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Abstract

OBJECTIVE: Little is known about midlife risk factors of future cardiac arrest. Our objective was to evaluate cardiovascular risk factors in midlife in relation to the risk of Cardiac Arrest (CA) of cardiac and non-cardiac origin later in life.

METHODS: We cross-matched individuals of the population based Malmö Diet and Cancer study (n=30447) with the local CA registry of the city of Malmö. Baseline exposures were related to incident CA.

RESULTS: During a mean follow-up of 17.6±4.6 years, 378 CA occurred, of whom 17.2% survived to discharge. Independent midlife risk factors for CA of cardiac origin included coronary artery disease {HR 2.84 (1.86-4.34) (P<0.001)}, diabetes mellitus {HR 2.37 (1.61-3.51) (P<0.001)} and smoking {HR 1.95 (1.49-2.55) (P<0.001)}. Dyslipidemia and history of stroke were also significantly associated with an elevated risk for CA of cardiac origin.

Independent midlife risk factors for CA of non-cardiac origin included obesity (BMI>30 kg/m2) {HR 2.37 (1.51-3.71) (P<0.001)}, smoking {HR 2.05 (1.33-3.15) (P<0.001)} and being on antihypertensive treatment {HR 2.25 (1.46-3.46) (P<0.001)}.

CONCLUSION: Apart from smoking, which increases the risk of CA in general, the midlife risk factor pattern differs between CA of cardiac and non-cardiac origin. Whereas CA of cardiac origin is predicted by history of cardiovascular disease, dyslipidemia and diabetes mellitus, the main risk factors for CA of non-cardiac origin are obesity and hypertension. In addition to control of classical cardiovascular risk factors for prevention of CA, our results suggest that prevention of midlife obesity may reduce the risk of CA of non-cardiac origin.

Introduction

Sudden cardiac arrest, defined as "the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation"[1], is a rare but potentially reversible condition if treated with cardiopulmonary resuscitation (CPR). The progression of the condition could lead to sudden cardiac death (SCD)[2], which in turn is defined as a sudden arrest of presumed cardiac origin occurring within 24 hours after onset of any symptoms that could retrospectively be interpreted as being of cardiac origin[3]. Cardiac arrest is commonly subdivided into in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA). The incidence of IHCA is about 1-5/1000 admissions[4] and for OHCA 0,5/1000 population[5]. Depending on location, the survival rates ranges from 10,3% (OHCA) to 28% (IHCA) according to the 2013 report from the Swedish Cardiac Arrest Registry (SCAR)[4]. Other sources claim lower survival rates such as 5-10% for OHCA[4] and 15-20% for IHCA[5].

The main cause of cardiac arrest is believed to be cardiac disease, which accounts for approximately 2/3 of all cases[4]. Cardiac arrest with a non-cardiac etiology constitutes about 15-25 percent of cases and the etiology includes bleedings, intracranial hemorrhages and pulmonary embolism[6].

Many researchers have investigated cardiac arrest, both IHCA and OHCA, however, mainly focusing on overall survival and peri-arrest factors such as early defibrillation[7-9]. One limitation is that comorbidities, cardiovascular risk factors and current medications rarely are known. Another limitation is that these studies are usually burdened with a selection bias since the patients included already have experienced OHCA or IHCA and therefore represent a more morbid selection. So far, no study has prospectively examined cardiovascular risk factor pattern in relation to incidence of CA during long-term follow-up. Here, we addressed this issue by relating cardiovascular risk factor exposure in midlife to risk of CA of cardiac and non-cardiac origin later in life in a large

population-based prospective cohort study. In addition, midlife cardiovascular risk factors as well as peri-arrest factors were related to survival in subjects who did suffer a CA.

Materials and methods

Inclusion

The Malmö Diet and Cancer study (MDCS) is a community-based, prospective observational study of 30,447 participants drawn from ~230,000 residents of Malmö, Sweden. Men aged 46 to 73 years and women aged 45 to 73 years were invited to participate and were enrolled between 1991 and 1996. Details of the MDC design have been previously reported[10]. The baseline investigation included a physical exam, anthropometry, blood pressure measurement, blood sampling including measurement of apolipoproteins and a questionnaire in which the participants answered questions about their lifestyle, diet, socioeconomic factors, current medication, current health and previous diseases.

The local cardiac arrest registry at Skåne University Hospital, Malmö, was created in 1999 and covers 2758 cases of cardiac arrest up until 2012. All suspected cardiac arrests result in initiation of an automatic alarm, which reaches the emergency team. After completing the resuscitation, data from every case is registered and sent to the local cardiac arrest registry. A specialized nurse reviews the data, further data is then collected from the medical records and a report is sent to the national cardiac arrest registry including information about outcome, initial cardiac rhythm, time to defibrillation and place of the arrest noted.

