Rehabilitation after Resuscitation

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Chapter 4

Out-of-hospital cardiac arrest survivors with cognitive impairments have lower exercise capacity

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Abstract

Background
Hypoxic brain injury is described in up to 40% of survivors after out-of-hospital cardiac arrest (OHCA). Besides cognitive impairments, lack of circulation may also affect exercise capacity. It is not known if exercise capacity of patients with cognitive impairments differs from other OHCA survivors.

Methods
This retrospective cohort study included patients ≥18 years with myocardial infarction (MI) as cause of OHCA admitted for cardiac rehabilitation between February 2011 and April 2014. Data in socio-demographic, OHCA and medical interventions were retrieved. Cognitive functioning was determined with the Mini-Mental State Examination, Cognitive Failures Questionnaire and the Informant Questionnaire on Cognitive Decline in the Elderly. Exercise capacity (VO2peak), workload (Watts) and blood pressure (mmHg) were measured at maximum cardiopulmonary exercise. Heart rate (bpm) was measured at rest and maximum exercise and Metabolic Equivalents of Tasks (MET) were calculated.

Results
65 patients after OHCA caused by MI were included (85% male, median age 60 years). Of 53 patients Cardio Pulmonary Exercise Test data was available of which nine patients showed cognitive impairments.
Significant differences ($p < 0.05$) in exercise capacity were found between patients with and without cognitive impairments: VO2peak (median 14.5 vs 19.7 ml/kg/min), workload (median 130.0 vs 143.5 W) and MET's (median 4.1 vs 5.6).

Conclusion
Based on this small study, there seems to be a correlation between cognitive impairments and lower exercise capacity in patients referred for rehabilitation after OHCA caused by MI. It seems sensible for rehabilitation programs to take the lower exercise capacity of patients with cognitive impairments into account.

Introduction

In Europe survival rate after out-of-hospital cardiac arrest (OHCA) is on average 10% [1]. Initial shockable rhythm show higher survival rates (44%) when compared to non-shockable rhythm (3%) [2]. Recent studies show higher survival rates in the Netherlands [3,4]. These higher survival rates might be due to short arrival times ambulance and increased use of Automatic External Defibrillators by bystanders.
OHCA can cause hypoxic brain injury which may lead to cognitive impairments [5]. In a systematic review, Moulaert et al. reported cognitive impairments in 42%-50% of all OHCA survivors [6]. One could postulate that patients with a more severe cardiac event have higher chances of cerebral oxygenation problems leading to cognitive impairments. Besides, the lack of circulation may not only cause cognitive impairments, but may also affect the cardiac muscle and thus affect exercise capacity [7]. However, data on this particular topic is scarce.
Up to 50% of the patients that survive an OHCA have a Myocardial Infarction (MI), and thus underlying cardiovascular disease, as cause of their cardiac arrest [8]. Exercising after MI significantly increases VO2peak (peak oxygen uptake), metabolic equivalents of tasks (METs) and anaerobic threshold (AT) [9–12]. Besides we know that physical exercises have a positive effect on both cognitive impairments and many of the established risk factors for cardiovascular disease [1,13,14]. Literature shows a relation between cardiovascular risk factors (CVR) and cognitive impairments: vascular disease and midlife hypertension, are correlated to progressive loss of memory and cognitive functions. Vascular cognitive impairments (VCI) is the umbrella term that covers the spectrum from mild cognitive deficits to vascular dementia [15–17]. Since many of the OHCA survivors suffer from cardiovascular disease, this may implicate that part of the cognitive impairments in the OHCA survivors were already present before the OHCA [18].
The aim of this prospective study is to determine whether there are differences in exercise capacity between MI-induced OHCA survivors with and without cognitive impairments. The results of this study are relevant for the design of rehabilitation programs after OHCA.

Methods

Study design

Data in this retrospective cohort study were collected as part of the integrated care pathway for OHCA survivors of the Rijnlands Rehabilitation Centre (RRC) in Leiden, the Netherlands. As all data were gathered for routine clinical care, the Medical Ethical Review Board of the Leiden University Medical Centre (LUMC) judged this study to be outside the remit of the Dutch Medical Research Involving Human Beings Act and provided a certificate of no objection.

