Trombofilija i druga stanja povezana s akutnim oblicima srčanožilnih bolesti

Thrombophilia and Other Conditions Associated with Acute Forms of Cardiovascular Disease

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RECEIVED: January 13, 2015

UPDATED: January 22, 2015

ACCEPTED: January 24, 2015

SAŽETAK: Svjedoci smo sve češćih slučajeva akutnih koronarnih sindroma u mlađih bolesnika, odnosno u bolesnika u kojih ne nalazimo prisutne tipične preinačive ili nepreinačive čimbenike rizika. Većina studija definira mlađe pacijente kao osobe dobi do 45 godina. U takvih se bolesnika obično dijagnosticira akutni infarkt miokarda (AIM) s normalnim koronarnim arterijama, odnosno koronarne arterije ne pokazuju intraluminalne nepravilnosti (stroga definicija) ili arterije s manjim stupnjem stenoze, ali hemodinamski bez značenja (u većini slučajeva < 30% stenoza). Nedavno objavljena studija (APPROACH) utvrdila je učestalost akutnog infarkta miokarda s normalnim koronarnim arterijama u iznosu od 2,8% u bolesnika podvrgnutih koronarnoj angiografiji kod AIM-a. Diferencijalna dijagnoza takvih akutnih koronarnih zbivanja uključuje miokarditis, stres miokardiopatije i sindrom baloniranja vrška lijeve klijetke. Ne postoji jedinstveno objašnjenje nastanka AIM-a s normalnim koronarnim arterijama, ali predloženo je nekoliko mogućih mehanizama: latentna ateroskleroza, vazospazam, tromboza i hiperkoagulabilno stanje, embolizacija i upala. Postoje stečeni i nasljedni sindrom trombofilije.

U ovom ćemo prikazu opisati povezanost između nasljednih oblika tromboflije u koje ubrajamo mutaciju faktora V Leiden, mutacija gena za protrombin, manjak proteina C i proteina S, manjak antitrombina i mutacija gena za glikoprotein inhibitor plazminogen aktivatora-1 s akutnim oblicima srčanožilnih bolesti.

SUMMARY: We are witnessing increasingly frequent cases of acute coronary syndrome in younger patients, or in patients who did not present the typical risk factors. Most studies define younger patients as persons under 45 years of age. Such patients are typically diagnosed with acute myocardial infarction (AMI) with normal coronary arteries, i.e. the coronary artery does not show intraluminal anomalies (strict definition) or with a smaller artery stenosis but hemodynamically insignificant (in most cases <30% stenosis). A recently published study (APPROACH) determined the prevalence of AMI with normal coronary arteries was 2.8% in patients who underwent coronary angiography for AMI. Differential diagnosis of such acute coronary events includes myocarditis, stress cardiomyopathy, and Takotsubo syndrome. There is no single explanation for the origin of AMI with normal coronary arteries, but a few possible mechanisms have been suggested: latent atherosclerosis, vasospasm, thrombosis and hypercoagulability, embolization, and inflammation. We differentiate between acquired and inherited thrombophilia syndrome.

In this report, we will describe a link between hereditary forms of trombophilia (a mutation of factor V Leiden, prothrombin gene mutation, deficiency of protein C and protein S, antithrombin deficiency, and mutations in the gene for glycoprotein plasminogen activator inhibitor-1) and acute forms of cardiovascular disease.

KLJUČNE RIJEČI: trombofilija, akutni koronarni sindrom, infarkt miokarda s urednim koronarnim arterijama.

KEYWORDS: thrombophilia, acute coronary syndrome, myocardial infarction with normal coronary arteries.