Using the Swedish personal identification number, we cross-matched individuals of the MDCS material with the local cardiac arrest registry of the city of Malmö. The local ethics committee of Lund University approved the study. The participants provided written consent upon inclusion in the MDCS but no consent was obtained for our study since most of the participants were deceased.

This procedure was approved by the ethics committee.

In the MDCS there were 518 incident cases of cardiac arrest. A medical doctor then reviewed each case in the medical records system "Melior". The following cases were excluded: 75 cases were not real cardiac arrests (seizures, fainting, stroke, non-pulseless VT, bradycardia, 34 cases were duplicates, 13 cases were lacking data. 11 cases had 2 separate cardiac arrests, of which only the first was included, 3 cases were suicides, 1 case was a procedure related accident (PCI) and 3 cases were accidents. Thus, 378 cases remained for further analysis. Cause of death was recorded by reviewing the autopsy reports of each individual case. In cases where no autopsy had been performed the cause of death was only recorded if clinically determined as "Sudden cardiac death" according to the previously mentioned definition[2]. In cases where the cause of death was not clinically determined nor autopsy was performed, we used the Utstein definition of cardiac origin[1]. All the cases of cardiac arrest were then divided into arrest of cardiac or non-cardiac origin.

Relevant baseline exposure data were obtained from the MDCS baseline exam whereas, factors with close temporal relationship to the cardiac arrest, i.e periarrest factors, were collected from the local cardiac arrest registry and additional data related to the cardiac arrest were collected from the medical records. Variables with missing values exceeding 20% were excluded from analysis.

Definitions

Obesity was defined as a body mass index (BMI) higher than 30 (kg/m^2). Diabetes mellitus was defined as self-report of a physician´s diagnosis of diabetes, having a fasting whole blood glucose of ≥6.1 mM (corresponding to plasma glucose of ≥7.0 mM) or being on antidiabetic medication. Hypertension was defined as being on antihypertensive medication. Socioeconomic variables (living alone, education) and current use of medications were retrieved from the MDCS baseline questionnaire. Blood samples were collected from MDCS participants at baseline and serum and plasma was separated within one hour and stored at -80 °C. Serum concentrations of Apolipoprotein

A1 (ApoA1) and B (ApoB) were measured by Quest Diagnostics (San Juan Capistraon, CA), blinded to case-control status, using an immunonephelometric assay run on the Siemens BNII (Siemens, Newark, DE). The inter-assay variability was < 4.0% for both ApoA1 and ApoB. Occurrence of cardiovascular diseases prior to the MDCS baseline exam were assessed by linking the Swedish personal identification number with the national inpatient registry. CAD was defined as fatal or non-fatal myocardial infarction or having had coronary artery by-pass grafting (CABG) or percutaneous coronary intervention (PCI). Myocardial infarction was defined on the basis of International Classification of Diseases 9th and 10th Revisions (ICD9 and ICD10) codes 410 and I21, respectively. PCI was defined based on the operation codes FNG05 and FNG02. CABG was identified from national Swedish classification systems of surgical procedures, the KKÅ system from 1963 until 1989 and the Op6 system since then. CABG was defined as a procedure code of 3065, 3066, 3068, 3080, 3092, 3105, 3127, 3158 (Op6) or FN (KKÅ97). Congestive heart failure was defined as diagnosis codes 427.00, 427.10 and 428.99 for International Classification of Diseases 8th Revision (ICD-8), 428 for the ICD9 and I50 and I11.0 for the ICD-10. Stroke was assessed using codes 430, 431, 434 and 436 (ICD9) and I60, I61, I63, and I64 (ICD10). Atrial fibrillation and atrial flutter was defined using diagnosis codes 427.92 (ICD-8), 427D (ICD-9) and I48 (ICD-10).

Statistical analysis

Mean and standard deviation (SD) were used as descriptive measures for normally distributed continuous variables, whereas median and interquartile range (IQR) was used for skewed distributions. For continuous variables students T-test or Mann-Whitney test was used to compare group means (medians) and Chi-square test and Fischer's exact test were used for comparison of group frequencies. Variables, which displayed significant differences between groups, were then analysed using either Cox proportional hazards model or logistic regression analysis creating a model of independent risk factors. Cox regression was used for event analyses with long-term

follow-up, while logistic regression was judged more appropriate in analyses that were not time dependent. A two-sided P-value <0.05 was considered as nominally statistically significant. All analyses were performed using SPSS statistical software version 21.0 for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Results

In the MDCS material, 60.2% were female and mean age at the time of screening was 58.0 years (SD 7.6). The mean follow-up time was 17.6 years (SD 4.6). The midlife characteristics, i.e. baseline characteristics (1991-1996) are shown in Table 1, with the population divided into subjects who did not develop cardiac arrest during follow up and those who developed cardiac arrest of cardiac and non-cardiac origin.

