cardiac arrest with good neurological outcome show considerable impairments of memory functioning

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ABSTRACT

Background: Deficits in cognitive function are a well-known dysfunction in survivors of cardiac arrest. However, data concerning memory function in this neurological vulnerable patient collective remain scarce and inconclusive. Therefore, we aimed to assess multiple aspects of retrospective and prospective memory performance in patients after cardiac arrest.

Methods: We prospectively enrolled 33 survivors of cardiac arrest, with cerebral performance categories (CPC) 1 and 2 and a control-group (n = 33) matched in sex, age and educational-level. To assess retrospective and prospective memory performance we administrated 4 weeks after cardiac arrest the “Rey Adult Learning Test” (RAVLT), the “Digit-Span-Backwards Test”, the “Logic-Memory Test” and the “Red-Pencil Test”.

Results: Results indicate an impairment in immediate and delayed free recall, but not in recognition. However, the overall impairment in immediate recall was qualified by analyzing RAVLT performance, showing that patients were only impaired in trials 4 and 5 of the learning sequence. Moreover, working and prospective memory as well as prose recall were worse in cardiac arrest survivors. Cranial computed tomography was available in 61% of all patients (n = 20) but there was no specific neurological damage detectable that could be linked to this cognitive impairment.

Conclusion: Episodic long-term memory functioning appears to be particularly impaired after cardiac arrest. In contrast, short-term memory storage, even tested via free-call, seems not to be affected. Based on cranial computed tomography we suggest that global brain ischemia rather than focal brain lesions appear to underlie these effects.

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1. Introduction

Global or regional cerebral hypoperfusion caused by stroke, traumatic brain injury and even coronary artery bypass (CABP) surgery, are well known as effectors for various types of dysfunction in cognitive performance including memory deficits.1–3 In regard to these findings, the potential effects of cardiac arrest on cognitive performance have been targeted. The cerebral performance category (CPC) scale is a well established tool for evaluation of neurological damage after cardiac arrest and describes patients mental ability from CPC 1 (=return to normal cerebral performance) to CPC 5 (=brain death).4 However, within animal-models both neuropathological and neuroimaging studies revealed specific vulnerability of hippocampal regions after global cerebral ischemia due to cardiac arrest.5–6 Human data in this context remain scarce and not conclusive. In terms of neurobiological effects studies appear to converge in indicating that global cerebral hypoperfusion may lead to focal lesions especially in the hippocampal region.7,8 The hippocampal region is essential for learning and the transfer of new information in the declarative memory. Site of long-term memory and short-term recall are the neo-cortex and numerous subcortical regions, with which the hippocampus has strong reciprocal connections (see Fig. 1).

In terms of psychological consequences, previous studies empirically testing the associated cognitive profile reported significant cognitive deficits in cardiac arrest survivors.9–14 However, the exact pattern of impairment still appears to be underspecified.15,16 While early reports have used rather crude methods of assessing cognitive functioning such as the Mini Mental State Examination,17 recently,
first studies have investigated cognitive functioning using a variety of established cognitive tests. Our study follows up on previous work exploring potential memory deficits in cardiac arrest survivors extending the existing literature in three aspects. First, we prospectively tested for potential memory deficits applying an age, sex and education matched control group. Second, we aimed at delineating potential memory deficits using a comprehensive battery of retrospective and prospective short and long-term memory measures. Third, we aimed at disentangling potentially different performance patterns in cardiac arrest patients according to their state of consciousness at time of admission to our department as well as according to their overall neurological status at time of testing.

2. Methods

2.1. Study population

We prospectively enrolled 33 patients (23 [70%] male, age 50 [±15] years) after cardiac arrest admitted to the Department of Emergency Medicine at Vienna General Hospital, a university affiliated tertiary care center. To be included in our study, patients had to be at least 18 years old and had to show CPC 1 or 2. Patients were excluded if they had insufficient knowledge of the German language, were unable to speak and if they had suffered any cerebrovascular incident or disease of the central nervous system prior to the cardiac arrest.

2.2. Data acquisition

Patient data were collected by instructed personnel and inserted into a predefined data record abstraction form. Data about the patient’s medical history, home drug treatment, neurological (CPC) and general physical status before the arrest, cardiac risk factors, first-aid and emergency medical service response intervals, extent and amount of emergency cardiac care and CPC on arrival and over a follow-up period of 4 weeks when the tests were collected. Memory tests were scheduled 4 weeks after cardiac arrest. Participants had to sign a written informed consent for inclusion in our study. After patient interviews were completed, a sex, age and education matched control group was tested for comparison. Recruitment of healthy controls was done by public postings and amounted to 33 healthy patients (23 [70%] male, age 51 [±14] years). The two interviewers were – especially by an experienced neuro-psychologist trained – medical doctors. The study was approved by the local ethics committee at Medical University of Vienna and was in accordance with the Declaration of Helsinki.

