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Ambulatory electrocardiographic monitoring as a diagnostic tool for ischemic heart disease in women

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Abstract

Introduction. Ischemic heart disease(IHD) is currently the leading cause of mortality in women. In this study we aimed to evaluate ambulatory electrocardiographic monitoring(AECGm) as a diagnostic test for IHD in women. **Material and method.** The study included 225 female who underwent AECGm divided into 2 groups: 136 previously diagnosed with IHD(IHD+) and 89 controls(IHD-). The IHD+ group was subdivided into AECGm ischemia subgroup(I+) and AECGm non-ischemia subgroup(I-). AECGm was assessed for presence of myocardial ischemia (ST segment depression >5mm), duration and ischemic load (the percentage that episodes of myocardial ischemia accounted throughout the recording). **Results and discussions.** Patients mean age was 62.31±12.51years. The IHD+ and IHD- groups were similar regarding associated risk factors (hypertension, obesity, dyslipidemia, diabetes mellitus), echocardiographic parameters (left ventricular size, ejection fraction, kinetic disorders), minimum and maximum heart rates(MaxHR) on AECGm. Statistically significant differences were identified regarding presence of atrial fibrillation episodes(AFibE) (IHD+:21.3% vs IHD-:8.9%), myocardial ischemia (IHD+:55.14% vs IHD-:42.69%), ischemic load (IHD+:15.23±30.54% vs IHD-:4.7±15.65%), duration of ischemia (IHD+:174.16±380.75 minutes vs IHD-:59.44 ± 209.02 minutes). In multivariate analysis, ischemia episodes, ischemic load and duration of ischemia were predicted by obesity, MaxHR and AFibE. Statistically significant differences were also identified regarding presence of AFibE (I+:30% vs I-:8.9%), MaxHR (I+:120 vs I-:111beats/minute), obesity (I+:20% vs I-:41%), diabetes mellitus (I+:16% vs I-:69%), hypertension (I+:76% vs I-:90%). **Conclusions.** Although myocardial ischemia was also present in IHD- group, our study demonstrated that the diagnosis of IHD can be established by AECGm using the threshold values of ischemic load (> 27%) and ischemic duration (> 315minutes).

Key words: *ischemic heart disease, ambulatory ECG monitoring, ischemic load, women, diagnostic tool,*

Introduction

Ischemic heart disease (IHD) has been considered as a men's disease but is currently the leading cause of death in both sexes. Moreover, annually, IHD causes a higher number of deaths among females than in males at older ages, according to World Health Organization statistics (1). Although IHD has been considered a disease of patients in high income countries, the cardiovascular mortality rate in women over 60 years is currently twice as high in developing vs. high income countries. This rate is higher in European middle-income countries, category in which Romania also falls, followed by the eastern Mediterranean region and the African regions (1).

Coronary angiography is considered gold standard in terms of the diagnostic tools for IHD. Women frequently present microvascular coronary disease therefor no pathological changes are detected on coronary angiography (2). The literature states that almost half of patients who underwent coronary angiography for symptoms of myocardial ischemia do not have obstructive coronary heart disease defined as stenosis >50% of the lumen of an epicardial artery (3,4).

Another diagnostic tool used for IHD is the exercise stress test. Because the physical condition is more precarious in females, patients cannot reach the maximal heart rate, so exercise stress test is often inconclusive (5).

Ambulatory electrocardiographic monitoring (AECGm) is an important non-invasive method for diagnosing IHD. Myocardial ischemia can occur in

asymptomatic patients, most often being intermittent, so the simple 12-lead ECG recording may not detect it. The introduction of AECGm has increased the chance of detecting myocardial ischemia (6). It has been shown that episodes of silent myocardial ischemia registered on AECGm have the same pathological significance as symptomatic ischemic episodes and it has been observed that the incidence of silent ischemia is much higher among the female population (7).

The need for a diagnostic tool more appropriate for women with IHD has thus emerged. In this study, we aimed to evaluate AECGm for this purpose.

