Gene polymorfism of angiotensin-converting enzyme and angiotensin II type 1 receptor in heart failure patients with atrial fibrillation

Polimorfismul genic al enzimei de conversie a angiotensinei şi a receptorului de tip 1 al angiotensinei II la pacienți cu insuficiență cardiacă şi fibrilație atrială

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Abstract

The angiotensin converting enzyme (ACE) and AT1 receptor genetic polymorphism influence the plasma ACE and angiotensin II (AII) levels, with the highest levels being registered in the DD associated with CC form. ***Objectives****: To investigate the genetic polymorphism of renin-angiotensin-aldosterone system in patients with heart failure and persistent atrial fibrillation.* ***Methods****: We studied 72 NYHA II, III and IV class heart failure patients, 43 males and 29 females, aged 67.87±11.96 years, of which 63.9% presented persistent atrial fibrillation. The distribution of ACE gene insertion, deletion (ID) and AT1 receptors A1166C gene polymorphism were determined. Analyses of ACE and AT1 receptors genotypes were performed by polymerase chain reaction (PCR).* ***Results****: The distribution of genetic ACE polymorphism was: DD-47.2% (34p); ID–29.2% (21p); II –23.6% (17p). The identified AT1 receptors genotypes were as follows: AA –51.4% (37p); AC- 36.1% (26p), CC– 12.5% (9p). Among the 63.88% (46p) of the patients with permanent atrial fibrillation, the distribution of genetic polymorphism was as follows: DD- 45.7% (21p), ID –26.1% (12p); II –28.3% (13p), AA- 65.2% (30p), AC-23.9% (11p), CC-10.9% (5p). The two types of genetic polymorphism were associated in 45.65% (21p) of the patients with atrial fibrillation: DD + AA – 57.14% (12p); DD + AC –28.57% (6p); DD + CC –14.28% (3p).* ***Conclusion****: Associated ACE and AT1 genetic polymorphism was registered in approximately half of the heart failure patients with permanent atrial fibrillation suggesting that high levels of ACE, respectively AII can contribute to the development of atrial fibrillation.*

Keywords: *heart failure, atrial fibrillation, genetic polymorphism, renin angiotensin aldosterone system.*

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Rezumat

Polimorfismul enzimei de conversie a angiotensinei (ECA) şi a receptorului angiotensinei II de tip I (AT1) influenţează nivele plasmatice ale ECA şi ale angiotensinei II (AII), nivelele cele mai ridicate fiind înregistrate la pacienţii care prezintă asocierea formelor CC şi DD. Obiectivele studiului investigarea polimorfismului genetic a sistemului renina-angiotensină-aldosteron la pacienţii cu insuficientă cardiacă şi fibrilaţie atrială. ***Material şi metodă:*** *au fost investigaţi un număr de 72 de pacienţi cu insuficienţă cardiacă (clasa NYHA II, NYHA III sau NYHA IV), 43 bărbaţi şi 29 femei, vârsta medie 67.87±11.96 ani, 63.9% prezentând fibrilaţie atrială cronică. A fost studiat polimorfismului genetic al inserţiei şi deleţiei (ID) genelor ECA, precum şi a receptorului AT1 A1166C. Analiza genotipului ECA şi a receptorului AT1 a fost efectuată utilizând metoda PCR (polimeraze chain reaction).* ***Rezultate:*** *distribuţia polimorfismului genetic a ECA a fost următoarea DD-47.2% (34p); ID –29.2% (21p); II –23.6% (17p).Genotipurile receptorului AT1 identificate au fost: AA –51.4% (37p); AC- 36.1% (26p), CC–12.5% (9p). La pacienţii cu fibrilaţie atrială permanentă distribuţia polimorfismului genetic a fost DD-45.7% (21p), ID –26.1% (12p); II –28.3% (13p), AA-65.2% (30p), AC-23.9% (11p), CC-10.9% (5p). Cele două tipuri de polimorfism genetic au fost asociate în 45.65% (21p) din pacienţii cu fibrilaţie atrială: DD + AA –57.14 (12p); DD + AC –28.57% (6p); DD + CC –14.28% (3p).* ***Concluzie:*** *asocierea polimorfismului genetic a ECA şi a AT1 la aproape jumătate din pacienţii cu insuficienţă cardiacă şi fibrilaţie atrială permanentă poate sugera faptul că nivelele ridicate ale ECA, respective ale angiotensinei II pot contribui la apariţia fibrilaţiei atriale.*