2.3. Testing procedures

Rey Adult Verbal Learning Test (RAVLT) was used to assess immediate, delayed free recall and recognition in several ways. The interviewer read aloud 15 words to the participant in 5 subsequent trials and participants had to recall as many words as possible after each trial. Each trial’s performance was noted separately. After the 5th trial an interference list of 15 different words (Interference Trial) was read to the participants and they had to recall those words. Performance in trials 1–5 and the interference list was taken as indicators for immediate free recall – as measured in single trial performance as well as a combined overall score. The relative increase in performance from trial 1–5 was used as a measure for the participant’s learning ability. For assessment of delayed recall participants had to recall the 15 words from trial 1–5 right after the interference list had been tested (trial 6) and about 30 min thereafter (trial 7). To examine participants recognition performance, in trial 8, they had to recognize the 15 words from trial 1–5 from an orally presented word list also containing 35 words from the interference list and phonetic or semantic similar distractor words.

Digit-span-backwards from Wechsler Adult Intelligence Scale-Revised (WAIS-R) was used for assessment of working memory. Here, the participant had to repeat increasing sequences of numbers in backward direction. The Red-Pencil-Test was used for assessment of prospective memory. At the beginning of the interview the participant was instructed to remember to say aloud “red pencil” whenever the interviewer uses the expression “red pencil”. The cue appeared 4 times across the test session.

The logical memory subscale from Wechsler Memory Scale-Revised (WMS-R) was performed to test performance in prose recall. A standardized story was read to the participant by the experimenter. Participants were asked to listen and, when the story was finished, to recall as many details as possible. The number of propositions correctly recalled was the prose recall score.

2.4. Statistical analysis

Continuous data are shown as median and interquartile range (IQR) if non-parametric distribution, discrete data as counts and percentages. Discrete data were analyzed using Chi-square test and Mann–Whitney-U-test for continuous variables. Data were tested for normal distribution using the Kolmogorov–Smirnov test. For normally distributed variables group differences in cognitive functioning were assessed by single factors analyses of variance (ANOVA) or mixed repeated-measures ANOVA, respectively. As within-subjects factor we used the respective RAVLT trials and as between-subjects factor patients versus controls or different patient subgroups were used in the respective ANOVAs. Where appropriate, the Tukey Honestly Significant Difference post hoc tests (Tukey HSD post hoc test) or planned comparisons using t-tests were performed and P-values were adjusted according to Bonferroni, or Greenhouse–Geisser (in the repeated measures data). We chose two-sided P-values <0.05 as statistical significant. Effect size is given in r² indicating proportion of explained variance. Statistical analyses were performed using SPSS 11.5 (IBM USA).

3. Results

Between May 1st, 2004 and April 30th, 2005 all patients admitted after cardiac arrest (n = 174) were screened and finally
33 patients were included in our study (Fig. 2). Bystander CPR was performed in 27.3% (n = 9) of those cases.

3.1. Rey Adult Verbal Learning Test (RAVLT)

3.1.1. Cardiac arrest patients versus healthy controls

Within an initial 5 (trials 1–5) × 2 (group) ANOVA, a significant group effect was found indicating impaired overall performance across trials 1–5 in cardiac arrest patients (P < 0.05; \( \eta^2 = 0.091 \)). In addition, a main effect for trial repetition was found indicating an increase in performance over time (P < 0.001; \( \eta^2 = 0.769 \)). Importantly, the ANOVA revealed a significant interaction qualifying the main effect of group (P < 0.001; \( \eta^2 = 0.219 \)). Planned comparisons revealed that the interaction effect was due to cardiac arrest patients showing impaired performance only in trials 4 and 5 while being equal to controls in trials 1–3 (see Fig. 3 – Panel A).

