DOI: 10.4149/BLL_2019_113

Bratisl Med J 2019; 120 (9)
676 – 679

CLINICAL STUDY

Holter ECG findings in diabetics with medial arterial calcification

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ABSTRACT
OBJECTIVES: Medial arterial calcification (MAC) is a nonobstructive condition leading to reduced arterial compliance. The disease most commonly occurs in diabetes mellitus. Decreased ankle-brachial pressure index (ABI) is a well-known marker of increased cardiovascular mortality. However, also the values of ABI above 1.3, typical in MAC, are associated with increased mortality.
METHODS: By means of Holter ECG monitoring, we investigated 41 patients (25 men, 16 women) with mean age of 59±8 years, suffering of type 2 diabetes mellitus and identified as having MAC, and Holter ECG monitoring with an average duration of recording 22.36 hours, was carried out by GE-Marquette MARS ECG Holter system.
RESULTS: We found frequent incidence of cardiac arrhythmias and myocardial ischemia in 22 patients (53.7 %). Only 19 patients (46.3 %) had normal Holter ECG recordings. ABI values were significantly higher in patients with abnormal ECG Holter recordings.
CONCLUSION: Our results confirm the importance of ABI estimation in clinical practice. As the central goal of therapy for patients with myocardial ischemia and/or complex forms of cardiac arrhythmias is the reduction or elimination of these episodes. Ambulatory Holter ECG monitoring plays an important role in the management of these patients *(Tab. 7, Ref. 16).* Text in PDF *www.elis.sk.*
KEY WORDS: medial arterial calcification, diabetes mellitus, Holter ECG monitoring, cardiac arrhythmias.

Introduction

Major cardiovascular and cerebrovascular events, including myocardial infarction, stroke and sudden cardiac death, often occur in individuals without known preexisting disease. Early risk assessment in these patients is necessary in clinical practice. Despite the intensive study of atherothrombosis and introduction of new therapeutic approaches cardiovascular diseases are the most common causes of morbidity and mortality of the population,. Several studies have shown that reduced ankle-brachial pressure index (ABI) is a reliable warning sign of increased cardiovascular risk (1). But also, ABI values above 1.3 in the presence of medial arterial calcification are associated with increased mortality due to cardiovascular causes (2). Calcification of the media or medial arterial calcification was first described by the German pathologist, J. G. Mönckeberg, in 1903 and is also known as Mönckeberg´s sclerosis.

ABI has become a well-known marker in screening patients with pre-existing but not yet clinically proven atherosclerosis. This method is used in angiology practice for determining the severity of peripheral arterial obliterative disease. In the recent years, ABI received attention in cardiology because of the growing evidence of the relationship between the value of ABI and cardiovascular mortality (3).

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Acknowledgement: This work was supported by grant MŠ VEGA 1/0807/18.

Objectives of the study

Aim of our study was to determine the incidence of cardiac arrhythmias and myocardial ischemia using Holter ECG monitoring in a group of patients with diabetes mellitus type 2 and medial arterial calcification (MAC). To point out, that the determination of the ABI is a simple but important and reliable marker of cardiovascular risk. Not only in subjects with decreased ABI, but also for those who have MAC.

Materials and methods

A total of 41 patients with type 2 diabetes mellitus (25 men and 16 women) with the mean age of 59 ± 8 years were examined. Medial arterial calcification was present in all members of our group. The baseline clinical characteristics of the study population are summarized in Table 1.

All the patients were treated for diabetes mellitus type 2, as shown in Table 2. The mean duration of DM was 12.6 ± 7.1 years and the value of glycated hemoglobin (HbA1c) was 60.7 ± 8.6 mmol/mol (IFCC). 25 patients (61 %) had chronic renal disease of whom 8 (32 %) were in the 4th stage according to K/DOQI classification (severe reduction in glomerular filtration). Mean BMI (kg/m^2) was 29.3 ± 4.4. Nearly all subjects, 35 (85.3 %), had arterial

Tab. 1. Baseline clinical characteristics of study population.

Parameter	n	%
Medial arterial calcification	41	100
Diabetes mellitus	41	100
Chronic renal disease	25	61.0
Metabolic syndrome	31	75.6
Arterial hypertension	35	85.3
State after MI	8	19.5
State after ischemic stroke	7	17.1

Tab. 2. Treatment of diabetes mellitus.

Type of diabetes mellitus treatment	n	%
Only dietary intervention	2	4.9
Oral antidiabetic drugs (OADs)	16	39.9
Insulin	21	51.2
Combination of insulin and OADs	2	4.9

Tab. 3. Prevalence of arterial hypertension.