CITATION: Cardiol Croat. 2015;10(1-2):23-27. | **DOI:** http://dx.doi.org/10.15836/ccar.2015.23

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Prikaz pacijenata

Tijekom 2013. godine na Odjelu kardiologije Županijske bolnice Čakovec bolnički je bilo liječeno osam pacijenata koji su preboljeli akutni koronarni sindrom, a u kojih su koronarografijom dokazane uredno prohodne epikardijalne krvne žile (MINCA, prema engl. Myocardial Infarction with angiographically Normal Coronary Arteries). Šest je bolesnika bilo mlađe od 40 godina, bez tipičnih čimbenika rizika za srčanožilne bolesti (pušenje, hiperlipidemija, arterijska hipertenzija) i bez pozitivne obiteljske anamneze. Dvije pacijentice s MINCA-om koje su bile starije od 40 godina bolovale su od reumatoidnog artritisa.

S obzirom na tehničke mogućnosti i suradljivost pacijenata, nismo bili u mogućnosti učiniti genetsku analizu i magnetnu rezonanciju (MR) srca kod svih pacijenata s MINCA-om i akutnim koronarnim sindromom pa stoga ovdje prikazujemo samo potpuno obrađene pacijente.

U dvije pacijentice u dobi od 40 godina, s preboljelim akutnim koronarnim sindromom i urednim nalazom koronarografije, no dokazanom ishemijom miokarda, s pomoću MR-a utvrdili smo da su PAI – 1 homozigot 4G (inhibitor plazminogen aktivatora-1-glikoprotein). Osim pacijenata s urednim koronarnim arterijama, čimbenike za trombofiliju dokazali smo i kod drugih oblika akutnih srčanožilnih bolesti.

U bolesnice u dobi od 29 godina, bez tipičnih čimbenika rizika s preboljelim akutnim koronarnim zbivanjem s elevacijom ST segmenta u koje je bila učinjena perkutana koronarna intervencija dokazana je jednožilna koronarna bolest srca i obavljena primarna implantacija stenta u desnu koronarnu arteriju, dokazali smo mutaciju za faktor II protrombin.

Pacijentici u dobi od 40 godina s preboljelom tranzitornom ishemijskom atakom, novootkrivenim otvorenim foramenom ovale, dokazanim sitnim nodoznim ishemijskim lezijama mozga s pomoću MR-a implantiran je Amplatzer septalni okluder i dokazan PAI–1 homozigot 4G.

Napominjemo da su u svih pacijentica bile uredne vrijednosti CRP-a, D-dimera i homocisteina te uredni osnovni testovi koagulacije (APTV, PV, fibrinogen).

Uvod

U modernoj kardiološkoj praksi svjedoci smo sve češćih slučajeva akutnoga koronarnog sindroma (AKS) u mlađih bolesnika, odnosno u bolesnika u kojih ne nalazimo prisutne tipične preinačive (pušenje, hiperkolesterolemija, arterijska hipertenzija, šećerna bolest, sedentarni način života) ili nepreivačive (dob, spol, obiteljsko nasljeđe) čimbenike rizika.[1-11] Danas znamo da postoje brojni okolišni i genski čimbenici povezani s aterosklerozom, odnosno aterotrombozom. Relativno mali broj studija ispitivao je utjecaj i povezanost markera trombofilije s akutnim koronarnim sindromom, odnosno povezanost genskih čimbenika i AKS-a s urednim koronarnim arterijama.[2] Unatrag nekoliko godina razvoj senzitivnijih testova omogućio je precizniju biokemijsku definiciju hiperkoagulabilnih stanja. Molekularna tehnologija genskih analiza otkriva nam mutacije gena odgovornih za kaskadu koagulacije.[1]

Case report

During 2013, the Cardiology Department of the Čakovec County Hospital treated eight patients that had had acute coronary syndrome, but coronarography showed normal lumen of coronary arteries (myocardial infarction with angiographically normal coronary arteries – MINCA). Six patients were under 40 years of age, with no typical risk factors for cardiovascular diseases (smoking, hyperlipidemia, arterial hypertension) and no positive family history. Two female patients with MINCA older than 40 years of age suffered from rheumatoid arthritis. Due to technical issues and lack of cooperation from the patients, we were unable to perform a genetic analysis and cardiac magnetic resonance imaging (MRI) for all the patients with MINCA and acute coronary syndrome, and will only present fully processed patients here.