Comparing performance in the two RAVLT delayed recall trials, single-factor ANOVA revealed a group difference in both trials (trial 6: P < 0.001; \( \eta^2 = 0.224 \); trial 7: P < 0.001; \( \eta^2 = 0.221 \)). A 3 (trials 5–7) × 2 (group) ANOVA revealed a significant group difference reflecting the impaired overall performance in cardiac arrest patients (P < 0.001; \( \eta^2 = 0.261 \)) in the rate of forgetting. More importantly, a main effect for trial repetition was found indicating overall forgetting; i.e., a decrease in performance across trial 5 to trial 7 (P < 0.001; \( \eta^2 = 0.384 \)). Finally, the ANOVA revealed no significant interaction indicating comparable rates of forgetting in both groups (P = 0.641; \( \eta^2 = 0.007 \)). Planned comparisons showed that there was significant forgetting from trial 5 to trial 6 in both groups (cardiac arrest: P < 0.001; healthy controls: P < 0.001), but no further forgetting from trial 6 to trial 7, again for both groups (cardiac arrest: P = 0.748; healthy controls: P = 0.563).

Comparing performance in the recognition trial, Mann–Whitney–U-test revealed no significant group difference in both indicators (hits: \( M_{\text{cardiac arrest}} = 84\% \) versus \( M_{\text{controls}} = 89\% \); P = 0.167; correct rejections: \( M_{\text{cardiac arrest}} = 93\% \) versus \( M_{\text{controls}} = 95\% \), P = 0.106). The same was found when combining both measures into one single measure of recognition discrimination sensitivity d’ (P = 0.443).

3.1.2. CPC 1 patients versus CPC 2 patients versus healthy controls

The 5 (trials 1–5) × 3 (group: controls versus CPC 1 versus CPC 2) ANOVA again revealed a significant overall group difference (P < 0.01; \( \eta^2 = 0.260 \)). This difference was due to healthy controls showing better overall performance than CPC 2 (P < 0.001) and CPC 1 showing better overall performance than CPC 2 (P < 0.05), but healthy controls and CPC 1 did not differ (P = 0.548). A main effect was also found for trial repetition indicating an increase in performance over time across all groups (P < 0.001; \( \eta^2 = 0.714 \)). Most importantly, an interaction between group and trial repetition was found (P < 0.001; \( \eta^2 = 0.243 \)). As depicted in Fig. 3 – Panel B, post hoc tests revealed a cross-over in performance on the CPC 1 group across trials. Trial 1: CPC 1 > healthy controls > CPC 2 (P < 0.05; P < 0.05, respectively); trial 2: CPC 1 = healthy controls > CPC 2 (P = 0.860; P < 0.05, respectively); trial 3: healthy controls > CPC 1 (P = 0.873), healthy controls > CPC 2 (P < 0.05), CPC 1 = CPC 2 (P = 0.067); trial 4: healthy controls > CPC 1 = CPC 2 (P < 0.05; P < 0.05; CPC 2 = CPC 1 = 0.017; P = 0.197, respectively). This interaction was due to significant group effects only emerging for trials 4 and 5 (trial 1: P = 0.163; trial 2: P = 0.252; trial 3: P = 0.078; trial 4: P < 0.01; trial 5: P < 0.001). Post hoc tests further revealed showed that the two latter differences were largely due to healthy controls being better than CPC ≤ 8 (trial 4: P < 0.001; trial 5: P < 0.001) but all other groups did not differ. Comparing performance in the interference list, a Mann–Whitney–U-test revealed no significant group difference (P = 0.753).

Additionally, we compared the patients’ cognitive performance according to GCS on hospital admission and CPC at the time of the interview in all other memory tests administered. However, besides the reported differences in RAVLT trials 1–5 no other differential effects regarding CPC or GCS subgroups were found.

3.2. Digit-span-backwards from Wechsler Adult Intelligence Scale–Revised

We could demonstrate within an ANOVA revealed lower working memory span for cardiac arrest patients (P < 0.001; \( \eta^2 = 0.279 \)) compared to the healthy controls.

3.3. Red-Pencil-Test

Concerning prospective memory function we were able to show significant impairment in cardiac arrest patients (P < 0.05) compared to the healthy controls.

3.4. Logical memory subscale from Wechsler Memory Scale–Revised

Moreover within probe recall, cardiac arrest patients recalled less details (P < 0.001; \( \eta^2 = 0.612 \)) than healthy controls.

