Earlobe crease relationship with coronary atherosclerotic burden and pericardial adiposity

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SOUHRN

Kontext: Vzhledem k omezenému množství údajů stále ještě panuje značná nejistota ohledně významu a korelace mezi záhybem ušního lalůčku (earlobe crease, ELC) a zátěží koronárních tepen aterosklerózou plus adipozitou perikardu.
Cíl: Cílem naší studie bylo zhodnotit souvislost mezi ELC a zátěží koronárních tepen aterosklerózou hodnocenou výpočtem kalciového skóre koronárních tepen (coronary artery calcium score, CAC), přítomností plátů a závažností koronárních stenóz i mezi ELC a objemem perikardiálního tuku (pericardial fat volume, PFV) u pacientů s podezřením na ischemickou chorobu srdeční.
Metody: Do studie bylo zařazeno 70 pacientů odeslaných na naše oddělení pro klinické podezření na ischemickou chorobu srdeční, u nichž bylo provedeno vyšetření 64řádkovou CT koronarografií; z uvedeného počtu jich 33 (47 %) mělo ELC.
Výsledky: Přítomnost ELC vykazovala po adjustaci na klasické faktory rizika vzniku koronárních příhod statisticky významně nezávislou korelaci se zvýšenou hodnotou CAC (OR [CI] = 3 [2–10]; $p < 0,01$), významnou koronární stenózou (OR [CI] = 3 [2–8]; $p < 0,01$) a s přítomností koronárních plátů (OR [CI] = 4 [3,5–9]; $p < 0,01$). Po adjustaci na klasické faktory rizika vzniku koronárních příhod byla přítomnost ELC ($p < 0,01$) nezávisle a významně spojena se zvýšenou hodnotou PFV.
Závěr: Přítomnost ELC je významně a nezávisle spojena se zátěží aterosklerózy koronárních tepen a zvýšenou adipozitou perikardu.

Keywords:
Coronary atherosclerosis
CT angiography
Earlobe crease
Pericardial fat

ABSTRACT

Background: There is still uncertainty or limited data regarding the relevance of earlobe crease (ELC) to coronary atherosclerosis burden and pericardial adiposity.
Objective: We aimed to assess the association between ELC with coronary atherosclerotic burden, including coronary artery calcium score (CAC), plaque presence, and coronary stenosis severity and pericardial fat volume (PFV) in patients with suspected coronary artery disease.
Methods: Seventy patients referred owing to clinical suspicion of coronary artery disease who underwent 64-slice coronary CT angiography, 33 of whom (47%) had ELC, were enrolled.
Results: ELC presence showed a significant independent association with increased CAC (OR [CI] = 3 [2–10], p <0.01), significant coronary stenosis (OR [CI] = 3 [2–8], p <0.01), and coronary plaque presence (OR [CI] = 4 [3.5–9], p <0.01) after adjustment for conventional coronary risk factors. ELC presence (p <0.01) was independently and significantly associated with increased PFV following adjustment for conventional coronary risk factors.
Conclusion: ELC is significantly and independently associated with coronary atherosclerotic burden and increased pericardial adiposity.

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Introduction

Earlobe crease (ELC) is a diagonal fold or deep wrinkle, either unilaterally or bilaterally, that extends from the tragus to the auricle.[1–3] This simple clinical sign that can be easily observed and was first described by Frank in routine clinical examination in 1973 ,who reported the significant association of ELC with increased risk for coronary artery disease.[1–5]

From that year forward, several studies have evaluated the potential link between ELC and coronary risk factors or coronary artery disease.[1,3,5] However, there is still uncertainty regarding the relevance of ELC to coronary atherosclerosis burden despite the notable number of studies available on this issue.

In the last decade, fat in pericardial cavity, owing to its anatomical proximity to heart and coronary vessels, was reported to be related to coronary atherosclerosis severity and prognosis via local release of inflammatory mediators on adjacent coronary arteries leading to local inflammation and pathophysiological changes, which may have a fundamental role in the development and progression of coronary atherosclerosis.[4,6–8] Nevertheless, data on the association between ELC and pericardial fat volume (PFV), as a marker of clinical and subclinical coronary atherosclerosis, are limited in the literature.