Material and methods

Study population

We enrolled 225 consecutive female inpatients from the Cardiology Department of Rehabilitation Clinical Hospital of Cluj-Napoca registered in the AECG laboratory throughout a year. Women were retrospectively enrolled in two groups: the ischemic heart disease group (IHD+, n=136) which consisted of women with previously established diagnosis of ischemic heart disease and the control group (IHD-, n=89) which consisted of women without diagnosis of ischemic heart disease. Exclusion criteria were paced rhythm or inadequate recordings from Holter monitoring. The IHD+ group was subdivided into AECGm ischemia and AECGm non-ischemia. The study was approved by the Ethical Committee of Iuliu Hatieganu University of Medicine and Pharmacy of Cluj-Napoca, Romania.

In addition to baseline characteristics, clinical and paraclinical details were collected. Participants in the study were monitored by AECGm and underwent M-mode, two-dimensional and Doppler echocardiography.

The two groups were compared regarding associated risk factors (hypertension, obesity, dyslipidemia, diabetes mellitus), echocardiographic parameters (left ventricular size – diastolic (LVSD) and systolic diameters (LVDD), ejection fraction, kinetic disorders) and parameters registered on Holter ECG (minimum and maximum heart rates, atrial fibrillation episodes, presence of myocardial ischemia episodes, duration and ischemic load).

Assessment of ambulatory ECG recordings

Participants in the study were monitored by 12-lead 24-hours AECG (Labtech Instruments® Recorder version: 5.1.10.2559). A medical student processed the AECG recordings and a physician reviewed them. A recording was considered eligible if the following criteria were met: over 12 h of analyzable data, both daytime and night-time periods available. Tracings were reviewed for evidence of horizontal or down sloping ST segment depression ≥5 mm, duration and ischemic load defined as the percentage that episodes of myocardial ischemia accounted throughout the recording**.**

2.3 Statistical analysis

The results obtained were statistically processed using Microsoft Excel version 18 and Stata version 14.2. Case control analysis was performed using chi-square and Z-test test for categorical and quantitative variables, respectively. For multivariate data analysis we used multiple regressions (logistic and linear regressions for categorical vs quantitative variables). Data is presented as n (%) or mean ± SD. Statistically significant values are considered when $p \leq 0.05$.

Results

From the 225 female patients included in the study (fig. 1), 60% (136 patients) were anterior diagnosed with ischemic heart disease and 40% (89 patients) constituted the reference group. Mean age of the patients included in the study was 62.31 ± 12.51 years.

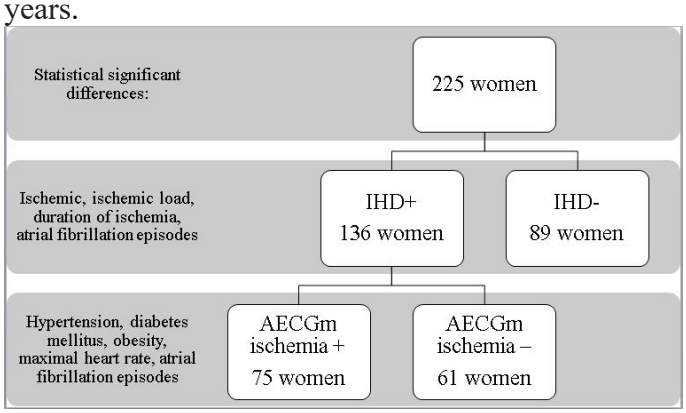

Fig. 1. Study design with results (IHD = ischemic heart disease, AECGm = ambulatory electrocardiographic monitoring)

Comparison of IHD+ and reference subjects

Table 1 compares the women in IHD+ group with reference subjects from IHD- group. Overall, no significant differences were noted regarding cardiovascular risk factors (hypertension, obesity, dyslipidemia, diabetes mellitus), echocardiographic parameters (left ventricular systolic and diastolic diameters, ejection fraction, kinetic disorders) and heart rate (maximal, minimal) on AECGm.

Statistically significant differences were identified regarding presence of atrial fibrillation episodes (more in IHD+), presence of myocardial ischemia episodes (more in IHD+), ischemic load (higher in IHD+) and episodic ischemia duration (longer in IHD+).

Table 1. Comparison of IHD+ and reference subjects.