Cuvinte cheie: *insuficienta cardiaca, fibrilaţie atrială cronică, sistemul renina – angiotensină - aldosteron, polimorfism genetic.*

Introduction

The angiotensin converting enzyme (ACE) and AT_1 receptor genetic polymorphism influence the plasma ACE and angiotensin II (AII) levels, with the highest levels being registered in the DD associated with CC form. Renin-angiotensin-aldosterone system (RAA system) and angiotensin II type 1 receptor have been involved in atrial structural and electrical remodeling. RAA system activates the mitogen-activated protein kinase resulting in myocyte hypertrophy and fibroblast proliferation. Angiotensin-gene polymorphism is associated with increased non-familial atrial fibrillation (AF) (1). Polymorphisms in the RAA system genes may affect the serum angiotensin II level. However, it has yet to be demonstrated that polymorphisms of the RAA system genes promote AF via alterations of atrial angiotensin II levels (2). More studies are trying to elucidate whether there is a mechanistic link between the observed association of RAA system gene polymorphisms and AF. In addition, RAA system is involved in the pathogenesis of heart failure. Raynolds et al. reported an association between the ACE genetic polymorphism and the presence of heart failure (3). The presence of AT_1 genetic mutation, especially in the homozygote form, may be associated with DD genotype (homozygote form) of ACE, the result being a high level of ACE.

The objective of this study was to investigate the genetic polymorphism of ACE and AT1 receptor in patients with heart failure and atrial fibrillation.

Methods

We studied 72 NYHA II, III and IV class heart failure patients, 43 males and 29 females, aged 67.87±11.96 years, of which 63.9% presented persistent atrial fibrillation.

ACE- insertion (I)/deletion (D) genotyping Genotyping for the insertion (I)/deletion (D) of the 287 bp in the ACE gene was performed in an Eppendorf thermocycler. The primers used had the following sequences: the forward primer 5'-CATCCTTTCTCCCATTTCTC -3' and the reverse primer 5'-TGGGATTACAGGCGTGATACAG-3'. The PCR conditions were: 1X PCR buffer (100mM

Table 1. Main patient characteristics

	Total patients with heart failure (No, %)	With atrial fibrillation (No, %)	Without atrial fibrillation (No, %)	p
No. (%)	72(100)	46(63.9)	26 (23.1)	
Age	67.87±11.96	69.54±11.11	64.92±13.03	NS
Women	29(40.3%)	19(41.3)	10(38.5)	NS
Hypertension	45(62.5)	28(60.9)	17(65.4)	NS
Diabetes mellitus	17(23.6)	9(19.6)	8(30.8)	NS
Obesity	30(41.7)	18(39.1)	12(46.2)	NS
NYHA II class	3 (4.16)	1(2.2)	2(7.7)	NS
NYHA III class	40(55.6)	23(50)	17(65.4)	NS
NYHA IV class	29(40.3)	22(47.8)	7(26.9)	0.06
Left atrium>50 mm	49(68.1)	38(82.6)	11(42.3)	0.001

tris- HCl, pH 8.8, 500mM KCl 0.8% (v/v) Nonidet P40), 20ng genomic DNA, 2.0mM $MgCl_2$, 200µM dNTPs, 0.2µM each primer, 2U Taq DNA polymerase. The PCR program was: denaturation at 95ºC for 10 min, followed by 35 cycles of amplification at 94ºC for 30 sec, 69ºC for 30 sec, 72ºC for 1min 30sec and a final extension step at 72ºC for 2 min. The product had 290bp and the deletion formed a product of 100bp.

AGTR1- A1166C genotyping For the analysis of the A1166C polymorphism we used the methods of Takemoto (1998) (4). The forward primer 5'-ATAATGTAAGCTCATCCACC-3' and the reverse primer 5'-GAGATTGCATTTCTG TCAGT-3' were used. The PCR reaction contained 1 X PCR buffer (100mM tris- HCl, pH 8.8, 500mM KCl 0.8% (v/v) Nonidet P40), 20ng genomic DNA, 2.0mM $MgCl_2$, 200µM dNTPs, 0.2µM each primer, 2U Taq DNA polymerase. Cycling PCR conditions were: one cycle at 95ºC for 10 min, 35 cycles of denaturation at 94ºC for 30 sec, annealing at 57ºC for 30 sec, extension at 72ºC for 1 min 30 sec and a final extension cycle at 72ºC for 2 min. The 350 bp amplified fragment was digested for 3h at 37ºC with 5U Ddel in a total volume of 10µl. The expected fragment sizes were 350bp for the wild-type A1166 allele and 211 and 139bp for the variant C1166 allele.