The main aim of the present study was to assess the association between ELC and coronary atherosclerotic burden, including coronary artery calcium score (CAC), plaque presence, and coronary stenosis severity and PFV in patients with suspected coronary artery disease.

Methods

This cross-sectional study was carried out at our Cardiology Centre between July 2020 and January 2021. Seventy patients with stable chest pain who underwent 64-slice multi-detector CT (MDCT) angiography to exclude occlusive coronary artery disease were recruited. Patients with poor examination or motion artifacts, previous coronary artery bypass surgery or previous coronary artery stenting, and difficulty in PFV segmentation or calculation were excluded from the study.

Information regarding conventional coronary risk factors was obtained from the each patient at the time of coronary MDCT examination including a positive family history of premature CAD (occurring before the age of 55 years in men and before 65 years in women), current smoking history (more than 10 cigarettes per day in the last year), a history of hypertension or use of anti-hypertension medications, a history of diabetes mellitus or use of insulin or diabetes lowering drugs, and measurement of body weight and height to calculate body mass index (BMI) and define obesity (BMI ≥30).[6] Verbal informed consent was obtained from all individuals included in the study. The study was approved by our institution.

Both earlobes were examined by 2 trained observers blinded to patients' results of MDCT angiography who determined by consensus whether ELC was present with the patient in the sitting position. An ELC was considered to be present when the patient has a wrinkle extending from the tragus to the outer border of the earlobe not related to sleeping position or wearing earrings. Patients with distorted earlobe anatomy were excluded.[9]

Fig. 1 – Earlobe crease. (A) Complete and (B) incomplete.

According the length of the ELC, ELC can be categorized as complete when it crosses the entire earlobe and incomplete when it is visible only partly through the earlobe as in Figure 1.

MDCT scan protocol

MDCT coronary angiography was performed with a 64-slice scanner (Aquilon 64, v. 4.51 ER 010; Toshiba Medical Systems, Tochigi, Japan). PFV was defined as any fat tissue located within the pericardial sac and measured 3-dimensionally in the contrast-enhanced phase. The layer of the pericardium was manually traced, and a 3-dimensional image of the heart was constructed. Then the pericardial fat volume was determined by measuring the total volume of the tissue whose CT density ranged from –250 to –20 HU within the pericardium by using a 3-dimensional workstation statistical analysis.[6] For other MDCT parameters of coronary atherosclerosis, a plaque was defined as a structure of >1 mm within and/or adjacent to the vessel lumen. Plaques were classified into calcified (plaque consisting of only calcium), non-calcified plaque (plaque that was free of calcium).[6,8]

The severity of coronary artery stenosis was visually graded as normal (normally appearing lumen to non-significant with a mean lumen diameter reduction of <50%) and significant with a mean lumen diameter reduction of ≥50% in a single vessel by comparing the lumen diameter of the narrowest segment with that of a more proximal or distal normal segment in 2 orthogonal projections. The CAC score was assessed as per our previous study.[8]

The analyses of MDCT images were examined by 2 trained radiologists in consensus.

Statistical analysis

Data were presented as mean ± standard deviation or as numbers with percentages, as indicated. CAC score values were non-normally distributed and presented as median (inter-quartile range [IQR]). The independent t-test or non-parametric test (Mann–Whitney U test) was used to assess the associations between ELC with PFV and CAC,

respectively. The categorical data, including coronary plaque and stenosis severity, were compared using chi-square test. Binary logistic regression analysis was used to analyze the association of ELC and conventional coronary risk factors, including BMI, age, hypertension, smoking, diabetes mellitus, and family history of premature coronary artery disease with coronary atherosclerotic markers. For the purpose of binary regression analysis, CAC was classified into two groups as the CAC = 0 group and CAC >0 group. The results were reported as odds ratios and confidence intervals (OR [CI]) for each variable of the binary regression analysis. Multivariate logistic regression analysis was conducted to assess the influence of ELC and conventional coronary risk factors on PFV. The results were reported as β-coefficient. Statistical significance was set at p <0.05. SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the data.

Results

A total of 70 patients (35 males and 35 females) with a mean age of 52±10 years were enrolled in the present study. The enrolled patients were assigned into two groups: one group was the non-ELC group (n = 37, 53%) and the other group was ELC group (n = 33, 47%). The clinical characteristics of the enrolled patients are shown in Table 1.