Characteristics	IHD+ (n=136)	IHD- (n=89)	p-value
Hypertension (patients / %)	112 / 82%	5 / 6%	NS
Obesity (patients / %)	40 / 29%	18 / 17%	NS
Dyslipidemia (patients / %)	31 / 23%	15 / 17%	NS
Diabetes mellites (patients / %)	92 / 68%	54 / 60%	NS
LVDD (mm)	49,95 ± 7,58	47,7 ± 4,72	NS
LVSD (mm)	32,27 ± 7,4	30,92 ± 6,41	NS
EF (%)	49,69 ± 2,17%	50% ± 0.1%	NS
Myocardial dyskinesia (patients)	4	0	NS
Maximal HR (beats/min)	116 ± 22	120 ± 25	NS
Minimal HR (beats/min)	51 ± 11	52 ± 9	NS
Atrial fibrillation episodes (patients)	29	8	0.013744
Ischemia episodes (patient / %)	75 / 55.14%	38 / 42.69%	0.067793
Mean duration of ischemic episodes (min)	174,16 ± 380,75	59,44 ± 209,02	0.003646
Ischemic load[1] (%)	15,23 ± 30,54%	4,7 ± 15,65	0.000703

LVDD = left ventricular diastolic diameter
LVSD = left ventricular systolic diameter
EF = ejection fraction
HR = heart rate
NS = not significant

1. ischemic load defined as percentage that episodes of myocardial ischemia accounted throughout the recording

A binominal logistic regression was run to understand the effects of age, IHD, hypertension, obesity, diabetes mellitus, dyslipidemia, LVDD, LVSD, EF, myocardial dyskinesia, maximal and minimal heart rate and atrial fibrillation episodes on the presence of ischemia on AECGm. Obesity (p = 0.007), maximal HR (p = 0.012) and atrial fibrillation episodes (p = 0.011) statistically significantly predicted exam success, but remaining variables did not (table 2).

Table 2. Results of multiple analysis upon ischemia episodes

Logistic regression — Number of obs = 225; LR chi2(13) = 39.85; Prob > chi2 = 0.0001; Log likelihood = -136.02939; Pseudo R2 = 0.1278

Ischemia	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age	1.004188	.0142048	0.30	0.768	.97673	1.032419
IHD	1.730164	.5484811	1.73	0.084	.9294948	3.220532
Hypertension	.722674	.291146	-0.81	0.420	.3281074	1.591728
Obesity	.3683073	.1363638	-2.70	0.007	.1782614	.7609623
Diabetesmellitus	.5885259	.2325449	-1.34	0.180	.2712872	1.276738
Dislipidemia	1.55152	.5032682	1.35	0.176	.8215843	2.929966
LVDD	.9840335	.0411271	-0.39	0.700	.906639	1.068035
LVSD	1.038028	.0348776	1.11	0.267	.9718712	1.108688
EF	.8078815	.2304445	-0.75	0.455	.4618982	1.413022
Myocardialdyskinesia	1.623583	1.216755	0.65	0.518	.3737335	7.053215
MaximaHR	1.019214	.0077498	2.50	0.012	1.004137	1.034517
MinimalHR	.9743879	.0151218	-1.67	0.095	.9451958	1.004482
Atrialfibrillation	3.226387	1.484271	2.55	0.011	1.30957	7.948848
_cons	7383.994	106625.4	0.62	0.537	3.77e-09	1.44e+16

IHD = ischemic heart disease
LVDD = left ventricle diastolic diameter
LVSD = left ventricle systolic diameter
EF = ejection fraction
HR = heart rate

A multiple regression was run to predict ischemic load from age, IHD, hypertension, obesity, diabetes mellitus, dyslipidemia, LVDD, LVSD, EF, myocardial dyskinesia, maximal and minimal heart rate and atrial fibrillation episodes (table 3). These variables explain 22.52% of the variability of ischemic load and statistically significantly predict the ischemic load, $F(13, 211) = 4.72$, $p < 0.00001$, the regression model being a good fit of the data. The general form of the equation to predict ischemic load from above listed variables is:

predicted ischemic load = -34.77 + (0.219 x age) + (6.271 x IHD) – (2.847 x hypertension) - (7.806 x obesity) - (5.020 x diabetes mellitus) + (6.611 x dyslipidemia) + (0.476 x LVDD) + (0.007 x LVSD) - (0.001 x EF) + (7.150 x myocardial dyskinesia) + (0.078 x maximal HR) - (0.146 x minimal HR) + (24.111 x atrial fibrillation)

Table 3. Results of multiple analysis upon ischemic load

Source	SS	df	MS	Number of obs =	225
				F(13, 211) =	4.72
Model	34377.5613	13	2644.42779	Prob > F =	0.0000
Residual	118247.748	211	560.415866	R-squared =	0.2252
				Adj R-squared =	0.1775
Total	152625.309	224	681.362987	Root MSE =	23.673