The data was analyzed using SPSS 16.0 (Demo Version). We calculated mean and standard deviation for normal distributed quantitative variables. Differences between quantitative variables were examined using the Student test (independent-sample T test), and for qualitative variables we used χ^2 test. A p value less than 0.05 was considered statistically significant.

Results

Patients' characteristics are presented in *Table 1*. The distribution of genetic ACE polymorphism was DD - 47.2% (34 patients); ID – 29.2% (21 patients); II –23.6% (17 patients). The identified AT_1 receptors genotypes were as follows: AA - 51.4% (37 patients); AC - 36.1% (26 patients), CC- 12.5% (9 patients). Not significant gender differences with respect to genetic polymorphism distribution were registered (*Table 2*).

Among the 63.88% (46 patients) of the patients with permanent atrial fibrillation (AF), the distribution of genetic polymorphism was as follows: DD- 45.7% (21 patients), ID –26.1% (12 patients); II –28.3% (13 patients), AA- 65.2% (30 patients), AC-23.9% (11 patients), CC-10.9% (5 patients) (*Figure 1*). The percent of DD and CC mutations was similar in patients with and

Table 2. The distribution of the two type of genotypes in women and men

Type of genotype	Women (No, %)	Men (No, %)	p
DD	13(44.8)	21(48.8)	NS
ID	10(34.5)	11(25.6)	NS
II	6(20.7)	11(25.6)	NS
CC	1(3.4)	8(18.6)	0.07
AC	13(44.8)	13(30.2)	NS
AA	15(51.7)	22(51.2)	NS

without atrial fibrillation (DD 45.7% vs. 50%, respectively CC 10.9% vs. 15.4%).

Considering patients less than 65 years of age, the prevalence of DD mutation was 58.3% in patients with and 53.8% in patients without AF (OR 1.2, CI 0.24 - 5.84). Also more AF patients present CC mutation: 25% vs. 15.4% (OR 1.8, CI 0.24 - 13.47).

It has to be mentioned that DD and CC mutations were associated in 8.3 % of the patients under 65 years, but in only 5.9% of the patients above 65 years of age.

With respect to ischemic and non-ischemic etiology of the atrial fibrillation, CC, DD mutations, but also their association was more frequently registered in ischemic ones. In atrial fibrillation patients, CC was present in 11.5% of the ischemic patients vs. 10% of non-ischemic patients (p=NS); the percentages registered for DD mutation were 50% and 40%, respectively (p=NS). In addition, CC + DD association was present in 7.7% of ischemic pa-

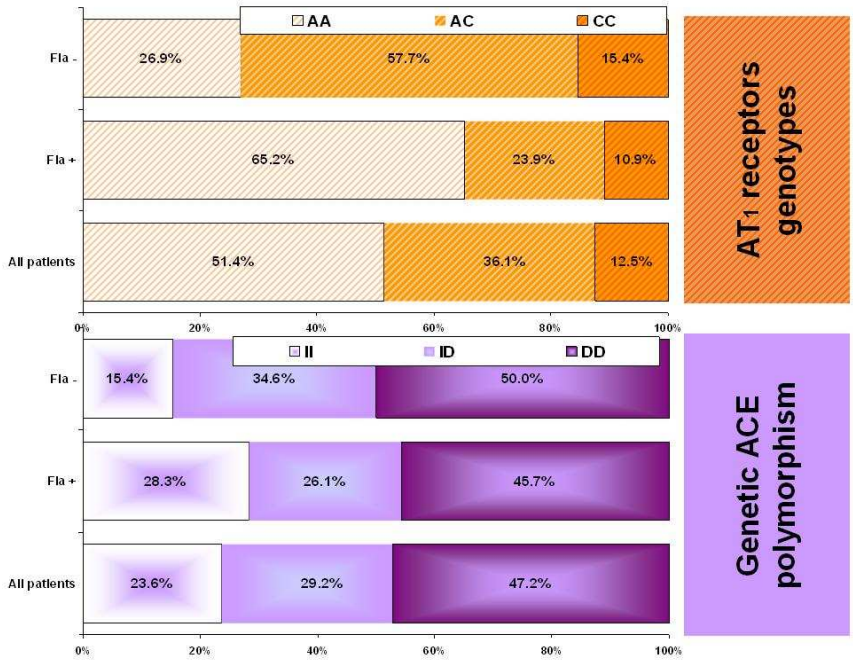

Figura 1. Distribution of genetic ACE polymorphism and AT1 receptor genotypes (Fla = atrial fibrilation)