Two female patients aged 40 that had had acute coronary syndrome in the past, with normal coronary catheterization results but myocardial ischemia detected with MRI, we determined the patient was homozygous for PAI 1 4G (plasminogen activator inhibitor-1 glycoprotein-1). We also found risk factors for thrombophilia in patients with other forms of acute coronary disease.

In a female patient aged 29, with no typical risk factors that had had an ST-segment elevation acute myocardial infarction and undergone percutaneous coronary intervention, we diagnosed single vessel coronary artery disease and preformed primary stent implantation in the right coronary artery, and found a prothrombin 20210 mutation.

In a female patient aged 40, who had had a transitory ischemic attack in the past, with newly diagnosed patent foramen ovale and small nodular ischemic brain lesions discovered with MRI, we implanted an Amplatzer Septal Occluder and found PAI–1 4G homozygosity.

We would like to note that all these patients had normal CRP, D-dimer, and homocysteine values as well as normal basic coagulation tests (APTV, PV, fibrinogen).

Introduction

In modern cardiologic practice, we are witnessing an increase in cases of acute coronary syndrome (ACS) in younger patients, i.e. in patients with no typical risk factors, either variable (smoking, hypercholesterolemia, arterial hypertension, diabetes, a sedentary lifestyle) or fixed (age, sex, family history).[1-11] Today we are aware of many environmental and genetic factors linked to atherosclerosis and atherothrombosis. Only a relatively small number of studies examined the influence and association of genetic factors and ACS with angiographically normal coronary arteries.[2] Several years ago, the development of more sensitive tests allowed more precise biochemical definition of hypercoagulable states. Molecular technology allows us to perform genetic analysis on gene mutations responsible for coagulation cascades.[1]

Myocardial infarction in patients with angiographically normal coronary arteries

The term myocardial infarction (MI) is used when there is evidence of myocardial necrosis in clinical conditions indicative

TABLE 1. Types of acute coronary syndrome in patients with normal coronary arteries.

Type 1 non-atherosclerotic causes of myocardial infarction

- Dissection of coronary arteries: in younger women (<50 years, most incidents occur during pregnancy or in the peripartal period, which implicates hormonal or hemodynamic risk factors)
- Pro-coagulant states (Factor V Leiden mutation, prothrombin gene mutation, deficiency of protein C and protein S, deficiency of anti-thrombin and plasminogen activator inhibitor-1gene mutation, antiphospholipid syndrome, high concentrations of Factor VII, IX, etc., acquired deficiency of antithrombin, eclampsia, nephrotic syndrome, etc.)[3]

Type 2 non-atherosclerotic causes of myocardial infarction

- Cocaine: a strong coronary vasoconstrictor that causes increased arterial pressure and heart rate, especially in combination with smoking
- Coronary artery embolism: most commonly as a complication during atrial fibrillation and infective endocarditis
- Coronary artery anomalies
- Anemia, hypotension, arterial hypertension, arrhythmias, etc.

Diseases with positive troponin and normal coronary arteries

- Takotsubo cardiomyopathy
- Myocarditis
- Pulmonary embolism, heart trauma, sepsis, renal insufficiency, etc.

Angioproliferative disorders and coronary heart disease

In rare angioproliferative disorders, the diagnosis is established via biopsy[3]:

- Kimura disease is a chronic inflammatory disease with no known cause, most commonly found in younger to middle-aged men. Patients present with lymphadenopathy, peripheral eosinophilia and elevated IgE levels, and endothelial proliferation. Coronarography describes small, aneurismatically changed, irregular epicardial arteries. Cardiac presentation of the disease is arrhythmia and/or acute myocardial infarction.
- Angiolymphoid hyperplasia with eosinophilia is a chronic inflammatory disease that characteristically manifests with papules, plaque, and knots in the areas of the head and neck. The lesions are, as opposed to Kimura disease, closer to the surface. We also find peripheral eosinophilia and elevated IgE levels. Epicardial arteries can be effected as well.