Ischemicload	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Age	.2194659	.150851	1.45	0.147	-.0779023	.5168342
IHD	6.271199	3.427472	1.83	0.069	-.4852756	13.02767
Hypertension	-2.847134	4.321127	-0.66	0.511	-11.36524	5.670977
Obesity	-7.806195	3.844032	-2.03	0.044	-15.38382	-.2285669
Diabetesmellitus	-5.020765	4.155353	-1.21	0.228	-13.21209	3.170561
Dislipidemia	6.611143	3.485105	1.90	0.059	-.2589419	13.48123
LVDD	.4764352	.4456534	1.07	0.286	-.4020683	1.354939
LVSD	.0071646	.3596844	0.02	0.984	-.7018706	.7161998
EF	-.0010572	.0049148	-0.22	0.830	-.0107456	.0086313
Myocardialdyskinesia	7.150117	7.844578	0.91	0.363	-8.313669	22.6139
MaximaHR	.0782602	.0792862	0.99	0.325	-.0780344	.2345547
MinimalHR	-.1465886	.1599359	-0.92	0.360	-.4618656	.1686884
Atrialfibrillation	24.11122	4.645394	5.19	0.000	14.95389	33.26854
_cons	-34.77811	22.58946	-1.54	0.125	-79.30805	9.751839

IHD = ischemic heart disease
LVDD = left ventricle diastolic diameter
LVSD = left ventricle systolic diameter
EF = ejection fraction
HR = heart rate

A multiple regression was run to predict duration of ischemia from age, IHD, hypertension, obesity, diabetes mellitus, dyslipidemia, LVDD, LVSD, EF, myocardial dyskinesia, maximal and minimal heart rate and atrial fibrillation episodes (table 4). These variables explain 17.26% of the variability of duration of ischemia and statistically significantly predict the duration of ischemia, $F(13, 211) = 3.39$, $p < 0.0001$, the regression model being a good fit of the data. The general form of the equation to predict ischemic load from above listed variables is:
Predicted duration of ischemia = -175.6 + (1.9 x age) + (74.27 x IHD) – (0.738 x hypertension) - (74.139 x obesity) - (88.673 x diabetes mellitus) + (75.339 x dyslipidemia) + (1.872 x LVDD) - (0.334 x LVSD) - (0.011 x EF) + (129.161 x myocardial dyskinesia) + (0.709 x maximal HR) - (1.643 x minimal HR) + (279.024 x atrial fibrillation)

Table 4. Results of multiple analysis upon ischemia episodes duration

Source	SS	df	MS	Number of obs =	225
				F(13, 211) =	3.39
Model	4164651.3	13	320357.792	Prob > F =	0.0001
Residual	19959882.5	211	94596.5994	R-squared =	0.1726
				Adj R-squared =	0.1217
Total	24124533.8	224	107698.811	Root MSE =	307.57

Durationofischemia	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Age	1.900349	1.959886	0.97	0.333	-1.963118	5.763815
IHD	74.27598	44.53038	1.67	0.097	-13.50546	162.0574
Hypertension	-.7381979	56.14093	-0.01	0.990	-111.4072	109.9308
Obesity	-74.13969	49.94242	-1.48	0.139	-172.5897	24.31034
Diabetesmellitus	-88.67388	53.98716	-1.64	0.102	-195.0972	17.74942
Dislipidemia	75.33912	45.27917	1.66	0.098	-13.91838	164.5966
LVDD	1.872663	5.790017	0.32	0.747	-9.541027	13.28635
LVSD	-.33482	4.67309	-0.07	0.943	-9.546744	8.877104
EF	-.0115627	.0638542	-0.18	0.856	-.1374366	.1143113
Myocardialdyskinesia	129.1631	101.9183	1.27	0.206	-71.74542	330.0717
MaximaHR	.7098575	1.030102	0.69	0.492	-1.320752	2.740467
MinimalHR	-1.643516	2.077919	-0.79	0.430	-5.739656	2.452625
Atrialfibrillation	279.0248	60.35387	4.62	0.000	160.051	397.9986
_cons	-175.6	293.4867	-0.60	0.550	-754.1417	402.9418