tients with atrial fibrillation, compared to only 5% of those with non-ischemic etiology.

As far as drug treatment was concerned, angiotensin-converting enzyme inhibitors (ACE inhibitors, ACEI) and/or angiotensin receptor antagonists (ARBs) were administrated to the 91.2 % of the patients with DD mutation and 77.8 % of the patients with CC mutation.

Discussion

Angiotensin II (AG II), through AT_1 receptor stimulation, plays an important role in the proliferation of cardiac fibroblasts increasing the transforming growth factor *beta* 1 (TGF-β1) synthesis (5, 6, 7). Stimulation of TGF-β1 secretion in mouse results in atrial, but not ventricular fibrosis (6). Also experimental studies on heart failure dogs demonstrate that atrial AG II level is increased in comparison with ventricular AG II level, with an increased TGF-β1 synthesis (7).

Local atrial angiotensin converting enzyme (ACE) synthesis results in enlarged atrial dimensions promoting atrial fibrillation and heart failure (8). In persistent atrial fibrillation, ACE synthesis is elevated, but an experimental study showed that ACE-inhibitors inhibit fibrosis and decrease AF duration (7). The role of AT_1 and AT_2 receptors in AF is unclear. It is supposed that the AT_1 receptor stimulation will activate a protein-kinase resulting in ventricular hypertrophy, but the AT_2 stimulation has antiproliferative properties (9).

The direct effects of AG II upon cellular electrophysiology are still controversial, but the majority of the experimental studies demonstrate increased L and T calcium currents in ventricular myocytes (10). Consequently, as the inactivation of L and T calcium currents (ICa,L, ICa,T) can prevent atrial fibrillation, the angiotensin II (AG II) inhibition through renin-angiotensin-aldosterone system antagonists could have the same beneficial effects upon acute atrial remodeling through Kv repolarization current inhibition (11,12).

Studies performed in a large number of families suggested that 50% of the inter-individual variability of the angiotensin converting enzyme (ACE) is due to the polymorphism of a major gene located on the 17q23 chromosome, the coding sequences being responsible for a protein with 1306 amino acids (13). Rigat identified a genetic polymorphism inside intron 16, consisting of the presence or absence of a fragment formed of 287 amino acid pairs. The presence of this fragment defines the allele I (insertion), while its absence defines the allele D (deletion) (14). Depending on the modality in which the two alleles combine, ACE genotype is characterized by three types: II, DD and ID (14). ACE serum levels depend on the ID polymorphism of the ACE gene, as higher titers are found in the DD form, which has also the highest cellular activity (14). Furthermore, three genetic types (15, 16, 17) of the AT_1 receptors have been identified (AA, CC and AC), according to the nucleotide present in the 1116 position on the sequence of the messenger RNA responsible for this receptor (18). The DD genotype is frequently associated with a CC homozygote genotype of the AT_1 receptors.

In our study, the incidence of genetic mutations in the patients with heart failure was as follows: DD - 47.2% of the cases (34 patients); ID in 29.2% (21 patients) and II in 23.6% (17 patients). The incidence reported by McNamura is somewhat different (DD-30.7%, ID-50.7% and II-18.6%). The differences may be accounted for by the relatively small number of patients in our study (19). McNamura emphasizes that the DD mutation is present in one third of the population with high ACE levels (19). We did not find literature data regarding the incidence of this mutation or the association between ACE and AT_1 receptors mutations in patients with heart failure.

It is likely that the increased incidence of atrial fibrillation in the setting of heart failure can be attributed to the toxic effects of hemodynamic and neurohormonal pathology on atrial structure and function. Whether these effects

obviate or enhance genetically determined susceptibilities to atrial fibrillation is unclear. Polymorphism of the ACE and the angiotensin II type receptor gene are common and may be associated with atrial fibrillation and heart failure.