Participants

All data of the consecutive OHCA survivors referred for integrated cardiac rehabilitation between 1 February 2011 and 30 April 2014 to the Rijnlands Rehabilitation Centre were included. Patients were selected if age ≥18 years and OHCA was caused by MI. Probable MI, possible MI and in-stent thrombosis with deficits on perfusion scan or Magnetic Resonance Imaging (MRI) were considered as MI. Patients were excluded if: MI occurred >48 h before OHCA; the cardiac arrest occurred in hospital.

In order to create comparable groups, this study only pertained patients with a MI as cause of the cardiac arrest. Their CVR factors are also taken into account. Integrated rehabilitation care pathway for OHCA survivors To achieve patient-centred cardiac and cognitive rehabilitation to all OHCA survivors and their spouses, cardiac and cognitive rehabilitation is coordinated in an integrated care pathway [19].

The integrated rehabilitation pathway, as used in the Rijnlands Rehabilitation Centre, focuses mainly on secondary prevention: restoration of exercise capacity and optimal cognitive functioning in order to achieve optimal participation in society, with minimal burden for spouses and society. Besides, tertiary prevention takes place in order to diminish the chance of new cardiovascular events. Therefore education was provided to all CA survivors and their family and a simple screening for cognitive problems was performed containing the Mini-Mental State Examination (MMSE), Cognitive Failure Questionnaire (CFQ) and the Informant Questionnaire on Cognitive Decline of the Elderly (IQCODE). Patients with possible cognitive impairments followed cardiac rehabilitation in a smaller group that was supervised both by a cardiac and a cognitive oriented physical therapist. Besides, patients

with cognitive impairments were offered an appointment with the cognitive rehabilitation physician. If needed, cognitive rehabilitation was started directly after the cardiac rehabilitation program [21].

Assessments

OHCA survivors were registered prospectively in the database of the integrated care path for OHCA survivors of the RRC. Data were imported from the Cardiac Rehabilitation Decision Support System 3.1.0 (Mediscore CARDSS, Itémedical, the Netherlands) and the medical record.

Socio-demographic characteristics, MI (location, Left Ventricle function: good >60%; reasonable 45–60%; moderate 35–45%; poor <35% based on the echo), data on acute treatment (Percutaneous Coronary Intervention, Coronary Artery Bypass Grafting and Internal Cardioverter Defibrillator) and risk factors (hypertension, hypercholesterolemia, diabetes mellitus, nicotine abuse and previous MI) were recorded. As part of the integrated care pathway all patients were screened on cognitive functioning within 2 weeks after hospital discharge and before the Cardio Pulmonary Exercise Testing (CPET). Unfortunately, no gold standard is available as a cognitive screening. The gold standard, to detect cognitive impairments, is an extensive neuropsychological test, that takes several hours. The MMSE, though no gold standard, is an often used short test to screen for cognitive deficits [20]. However, this test has a ceiling effect. In order to be more sensitive than the MMSE alone, we added the CFQ questionnaire about cognitive slips [21]. Besides we added the only well validated questionnaire for the recognition of cognitive impairments by caregivers: the IQCODE [22].

The MMSE is a well validated short, 24 item, face-to-face performed cognitive screening (scale ranging from 0 to 30 points). The test assesses multiple domains of cognitive functioning: orientation, memory, concentration, language and praxis. Unfortunately, the MMSE has a ceiling effect, which negatively influences the sensitivity. In this study therefore a relatively high cut off score of <28 was used based on the results of Bour et al. [23].