Category of arterial hypertension (ESC/ESH)	n	%
Grade 1 hypertension	2	4.9
Grade 2 hypertension	13	31.7
Grade 3 hypertension	20	48.8

hypertension. The classification in categories according to ESC/ /ESH Guidelines 2018 is summarized in Table 3.

During one-year follow-up, 4 patients died in domestic environment ;autopsy was not performed. Holter ECG monitoring with an average duration of recording 22.36 hours, was carried out by means of GE-Marquette MARS PC ambulatory ECG Holter system. The system captures and stores every heartbeat of the patient, and then provides a computerized ECG analysis using a full suite of GE-Marquette algorithms. The device enables the analysis of arrhythmias and ischemia even though the ST-segment horizontal descent is the sign most commonly diagnosed in the presence of myocardial ischemia.

Each record was also subjected to manual visual inspection with correcting electrocardiographic interpretation of automatic evaluation software by experienced physician. Clean recording with no artefacts and interference during the entire period of examination is essentially conditioned by optimal placement of electrodes. Our equipment is using a three-channel system. Medial arterial calcification was detected by the BOSO, ABI – system 100 (Germany) using the oscillometric method of measuring blood pressure. The sophisticated software accurately calculates ABI on each side (left and right). ABI measurement is a noninvasive, simple and reproducible examination method. Measurement was carried out with patient in supine position after 5 to 10 minutes of rest. Compression sleeves were placed on both arms and lower limbs and the values of blood pressure were measured simultaneously. ABI value was calculated as a ratio of the value of higher pressure in the legs to the higher pressure on the upper extremities.

Results

Normal findings during the evaluation of Holter ECG records - no arrhythmias and no signs of myocardial ischemia were present in 19 examined patients (46.3 %). Twenty-two patients (53.7 %) had findings of cardiac arrhythmias and/or ischemia. In 18 examined records (43.9 %), we found a complex form of cardiac arrhythmias of Lown type III B or type IV A. The results of all Holter ECG examinations are summarized in Table 4.

Mean ABI value was 1.615 ± 0.193 (lowest 1.34, highest 2.07). There was significant correlation of ABI with age (Pearson r = 0.511; p < 0.001). However, there was no significant correlation with duration of DM, systolic and diastolic blood pressure values, BMI or HbA1c. The complete result of correlation analysis is shown in Table 5.

For further analysis, patients were split in 2 groups according to the presence or absence of normal ECG Holter record and also according to the presence or absence of ischemia. Patients with abnormal ECG Holter record had significantly higher ABI values (1.718 ± 0.189 vs 1.496 ± 0.114; p < 0.001) and were older (71.2 ± 10.3 vs 65.2 ± 6.5; p < 0.05). No significant differences were observed for duration of DM, systolic and diastolic blood pressure, BMI or HbA1c; details are shown in Table 6. Using chi-square test, we found no significant association of presence or absence of normal ECG record with sex, presence of chronic kidney disease, hypertension, metabolic syndrome, history of myocardial infarction or stroke, type of DM treatment and grade of hypertension.

The analysis of subgroups according to the presence or absence of ischemia on Holter ECG record has shown that patients with ischemia had significantly higher ABI values

(p < 0.01). No differences were observed for age, duration of DM, systolic and diastolic blood pressure values, BMI or HbA1c°;

Tab. 4. Results of Holter ECG monitoring.

ECG Holter recording finding	n	%
Normal recording – without ischemia or arrhythmia	19	46.3%
Atrial fibrillation	6	14.6%
Complex forms of arrhythmia – Lown III B	12	29.2%
Complex forms of arrhythmia – Lown IV A	6	14.6%
2nd degree A–V block Mobitz type I	1	2.4%
Myocardial ischemia	10	24.4%

Some patients had multiple conditions.

Tab. 5. Correlation analysis.

Parameter	ABI
Age	r = +0.511; p<0.001
Duration of DM	r = +0.245; p=0.122
Systolic BP	r = –0.174; p=0.276
Diastolic BP	r = –0.126; p=0.433
BMI	r = –0.081; p=0.616
HbA1c IFCC	r = 0.013; p=0.935

Tab. 6. Comparison according to normal or abnormal ECG Holter record.