As noticed, patients with ELC were older and had a significantly higher prevalence of diabetes mellitus than those without ELC. The distribution of BMI, hypertension, smoking, male sex, and family history of premature coronary artery disease showed no significant differences between ELC and non-ELC groups.

With regards to the distribution of coronary atherosclerotic markers and PFV, around three quarters of patients with ELC presence had coronary artery disease in the present study. Coronary calcification, CAC, calcified plaque, and significant coronary stenosis were significantly more prevalent among ELC group than non-ELC group (p <0.01). There was no significant difference in the frequency of non-calcified plaque presence between ELC patients and patients without ELC (18% vs 14%, p = 59). PFV values were significantly higher in ELC group than in non-ELC group (145 vs 92, p <0.01), as in Table 1.

Table 1 – Patients' characteristics

Variables	Non-ELC group n = 37	ELC group n = 33	*p*-value
Age (years), mean ± SD	48±9	57±8	<0.01
BMI, mean ± SD	28±3	29±4	0.08
Male, n (%)	19 (51%)	14 (42%)	0.45
Hypertension, n (%)	19 (51%)	22 (66%)	0.19
Diabetes mellitus, n (%)	9 (24%)	18 (54%)	0.01
Smoking, n (%)	13 (35%)	16 (48%)	0.25
Family history, n (%)	13 (35%)	10 (30%)	0.66
CAC, median (IQR)	0 (0–6.5)	57 (15–86)	<0.01
Coronary calcification (CAC >0), n (%)	10 (27%)	26 (79%)	<0.01
Coronary plaque, n (%)	14 (38%)	32 (97%)	<0.01
Calcified plaque	9 (24%)	27 (82%)	<0.01
Non-calcified plaque	5 (14%)	6 (18%)	0.59
Non-significant coronary stenosis, n (%)	29 (78%)	4 (12%)	<0.01
Significant coronary stenosis (≥50%), n (%)	8 (22%)	29 (88%)	<0.01
PFV (cm^3), mean ± SD	92±25	145±26	<0.01

BMI – body mass index; CAC – coronary artery calcium score; ELC – earlobe crease; IQR – interquartile range; PFV – pericardial fat volume; SD – standard deviation.

Regression analysis

ELC presence showed a significant independent association with increased CAC (OR [CI] = 3 [2–10], p <0.01), signifi-

Table 2 – Binary regression model of association between coronary artery disease risk factors and earlobe crease presence to predict coronary atherosclerosis markers

CAC		
Predictor	**OR (CI)**	***p*-value**
Age	1 (0.9–1.1)	0.13
Male	0.5 (0.1–2)	0.44
BMI	1 (0.8–1.2)	0.50
Hypertension	0.1 (0.1–0.9)	0.04
Diabetes mellitus	2 (0.4–7)	0.31
Smoking	0.7 (0.1–4)	0.75
Family history	0.3 (0.1–1.3)	0.12
Earlobe crease	3 (2–10)	<0.01
Significant coronary stenosis		
Predictor	**OR (CI)**	***p*-value**
Age	1 (0.9–1.2)	0.02
Male	0.6 (0.4–4)	0.71
BMI	1 (0.8–1.4)	0.35
Hypertension	0.2 (0.1–1.1)	0.06
Diabetes mellitus	1 (0.1–5)	0.90
Smoking	0.6 (0.1–5)	0.69
Family history	0.8 (0.1–4)	0.83
Earlobe crease	3 (2–8)	<0.01
Coronary plaque presence		
Predictor	**OR (CI)**	***p*-value**
Age	1 (1–1.2)	0.02
Male	0.6 (0.1–5)	0.71
BMI	1 (0.8–1.4)	0.41
Hypertension	0.2 (0.1–0.8)	0.03
Diabetes mellitus	1 (0.1–5)	0.68
Smoking	0.4 (0.1–4)	0.51
Family history	1 (0.2–5)	0.91
Earlobe crease	4 (3.5–9)	<0.01

CI – confidence interval; OR – odds ratio.