The CFQ is a 25 item questionnaire in which patients rate their perception of frequency of various cognitive slips in daily life. The items are related to memory and attention. The questionnaire takes about 10 min to complete and the scale ranges from 0 to 100. A higher score indicates worse perceived cognitive functioning. A score of >32 was used as cut off, based on the mean score of 31.8 (SD 11.1) Ponds

found in healthy subjects [24].
The partner was asked to complete the Dutch version of the short IQCODE. The 16 item questionnaire aims at cognitive functions like everyday memory and instrumental activities of daily living and compares the present functioning with the situation prior to the cardiac arrest. A higher score (range from 1 to 5) indicates a greater decline. Based on the findings of Jorm et al. we used the cut-off point of >3.6 [24].
Cognitive impairments were considered present if the score on the MMSE was <28 or the IQCODE was >3.6 or the CFQ was >32. Exercise capacity was measured 6–8 weeks after the MI, at the start of the cardiac rehabilitation by means of CPET on a bicycle ergometer with the following parameters: VO2peak; heart rate, blood pressure (systolic and diastolic), MET's and anaerobic threshold.
A twelve lead ECG was made during the CPET to retain heart rate. During CPET blood pressure was measured with a blood pressure monitor which was automatically controlled by the computer by using a cuff on the right arm of the patient (Riva-Rocci method) [25]. Blood pressure at maximum exercise and heart rate at rest and at maximum exercise were used for analysis.
Increasing the intensity of exercise will cause the heart rate and the systolic blood pressure to increase [26]. Systolic blood pressure and heart rate at maximum exercise were collected in order to be informed about the maximum effort patients gave.

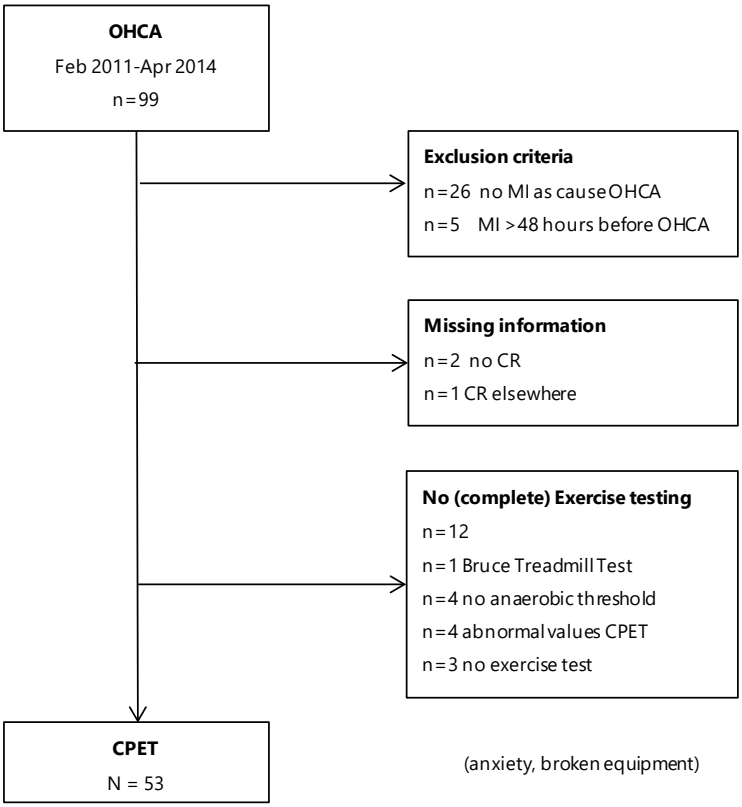
Statistical analysis
All statistical analyses were performed using IBM SPSS Statistics 22 software package. Descriptive statistics were used to present socio-demographic characteristics, OHCA and treatment results of CPET. Differences in exercise capacity between patients with and without cognitive impairments were determined with the Mann-Whitney U test. Because of the small sample sizes, dichotomous variables were tested 2-sided with use of the Fisher's exact test, unknown variables were left out. For all analyses a p-value of ≤0.05 was used as statistically significant.

Results

Participants

Between 1 February 2011 and 30 April 2014, 99 OHCA survivors were referred for cardiac rehabilitation. Patients were excluded when the OHCA was not caused by an MI (n = 26) or in case of not starting cardiac rehabilitation (n = 3). In total 65 patients with myocardial infarction were included for this study (Fig. 1) of which 53 patients had an adequate CPET.