Parameter	ECG Holter record normal (n=19)	ECG Holter record abnormal (n=22)	Sign.
ABI	1.496±0.114	1.718±0.189	p<0.001
Age (years)	65.2±6.5	71.2±10.3	p<0.05
Duration of DM (years)	11.2±6.4	13.9±7.7	p=0.233
Systolic BP (mmHg)	134.0±8.8	131.8±10.5	p=0.489
Diastolic BP (mmHg)	82.9±5.8	80.8±4.1	p=0.193
BMI (kg/m^2)	33.26±4.04	36.11±11.01	p=0.292
HbA1c IFCC (mmol/mol)	58.06±16.89	62.85±22.69	p=0.454

Tab. 7. Comparison according to presence or absence of ischemia on ECG Holter record.

Parameter	Ischemia present (n=10)	Ischemia absent (n=31)	Sign.
ABI	1.755±0.224	1.570±0.161	p<0.01
Age (years)	71.4±9.7	67.5±9.0	p=0.245
Duration of DM (years)	14.1±5.9	12.1±7.6	p=0.456
Systolic BP (mmHg)	129.1±7.9	134.0±10.0	p=0.166
Diastolic BP (mmHg)	81.8±3.3	81.8±5.5	p=0.989
BMI (kg/m^2)	33.10±4.24	35.34±9.52	p=0.479
HbA1c IFCC (mmol/mol)	70.86±27.23	57.33±16.46	p=0.063

details are shown in Table 7. Similarly to previous analysis, chi-square test did not find any significant association between the presence or absence of ischemia on Holter ECG record and sex, presence of chronic kidney disease, hypertension, metabolic syndrome, history of myocardial infarction or stroke, type of DM treatment and grade of hypertension.

Discussion

Arterial calcification is common in diabetes, and is associated with incidents of cardiovascular disease events independent of traditional risk factors. However, in individuals with diabetes, the arterial calcification may reflect at least two distinct vascular pathologies, namely intimal calcification associated with atherosclerosis, and medial arterial calcification.

Medial arterial calcification is classified as a disease with a sclerotic tendency. Since it does not affect the intima of arteries, occlusive symptoms do not arise. It occurs most frequently in patients with diabetes mellitus, chronic renal insufficiency, hyperparathyroidism, smoking and history of hyperuricemia. In MAC, the calcium salts are deposited in the media of arteries, thus reducing the elasticity and compressibility of affected arteries. This is the reason why we obtain falsely high values of the local systolic blood pressure in the affected arteries of the lower extremity. High ABI is a reliable predictor of MAC. Native X-ray of affected lower limb arteries shows continuous tubular shadows of the media, unlike the complicated calcified atherosclerotic plaques, in which native X-ray shows spotted intermittent drawings of the plaques in the intima. MAC is also more frequently observed in patients with autonomic neuropathy. Similar calcifications, which develop in diabetics with autonomic neuropathy, are also found in non-diabetic patients after lumbar sympathectomy. Therefore, sympathetic denervation seems to be an important factor responsible for specific calcification of the medial layer of medium-sized and large arteries without affecting the intima (4). MAC is also a marker for increased risk of amputation (5, 6). Morphological findings in MAC differ from calcifications of the *lamina elastica interna* present at giant-cell arteritis. Typical histopathological finding in giant-cell arteritis is a granuloma and focal inflammation in the media (6). All layers of the vessel wall are affected, but dominantly in the media. It leads to fissures and fragmentation of internal elastic membrane with the findings of calcification, which is one of the typical features of giant-cell arteritis (7). ABI measurements exceeding 1.3 have been associated with CVD events and all-cause mortality in several studies in the general population (8).

If high ABI measurements are specific for MAC in this setting, MAC may represent a novel CVD risk factor in general community.

Atherosclerosis is a complex systemic, generalized obliterating arterial system disease which leads to various combinations of changes in the arterial intima consisting of focal accumulation of lipids, blood products, connective tissue and calcium deposits. The integrity of atherosclerotic plaque can be violated by fissure, disruption or rupture of fibrous cap, which leads to the formation of unstable plaque with thrombus, and consequently causes vasoconstriction with a varying degree of dynamic arterial obstruction. The calcification of the intima is a feature of atheroma (atherosclerotic calcification), it is eccentric associated with luminal narrowing and tends to be more proximal. MAC tends to be concentric and symmetrical, and in diabetes, it is a common feature in more distal arteries.