Infarkt miokarda u pacijenata s urednim koronarnim arterijama

Terminom infarkt miokarda (IM) koristimo se kada postoje dokazi nekroze miokarda u kliničkim uvjetima u skladu s ishemijom miokarda. U tim uvjetima postoje jasno definirani kriteriji za dijagnozu akutnog infarkta miokarda (AIM). Klasifikacija IM-a s obzirom na patofiziološke, kliničke i prognostičke čimbenike razlikuje pet tipova infarkta.[12] Infarkt miokarda s urednim koronarnim arterijama (MINCA) pripada u tip 1 (neaterosklerotski uzroci) (**tablica 1**). Ne postoji jedinstveno objašnjenje nastanka AIM-a s normalnim koronarnim arterijama, ali predloženo je nekoliko mogućih mehanizama: latentna ateroskleroza, vazospazam, tromboza in situ i hiperkoagulabilno stanje, embolizacija i upala.[11] Danas je prihvaćeno mišljenje da koronarografija nije najbolji prediktor destabilizacije koronarne bolesti srca. Traže se alternativne tehnike koje bi bolje pridonijele kliničkoj ulozi identifikacije tzv. nestabilnoga plaka. Te tehnike uključuju intravaskularni ultrazvuk, optičku koherentnu tomografiju, višeslojnu kompjutorsku tomografiju i magnetnu rezonanciju.[11]

Genski čimbenici rizika u akutnome koronarnom sindromu

Mnogi poremećaji koagulacijske kaskade koje uvrštavamo u sindrom trombofilije nisu nasljedni, nego stečeni (npr. an-

of myocardial infarction. There are clearly defined criteria for establishing a diagnosis of acute myocardial infarction (AMI) in those conditions. MI classification recognizes five types of infarction depending on pathophysiological, clinical, and prognostic factors.[12] Myocardial infarction with angiographically normal coronary arteries (MINCA) falls under type 1 (non-atherosclerotic causes) (**Table 1**). There is no definite explanation of the causes of MINCA, but several mechanisms have been suggested: latent atherosclerosis, vasospasms, thrombosis in situ and a hypercoagulable state, embolization, and inflammation.[11] Today, coronarography is not considered the best predictor of coronary heart disease destabilization. Alternative techniques are being considered that would contribute better to the clinical role of identifying so called unstable plaque. These techniques include intravascular ultrasounds, optical coherence tomography, multilayer computed tomography, and MRI.[11]

Genetic risk factors in acute coronary syndrome

Many coagulation cascade disorders classified under thrombophilia are not hereditary but rather acquired (e.g. antiphospholipid syndrome, high concentrations of Factor VII, IX, acquired deficiency of antithrombin in disseminated intravascular coagulation (DIC), eclampisa and nephrotic syndrome), but the rest of this text will primarily discuss hereditary, genetically influenced thrombophilia.[10]

tifosfolipidni sindrom, visoke koncentracije faktora VII, IX..., stečeni manjak antitrombina kod diseminirane intravaskularne koagulacije, eklampsije, nefrotskog sindroma i dr.), no u daljnjem će tekstu biti riječi većinom o nasljednoj, genski uvjetovanoj trombofiliji.[10]

Uz već tradicionalne imunološke i funkcionalne testove ispitivanja nasljednog manjka antitrombina, proteina C i S, koji se ipak najčešće manifestiraju venskim tromboembolizmom, danas imamo na raspolaganju i genske testove kojima verificiramo mutacije bitne za trombogenezu u akutnim oblicima srčanožilnih bolesti.[3]

Mutacija faktora V Leiden (posljedica mutacije jest zamjena arginina glutaminom na mjestu 506 proteina za faktor V) manifestira se nasljednom rezistencijom za inaktivaciju faktora V aktiviranim proetinom C, tzv. APC rezistencija. Nasljeđuje se autosomno resecivno, heterozigoti imaju 5 – 10%, a homozigoti 50 – 100% veću učestalost tromboza. Prevalencija mutacije u općoj populaciji iznosi oko 5%.

