HEART ISCHAEMIA AND VE-CADHERIN. AGE CORRELATIONS

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Abstract. Objective: We investigated a possible connection between VE-cadherin (vascular endothelial cadherin) and age, in human ischemic heart disease. Method: Our study was conducted on two groups - ischemic heart disease group (65.6 ± 9.0) years, n = 15 and health group (67.1 ± 7.0) years, n = 12. Venous blood was used for obtaining serum, stored below -70 Celsius degrees for 6 months. Serum VE-cadherin was determined on a Statfax 2100 micro plate reader, through ELISA RD kit (DCADV0) at 450 nm. We used a SPSS program for determining Pearson correlation coefficients and statistic significances. Results: Our data shows an inverse and significant correlation between serum VE-cadherin and age (r = - 0.557, p = 0.03, n = 15) in ischemic heart disease group. Health group has no correlation between VE-cadherin and age (r = - 0.546, p = 0.07, n = 12). Conclusion: VE-cadherin, factor implicated in modulating vascular structure, decrease with age in ischemic heart disease, but not in health group; this being an aggravation mechanism in vascular pathology including heart disease.

Rezumat. Obiectiv: Am investigat o posibilă legătură între VE-caderină (caderina endoteliului vascular) și vârstă, în boala cardiacă ischemică umană. Metodă: Studiul nostru a fost efectuată pe două loturi – grupul cu boală cardiacă ischemică (65,6 ± 9,0) ani, n = 15 și grupul sanătos (67,1 ± 7,0) ani, n = 12. Sângele venos a fost folosit pentru obținerea serului care s-a păstrat la temperaturi sub -70 grade Celsius pentru o perioadă de pană la 6 luni. VE-caderina serică a fost determinată pe un cititor de micro plăci Statfax 2100, prin kit ELISA RD (DCADV0) la 450 nm. Am folosit un program SPSS pentru determinarea coeficienților de corelație Pearson și a semnificațiilor statistice. Rezultate. Datele noastre arată o corelație inversă şi semnificativă statistic între VE-caderină serică și vârsta (r = - 0,557, p = 0,03, n = 15) în grupul cu boală cardiacă ischemică. Grupul sănătos nu prezintă nici o corelație între VE-caderină și vârsta (r = - 0,546, p = 0,07, n = 12). Concluzii: VE-caderină, factor implicat în modularea structurii vasculare, scade odată cu vârsta în boala cardiacă ischemică, dar nu în grupul sănătos; această scădere devenind un factor agravant al patologia vasculară incluzând bolile cardiace.

INTRODUCTION

Cadherin are transmembrane proteins involved in cell adhesion ion dependent (Ca^{2+}), hence the name (calcium-dependent adhesion proteins).

Synthesized as polypeptide (720-750 amino acids) they change posttranslational, becoming cellular proteins implicated in mediating adhesion and cell recognition. Each has a cytoplasm component, one transmembrane and one extracellular. Their structure has repetitive areas for binding extracellular Ca^{2+}. The cadherin super-family includes cadherins, protocaderine, desmogline, desmocoline etc. There are several classes of cadherins named by a prefix specifique for each type of tissue which it is associated. There are over 100 cadherins. Some of these with known amino acid sequence (Kurita et al., 2013). CDH1 - E-cadherin (epithelial) CDH2 - N-cadherin (neural) CDH12 - cadherin 12, type 2 (N-cadherin 2) CDH3 - P-cadherin (placental) CDH4 - R-cadherin (retinal) CDH5 - VE-cadherin (vascular endothelial) CDH6 - K-cadherin (kidney) CDH11 - OB-cadherin (osteoblast) CDH13 - T-cadherin - H-cadherin (heart) CDH17 - LI-cadherin (liver-intestine).

Cells which contain a certain type of tend to form clusters with the same type of cadherine. For example, cells that have N-cadherine tend to form clusters with other cells containing N-cadherine. Is possible to have heterotypic with different properties. A proposed model seems to denote that cells distinguish between different subtypes of cadherin-on kinetic parameters than thermodynamic ones and clusters are different in life time. (Bayas MV ET AL., 2006).