Figure 1. Flow chart of patient inclusion



OHCA Out of Hospital Cardiac Arrest; MI Myocardial Infarction; CR Cardiac Rehabilitation; CPET Cardio Pulmonary Exercise Test

In 12 of the 65 patients no adequate CPET data were available. One patient was excluded because the Bruce Treadmill Test was performed instead of CPET. In four patients no AT was found caused by extreme tiredness before reaching AT. In five patients no CPET data was available due to a temporarily technical defect in the recording of the data. One patient was too afraid to start CPET and of one patient no CPET data could be retrieved in medical record other than CPET that was performed. Three of these 12 patients had cognitive impairments based on the MMSE, CFQ or IQCODE.

Characteristics of patients admitted for rehabilitation

Table 1 shows the sociodemographic and disease characteristics of the patients. The time between OHCA and CPET (median 4, range 2–32 weeks) was within the aimed time frame of maximal 8 weeks after the OHCA as protocolled in the rehabilitation centre. Although it was not a significant difference ($p = 0.192$) it seems that patients with cognitive impairments start later with cardiac rehabilitation (10 weeks vs 4 weeks) than patients without cognitive impairments.

Nine of the remaining 53 patients had cognitive impairments after OHCA according to one or more of the three instruments for cognitive functioning: 4 scored below the cut-off on the MMSE, 3 on the IQCODE and 3 on the CFQ (one patient scored on both CFQ and IQCODE).

Table 1 shows that, apart from relatively fewer patients with diabetes in the group of patients without cognitive impairments ($p = 0.03$), there were no statistically significant differences between the two subgroups. Left ventricular function was more often unknown for patients with cognitive deficits (56% vs 25%).

Table1 Characteristics at baseline of 65 OHCA survivors with myocardial infarction

	all patients	CPET			
		total patients	no cognitive impairments	cognitive impairments	p-value[a]
	n=65	n=53	n=44	n=9	
Age in years, median (range)	60 (36-84)	61 (10.1)	60 (42-84)	62 (49-74)	.492
Body Mass Index, median (range)	26.1 (19.5-37.9)	26.4 (19.5-37.9)	26.2 (19.5-33.3)	26.8 (21.5-37.9)	.421
Time CPET after CA (week), median (range)	4.4 (2.0-31.7)	4.4 (2.4-31.7)	4.3 (2.4-31.7)	9.9 (2.4-18.7)	.192
Male gender, n (%)	55 (84.6)	45 (84.9)	38 (86.4)	7 (77.8)	.611
Infarct location, n (%)					1.000
Anterior, anterolateral or anteroseptal	25 (38.5)	18 (33.9)	15 (34.1)	3 (33.3)	
Inferior, infero-posterior or apical	23 (35.4)	20 (37.7)	17 (38.6)	3 (33.3)	
NSTEMI	3 (4.6)	2 (3.8)	2 (4.5)	-	
Location unknown	14 (21.5)	13 (24.5)	10 (22.7)	3 (33.3)	
Acute treatment, n (%)					
PCI	54 (83.1)	42 (79.2)	35 (79.5)	7 (77.8)	1.000[a]
CABG	10 (15.4)	10 (18.9)	8 (18.2)	2 (22.2)	1.000[a]
ICD	8 (12.3)	8 (15.1)	5 (11.4)	3 (33.3)	.124[a]
Beta blockers, n (%)	64 (98)	51 (96.2)	43 (97.7)	8 (88.9)	.313
Risk factors, n (%)					
Diabetes	5 (7.7)	5 (9.4)	2 (4.5)	3 (33.3)	.030
Hypertension	29 (45.3)	24 (45.3)	20 (45.5)	4 (44.4)	1.000
Hypercholesterolaemia	27 (42.2)	22 (41.5)	17 (37.8)	5 (55.6)	.464
Nicotine use before CA	29(44.6)	25 (47.2)	20 (44.7)	5 (55.6)	.719
Left ventricle function, n (%)					.381
good	23 (35.4)	21 (39.6)	18 (40.9)	3 (33.3)	
reasonable	7 (10.8)	6 (11.3)	6 (13.6)	-	
moderate	10 (15.4)	7 (13.2)	7 (6.8)	-	
poor	3 (4.6)	3 (5.7)	2 (34.1)	1 (11.1)	
unknown	22 (33.8)	16 (30.2)	11 (4.5)	5 (55.6)	
Previous myocardial infarction	6 (9.2)	5 (9.4)	3 (6.8)	2 (22.2)	.196