IHD = ischemic heart disease
LVDD = left ventricle diastolic diameter
LVSD = left ventricle systolic diameter
EF = ejection fraction
HR = heart rate

Ischemia on Holter ECG

In the IHD+ group, 55% (75/136) had at least one episode of ST depression on AECGm compared to 43% (38/89) subjects in the reference group. Among IHD+ subjects, we compared those with AECGm ischemia to those without AECG ischemic ST depressions (table 5) and found no differences in echocardiographic parameters and minimal heart rate on AECGm. The two groups differed regarding associated risk factors like hypertension, obesity and diabetes mellitus with higher rates in AECG ischemia group. The mean maximal heart rate was found to be 120 ± 23 bpm significantly higher in the AECG ischemia group.

Table 5. Comparison of IHD+ subjects stratified by Holter ECG ischemia

Characteristics	Holter ECG ischemia+ (n=75)	Holter ECG ischemia- (n=61)	p-value
Mean age (years)	66	60	NS
Hypertension (patients / %)	57 / 76%	55 / 90%	0,041
Obesity (patients / %)	15 / 20%	25 / 41%	0,009
Dyslipidemia (patients / %)	54 / 72%	38 / 38%	NS
Diabetes mellites (patients / %)	12 / 16%	19 / 31%	0,042
LVDD (mm)	49,6 ± 6.8	49,3 ± 4,8	NS
LVSD (mm)	33 ± 8,7	31,3 ± 5,3	NS
EF (%)	49,4 ± 2,89%	50% ± 0.1%	NS
Myocardial dyskinesia (patients)	8	7	NS
Maximal HR (beats/min)	120 ± 23	111 ± 19	0,019
Minimal HR (beats/min)	51 ± 12	52 ± 9	NS
Atrial fibrillation episodes (patients / %)	23 / (30%)	6 (10%)	0,003
Mean duration of ischemic episodes (min)	315,81 ± 468,13		
Ischemic load[1] (%)	27,79 ± 36,85%		

NS = not significant
LVDD = left ventricular diastolic diameter
LVSD = left ventricular systolic diameter
EF = ejection fraction
HR = heart rate
1. ischemic load defined as percentage that episodes of myocardial ischemia accounted throughout the recording

Ischemic load

The percentage represented by myocardial ischemia throughout the AECG recording was defined as ischemic load. Among the IHD+ women, 15 out of 75 (54%) presented episodes of ischemia on Holter ECG and 38 out of 69 (43%) among IHD- women. But the IHD+ group had a higher mean ischemic load (15%) compared with IHD- group (4,7%) (fig. 2), a difference that was highly significant (p<0,01). The ischemic load of patients who presented both anterior diagnosis of IHD and ischemia on AECGm was 27.79%.

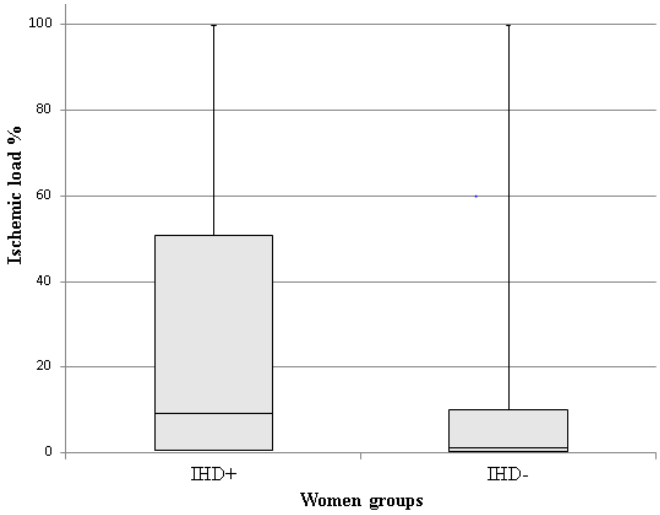

Fig. 2. Representation of ischemic load in percentage (IHD+ = ischemic heart disease group, IHD- = control group)

Duration of ischemia

The mean duration of ischemic episodes was 174,16 ± 380,75 minutes with limits between 1 and 2063 minutes in the IHD+ group and 59,44 ± 209,02 minutes in the IHD- group (p<0.01) with limits between 1 and 1436 minutes (fig. 3). The mean duration of patients who presented both anterior diagnosis of IHD and ischemia on AECGm was 315.81 min.