Cadherin 5, type 2,or VE-cadherin (vascular endothelial) named like CD144 (Cluster of Differentiation 144) is coded by

human gene CDH5 (SUZUKI S ET AL. 1991). It is a calcium dependent adhesion glycoprotein for cell to cell interaction, composed by 5 repetitive cadherin extracellular domains, a region transmembranare and a cytoplasm tail. Functioning as a classical cadherine it provides the ability to adhere homophile cells together. In this way, VE-cadherin may play an important role in endothelial cell biology, in controlling cohesion and intercellular junctions organizing (CORADA M ET AL., 2001. The integrity of these is a major determinant in endothelial permeability, and those in which it is implicated VE-cadherin is considered to be particularly important. VE-cadherin is known to be required to maintain a restrictive endothelial barrier. VE-cadherin is indispensable for proper vascular development [Carmeliet P ET AL., 1996; GORY-Faure S ET AL., 1999]. In the absence of VE-cadherin, forming vessels collapse and are dissembled (CV CROSBY ET AL., 2005). Several cadherin genes have promoter regions that are regulated by methylation processes and thus can under the influence of epigenetic processes (F GRAZIANO et al., 2004). The same methylation process is operated by intermediate agents such as vitamin B9 and B12. They are the protective factors in cardiovascular diseases in aging and a possible mechanism is by decreasing risk factors that homocysteine (VALUCH ET AL., 2012).

Studies with blocking antibodies to VE-cadherin increased monolayer permeability in cell cultures [CORADA M ET AL., 2001] and led to interstitial edema and hemorrhage in vivo [CORADA M ET AL., 2002]. Myocardial ischemia is accompanied by alterations of vascular endothelium. More often it was associated with the alterations of vascular endothelial and circulatory system in general. Therefore we felt that is possible to produce a change in VE-cadherin that is implicated in the mechanism of endothelial homeostasis. In these conditions (VE cadherin involvement in regulating endothelial and vasculogenesis) we proposed to study on two groups of human subjects (control and cardio ischemia disease) some changes in VE-cadherin and other correlations with clinical and preclinical parameters taken into study, including age.

METHOD

The selection criteria were:

• Exclusion criteria for healthy subjects: CARDIOISCHEMIA DISEASE, DIABETES, MYOCARDITIS / PERICARDITIS, rheumatism, pulmonary embolism, ACUTE INFECTIONS, cancer

• Exclusion criteria for subjects with cardiovascular pathology: DIABETES, MYOCARDITIS / PERICARDITIS, rheumatism, pulmonary embolism, ACUTE INFECTIONS, cancER

• Inclusion criteria for patients with cardiovascular pathology: CARDIOISCHEMIA DISEASE.

We chose two groups of patients: group 1 (BCI with HTA) and group 2 (control without HTA).

The blood collected was processed to obtain serum for storing at -70^0 C. VE-cadherin was determined at 450 nm by ELISA kit RD system, catalog code DCADV0 on a Statfax 2100 device. The data were statistically processed to obtain Pearson correlation coefficients between the various parameters and age.

RESULTS AND DISCUSSION

Vascular endothelial cadherin is exclusively expressing on interendothelial junctions in normal and tumor vessels (BREIER ET AL., 1996; LAMPUGNANI ET AL., 1992). VE-cadherin is implicated in regulation of vascular neogenesis. In her absence the process is disturbed and is induced alterations of vascular endothelium and cardiovascular system in general (CV CROSBY ET AL., 2005). Myocardial ischemia is accompanied by a series of endothelial dysfunctions and was expected to be accompanied by change in VE-cadherin values and eventually correlated

with systolic and diastolic blood pressure. The two groups of patients, one with heart ischemia and controls were analyzed using Pearson coefficient correlation tables. The data were able to show that heart group ischemia present a negative significant correlation between the VE-cadherin and age (Table 1, r = - .557, p = 0.03, n = 15). The control group has not significant correlation between VE-cadherin and age (Table 2, r = -0.546, p = 0.07, n = 12). The data obtained suggest that the cardiac ischemia produce a decrease and a disorder with age for the capacity of neovascularization, mediated by the VE-cadherin.