OHCA out of hospital cardiac arrest, CPET cardio pulmonary exercise testing, NSTEMI Non ST-segment elevation myocardial infarction, PCI Percutaneous coronary intervention, CABG Coronary artery bypass graft, ICD Implantable cardioverter defibrillator, CA cardiac arrest
[a] Fisher exact or Mann-Whitney U test

In Table 2 parameters of exercise capacity of the total CPET group and the two subgroups are presented. No differences were found for heart rate, systolic and diastolic blood pressure in rest and at maximum exertion.

Patients with cognitive impairments showed a significant lower VO2peak (median 14.5 ml/kg/min) if compared with patients with no cognitive impairments (median 19.7 ml/kg/min).

This difference was also consistently found for workload (p = 0.004) and METs (p = 0.003). Patients with cognitive impairments showed a lower workload than patients with no cognitive impairments (median 130.0; IQR 103.0–151.0 vs median 143.5; IQR 114.5–167.5) and lower METs (median 5.6; IQR 4.9–7.1 vs median 4.1;IQR 3.3–5.2 MET).

Table 2 Values Cardiopulmonary exercise testing (CPET) at baseline.

	all patients	**cognitive impairments**		
	n=53	No (n=44)	Yes (n=9)	p-value*
	median (IQR)	median (IQR)	median (IQR)	
VO2peak (ml/kg/min)	19.3 (15.2-23.9)	19.7 (16.9-24.8)	14.5 (11.3-18.1)	.004
VO2AT (ml/kg/min)	15.6 (13.1-18.4)	16.4 (14.0-19.5)	13.8 (9.7-15.5)	.006
Load (W)	139.0 (110.5-165.0)	143.5 (114.5-167.5)	130.0 (103.0-151.0)	.004
Load (%)	90.0 (73.5-111.5)	102.0 (79.5-116.0)	68.0 (52.0-86.5)	.006
Load AT (W)	98.0 (73.5-112.5)	99.0 (78.0-117.8)	72.0 (60.5-94.5)	.021
METs	5.5 (4.4-6.7)	5.6 (4.9-7.1)	4.1 (3.3-5.2)	.003
METs (%)	81.0 (62.5-96.00)	89.0 (69.3-97.8)	61.0 (54.0-70.5)	.003
HRrest (beat/min)	61.0 (52.5-70.5)	60.0 (51.3-69.5)	65.0 (61.0-74.0)	.115
HRmax (beat/min)	120.0 (107.0-135.0)	120.5 (107.3-141.8)	112.0 (104.5-125.0)	.184
RR_{max} systolic (mmHg)	185.0 (155.0-200.0)	187.0 (156.5-205.3)	177.0 (139.5-192.5)	.142
RR_{max} diastolic (mmHg)	77.0 (72.0-85.0)	78.5 (75.0-88.75)	75.0 (62.5-80.0)	.086

VO2peak Peak oxygen consumption, VO2AT Oxygen consumption anaerobic threshold, W Watt, MET Metabolic Equivalent of Tasks HRrest Heart Rate in rest, HRmax Heart Rate at maximum exercise; RRmax Riva-Rocci at maximum exercise.
* Mann-Whitney U test

Discussion

Based on this small study, there seems to be a correlation between cognitive impairments and lower exercise capacity in patients referred for rehabilitation after OHCA caused by MI. Effects were seen in VO2peak, work load and METs.