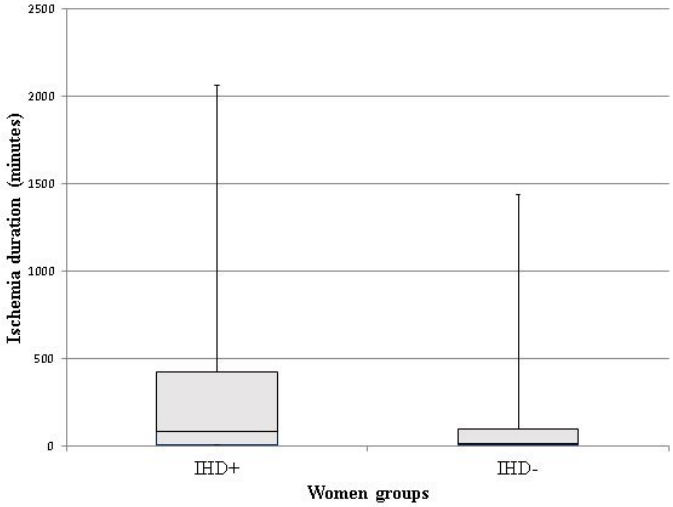

Fig. 3. Representation of ischemia episodes duration in minutes (IHD+ = ischemic heart disease group, IHD- = control group)

Discussions

Cardiovascular risk factors

Declining trends in cardiovascular risk factors have been observed predominantly regarding lower smoking rates, serum cholesterol and blood pressure (8,9). The incidence of fatal myocardial infarction has decreased in both sexes, but studies suggest that the reduction in non-fatal myocardial infarction may be lesser in middle-aged and younger women than in men of the same age (10). In our study, cardiovascular risk factors were frequently encounter in the IHD+ group but with no statistically significant difference between women with and those without IHD diagnosis. In the group of women with IHD and ischemic episodes on AECGm, a significant higher prevalence of cardiovascular risk factors (hypertension, obesity and diabetes mellitus) was observed. Obesity was the more important cardiovascular risk factor seen in our results, with a significant contribution to ischemia episodes and ischemic load.

Echocardiographic parameters

Quantitative assessment of cardiac function is important for diagnosis and management of cardiovascular diseases. Even though it is not the best tool, left ventricular ejection fraction is the most commonly assessed parameter for cardiac function and is frequently mentioned in guidelines for diagnosis and treatment of ischemic and non-ischemic heart disease, arrhythmias, valvular heart disease, heart failure, etc (11). In our study, no difference was observed between women in IHD+ group vs. IHD- group or ischemia group vs non-ischemia group regarding echocardiographic parameters.

AECGm parameters

Heart rate

AECGm provides minimal, mean and maximal heart rate (HR), heart rate variability, arrhythmic and ischemic events. The mean resting HR in patients with IHD increases approximately 20 bpm prior to the onset of ischemic episodes; therefore, the explanation of ST segment depression could be demand related ischemia (12). No difference was observed in our study regarding heart rate values between IHD+ and IHD- group or ischemia group vs non-ischemia. Maximal heart rate was observed as having a significant contribution in ischemic episodes prediction in our study.

Atrial fibrillation

Ischemia episodes are associated with anatomic changes in myocytes like cellular degeneration, hypertrophy and fibrosis demonstrated through anatomopathological studies (13) and are considered factors that increase rates of arrhythmias in patient with IHD. Reports suggest that atrial fibrillation is associated with increased mortality in patients with IHD (14). In our study, there have been significantly more patients with atrial fibrillation in the IHD+ group than in the IHD- group. We documented a significantly high number of patients (20%) which presented both ischemic episodes and atrial fibrillation episodes on AECGm. The presence of atrial fibrillation had a significant contribution in all major variables from our study: ischemia episodes, ischemic load and duration of ischemic episodes.

Ischemia episodes

Detection of cardiac ischemia is of major importance in the prevention of sudden cardiac death and acute myocardial infarction, therefore patients with minimal symptoms of ischemic heart disease should be investigated to establish the diagnosis of IHD. AECGm is a low-cost, easy-to-perform, easy-to-interpret diagnostic tool that has a high value in diagnosing IHD (15). It is an effective tool for: diagnosing silent ischemia episodes in patients without prior diagnosis of IHD; assessing the frequency and duration of ischemic episodes for patients with IHD and for risk stratifying by identifying those at increased risk for future cardiovascular events or death; monitoring of the effectiveness of therapy in patients with IHD (16).