Mutacija gena za faktor II protrombin (zamjena gvanina adeninom u nukleotidu G20210A) praćena je pojačanom ekspresijom gena te u konačnici povećanom razinom protrombina, tj. prokoagulantnim stanjem. Prevalencija iznosi oko 2 – 3%, heterozigoti imaju 30% povišene razine protrombina u plazmi, a homozigoti su rijetkost.

Pri ispitivanju polimorfizma za PAI-1 (inhibitor plazminogen aktivatora-1- glikoprotein koji regulira fibrinolitički sustav, prije svega inhibirajući tkivni i urokinazni aktivator plazminogena (tPA i uPA) genotip 4G/4G dodatni je čimbenik rizika za infarkt miokarda pacijenata mlađe dobi i u pacijenata s AKS-om i urednim koronarnim arterijama. U promotorskoj regiji PAI-1 gena utvrđeno je postojanje specifičnog polimorfizma 4G/5G koji utječe na ekspresiju PAI-1. Studije su pokazale da homozigotne osobe 4G/4G imaju u plazmi koncentraciju PAI-1 25% višu nego homozigotne osobe genotipa 5G/5G te time i povećan rizik od tromboze zbog jače inhibicije fibrinolitičkog sustava. Heterozigotne osobe 4G/5G također imaju povećanu razinu PAI-1 u plazmi, no rizik od tromboze u njih je u mnogo manji i ovisi od slučaja do slučaja. Napomenimo da, osim endotela, PAI-1 luče i adipociti – jedan od čimbenika trombogeneze u pretilih pacijenata, tj. u bolesnika s metaboličkim sindromom, a da se u trudnoći iz placente luči i PAI-2. Prema novijim istraživanjima, povišenje PAI-1, osim toga što vodi do hipofibrinolize, smanjuje aktivnost matrix metaloproteaza (MMP) i staničnu adheziju.

Mutacija MTFHR (postoji više polimorfizama, odnosno varijanti, no najzančajnija je 677 TT) kodira enzim metilentetrahidrofolat reduktazu koji sudjeluje u stvaranju kosupstrata za remetilaciju homocisteina u metionin. U homozigota (genotip 677 TT) posljedica je termolabilan enzim te u konačnici skretanje metabolizma prema proizvodnji homocisteina koji ubrzava aterosklerotski proces. Heterozigoti 677 CT imaju tek neznatno povišen rizik od tromboze jer normalni alel čini enzim dovoljno termostabilnim.[10]

Od stečenih trombofilija spomenut ćemo antifosfolipidni sindrom (može biti izolirana bolest – primarni ili sekundarni u sklopu drugih autoimunosnih bolesti ili zloćudnih tumora). Uz arterijske i venske tromboze, karakteriziraju ga i spontani pobačaji te trombocitopenija. Antifosfolipidna protutijela uključuju protutijela koja uzrokuju lažno pozitivne rezultate nekih testova,

Beside the traditional immunological and functional tests examining the hereditary lack of antithrombin and protein C and S that still most commonly manifest in venous thromboembolism, today we can also apply genetic tests that verify mutations related to thrombogenesis in acute cardiovascular disease.[3]

Factor V Leiden mutation (a consequence of the mutation is a replacement of arginine by glutamine at the place 506 protein for factor V) leads to hereditary activated protein C resistance (APCR). It is an autosomal recessive disease with an increased thrombosis prevalence of 5-10% in heterozygous patients, and 50-100% in homozygous patients. The prevalence of the mutation in the general population is estimated at 5%.

The prothrombin 20210 mutation (replacement of guanine with adenine at nucleotide G20210A), also called Factor II mutation, results in increased gene expression and consequently higher levels of prothrombin, i.e. a procoagulant state. The prevalence is estimated at 2-3%; heterozygous patients have levels of prothrombin increased by 30%, and homozygous patients are rare.