The distribution of genetic polymorphism in our study in the patients with atrial fibrillation and heart failure was as follows: DD - 45.7% (21 patients), ID - 26.1% (12 patients), II - 28.3% (13 patients), AA - 65.2% (30 patients), AC - 23.9% (11 patients), CC - 10.9% (5 patients). In GRACE study, which enrolled 479 heart failure patients, atrial fibrillation was present in 51 patients (15%) and was significantly associated with ACE DD mutation (OR 1.5). In fact, the results are similar with those reported by us: DD mutation in 45.1% in comparison with 45.7% in our study (20).

Gensini compared patients with and without AF and with preserved left ventricular function and no heart failure, and observed a significant association between the D allele and AF (odd ratio>3) (21). In the Copenhagen City Heart Study, subjects that initially presented sinus rhythm were followed for 26 years, and ACE and angiotensinogen mutation were determined. During follow-up, AF was registered in 968 subjects, especially in those with double or triple homozygots associations (22). A more recent study which studied the angiotensinogen, ACE mutation, but also mutations of AT_1 receptor, did not establish a significant association between each of the mutation and AF (23). In turn, the associations of ACE ID polymorphism and angiotensinogen gene haplotypes, AT1R A1166C polymorphism and angiotensinogen gene haplotypes, respectively between ACE ID, AT1R A1166C and angiotensinogen gene haplotypes were detected in significant number of AF patients (23). Also in a recent Chinese study, the prevalence of DD genotype of the ACE gene was significantly increased in AF patients in comparison with those without AF (24). In contrast, Yamashita et al. found no significant association between the DD genotype and AF in the patients without apparent structural heart disease (25).

To the best of our knowledge, there are no studies considering the association of ACE and AT_1R A1166C genetic polymorphism in heart failure patients.

Fatini investigated the role of the ACE ID polymorphism in relation to the different clinical forms of AF lone and secondary non-valvular atrial fibrillation (26). In this study, ACE D allele was significantly associated with both secondary and lone AF (26). The present research revealed the predominance of CC and DD type mutation in ischemic patients with AF in comparison with non-ischemic ones: 11.5% vs. 10% (p=NS), respectively 50% vs. 40 % (p=NS). This is in agreement with increased prevalence of DD genotype in ischemic heart failure independently of the cardiac risk (27, 28, 29). Moreover, some data suggests that ACE ID polymorphism represents a risk factor for fatal myocardial infarction (MI) and cardiac death (30). Also, the homozygote CC type of AT1-R increases the risk for MI (31) and generally for the event-rate in ischemic patients in comparison with AC or AA – types (10.8%, 5.7% respectively 8%) (32). The association between DD and CC mutation was also more prevalent in ischemic (7.7%) than in non-ischemic (5%) atrial fibrillation.

At the same time, there are no data about the gene polymorphism in relationship with age or gender AF patients, but our study suggests that CC or DD genotypes is more frequent in patients under 65 years of age, even if the differences were not statistical significant.

Therefore, the clinical relevance of the studies may be related to the possible characterization of the patients with AF and to the use of RAA system inhibitor therapy able to improve the arrhythmogenic substrate. Observational and experimental studies in humans and animals support the role of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARBs) in the prevention of atrial fibrillation (33, 34). A meta-analysis of the use of ACEI and

ARBs showed an overall effect of 18% risk reduction in new-onset AF across the trials and 43% risk reduction in patients with heart failure (35).

The use of ACEI and/or ARBs results in a preventive effect against atrial fibrillation, mainly in hypertensive patients with LV hypertrophy after myocardial infarction, with left ventricular dysfunction or congestive heart failure. The effect is obtained through regression in atrial and ventricular remodeling, normalization of refractory periods and of physiological adaptation rate (36, 37, 38). At the same time, the genetic polymorphism of the RAA system was associated with an increased incidence of non-familial AF; in these patients, ACE inhibitors represented the drug to be preferred (1). In our research, ACEI and/or ARBs were used in 91.2 % of the patients with DD mutation, respectively in 78% of the patients with CC mutation.

Conclusion

The association of ACE and AT_1 genetic polymorphism was registered in approximately half of the heart failure patients with permanent atrial fibrillation suggesting that high levels of ACE, respectively angiotensin II can contribute to the development and maintenance of atrial fibrillation.

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