Ischemia episodes occur during physical exertion or at rest in about 70-80% of patients with IHD and interfere with daily activities in 30-50% of them (15). It was previously shown that episodes of ST-segment depression events during AECGm correlate with the exercise ECG findings (16). AECG detection of ischemia episodes has significant prognostic information beyond the findings that are obtainable during exercise testing (16). In a study, 86 patients with IHD and abnormal exercise ECGs were followed for a mean of 12.5 months: during follow-up, there were 21 major cardiovascular events, excepting 1, all of these events occurred in patients with AECGm evidence of ST-segment depression. By multivariable analisys, only ST-

segment depression during AECGm and not ST-segment depression during exercise testing, significantly predicted worse outcomes (17). In our study, only obesity, maximal heart rate and atrial fibrillation episodes were found to significantly predict ischemic episodes in multivariate analysis. Continuous ECG monitoring could detect episodes of ischemia secondary to microvascular coronary disease, which are not detected at coronary angiography, currently considered the gold standard. In our study we demonstrate that ischemia detected by ST segment depressions on 24-hour AECGm is prevalent in over half of women included in the study, 53 % vs 42% in the IHD+ compared to matched reference subjects (IHD-). The distinction between these two groups consisted of different duration and ischemic load.

It has been shown that the presence of myocardial ischemic episodes with increased duration is associated with increased incidence of acute coronary events and mortality (2). In our study the duration of ischemic episodes was longer in the IHD+ group with statistically significance. The threshold value for an ischemic episode that is associated with potential IHD from our findings was establish as greater than 174 minutes. The value for duration episodes in IHD+ women that had also ischemic episodes on AECGm was 315 minutes. We recommend this value in using AECGm as a tool for IHD diagnosis. In multivariate analysis was observed that only presence of atrial fibrillation was significantly predicting duration of ischemic episodes.

Studies (18,19) demonstrated that ischemic episodes on AECGm independently predict adverse outcomes. In a study of 107 patients with chronic stable angina, 43% subjects with one or more ischemic episode were found to have a threefold increase in risk of cardiac death in the two year follow up period compared to those with no ischemic episodes (19). Our study demonstrated a high burden of ischemia in IHD+ women, consistent with prior reports (20) with obesity and atrial fibrillation episodes being predictors for ischemic load. The threshold values for ischemic load in our study was observed to be greater than 15%. The value for ischemic load in IHD+ women that had also ischemic episodes on AECGm was 27% minutes. We recommend this value in using AECGm as a tool for IHD diagnosis.

AECGm could be useful for detecting ischemic episodes in other patients like heart transplantation and coronary vascular allograft reciepents (21). Due to the fact that they have denervated hearts, they rarely present typical angina symptoms. Our proposed model of ischemia episodes detection and characterisation through episodical duration and ischemic burden could be helpfull in this specific cathegory of patients, but further research is nedeed.

Study limitations

A limitation of our study is the fact that we did not made a differentiation between silent and symptomatic episodes of myocardial ischemia. We also did not systematically collect information on sleep, physical, and mental activity, conditions that could modify heart rate and ST segment changes.

Conclusion

Although myocardial ischemia episodes were also present in IHD- group, our study demonstrated that the diagnosis of IHD can be established by AECGm using the threshold values of ischemic load (> 27%) and episodical ischemic duration (> 315 minutes). The use of AECGm increased the chance of detecting myocardial ischemia. The results of this study are important because they demonstrate the usefulness of AECGm as a reliable tool for diagnosis of IHD in a population that globally, is underdiagnosed and undertreated due to classical diagnostic methods which have a low efficiency in female population.

Declaration of interest: The authors report no declarations of interest.