In literature a broad range of VO2peak is found in patients after MI with a variation of 13.9 up to 32.3 ml/kg/min [11,12]. Our patients after OHCA caused by MI showed a median VO2peak of 19.3 ml/kg/min, which is within range of patients after MI without OHCA. Even the cognitive impaired patients, that score significantly below patients without cognitive impairments, score within this range (14.5 ml/kg/min). Consistent data were found for workload and METs in which also significant differences were found between patients with and without cognitive impairments (respectively 130W vs 143.5W and 4.1 vs 5.6 MET). Although the aetiology of the difference in exercise capacity for OHCA patients with and without cognitive impairments is not yet clear one might postulate that patients with cognitive impairments suffered from more severe hypoxia, which may also effect other organ systems. A study by Picano et al. supports this: They describe the influence of different physiological characteristics of cardiovascular hemodynamics and their mutual cohesion. One of their conclusions is that cognitive performance is associated with the maximum aerobic exercise capacity which is dependent on size infarction and ventricular function [9]. Unfortunately one of the limitations of this study is the lack of data indicating the size of the infarction, as could have been measured for instance with an area under the curve estimations of creatine kinase. Also, left ventricular function was not conclusive due to small numbers and >50% missing data in the cognitive impaired group.

One could also argue that patients with a lower exercise capacity and cognitive impairments after OHCA suffered already premorbid from a more severe cardio vascular disease. This theory is supported by the higher observed incidence of diabetes in the cognitive impaired group, since patients with diabetes have an increased risk of both cardio vascular diseases and cognitive deficits [18,27,28].

This idea is supported by the findings of Gottesman et al. They found that cardio vascular disease, hypertension and elevated systolic blood

pressure, is associated with more cognitive decline [29]. A bias in this study might be the relatively low percentage of patients with cognitive impairments after OHCA, since in this study we only found 18.8% of the patients to have cognitive impairments which is remarkably lower than the 42–50% found in literature [7]. Most probably, this difference can be explained by a selection bias: only patients that are fit enough are actually referred for rehabilitation after hospital discharge. Due to a structured care pathway in the affiliated area of the rehabilitation centre 80% of the OHCA survivors are referred for cardiac rehabilitation [30]. The 20% non-referrals went to nursing homes or had comorbidity preventing participation in rehabilitation (unpublished data). The non-referral group might have higher chances of cognitive impairments.

Another bias in this study might be caused by the screening. The IQCODE is not used in its original version ('10 years decline' in the original version versus 'prior to the cardiac arrest'). Thereby the cut-off value as used for the original version of the IQCODE (score 3.6) is not validated for the much shorter time-frame which is used in this study. Also for the CFQ no validated cut-off point was available and we used a cut-off at 32 (instead of a cut off at 21, mean –1SD). One might argue that the cut-offs, used in order not to overlook any patients, might be too wide [24,26].

This study indicates that patients with cognitive impairments after OHCA may have more severe cardiac impairments. Cognitive impairments may have a negative effect on the outcome of cardiac rehabilitation [31,32]. On the other hand physical exercises have a positive effect on both cognitive impairments and many of the established risk factors for cardiovascular disease [33–35].

We therefore strongly suggest that all survivors of cardiac arrest have both a check-up for cognitive impairments and cardiac impairments when attending a rehabilitation program. The cognitive screening should contain at least the MMSE or Montreal Cognitive Assessment. The screening can be performed during a face-to-face contact by a specialised nurse or physician assistant before the start of the outpatient rehabilitation program. In our experience, taking cognitive impairments into consideration prevents drop out of the cardiac rehabilitation group. The cognitive screening and psycho-education are highly appreciated by all patients and spouses, taking away

worries for those without cognitive impairments and providing the opportunity to tailor the rehabilitation program to individual needs for those with impairments. For patients with severe cognitive deficits, we recommend not to forget to perform CPET in order to be informed about their cardiac capacity.

Rehabilitation programs can take the lower exercise capacity of patients with cognitive impairments into account in order to provide individualised patient-centred rehabilitation care aiming at optimal participation.

Conclusion

This study shows that patients with cognitive impairments seem to have a lower exercise capacity when starting a rehabilitation program than patients without cognitive impairments after OHCA caused by MI. More research in larger prospective studies is needed.

Conflicts of interest

The authors report no conflicts of interest.

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