When testing for PAI-1 polymorphism (plasminogen activator inhibitor-1 gene mutation that regulates the fibrinolytic system, primarily by inhibiting the tissue- and urokinase-type plasminogen activator (tPA and uPA)), the 4G/4G genotype represents an additional risk factor for myocardial infarction in younger patients and in patients with MINCA. The existence of a specific 4G/5G polymorphism has been established in the PAI-1 promoter region that which influences PAI-1 expression. Studies have shown that homozygous 4G/4G patients have 25% higher PAI-1 plasma concentration than 5G/5G homozygous patients, and consequently also a higher risk of thrombosis due to stronger inhibition of the fibrinolytic system. Patients with 4G/5G heterozygosity also have increased PAI-1 plasma levels, but the risk of thrombosis is significantly lower and varies from case to case. It is worth noting that PAI-1 is also secreted by adipocytes as well as endothelial cells – a thrombogenesis factor in obese patients, i.e. patients with metabolic syndrome, and that during pregnancy PAI-2 is secreted from the placenta. According to recent studies, not only do increased PAI-1 levels cause hypofibrinolysis, they also reduce the activity of matrix metalloproteinase (MMP) and cell adhesion.

Methylene tetrahydrofolate reductase (MTHFR) gene mutation (the most significant polymorphism being 677 TT) codes the MTHFR enzyme that participates in the generation of substrates for remethylation of homocysteine into methionine. Homozygosity (genotype 677 TT) leads to a thermolabile enzyme that ultimately causes the metabolism to produce homocysteines that speed up the atherosclerotic process. Patients with 677 CT heterozygosity have only slightly increased risk of thrombosis since the normal allele results in an adequately thermostable enzyme.[10]

Regarding acquired thrombophilia, we will touch upon antiphospholipid syndrome (it can be a isolated, primary, or secondary disease as part of other autoimmune disease or carcinoma). In addition to arterial and vein thrombosis, antiphospholipid syndrome is characterized by spontaneous abortions and thrombocytopenia. Antiphospholipid antibodies include antibodies that cause false-positive results in some tests, for instance the Veneral Disease Research Labo-

npr. VDRL (Veneral Disease Research Laboratory test), LAC (lupus antikoagulans, označuje produljenje APTV-a koje se ne korigira kada se bolesnikova plazma razrijedi s normalnom), antikardiolipinska protutijela i protutijela na beta-2 glikoprotein.[3]

Zaključak

S obzirom na to da je trombofilija nasljedna, gensko testiranje može se primijeniti ne samo u osobe u koje je dokazan određeni polimorfizam nego i u ostalih članova uže obitelji. Spoznaja o genskoj predispoziciji može spriječiti izlaganje čimbenicima koji mogu pospješiti razvoj trombogeneze. Stoga u mlađih pacijenata s preboljelim kardiovaskularnim, cerebrovaskularnim i perifernim tromboembolijskim zbivanjem, a u kojih nisu prisutni tipični čimbenici rizika, moramo učiniti gensku analizu. Važnost dokazivanja markera trombofilije sastoji se u valjanom liječenju i svjesnosti postojanja rizika koje takva osoba nosi cijeli život, što nameće potrebu za širenjem koncepta tzv. konvencionalnih čimbenika rizika. Ova tema uvelike premašuje okvire ovoga prikaza jer pitanje tromboembolijskih bolesti koje su znatan uzrok mortaliteta i morbiditeta nismo niti otvorili. Budućnost medicine teži pravilnoj identifikaciji nasljednih čimbenika rizika, što će zajedno s genskim ispitivanjem i savjetovanjem, omogućiti još bolju suradnju pacijenata i liječnika i najefikasnije liječenje.