References:

1. World Health Organization. 10 leading causes of death in female 2020 (internet). Available from: https://www.who.int/gho/women_and_health/mortality/situation_trends_causes_death/en/
2. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. Circulation. 2003 Sep 9;108(10):1263-77.
3. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, Pepine CJ, Merz CN. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James

Women Take Heart Project. Arch Intern Med. 2009 May 11;169(9):843-50.
4. Pepine CJ, Ferdinand KC, Shaw LJ, et al. Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography. J Am Coll Cardiol. 2015;66(17):1918-1933.
5. Negrusz-Kawecka M, Moszczyńska-Stulin J, Zytkiewicz-Jaruga D, Salomon P. Czestość wystepowania bezbólowej postaci choroby niedokrwiennej serca u chorych na cukrzyce (Frequency of silent ischemic heart disease in patients with diabetes mellitus). Pol Merkur Lekarski. 1997 Aug;3(14):53-6.
6. Su L, Borov S, Zrenner B. 12-lead Holter electrocardiography. Review of the literature and clinical application update. Herzschrittmacherther Elektrophysiol. 2013 Jun;24(2):92-6.
7. Negrusz-Kawecka M, Moszczyńska-Stulin J. Czestość wystepowania bezbólowej choroby niedokrwiennej serca (Incidence of painless ischemic heart disease). Pol Tyg Lek. 1996 Mar;51(10-13):135-7.
8. Mannsverk J, Wilsgaard T, Mathiesen EB, Løchen ML, Rasmussen K, Thelle DS, Njølstad I, Hopstock LA, Bønaa KH. Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population. Circulation. 2016 Jan 5;133(1):74-81.
9. Persson CU, Collén AC, Rosengren A, Mandalenakis Z, Zverkova Sandström T, Fu M, Dellborg M, Johansson S, Hansson PO. Secular trends in cardiovascular risk factors among women aged 45-54 years in Gothenburg, Sweden, from 1980 to 2014. BMC Public Health. 2020 Jul 1;20(1):1042.
10. Rosengren A, Thelle DS, Köster M, Rosén M. Changing sex ratio in acute coronary heart disease: data from Swedish national registers 1984-99. J Intern Med. 2003 Mar;253(3):301-10.
11. Zhao L, Lu A, Tian J, Huang J, Ma X. Effects of Different LVEF Assessed by Echocardiography and CMR on the Diagnosis and Therapeutic Decisions of Cardiovascular Diseases. Front Physiol. 2020 Jun 16;11:679. doi: 10.3389/fphys.2020.00679.
12. Roy R, Aldiwani H, Darouian N, et al. Ambulatory and silent myocardial ischemia in women with coronary microvascular dysfunction: Results from the Cardiac Autonomic Nervous System study (CANS). Int J Cardiol. 2020;S0167-5273(19)36040-1.
13. Hess OM, Schneider J, Nonogi H, Carroll JD, Schneider K, Turina M, Krayenbuehl HP. Myocardial structure in patients with exercise-induced ischemia, Circulation 1998;77:967–977.
14. Raunsø J, Pedersen OD, Dominguez H, Hansen ML, Møller JE, Kjaergaard J, Hassager C, Torp-Pedersen C, Køber L; EchoCardiography and Heart Outcome Study Investigators. Atrial fibrillation in heart failure is associated with an increased risk of death only in patients with ischaemic heart disease. Eur J Heart Fail. 2010 Jul;12(7):692-7.
15. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med. 1986 May 8;314(19):1214-9.
16. Wimmer NJ, Scirica BM, Stone PH. The clinical significance of continuous ECG (ambulatory ECG or Holter) monitoring of the ST-segment to evaluate ischemia: a review. Prog Cardiovasc Dis. 2013 Sep-Oct;56(2):195-202.
17. Rocco MB, Nabel EG, Campbell S, Goldman L, Barry J, Mead K, Selwyn AP. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. Circulation. 1988 Oct;78(4):877-84.
18. Conti CR, Bavry AA, Petersen JW. Silent ischemia: clinical relevance. J Am Coll Cardiol. 2012 Jan 31;59(5):435-41.
19. Garzillo CL, Hueb W, Gersh B, Rezende PC, Lima EG, Favarato D, Franchini Ramires JA, Kalil Filho R. Association Between Stress Testing-Induced Myocardial Ischemia and Clinical Events in Patients With Multivessel Coronary Artery Disease. JAMA Intern Med. 2019 Jul 22;179(10):1345–51.
20. Crea F, Gaspardone A. New look to an old symptom: angina pectoris. Circulation. 1997 Nov 18;96(10):3766-73.
21. Lee MS, Finch W, Weisz G, Kirtane AJ. Cardiac allograft vasculopathy. Rev Cardiovasc Med. 2011;12(3):143-52.