TABLE 1. CORRELATIONS BETWEEN AGE, VE- CADHERINE AND DIFFERENTS VARIABLES ON A CARDIAC-ISCHEMIA GROUP ; N=15, age=(65.6 ± 9.0) years, HTAmax = (15.3 ± 1.4) mmHg, HTAmin = (8.2 ± 0.8) mmHg. Datele obtinute au aratat ca grupul cu cardiopatie ischemica prezinta o corelatie inversa semnificativa intre ve-caderina şi varsta (r = -0.557, p = 0.03, n =15).

		AGE (years)	LEUKOCYTE (nr/ul)	HDL (mg/dl)	LDL (mg/dl)	THROMBOCYTE (nr/ul)	VE-CAD (ng/ml)	HTA max (mmHg)	HTA min (mmHg)
AGE (years)	r	1	-0.704	0.062	0.004	-0.376	-0.557	-0.058	-0.059
	Sig. (2-tailed)		0.003	0.827	0.988	0.167	0.031	0.837	0.834
	N	15	15	15	15	15	15	15	15
VE-CAD (ng/ml)	r	-0.557*	0.327	-0.314	-0.017	0.276	1	0.162	-0.020
	Sig. (2-tailed)	0.031	0.235	0.254	0.953	0.320		0.564	0.942
	N	15	15	15	15	15	15	15	15
HTA max (mmHg)	r	-0.058	-0.113	-0.143	-0.231	0.158	0.162	1	0.663
	Sig. (2-tailed)	0.837	0.688	0.612	0.407	0.575	0.564		0.007
	N	15	15	15	15	15	15	15	15
HTA min (mmHg)	r	-0.059	-0.002	0.285	-0.461	0.102	-0.020	0.663	1
	Sig. (2-tailed)	0.834	0.995	0.303	0.084	0.717	0.942	0.007	
	N	15	15	15	15	15	15	15	15

**. Correlation is significant at the 0.01 level (2-tailed). r- Pearson correlation

*. Correlation is significant at the 0.05 level (2-tailed).

TABLE 2 . CORRELATIONS BETWEEN AGE, VE- CADHERINE AND DIFFERENTS VARIABLES ON A NON CARDIAC-ISCHEMIA GROUP ; N=12, age=(67.1 ± 7.0) years, HTAmax = (12.5 ± 0.7) mmHg, HTAmin = (7.5 ± 0.8) mmHg. Datele obtinute au aratat ca grupul martor nu prezinta o corelatie semnificativa intre ve-caderina şi varsta (r = -0.546, p = 0.07, n =12).

		AGE (years)	LEUKOCYTE (nr/ul)	HDL (mg/dl)	LDL (mg/dl)	THROMBOCYTE (nr/ul)	VE-CAD (ng/ml)	HTA max (mmHg)	HTA min (mmHg)
AGE (years)	r	1	-0.177	-0.086	-0.287	-0.447	-0.546	0.192	0.195
	Sig. (2-tailed)		0.583	0.790	0.365	0.145	0.067	0.550	0.545
	N	12	12	12	12	12	12	12	12
VE-CAD (ng/ml)	r	-0.546	-0.332	0.163	0.173	0.031	1	-0.133	-0.416
	Sig. (2-tailed)	0.067	0.292	0.612	0.590	0.925		0.681	0.178
	N	12	12	12	12	12	12	12	12
HTA max (mmHg)	r	0.192	0.553	-0.302	-0.187	0.059	-0.133	1	0.676
	Sig. (2-tailed)	0.550	0.062	0.340	0.561	0.856	0.681		0.016
	N	12	12	12	12	12	12	12	12
HTA min (mmHg)	r	0.195	0.664	-0.203	-0.132	0.360	-0.416	0.676	1
	Sig. (2-tailed)	0.545	0.019	0.526	0.683	0.250	0.178	0.016	
	N	12	12	12	12	12	12	12	12

*. Correlation is significant at the 0.05 level (2-tailed). r-Pearson correlation

**. Correlation is significant at the 0.01 level (2-tailed).

CONCLUSIONS

VE-cadherin is inversely correlated with age in cardiac ischemia ($r = - 0.557$, $p = 0.03$, $n = 15$) but not in the control. This suggests that the VE-cadherin, neovascularization adjustment factor, decreases with age in cardiac ischemia and may be a mechanism for aggravating vascular pathology, including cardio ischemia disease.