4. Discussion

Sudden cardiac arrest survivors, who were categorized as neurologically intact according to conventional CPC measures, were
revealed to show reduced memory performance in several but not all examined memory dimensions. Especially, resource-demanding memory tests such as delayed free recall, learning, working memory, prospective memory and prose recall were affected. However, short-term memory processes, even though tested via free recall tests, as well as recognition memory were revealed to be comparable to the control group. With respect to immediate free recall and learning performance, the present results are partly in line with previous studies, but also reveal differential effects when applying a more fine-grained analytical approach. For example, van Alem et al. found that patients 6 months after cardiac arrest scored impaired for immediate free recall using the same instrument (RAVLT) as the present study. Similarly, Sauve et al. also reported similar results using the RAVLT but additionally showed an improvement of performance within the first 6 months following the cardiac arrest, which confirmed earlier findings. However, our results suggest that more detailed analyses of the first 5 trials reveals a new insight into this cognitive deficit. Our patients scored equal for the first 3 trials of the RAVLT and for the interference list indicating that short-term free recall might not be impaired at all (except for patients with CPC 2 who were impaired in all 5 trials. The fact that the difference in performance became significant only during the trials 4–5 shows that rather resource demanding memory functions requiring the ability to organize and re-construct acquired information might be (particularly) impaired. Comparing our results with previous published data reveals another interesting pattern. In the Van der Elst study that focused on age differences across adulthood younger adults were found to outperform older adults mainly because of a better performance on Trial 1 – the learning pattern was similar across age groups. In contrast, within our study, patients showed comparable performance at the beginning but differed in their subsequent learning gains. This suggests that cardiac arrest-related differences in RAVLT performance were especially manifest in a qualitative and not just in a quantitative way. Interestingly, the rate of forgetting during the RAVLT did not differ between groups. In contrast to previous studies our patients...
Table 1
Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 33)</th>
<th>Controls (n = 33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>4 (12)</td>
<td>0</td>
<td>0.114</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>5 (15)</td>
<td>0</td>
<td>0.053</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (27)</td>
<td>1 (3)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>4 (12)</td>
<td>0</td>
<td>0.114</td>
</tr>
<tr>
<td>Chronic obstructive lung disease, n (%)</td>
<td>3 (9)</td>
<td>0</td>
<td>0.238</td>
</tr>
<tr>
<td>Peripheral arterial or cerebrovascular disease, n (%)</td>
<td>4 (12)</td>
<td>0</td>
<td>0.114</td>
</tr>
<tr>
<td>Psychopharmacaa at the time of the test, n (%)</td>
<td>7 (21)</td>
<td>2 (6)</td>
<td>0.149</td>
</tr>
<tr>
<td>ACE-I or ATB therapy at the time of the test, n (%)</td>
<td>19 (58)</td>
<td>1 (3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Cause of cardiac arrest  Initial ECG rhythm

<table>
<thead>
<tr>
<th></th>
<th>Ventricular fibrillation, n (%)</th>
<th>Time from collapse to ROSC min. (SEM)</th>
<th>Defibrillations needed to ROSC n (SEM)</th>
<th>Total dose of epinephrine within CPR mg (SEM)</th>
<th>pH-value on admission (SEM)</th>
<th>Serum lactate on admission mmol L⁻¹ (SEM)</th>
<th>Use of therapeutic hypothermia n (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac, n (%)</td>
<td>22 (67)</td>
<td>23 (70)</td>
<td>13.1 (2.5)</td>
<td>2.2 (0.5)</td>
<td>2.2 (0.4)</td>
<td>7.2 (0.03)</td>
<td>6.2 (0.6)</td>
</tr>
<tr>
<td>Pulmonary, n (%)</td>
<td>4 (12)</td>
<td>1 (3)</td>
<td>2.2 (0.5)</td>
<td>2.2 (0.4)</td>
<td>7.2 (0.03)</td>
<td>6.2 (0.6)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Intoxication, n (%)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>2.2 (0.5)</td>
<td>2.2 (0.4)</td>
<td>7.2 (0.03)</td>
<td>6.2 (0.6)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Hypothermia, n (%)</td>
<td>1 (3)</td>
<td>7 (21)</td>
<td>2.2 (0.5)</td>
<td>2.2 (0.4)</td>
<td>7.2 (0.03)</td>
<td>6.2 (0.6)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>4 (12)</td>
<td>1 (3)</td>
<td>2.2 (0.5)</td>
<td>2.2 (0.4)</td>
<td>7.2 (0.03)</td>
<td>6.2 (0.6)</td>
<td>17 (22)</td>
</tr>
</tbody>
</table>

Discrete data are demonstrated in counts (%), continuous data as mean (standard error of the mean). Differences in baseline characteristic in patients and controls are demonstrated within discrete data and were analyzed using Chi-Square test. Bold values demonstrating statistical significance.