Table 3 – Multivariate regression model of association of coronary risk factors and earlobe presence with PFV

PFV		
Predictor	***p*-value**	***p*-value**
Age	0.09	0.27
Male	–0.00	0.93
BMI	0.44	<0.01
Hypertension	–0.04	0.57
Diabetes mellitus	0.08	0.32
Smoking	0.02	0.77
Family history	0.10	0.13
Earlobe crease	0.56	<0.01

cant coronary stenosis (OR [CI] = 3 [2–8], p <0.01), and coronary plaque presence (OR [CI] = 4 [3.5–9], p <0.01) after adjustment for conventional coronary risk factors, as in Table 2. Also, ELC presence (p <0.01) was independently associated with increased PFV following adjustment for conventional coronary risk factors, as in Table 3.

Discussion

In the present study, a significant independent association was found between coronary atherosclerotic markers, including CAC, significant coronary stenosis, and plaque presence and ELC than between coronary atherosclerotic markers and other risk factors for coronary artery disease.

The pathophysiological mechanisms linking ELC to coronary atherosclerosis are largely unknown or not fully understood. Some hypotheses have been proposed to explain the possible mechanisms for the association between ELC and coronary atherosclerosis. The proposed mechanisms might include degeneration of elastin and unbalanced ratio of collagen to elastin. These changes were similarly seen in biopsy specimens taken from the earlobes and the coronary vessels, suggesting that ELC may reflect skin ageing and the ageing process of the major arteries, supporting the hypothesis that ELC may represent a marker of diffuse atherosclerotic disease.[3,10,11]

It has been also suggested that ELC and coronary atherosclerosis may share a common mechanism of age-related microvascular changes associated with weakening of elastic fibers of earlobes and in coronary arteries, as both the earlobe and myocardium are supplied by end-arteries of the same genetic origin with few collateral vessels. Thus, ear lobe tissues might undergo a diminished blood supply similar to that of myocardium.[12,13]

In an autopsy study, Cumberland et al. found that ELC presence was significantly associated with severe coronary artery stenosis (more than 75% stenosis of ≥1 major coronary artery) (p <0.01) and that the absence of ELC is an accepted predictor of the absence of severe coronary atherosclerosis.[1,14]

Along the same lines, ELC was significantly associated with coronary stenosis severity and plaque presence assessed by CT angiography (p <0.01). The association of ELC with coronary atherosclerotic markers remained even after adjusting for other conventional risk factors for coronary artery disease.[5]

According to the results of large meta-analysis study, which included more than 31,100 individuals, around 62% of patients with coronary artery disease have ELC. The risk of coronary artery disease is three fold higher in patients with ELC compared to those without ELC.[13]

In the literature, previous studies have explored the association between ELC and obesity or metabolic syndrome but data on the associations between ELC and other adiposity markers such as PFV assessed by 3-dimensional MDCT are lacking.[2] Only one study explored the association between pericardial adipose thickness measured by 2-dimentional echocardiography and earlobe crease presence among 65 apparently healthy individuals free of clinical cardiovascular disease with ELC and 65 age- and sex-matched controls without ELC. A significant and independent association between the presence of ELC and increased pericardial fat thickness was reported in this study.[4]

Pericardial adiposity was reported to contain and secrete higher levels of inflammatory markers that act locally to induce and accelerate atherosclerotic process through endothelial dysfunction.[15]

Importantly, ELC was found to be associated with lower flow-mediated vasodilation and increased carotid intima media thickness in previous studies. These findings may support the hypothesis that DELC is associated with endothelial dysfunction.[3,16]

Taken together, ELC may act as a mirror of endothelial dysfunction which is enhanced by inflammatory mediators secreted by pericardial adiposity.

There were some limitations in the present study. This study was cross-sectional, relatively small size, and single-center design of patients with suspected coronary artery disease based on physician referral, which may not reflect the general population. Data on dyslipidemia were not included in the statistical analysis because of absence of lipid profile data or patients were already on lipid lowering drugs. Despite these limitations, this study may provide a valuable insight into the significance of ELC in coronary atherosclerosis because it focused on different atherosclerotic markers assessed by 3-dimentional MDCT modality, in contrast to previous studies.

Conclusion

ELC is significantly and independently associated with coronary atherosclerotic burden, including CAC, calcified plaque, and significant coronary stenosis and increased pericardial adiposity.

Conflict of interest

The authors declare that they have no conflict of interest.

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