REFERENCES

[1] Bayas MV, Leung A, Evans E, Leckband D. Lifetime Measurements Reveal Kinetic Differences between Homophilic Cadherin Bonds. Biophysical Journal 2006, 90, 1385–1395.

[2] Breier G , Breviario F , Caveda L , Berthier R , Schnurch H , Gotsch U , Vestweber D , Risau W , Dejana E. Molecular cloning and expression of murine vascular endothelial-cadherin in early stage development of cardiovascular system. Blood, 1996, 87: 630- 41.

[3] Carmeliet, P., Ferreira, V., Breier, G., Pollefeyt, S., Kieckens, L., Gertsenstein, M., Fahrig, M. Vandenhoeck, A., Harpal, K., Eberhardt, C., Declercq, C., Pawling, J., Moons, L., Collen, D., Risau, W. and Nagy, A.. Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. Nature 1996, 380, 435-439.

[4] Crosby CV, Fleming PA, Argraves WS, Corada M, Zanetta L, Dejana E, Drake CJ. VE-cadherin is not required for the formation of nascent blood vessels but acts to prevent their disassembly. Blood, 2005 ,105, 7, 2771-2776.

[5] Gory-Fauré S, Prandini MH, Pointu H, Roullot V, Paintrand IP, Vernet M, Huber P. Role of vascular endothelial-cadherin in vascular morphogenesis. Development 1999, 126, 2093-2102.

[6] Graziano, F. Arduini, A. Ruzzo, A. Mandolesi, I. Bearzi, R. Silva, P. Muretto, E. Testa D. Mari, M. Magnani, M. Scartozzi & S. Cascinu. Combined analysis of E-cadherin gene (CDH1) promoter hypermethylation and E-cadherin protein expression in patients with gastric cancer: implications for treatment with demethylating drugs. Annals of Oncology 2004, 15, 489–492.

[7] Kurita S, Yamada T, Rikitsu E, Ikeda W, Takai Y. Binding between the Junctional Proteins Afadin and PLEKHA7 and Implication in the Formation of Adherens Junction in Epithelial Cells. J. Biol. Chem. 2013, 288: 29356-29368.

[8] Lampugnani MG , Resnati M , Raiteri M , Pigott R , Pisacane A , Houen G , Ruco LP , Dejana E. A novel endothelial-specific membrane protein is a marker of cell-cell contacts. J Cell Biol. 1992, 118: 1511- 22.

[9] Monica Corada, Fang Liao, Maria Lindgren, Maria Grazia Lampugnani, Ferruccio Breviario, Ronald Frank, William A. Muller, Daniel J. Hicklin, Peter Bohlen, and Elisabetta Dejana. Monoclonal antibodies directed to different regions of vascular endothelial cadherin extracellular domain affect adhesion and clustering of the protein and modulate endothelial permeability. Blood, 2001, 97, 6, 1679-1684.

[10] Monica Corada, Lucia Zanetta, Fabrizio Orsenigo, Ferruccio Breviario, Maria Grazia Lampugnani, Sergio Bernasconi, Fang Liao, Daniel J. Hicklin, Peter Bohlen, and Elisabetta Dejana.. A monoclonal antibody to vascular endothelial-cadherin inhibits tumor angiogenesis without side effects on endothelial permeability. Blood, 2002, 100, 3, 905-911.

[11] Suzuki S, Sano K, Tanihara H. Diversity of the cadherin family: evidence for eight new cadherins in nervous tissue. Cell Regul.1991, 2, 4, 261–70.

[12] Valuch Anton, Andrei Victoria, Simona Opris, Elena Lupeanu. Factori de protecţie in îmbătranirea umană a sistemului cardiovascular. p. 65. A-37-a Conferinţă Naţională de Geriatrie şi Gerontologie, cu Participare Internaţională. Anul longetivităţii active. La 60 de ani de geriatrie şi gerontologie in Romania. Institutul Naţional de Gerontologie şi geriatrie “Ana Aslan”, Otopeni, 18-21 octombrie 2012.