Table 2
Cognitive test performance.

<table>
<thead>
<tr>
<th></th>
<th>Cardiac arrest patients</th>
<th>Healthy control patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT recognition hits (IQR)</td>
<td>13 (11–15)</td>
<td>14 (13–15)</td>
<td>0.167</td>
</tr>
<tr>
<td>RAVLT recognition correct rejections (IQR)</td>
<td>34 (33–35)</td>
<td>35 (34–35)</td>
<td>0.106</td>
</tr>
<tr>
<td>Digit span backwards (SEM)</td>
<td>5.25 (0.36)</td>
<td>7.82 (0.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complex prose recall (SEM)</td>
<td>10.78 (0.83)</td>
<td>20.73 (0.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Red pencil test [3 correct]</td>
<td>45</td>
<td>73</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Continuous data are presented as median (interquartile range) and mean (standard error of the mean). Differences in test-performance are demonstrated within categorical data and were analyzed using Mann-Whitney U test. Bold values demonstrating statistical significance.

scored impaired in working memory as well.̓ This inconsistency might result from the different time interval between the cardiac arrest and the interview as our test was performed much earlier after the cardiac arrest so working memory might improve over time. However, as working memory span can be seen as a rather resource intensive memory function requiring the simultaneous storage and adaptation of information, the result obtained seems to fit nicely to the overall pattern observed in the present data set. Our study is the first to reveal an impairment of cardiac arrest survivors in prospective memory. Conceptually, this is in contrast to some current models of prospective memory – e.g., the Multiprocess View 23 – which assume prospective memory tasks such as the red pencil test to be associated with rather automatic retrieval processes that should be spared in a population with intact recognition abilities. However, other frameworks such as Craik’s 24 seminal memory framework suggest that prospective memory performance might be a rather resource demanding task as it requires the self-initiated execution of an intention. However GCS on admission reflects the immediate effect of cerebral ischemia on neurological function of patients after cardiac arrest. Therefore, we expected that cognitive performance of patients arriving conscious at the emergency department after only short cardiopulmonary resuscitation (e.g. only defibrillation for witnessed ventricular fibrillation) would be decisively better than performance of patients who were comatose upon arrival (Tables 1 and 2). Our results largely contradict this assumption as patients who regained consciousness right after resuscitation seem to have no deficits in immediate recall and learning but present with the same cognitive impairments as unconscious cardiac arrest survivors in all other areas suggesting extremely vulnerable neurons being responsible for most memory functions. This finding is supported by Weigl et al. who found cognitive deficits in patients after implantable cardioverter defibrillator implantation whose cumulative cardiac arrest times were only 25 s.̓

Clearly, further studies will have to follow up on this initial finding and specifically target prospective memory in cardiac arrest survivors. From a clinical perspective, given the relevance of prospective memory and learning for independence and everyday functioning, it will be important to further examine potential everyday consequences of the obtained prospective memory deficit. Based on a potential influence of the mentioned impairment in the patients’ quality of life and ability to work, it seems crucial to target memory-function specific rehabilitation addressing “mnemotechnic” exercises. A targeted rehabilitation in this field may improve the quality of life and result in a faster return of the patients’ ability to work. Undoubtedly the contemplated potential of cerebral recovery is depending on a variety of confounding factors. Those factors need to be elucidated in further studies.

5. Limitations

As one potential limitation one might argue that it seems quite early to perform extensive cognitive testing 4 weeks after a cardiac arrest. However, previous studies have successfully tested patients a few weeks after cardiac arrest, stroke and traumatic brain injury. A potential lack in follow-up analysis, as well as a lack in the analysis of recovery or decline in the study population has to be mentioned as a limitation. Nevertheless, examining the research questions of the present study using longer follow up times is clearly needed to corroborate the results obtained and/or explore potential recovery processes. Moreover the small sample size of our study population
represents a major limitation. However a lack in evaluation of baseline memory function before cardiac arrest could also be addressed as a potential limitation, but seems to be almost impossible to elucidate. As a statistical bias, the control group was not matched for co-morbidities, which might be cofounding factors.

6. Conclusion

Our findings have several conceptual, clinical and methodological implications. From a conceptual perspective, memory function after cardiac arrest was found to be particularly impaired in resource demanding memory qualities such as delayed recall or working and prospective memory. In contrast, basic short-term memory storage appeared to be spared. Future studies will have to delineate possible conceptual loci of this impairment.

Conflicts of interest statement

No conflicts of interest to declare.

References