Atherothrombosis is the most common etiopathogenetic process causing coronary artery disease as well as ischemic strokes, two most common causes of mortality at older age. Reduced values of ABI are a reliable warning sign of increased cardiovascular risk. When compared with subjects with normal ABI values (range from 0.9 to 1.1), ABI values below 0.7 indicate a significantly worse prognosis for survival as well as for the occurrence of serious cardiovascular events (9). Criqui et al (10) showed that mortality from cardiovascular causes during a 3-year follow-up depending on ABI value was comparatively high in cases of severe ischemia (ABI below 0.7) as well as findings of medial arterial calcification (ABI 1.3 and more). Similar results were also found in a six-year follow-up mortality from cardiovascular causes. In the present study, 53.7% patients with MAC had abnormal Holter ECG records. Our results confirm that both critical limb ischemia and MAC are major risk factors for cardiovascular complications.

These results are not surprising, as MAC typically occurs in diabetes mellitus, as well as renal insufficiency, both of which are one of the major risk factors of fatal cardiovascular complications. In addition to the entire myocardial structure, i.e. cardiac muscle, connective tissue, and conductive system, diabetes mellitus can affect also the coronary arteries. Coronary artery atherosclerosis in diabetics occurs earlier than in non-diabetic patients and reaches a wider range (11). Intracellular glucose induces tissue damage through four mechanisms, namely (I) activation of the polyol pathway resulting in increased oxidative stress, (II)) induction of an inflammatory response by age, (III) activation of the protein kinase-C pathway, leading to decreasing nitric oxide and increasing endothelin-1, and (IV). stimulation of N-acetyl glucosamine via the hexosamine pathway, which causes increased plasminogen activator inhibitor-1 and TGF-β (12). In our group of diabetics, 15 patients (36.6 %) have already overcome major vascular complications (myocardial infarction or ischemic stroke). These findings are consistent with the occurrence of metabolic syndrome (MS) in our study group (75.6 %), since MS is associated with increased overall and cardiovascular mortality (13). Classifications and definitions of the metabolic syndrome indicate that there are four fundamental components participating in its pathogenesis as well as resulting complications, namely obesity, insulin resistance, endothelial dys-

function and aggregation of other components linking the complex variable of MS. Obesity causes changes in the basic characteristics of circulation, such as cardiac output and stroke volume, peripheral vascular resistance, changes in the distribution of blood flow. Together with other risk factors, it leads to the development of arterial hypertension and coronary heart disease. The body fat distribution affects the morphology and density of muscles' capillary network. Obesity is firmly associated with hypertension; several central and peripheral mechanisms causing the formation and development of hypertension were identified. They involve the sympathetic autonomic nervous system, renin-angiotensin-aldosterone system, leptin, endothelial dysfunction and renal abnormalities (14). Obesity, especially the abdominal type of obesity, is associated with deterioration of the respiratory function. Increased abdominal mass present in the metabolic syndrome, limits the movement of the diaphragm and increases the intrathoracic pressure. Lung parenchymal compression leads to a decrease in compliance of the lungs, expiratory reserve volume and functional residual capacity. Obesity and visceral fat tissue accumulation are risk factors for the development of syndromes of sleep apnea and alveolar hypoventilation as well as resistant hypertension (15). Metabolic syndrome pathogenesis is a complex process affected by many components.In an addition to the role of abdominal obesity, importance should be ascribed also to the impact of insulin resistance .

However, some other components, including proatherogenic dyslipoproteinemia and proinflammatory state also participate significantly in the development of MS and its cardiovascular complications. We cannot omit the factor of age which affects all levels of the pathogenesis and accounts for the increasing prevalence of MS in ageing population (16). Very important is also the presence of arterial hypertension, which was present – almost in all our patients (85.3 %). The diagnosis and treatment of hypertension should be therefore addressed with appropriate attention.

Learning points

- Medial arterial calcification (MAC) is associated with increased mortality due to cardiovascular causes.
- High incidence of cardiac arrhythmias and/or myocardial ischemia was found during Holter ECG monitoring.
- Holter ECG monitoring in patients with MAC is therefore highly recommended.

Conclusions

High incidence of cardiac arrhythmias, including complex forms of arrhythmia, as well as myocardial ischemia (together 53.7 %) was found during Holter ECG monitoring in a group of 41 patients with diabetes mellitus and medial arterial calcification. Only 46.3 % of our patient group had normal Holter ECG recording. Patients proven to suffer from MAC are threatened by serious cardiac complications, including sudden cardiac death, and are in need of interdisciplinary care. ABI examination can reveal patients with increased cardiovascular risk. It is a simple, non-invasive and reproducible method. Patients at higher risk are not only those with reduced ABI, but also the ones with the finding of suggestive medial arterial calcification. Holter ECG monitoring in patients with MAC is highly recommended since subsequent cardiology management can improve their prognosis.

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Received June 10, 2019.
Accepted July 12, 2019.