During follow-up, over-all 378 incident cases of cardiac arrest occurred, and of these 65.9% were males. Mean age at cardiac arrest was 74.6 years (SD±7.1) and 63.5% were OHCA. Return of spontaneous circulation (ROSC) was reached in 37.3% of CA cases, but in total, only 17.2% were discharged alive from the hospital. The cause of the arrest was determined to be cardiac in 68.7% of the cases. Independently of IHCA or OHCA, an initial shockable rhythm of either ventricular fibrillation (VF) or ventricular tachycardia (VT) occurred in 26.2%, while 59.5% had asystole and 14.3% pulseless electrical activity (PEA). Nineteen percent of the cases were admitted to a ward with supervision by telemetry. Survival to discharge differed depending on the origin of CA; 21% survived among the patients suffering a CA of cardiac origin while only 7.5% survived among those with CA of non-cardiac origin. Concerning presenting diagnosis, 20.1% of the patients had ST-elevation myocardial infarction (STEMI), followed by non ST-elevation myocardial infarction (NSTEMI) (9.3%), chronic heart failure (7.4%) and chronic ischemic heart disease (6.6%). The

non-cardiac causes were dominated by respiratory failure (6.3%), pulmonary embolism (5.3%) and ruptured aortic aneurysm (4.5%).

In table 2 the final multivariate models for risk of arrest of cardiac and non-cardiac origin are presented. The risk profiles differ greatly; arrest of cardiac origin seem to be clearly associated with prevalent cardiovascular disease and classical risk factors for developing cardiovascular disease such as male sex, age, dyslipidemia, diabetes and smoking. In the risk profile of arrest of non-cardiac origin, the most important factors seem to be smoking, obesity and being on antihypertensive treatment. Exclusion of cases of CA of non-cardiac and cardiac origin respectively from the "non-event comparison group" did not change the results (data not shown).

In table 3, the relationship between all known pre- and peri-arrest factors known and survival are listed. Adding those variables from table 3 showing a significant association with survival and adjusting for sex and age at cardiac arrest produced a model shown in table 4. Shockable rhythm, arrest of cardiac origin and history of atrial fibrillation or flutter improved survival to discharge whereas OHCA reduced it.

Discussion

To our knowledge, this is the first study examining mid-life risk factors for cardiac arrest during long-term follow-up, as well as examining separately risk factors for cardiac arrests of cardiac and non-cardiac origin, respectively. We find a clear difference in midlife risk factors between cardiac arrest of cardiac and non-cardiac origin. In the group with arrest of cardiac origin the results show a typical cardiovascular risk factor pattern. In addition, a finding that surprised us was that living alone seems to be associated with a lower risk of CA of cardiac origin. The reason for this finding remains unclear, but in a subanalysis women were living alone in more often than men (28.3%, vs 18.9% p<0.001) and thus female sex, which by itself is protective against CA, may be one

explanation. We therefore tested for interaction between the variable of living alone and both gender and age on the outcome of CA of cardiac origin and found a non-significant interaction with gender (p=0.150) and a significant interaction with age (p=0.008). Subsequent stratification of the age variable (above or below mean age) in a Cox regression analysis showed that patients older than the mean age of 58 years explained the interaction of age on the "living alone"-variable (age<58 years: HR 1.29 CI 0.76-2.19, p=0.34, age>58 years: HR 0.45, CI 0.28-0.72, p=0.001).

In the group with cardiac arrest of non-cardiac origin, midlife smoking exposure and antihypertensive treatment are important risk factors. Interestingly, obesity was also significantly associated with an elevated risk of arrest of non-cardiac origin. Although our study is observational, and thus cannot prove causality between exposures and outcome, they suggest an important clinical implication; i.e. that apart from intensive cardiovascular risk factor control for prevention of cardiac arrest of cardiac origin, reduction of midlife obesity might prevent the risk of cardiac arrest of non-cardiac origin.

The cardiovascular risk factor pattern for arrest of cardiac origin resembles that in previous studies of sudden cardiac death. Although sudden cardiac death is a different entity (e.g. by definition always being fatal) than arrest of cardiac origin, these similarities in midlife risk factor pattern might be expected as there is overlap between the two[11-13]. This finding emphasizes the importance of aggressive preventive measures of cardiovascular risk factors since the ultimate outcome in the shape of a cardiac arrest carries such a high mortality rate.