ratory test (VDRL), Lupus Anti Coagulant test (LAC; represents prolonged APTV which does not improve when the patient's plasma is diluted with normal plasma), anticardiolipin antibody tests, and anti-beta(2)-glycoprotein I antibody tests.[3]

Conclusion

Since thrombophilia is hereditary, genetic testing can benefit not only the person with a particular polymorphism but also other close members of the family. Being aware of a genetic predisposition can prevent exposure to factors that can facilitate thrombogenesis. Thus, genetic analysis must be performed in younger patients that had cardiovascular, cerebrovascular, and peripheral thromboembolic events but have no typical risk factors. The importance of proving the existence of genetic markers for thrombophilia is in the resulting proper treatment and awareness of risk that the patient must carry for the rest of their lives. This in turn necessitates an expansion of the concept of conventional risk factors. That topic is well beyond the scope of this article, since we have not yet even addressed the question of thromboembolic diseases that are a significant cause of morbidity and mortality. The future of medicine is in correct identification of hereditary risk factors which will, together with genetic testing and consultation, allow even better cooperation between patients and physicians and lead to most effective treatment.

LITERATURE

1. Khare A, Ghosh K, Shetty S, Klukarni B, Mohanty D. Combination of thrombophilia markers in acute myocardial infarction of the young. Indian J Med Sci. 2004;58(9):381–8. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/15470279?dopt=Abstract
2. Sharifi M, Frohman TG, Silverman IM. Myocardial infarction with angiographically normal coronary arteries. Chest. 1995;107(1):36–40. **DOI:** http://dx.doi.org/10.1378/chest.107.1.36
3. Simeonidou E. Thrombophilia and other conditions associated with acute cardiovascular syndromes. Hospital Chronicles. 2007;2(4):164–6.
4. Gaspar J, Benchimol C, Gadelha T, Penna GL. Arterial thrombosis and acute myocardial infarction with angiographically normal coronary arteries in a woman heterozygous for both factor V Leiden and prothrombin mutation. Rev Port Cardiol. 2011;30(9):727–9. **DOI:** http://dx.doi.org/10.1016/S0870-2551(11)70016-6
5. Thomas PV, Shipeng Y, Blair PG, et al. Recurrent myocardial infarctions in a young football player secondary to trombophilia, associated with elevated factor VIII acivity. Intern Case Report Jour. 2014;7:147–54.
6. Puricel S, Lehner C, Oberhansli M, et al. Acute coronary syndrome in patients younger than 30 years - aetiologies, baseline characteristics and long-term clinical outcome. Swiss Med Wkly. 2013;143:w13816. **DOI:** http://dx.doi.org/10.4414/smw.2013.13816
7. Maor E, Fefer P, Varon D, Rosenberg N, Levi N, Hod N, et al. Thrombophilic state in young patients with acute myocardial infarction. J Thromb Thrombolysis. 2015 Jan 15; [Epub ahead of print] **DOI:** http://dx.doi.org/10.1007/s11239-014-1166-2
8. Miranda CH, Gali LG, Marin Neto JA, Louzada Junior P, Pazin-Filho A. Coronary thrombosis as the first complication of antiphosholipid syndrome. Arq Bras Cardiol. 2012;98(4):e66–9. **DOI:** http://dx.doi.org/10.1590/S0066-782X2012000400014
9. Alihanoglu YI, Kilic D, Yildiz BS. Non-atherosclerotic causes of acute coronary syndrome and management of the patients. Eur J Gen Med. 2013;10:22–31.
10. Khan S, Dickerman JD. Hereditary trombophilia. Thromb J. 2006;4:15. **DOI:** http://dx.doi.org/10.1186/1477-9560-4-15
11. Kardasz I, De Caterina R. Myocardial infarction with normal coronary arteries: a concudrum with multiple aetiologies an variable prognosis: an update. J Intern Med. 2007;261(4):330–48. **DOI:** http://dx.doi.org/10.1111/j.1365-2796.2007.01788.x
12. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J. 2007;28(20):2525–38. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehm355