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CELL-FREE DNA AS A NEW INDICATOR OF CELLULAR ISCHEMIA IN ISOLATED CORONARY ARTERY ECTASIA

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Summary

Background: Coronary artery ectasia (CAE) is the diffuse or localized enlargement of the epicardial coronary arteries without any particular symptoms. Cell-free DNA (cfDNA) is defined as the DNA originating from nucleated cells which circulates freely in circulatory system. In our study, we aimed to measure the cfDNA levels, an indicator of ischemia at cellular level, which is shown to be elevated in non-invasive exercise tests and perfusion scintigraphies.

Methods: 41 patients with isolated CAE and 39 patients with normal coronary angiograms (NCA) were included in the study. Coronary angiography was performed in case of typical angina or a positive exercise test. The amount of cfDNA was determined by centrifugation of peripheral blood samples from both groups.

Results: Plasma cfDNA levels were 5.86 ± 4.41 ng/µl in isolated CAE patients and 2.36 ± 1.32 ng/µl in NCA group (p=0.000). When angiographic types were evaluated based on Markis Classification, cfDNA levels were found as follows: type I (n=7) 10.15±5.25, type II (n=5) 6.42±3.91, type III (n=4) 5.15±3.74 and type IV (n=25) 4.66±3.78. The level of cfDNA was found significantly higher in type I CAE group when compared to other groups based on the Markis Classification (p=0.028).

Conclusion: High levels of cfDNA in patients with CAE suggest that impaired myocardial perfusion and the resulting ischemia cause myocardial cell lysis or rapid apoptosis that leads to earlier programmed cell death. High levels in cfDNA in these patients might be used as a marker of increased cardiovascular risk.

Key words: *coronary angiography, myocardial ischemia, cell-free nucleic acids, coronary aneurysm, exercise test.*

Introduction. Coronary artery ectasia (CAE) is the luminal dilation of epicardial coronary arteries up to 1.5 times of the normal coronary arteries without any specific symptom [1, 2]. It may be acquired or congenital and the incidence is between 0.3–5% [3]. Some studies have reported that isolated CAE is rare and angiographic measurements have revealed that it occurs in 0.1 – 0.79% of all patients [3; 4]. A majority of the patients with CAE present various symptoms including atypical and exercise-induced angina and myocardial infarction (MI) [5; 7]. Many studies have investigated myocardial ischemia using either invasive or non-invasive methods and it has been shown that myocardial ischemia was significantly higher in patients with CAE.

A number of factors such as congenital factors, atherosclerosis, inflammatory or connective tissue disorders may influence the development of CAE; however, despite the advances in technology and the previously published reports, the mechanism of action of this disease is still unclear [3]. CAE can be differentially diagnosed with coronary angiogram by measuring the slow coronary filling, phenomenon of segmental backflow, and stasis in ectatic segments [5]. It has been shown that activation of interleukin – 1β, tumor necrosis factor-α and enhanced thrombogenicity is associated with CAE [8].

Markis et al. have grouped CAE in four different types as Type I, II, III and IV [3]. Type I is diffuse ectasia in 2-3 arteries, type II is diffuse disease in a single artery and local disease in another, type III is diffuse disease in a single artery, and type IV is localized or segmental ectasia [3].

Cell-free DNA (cfDNA) is a DNA type which circulates freely in blood after being released from nucleated cells [9; 10]. The origin of the cfDNA has not been elucidated yet, but it has been proposed that cfDNA is released after a cell dies with mechanisms such as necrotic cell death, apoptosis, cell lysis, and active release [11]. In 1948, Mandel et al. have reported circulating nucleic acids in human blood [12]. In several studies conducted shortly after this study, it was suggested that the cfDNA may occur as a result of metastasis. Studies with quantitative measurement of cfDNA isolated from the plasma and serum samples of patients with leukemia, systemic lupus erythematosus, chronic glomerulonephritis, rheumatoid arthritis and cancer have revealed that levels of cfDNA were generally higher than the levels of normal individuals and cfDNA could be used as a marker in diagnosis of these diseases [13; 17]. Literature review shows that the quantitative values of the cfDNA are investigated in many other diseases with the developing technical methods and it is also investigated

whether genetic analyses including the next generation sequencing can be performed using the cfDNA [18; 19].

There was diffused or localized vasodilation in the CEA coronary arteries and its pathogenesis could not be determined clearly. Previously we found relations of the cfDNA levels and coronary slow-flow phenomenon [38]. In present study, we aimed to show whether there is an increase in levels of cfDNA, an indicator of ischemia at cellular level, especially in CEA cases.

Materials and methods. Study population. 41 patients with isolated CAE and 39 patients with normal coronary angiograms (NCA) who underwent coronary angiography between August 2016 and January 2019 were enrolled. The indications for coronary artery were typical angina or atypical chest pain and a positive exercise test. The patients' clinical data such as gender, age, dyslipidemia, diabetes mellitus, hypertension and smoking status were recorded. The patients with percutaneous coronary intervention, congenital heart disease, moderate to severe valvular heart diseases, left ventricular hypertrophy, previous history of myocardial infarction, rhythms other than sinus, left ventricular dysfunction (Ejection fraction (EF) lower than 50%), active infection, chronic obstructive pulmonary disease, renal failure, cor pulmonale, chronic systemic illness and neoplastic disease were not included in the study. The patients with (STeMI or nSTeMI) acute coronary syndrome or unstable angina pectoris were also excluded. The ethics and medical committee of the institution approved the study. The written consent of the patients was obtained before the study.

Coronary angiography. Selective left and right coronary angiography was performed using the standard techniques with radial or femoral arterial approach and a blind expert analyzed the angiographic data. Iohexol was used as opaque substance in all patients. Isolated CAE was accepted as the dilation of at least one epicardial coronary artery by 1.5 folds in diameter when compared to the normal vessel and lack of critical stenosis (more than 50%) in any coronary artery. The NCA was accepted as the lack of angiographic atherosclerosis during routine coronary angiography.

cfDNA measurement. Approximately 10 mL of peripheral blood samples were drawn in tubes and the samples were centrifuged for 10 min at 2500xg and then the supernatant was transferred into a new sterile tube which was centrifuged for 10 min at 16,000xg. The new supernatant was kept at -80 Co in a sterile tube. The Plasma/Serum Cell-Free Circulating DNA Purification Micro Kit [Norgen Biotek, Thorold, ON, Canada, Cat no: 55500] was employed for extraction of DNA. The amount and purity of the DNA was calculated using the Nanodrop ND1000 spectrophotometry (Thermo Fisher Scientific, Waltham, MA, USA).

Statistical analyses. SPSS 16 was used for all statistical analyses (SPSS for Windows, v. 16.0, Chicago, USA). Percentage and mean values were calculated with standard deviations. Tukey post hoc and ANOVA tests were used to compare the parametric variables between the groups. The non-parametric values and percentages were compared using Chi-square test. $p \leq 0.05$ showed statistical significance.

Results. In this study, 41 patients with isolated CAE and 39 patients with NCA who underwent coronary angiography were recruited. The mean age of CAE patients was 58.7±8.3 years and 57.3±8.1 years for the NCA patients. The patients in both groups had no statistically significant difference in terms of smoking status, age, hyperlipidemia, family history of coronary artery disease (CAD), hypertension and diabetes mellitus. Both groups had similar number of patients using drugs such as antidiabetics and antihypertensives (Table 1). Serum glucose, urea, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, total cholesterol, thyroid stimulating hormone (TSH) and hematocrit levels were similar in both groups (Table 2).

Table 1. *Clinical characteristics of patients with CAE and NCA.*

Age (years)	**CAE (n=41)**	**NCA (n=39)**	**p-value**
	58.7 ± 8.3	57.3 ± 8.1	NS
Gender (M/F)	28/13	22/17	NS
Hypertension (n)	33 (%80)	26 (%67)	NS
Diabetes mellitus (n)	12 (%29)	10 (%27)	NS
Hyperlipidemia (n)	16 (%39)	11 (%28)	NS
Family history of CAD (n)	14 (%34)	10 (%27)	NS
Smoking (n)	30 (%73	22 (%56)	NS
B-blocker (n)	11	7	NS
Ca channel blocker (n)	9	8	NS
Diuretic (n)	16	12	NS
ACE inhibitor (n)	12	11	NS
ARB (n)	8	8	NS
Alfa blocker (n)	3	2	NS
Oral antidiabetic drug (n)	9	9	NS
Insulin (n)	3	1	NS

Table 2. *Laboratory data of the patients with CAE and NCA.*

Fasting blood glucose (mg/dl)	**CAE (n=41)**	**NCA (n=39)**	**p-value**
	107±11	106±10	0.528
Urea (mg/dl)	34.7±9.6	34.2±8.4	0.794
Serum creatinine (mg/dl)	0.88±0.19	0.88±0.23	0.906
Total cholesterol (mg/dl)	191±41	189±35	0.891
Triglycerides (mg/dl)	147±43	142±47	0,668
LDL cholesterol (mg/dl)	124±28	115±24	0,153
HDL cholesterol (mg/dl)	40±9	42±8	0.569
TSH (mIU/l)	1.37±0.80	1.43±0.81	0.746
Hematocrit	43.9±3.5	44.1±3.7	0.823

The indication for coronary angiography was demonstrated by the positivity of the treadmill exercise test (Symptom or ST depression) or the presence of ischemia in the myocardial perfusion scintigraphy (MPS). In the CAE group, 31 patients had positive treadmill exercise test and 10 patients had ischemia in MPS. However, in NCA group, the numbers were 28 and 11, respectively. According to the results of the treadmill exercise test and the ischemia in MPS, there was no significant difference between the groups.

Plasma cfDNA levels were 5.86±4.41 ng/µl in isolated CAE patients and 2.36±1.32 ng/µl in NCA group (p=0.000). When angiographic types were evaluated based on Markis Classification, cfDNA levels were found as follows: type I (n=7) 10.15±5.25, type II (n=5) 6.42±3.91, type III (n=4) 5.15±3.74 and type IV (n=25) 4.66±3.78. cfDNA was highest in type I CAE group and it was statistically significant among the four types based on Markis classification (p=0.028) (Figure 1). When patients with NCA were compared to the patients with CAE (type I, II and IV) one-by-one, a statistically significant difference was found between the groups (p=0.000, 0.44 and 0.31, respectively). The difference between type III and NCA was not statistically significant. A possible explanation for this could be the low number of patients in type III group (Table 3).

Table 3. *Treadmill exercise test, myocardial perfusion scintigraphy and cfDNA measurement.*

Treadmill exercise test (n)	**CAE (n=41)**			**NCA (n=39)**	**P value**
	31			28	
Ischemia in myocardial perfusion scintigraphy (n)	10			11	
cfDNA	5.86±4,41			2.36±1.13	0.000
Angiographic types according to Markis classification for CAE and cfDNA measurement	Type I	10.15±5.25	P value 0.028	2.36±1.13	0.000
	Type II	6.42±3.91		2.36±1.13	0.044
	Type III	5.15±3.74		2.36±1.13	0.398
	Type IV	4.66±3.78		2.36±1.13	0.031

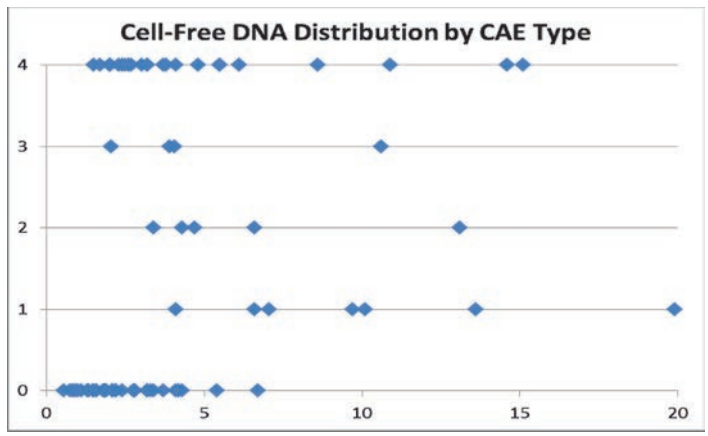

Figure 1. *Distribution of Cell-Free DNA in ng/µl by CAE Type. (1, 2, 3, 4 – Types of CAE; 0 – NCA Group)*

Discussion. The cfDNA can be detected in the plasma after particular events such as ischemia and apoptosis. In the present study, we found that the levels of cfDNA were increased significantly in patients with isolated CAE.

CAE is dilation of the coronary arteries up to 1.5 folds of the normal artery diameter and the main reasons of this situation are deposition of collagen instead of elastin and the loss of musculo-elastic layers of the arterial tunica media which leads to thin arterial walls [1; 3; 20]. As the intraluminal pressure increases, the media is injured, the vessel dilates and ectasia forms [20; 21]. In a study by Yilmaz et al. more than 50% of patients have been detected with atherosclerosis, however, vacuities of large vessels and connective tissue disorders can also be present [21].

CAE has similar histopathological characteristics like coronary artery disease but the underlying cause of luminal dilation is still unclear [3]. While stenotic CAD is presented with negative remodeling, CAE is presented with positive remodeling [3]. These findings suggest that positive remodeling in the vessel wall, an uncommon feature of the atherosclerotic process, plays an important role in the etiopathogenesis of the CAE [3].

Some of the most important flow characteristics of CAE can be attributed as stasis in ectatic segments, slow forward coronary filling, phenomenon of segmental backflow which all become even more important as the diameter of the coronary artery [3; 22].

In studies performed with stable isolated CAE patients, it has been shown that the coronary flow dynamics is impaired and myocardial perfusion is defected. In addition, different studies have shown that coronary ischemia in these patients can be measured using noninvasively and invasively with various stress tests. Recent studies using coronary arteriography have listed the possible symptoms of myocardial ischemia as segmental back flow, impaired coronary blood flow or deposition of dye in the coronary artery [22; 23; 24]. Papadakis et al. have measured the coronary flow velocity using the TIMI frame count method and they have found that the velocity was lower in patients with CAE when compared to the patients in obstructive CAD and control groups [24; 25].

Huang et al. have performed the treadmill test in angiographically detected isolated coronary ectasia patients and they have shown that the effort test for these patients had significantly become positive compared to the control group with NCA [26].

In a group of 30 patients with isolated CAE of the proximal left anterior descending (LAD) coronary artery, it has been shown that total and diastolic coronary flow volume have decreased significantly after intravenous glycerin administration when compared to the control group [27].

Ismail et al. have used 99mTc-sestamibi scintigraphy imaging technique and they have shown that basal and mid segments of the myocardium could be affected by the defects of reversible myocardial perfusion in patients with isolated CAE [22]. It has also been reported that patients with reversible myocardial perfusion defects had diffuse CAE more frequently than those who underwent normal myocardial perfusion scan [22]. 99mTc-sestamibi myocardial perfusion imaging has revealed reversible myocardial perfusion defects in 62.9% of patients with isolated CAE [22].

In a study using an invasive method such as coronary Doppler flow wire in 17 consecutive patients with isolated CAE, hyperemic average coronary blood flow was significantly slower and the coronary flow reserve was significantly lower when compared to the controls [28]. Another similar study using coronary Doppler flow wire in 19 patients with isolated coronary aneurysms, the coronary flow reserve has been found to be significantly lower and the coronary vascular resistance was higher than the controls [29]. In another study, coronary sinus lactate measurement under incremental atrial pacing method has been used to detect the myocardial ischemia and the patients with isolated CAE were found to have myocardial ischemia more frequently [23]. In a retrospective study recruiting 45 patients with isolated CAE who underwent elective coronary angiography, it has been reported that 54% and 29% of ectatic arteries had grade 3 TIMI flow and myocardial blush, respectively [30]. Same study reports that myocardial blush rate has reduced in 45% of ectatic arteries with TIMI flow grade 3 which suggests that normal epicardial coronary flow continues even though tissue-level perfusion is impaired [30].

Circulating cfDNA occurs after acute cellular injury or apoptosis and it can be used as a marker of cellular damage. The serum or plasma of healthy individuals can be used to assess the level of cfDNA even at low concentrations due to apoptosis [31; 32]. Recent studies have reported high concentrations of cfDNA in autoimmune diseases, sepsis, trauma and infection [31; 32].

It has been shown that the average concentration of cfDNA in patients with myocardial infarction is up to 10 times higher than the concentration levels of the control subjects [33; 34; 35]. In another study, DNA-based Alu assay have revealed the plasma cfDNA concentrations have increased significantly in patients with acute coronary syndrome when compared to the healthy people [36].

The etiopathogenesis of the CAE, the aneurysmatic dilatation of the coronary arteries, has not been clarified yet. Different studies on myocardial infarction revealed that the cfDNA released from myocardium exposed to ischemia was statistically significantly high. Different invasive and noninvasive studies conducted on patients with the CAE have also shown myocardial ischemia. In the present study, it was determined that the significance of cfDNA, which is an indicator of the ischemia and the damage at the cellular level, was high in isolated CEA patients. cfDNA amounts in all 4 types of CAE were found higher than the patients with NCA. This difference was statistically significant in the patients with type I, II and IV when compared to the ones with NCA. cfDNA was also high in type III, but since the number of patients with type III was low, that difference was not statistically significant. In addition, it was found that the elevation in type I was statistically significant according to the comparison between all 4 types. Type I CAE is the diffuse dilatation of 2-3 coronary arteries and high levels of cfDNA has been found to be related to the size of the ectatic segment. Markis et al. and Timir et

al. have stated that the presence of CAE means a higher cardiovascular risk [2, 37].

Conclusion. High levels of cfDNA in patients with CAE suggest that impaired myocardial perfusion and the resulting ischemia cause myocardial cell lysis or rapid apoptosis that leads to earlier programmed cell death. The high levels in cfDNA in these patients might be a marker of increased cardiovascular risk.

Limitations. Although the present study provides some significant results, it also some limitations. First, the number of patients could be more to represent the population better. Second, correlation coefficient for the parameters such as ectatic coronary artery localization and ectasia size or volume cannot be calculated.

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ЖАСУШАДАН ТЫС ДНҚ РЕТІНДЕ КОРОНАРЛЫҚ АРТЕРИЯНЫҢ ОҚШАУЛАНҒАН ЭКТАЗИЯСЫНДАҒЫ ЖАСУШАЛЫҚ ИШЕМИЯНЫҢ ЖАҢА КӨРСЕТКІШІ

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Түйінді

Өзектілігі: Коронарлық артерия Эктазиясы (КАЭ) - бұл қосымша белгілері жоқ эпикардиальды коронарлық артериялардың диффузды немесе жергілікті кеңеюі. Жасушадан тыс ДНҚ (жтДНҚ) қан айналымы жүйесінде еркін айналатын ядролық жасушалардан алынған ДНҚ ретінде анықталады. Біздің зерттеуімізде біз инвазивті емес жаттығулар мен перфузиялық сцинтиграфия сынақтарында жоғарылағаны көрсетілген жасушалық деңгейдегі ишемия индикаторы жтДНҚ деңгейін өлшеуге тырыстық.

Әдістері: Зерттеуге оқшауланған КАЭ бар 41 пациент және қалыпты коронарлық ангиограммасы (ҚКА) бар 39 пациент енгізілді. Коронарография әдеттегі стенокардия немесе оң жүктеме сынағы үшін жасалды. жтДНҚ мөлшері екі топтың перифериялық қан үлгілерін центрифугалау арқылы анықталды.

Нәтижелер: Плазмадағы жтДНҚ деңгейі оқшауланған КАЭ пациенттерінде 5,86 ± 4,41 нг/мкл және ҚКА пациенттерінде 2,36 ± 1,32 нг/мкл (p = 0,000) құрады. Маркис классификациясына негізделген ангиографиялық типтерді бағалау кезінде вкднқ деңгейлері келесідей болды: I тип (n=7) 10,15±5,25, II тип (n=5) 6,42±3,91, III тип (n=4) 5,15±3,74 және IV тип (n=25) 4,66±3,78. Ccdna деңгейі I типті САЕ тобында Маркис классификациясына негізделген басқа топтармен салыстырғанда едәуір жоғары екендігі анықталды (p = 0,028).

Қорытынды: КАЭ бар емделушілерде ccdna-ның жоғары деңгейі миокард перфузиясының бұзылуы және нәтижесінде пайда болатын ишемия миокард жасушаларының лизисін немесе жылдам апоптозды тудырады, бұл ертерек бағдарламаланған жасуша өліміне әкеледі деп болжайды. Бұл науқастарда ccdna жоғары деңгейі жүрек-қан тамырлары қаупінің жоғарылауының белгісі ретінде пайдаланылуы мүмкін.

Кілт сөздер: *коронарография, миокард ишемиясы, жасушадан тыс нуклеин қышқылдары, коронарлық аневризма, жүктеме сынағы.*

ВНЕКЛЕТОЧНАЯ ДНК КАК НОВЫЙ ИНДИКАТОР КЛЕТОЧНОЙ ИШЕМИИ ПРИ ИЗОЛИРОВАННОЙ ЭКТАЗИИ КОРОНАРНОЙ АРТЕРИИ

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Аннотация

Актуальность: Эктазия коронарных артерий (КАЭ) представляет собой диффузное или локальное расширение эпикардиальных коронарных артерий без дополнительных симптомов. Внеклеточная ДНК (вкДНК) определяется как ДНК, происходящая из ядерных клеток, которая свободно циркулирует в системе кровообращения. В нашем исследовании мы стремились измерить уровни вкДНК, индикатора ишемии на клеточном уровне, который, как показано, повышен при неинвазивных тестах с физической нагрузкой и перфузионной сцинтиграфии.

Методы: В исследование был включен 41 пациент с изолированной КАЭ и 39 пациентов с нормальной коронарной ангиограммой (НКА). Коронарографию выполняли при типичной стенокардии или положительной нагрузочной пробе. Количество вкДНК определяли центрифугированием образцов периферической крови обеих групп.

Результаты: Уровни вкДНК в плазме составили 5,86 ± 4,41 нг/мкл у изолированных пациентов с КАЭ и 2,36 ± 1,32 нг/мкл у пациентов с НКА (p = 0,000). При оценке ангиографических типов на основе классификации Маркиса уровни вкДНК оказались следующими: тип I (n=7) 10,15±5,25, тип II (n=5) 6,42±3,91, тип III (n=4) 5,15±3,74 и IV тип (n=25) 4,66±3,78. Уровень вкДНК был обнаружен значительно выше в группе КАЭ типа I по сравнению с другими группами на основе классификации Маркис (p = 0,028).

Заключение: Высокий уровень вкДНК у пациентов с КАЭ предполагает, что нарушение перфузии миокарда и возникающая в результате ишемия вызывают лизис клеток миокарда или быстрый апоптоз, что приводит к более ранней запрограммированной гибели клеток. Высокий уровень вкДНК у этих пациентов может быть использован в качестве маркера повышенного сердечно-сосудистого риска.

Ключевые слова: *коронарография, ишемия миокарда, внеклеточные нуклеиновые кислоты, коронарная аневризма, нагрузочный тест.*

Конфликт интересов. *Все авторы заявляют об отсутствии потенциального конфликта интересов, требующего раскрытия в данной статье.*

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