Identification of midlife risk factors for cardiac arrest of non-cardiac origin is on the other hand completely new. Obesity is a growing global problem[14] and our finding adds cardiac arrest of non-cardiac origin as a novel and severe risk associated with being obese which further underlines the need of population strategies and individual patient efforts to prevent and treat obesity. Furthermore, our data encourages inclusion of cardiac arrest of non-cardiac origin, as well as its potential underlying triggering diseases, in ongoing and planned surgical and pharmacological intervention

trials for weight reduction.

It could be speculated that obesity is related to the most common cause of arrest of non-cardiac origin in our material, which was respiratory failure[15]. Pulmonary embolism was the second most common cause and its relation to obesity and hypertension has previously been investigated by several authors, among them Ageno et al[16]. Finally, smoking and hypertension are known risk factors for aortic aneurysm development[17], which could explain why ruptured aortic aneurysm was the third most common cause of arrest of non-cardiac origin.

Concerning factors at arrest, shockable rhythm and cardiac origin were clearly favorable for survival while out-of-hospital cardiac arrest was not. The increased survival of an arrest of cardiac origin could then possibly explain the finding of a lower ApoA1 being associated with improved survival. Interestingly, a history of atrial fibrillation or flutter was significantly associated with increased survival. The cause for this observation remains unclear, but there are probably confounders. Several mechanisms are possible; many patients in Sweden with atrial fibrillation are treated with anticoagulants[18]. This would protect against pulmonary embolism[19] and may therefore increase survival. Another possibility is that patients with arrhythmia are more prone to be admitted to a ward with telemetry, which is also known to increase survival[20].

One of the limitations of this study was that the participants of the MDCS were healthier than the non-participants, the incidence of cancer and the total mortality were lower among the participants[21]. Age was not significantly associated with survival in this study, but a clear limitation concerning this variable was a selection bias since only patients between 44 and 74 years of age were included in the MDCS-material. Another possible source of selection bias was that cases of CA potentially were missed between the inclusion to the MDCS (1991-1996) and the start of the local CA registry (1999). Unfortunately, post-arrest variables such as hypothermia and invasive

coronary angiography, which could affect the survival data were not recorded in this study.

Competing risk is another possible limitation that possibly could weaken the associations between risk factors and CA. However, we find it unlikely that the observed associations are exaggerated. Furthermore, our previous finding that heart rate and sodium were significantly associated with survival[20] could not be validated, due to missing data for these variables.

In conclusion, apart from smoking, which increases the risk of cardiac arrest in general, the midlife risk factor pattern differs between arrest of cardiac and non-cardiac origin. Whereas cardiac arrest of cardiac origin is predicted by history of cardiovascular disease, dyslipidemia and diabetes mellitus, the main risk factors for cardiac arrest of non-cardiac origin are obesity and hypertension. In addition to control of classical cardiovascular risk factors for prevention of arrest of cardiac origin, our results suggest that prevention of midlife obesity may reduce the risk of cardiac arrest of non-cardiac origin.

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Table 1. Basic characteristics, univariate analysis

Variable	Control group	Arrest of cardiac origin		Arrest of non-cardiac origin	
	(n=30069), n (%)	(n=272), n (%)	*p*	(n=106), n (%)	*p*
Male sex	n=11872 (39.5)	n=194 (71.3)	<0.001*	n=55 (51.9)	0.011*
Age (years)‖	57.6 (12.9)	62.3 (9.4)	<0.001†	62.6 (9.6)	<0.001†
Finished elementary school or higher (yes/no)	27905 (99,1)	254 (98.8)	0.582*	97 (100)	0.360*
Living alone (yes/no)	6965 (24,7)	43 (16.7)	0.003*	17 (17.5)	0.105*
Smoking (yes/no)	7961 (28,2)	93 (36.0)	0.006*	33 (34.0)	0.211*
Obesity (yes/no)	4167 (13,9)	47 (17.3)	0.110*	31 (29.2)	<0.001*
ApoA1 (mg/L)	156.8 (SD 28.2)	146.1 (SD 26.5)	<0.001‡	152.5 (SD 25.2)	0.149‡
ApoB (mg/L)	107.1 (SD 26.1)	117.6 (SD 25.1)	<0.001‡	108.2 (SD 21.6)	0.701‡
Systolic BP (mm/Hg)	141.0 (SD 20.0)	150.2 (SD 21.0)	<0.001‡	149.1 (SD 21.6)	0.145‡
Antiypertensive treatment (yes/no)	4558 (15,2)	68 (25.0)	<0.001*	35 (33.0)	<0.001*
Lipid lowering treatment (yes/no)	891 (3,0)	23 (8.5)	<0.001*	5 (4.7)	0.306*
Antidiabetic treatment (yes/no)	476 (1,6)	19 (7.0)	<0.001*	6 (5.7)	0.001*
Antiplatelet drug therapy (yes/no)	721 (2,6)	16 (6.3)	<0.001*	4 (4.0)	0.331*

History of prevalent CAD (yes/no)	732 (2,4)	33 (12,1)	<0.001*	8 (7,5)	0,001*
History of prevalent stroke (yes/no)	315 (1.0)	12 (4,4)	<0.001*	6 (5,7)	<0.001*
History of prevalent heart failure (yes/no)	83 (0.3)	3 (1.1)	0.043§	1 (0.9)	0.262§
History of prevalent atrial fibrillation or flutter (yes/no)	306 (1,0)	5 (1.8)	0.181*	1 (0.9)	1.00§
History of prevalent diabetes mellitus (yes/no)	1293 (4,3)	37 (13.6)	<0.001*	10 (9.4)	0.011*

*=Chi square, †=Mann-Whitney, ‡=Students T-test, §=Fischer's exact test, ||=median (interquartile range)

BP=blood pressure, CAD=Coronary artery disease

Table 2. Final multivariate predictors for arrests of cardiac and non-cardiac origin

Variable	Cardiac origin		
	HR	CI (95%)	p
Male sex	2.59	1.93-3.48	<0.001
Age (years)	1.09	1.07-1.11	<0.001
Living alone (yes/no)	0.68	0.48-0.96	0.026
Smoking (yes/no)	1.95	1.49-2.55	<0.001
ApoA1 (mgdL)	0.99	0.99-1.00	0.009
ApoB (mgdL)	1.01	1.01-1.02	<0.001
Antihypertensive treatment (yes/no)	1.19	0.88-1.61	0.257
History of stroke (yes/no)	1.60	1.32-1.94	<0.001
History of CAD (yes/no)	2.84	1.86-4.34	<0.001
History of heart failure (yes/no)	2.84	1.86-4.34	0.178
History of diabetes mellitus (yes/no)	2.37	1.61-3.51	<0.001

Variable	Non-cardiac origin		
	HR	CI (95%)	p
Male sex	1.86	1.25-2.78	0.002
Age (years)	1.09	1.06-1.13	<0.001
Smoking (yes/no)	2.05	1.33-3.15	0.001
Antihypertensive treatment (yes/no)	2.25	1.46-3.46	<0.001

Obesity (yes/no)	2.37	1.51-3.71	<0.001

CAD=Coronary artery disease, HR= Hazard ratio

Table 3. Univariate analysis of Survival, factors at arrest

Variable	Survival	Non-survival	p
	(n=65), n (%)	(n=313), n (%)	
Age (years)‡	73.7 (7.7)	75.3 (9.6)	0.505†
Male sex	42 (64.6)	207 (66.1)	0.814*
Telemetry (yes/no)	19 (29.2)	53 (16.9)	0.022*
Shockable rhythm (yes/no)	49 (75.4)	50 (16.0)	<0.001*
STEMI (yes/no)	21 (32.3)	55 (17.6)	0.007*
OHCA (yes/no)	26 (40.0)	214 (68.4)	<0.001*
Cardiac origin (yes/no)	57 (87.7)	215 (68.7)	0.002*
History of stroke (yes/no)	9 (13.8)	40 (12.8)	0.816*
History of CAD (yes/no)	43 (66.2)	169 (54.0)	0.072*
History of heart failure (yes/no)	19 (29.2)	46 (14.7)	0.005*
History of atrial fibrillation or flutter (yes/no)	24 (36.9)	62 (19.8)	0.003*
History of diabetes mellitus (yes/no)	16 (24.6)	77 (24.8)	0.970*

*=Chi square, †=Mann-Whitney, ‡=median (interquartile range)

CAD=Coronary artery disease, OHCA=Out-of-hospital cardiac arrest, STEMI=ST-elevation myocardial infarction

Table 4. Multivariate model of survival, factors at arrest

Variable	OR	CI (95%)	*p*
Shockable rythm (yes/no)	16.04	7.92-32.47	<0.001
Cardiac origin (yes/no)	2.80	1.05-7.48	0.041
OHCA (yes/no)	0.20	0.10-0.41	<0.001
History of atrial fibrillation or flutter (yes/no)	2.32	1.15-4.65	0.019

Adjusted for sex and age

OHCA=Out-of-hospital cardiac arrest, OR=Odds ratio,