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HEART AND BLOOD VESSELS

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Review article

Cardiac complications in patients with COVID-19 infection

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Abstract COVID 19 infection in three phases: Phase I: Early infection, this phase is characterized with intrusion and direct invasion of COVID 19 into sensitive tissues. In this phase, virus is confronted only by the innate non-specific immunity. Symptoms are moderate in intensity. A more pronounced immune response is taking place, and in some cases a cessation of symptoms occurs. If the infection does not end here, a second phase develops. Phase II: pulmonary phase, pulmonary tissue invasion takes place and leads to direct tissue damage with added pulmonary vasodilation, enhanced endothelial permeability, leucocyte invasion as a cellular immune response to infection. This is clinically represented by further lung damage, and added burden on cardiovascular system. Phase III: Hyperinflammatory phase, this phase is presented as an escalation of immune response, which incorporates ARDS locally, acute myocardial damage, heart failure development, and systemic inflammatory response-multiorgan failure. This is complicated by secondary bacterial infection and enhanced intravascular coagulability. Arrythmia is the most common, but also most benign cardiovascular complication in COVID 19 patients. Viral myocarditis, with heart failure elements, is a complication which has to be always thought of, especially in patients with unusually prolonged dyspnea. COVID 19 infection did not have a direct effect on coronary artery disease incidence, but on the other hand had a major effect on time to first contact of the patients with medical service and to the decision making in the treatment process.

Kew words COVID-19, cardiovascular complications

Introduction

Officially the first COVID 19 patient was registered in Serbia on March the 6th of 2020. The illness had a pandemic character with severe virulency but fortunately with fatality rate 2.2% of total number of cases[1,2]. COVID 19 got its name as an acronym from Corona Virus Disease detected in 2019. In this way a new breed of Corona virus was registered, out of already well-known family of Corona viruses which caused common cold syndrome. COVID 19 is characterized by high virulency, but 80% of patients have asymptomatic form or mild form of the disease[1,2]. The rest of them, 20%, require hospitalization[1,2], and out of those most common presentation is of bilateral interstitial pneumonia, while 5-10% require some form of oxygen therapy and support. The data showed that patients with cardiovascular comorbidities had a greater chance of acquiring bilateral pneumonia, and on the other hand 25% of patients with pneumonia developed at least one cardiovascular complication. Out of those, some 26% were treated in intensive care unit[3]. Patients with preexisting cardiovascular comorbidities had a much worse prognosis in COVID 19 infection. The therapy used in COVID 19 patients is still very unspecific. Unfortunately, there is no specific drug which is targeting the virus itself. Some antiviral drugs are used, like Aluvia (Kalitrea), well known anti-retroviral drug. Remdesivir is another drug that is utilizing viral RNK polymerase inhibition. It was developed as a treatment for Ebola infection, and showed somewhat more efficacy against COVID 19 than the other antiviral drugs. On the other hand, the latest WHO paper renounces the use of remdesivir as inefficient.Standard therapy of COVID 19 infection incorporates the use of antibiotics, but as treatment and/or prevention of bacterial superinfection.

COVID-19 and cardiovascular complications

The main question is how this virus affects human body, and how we got from harmless virus, characterized by mild upper respiratory tract symptoms to this new form of Corona virus, which presents itself in some cases with severe bilateral interstitial pneumonia and sometimes very rapid development of ARDS with unpredictable outcome. Goha et al.[5], divided COVID 19 infection in three phases:

Phase I: Early infection, this phase is characterized with intrusion and direct invasion of COVID 19 into sensitive

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tissues. In this phase, virus is confronted only by the innate non-specific immunity. Symptoms are moderate in intensity. A more pronounced immune response is taking place, and in some cases a cessation of symptoms occurs. If the infection does not end here, a second phase develops.

Phase II: pulmonary phase, pulmonary tissue invasion takes place and leads to direct tissue damage with added pulmonary vasodilation, enhanced endothelial permeability, leucocyte invasion as a cellular immune response to infection. This is clinically represented by further lung damage, and added burden on cardiovascular system.

Phase III: Hyperinflammatory phase, this phase is presented as an escalation of immune response, which incorporates ARDS locally, acute myocardial damage, heart failure development, and systemic inflammatory response-multiorgan failure. This is complicated by secondary bacterial infection and enhanced intravascular coagulability.

Ma et al.[6], describe the influence of COVID 19 infection on cardiovascular system as:

- Direct viral cell invasion
- Indirect damage-immune system mediated
- Large presence of proinflammatory cytokines
- Electrolyte and fluid retention
- Enhanced sympathetic activity
- Platelet activation and procoagulability
- Pneumonia-hypoxia

Data from Wuhan[3] showed that 16.7% of patients developed any form of arrythmia, 7.2% acute coronary syndrome, and in some number of patients a Troponin increase was interpreted as a myocardial lesion due to myocarditis. Part of those patients developed heart failure symptoms.

Myocarditis represents virus invasion of cardiomyocytes with tissue destruction. The disease has it's acute and chronic phase. The acute phase of myocarditis is consequence of direct cell invasion with virus particles which in turn leads to cardiomyocyte damage under the cytotoxic effects of the virus. On day 0. Of the infection, virus genome is being replicated inside the cardiomyocytes. This process is taking place during the first week, so on the 6th day it is in its peak. On the 10th day of the infection, replication ceases, as well as the direct cardiomyocyte damage caused by virus replication in it. In this phase, the clinical picture is oligosymptomatic. However, cardiomyocyte lesion is predisposing factor for starting humoral immune reaction to infection, and is practically followed by the chronic phase of myocarditis, characterized by autoimmune damage mediated by inflammatory cell invasion and autoantibody activation. An unspecific immune response, cellularly mediated is being activated, it incorporates activated leucocytes, lymphocytes (CD4, CD8), macrophages. These cells are directly damaging and destroying virus host cells, in this case cardiomyocytes, but also they are releasing a large quantity of inflammation factors and mediators , which in turn cause "Cytokine storm", on the other hand blamed to be the main mechanism of further destruction of the host cells after the virus itself. This phase can last a variable amount of time, and is represented by the clinical presentation of myocarditis, but also sometimes with heart failure symptoms. This "Cytokine storm" is followed by the autoimmune response, mediated by the activation of the specific immune answer and the appearance of the antibodies to the virus particles , but also by the appearance of the cross reaction and development of the auto-antibodies to sarcolemma, myolemma, mitochondrial proteins, actyn, myosin, collagen, and beta receptors. This mechanism leads to additional cardiomyocyte lesion, which can be clinically represented with mild, moderate or severe heart failure symptoms even weeks or month/s after the acute phase of the infection. A group of German authors followed 100 patients after resolved COVID 19 infection, out of which only 33% were hospitalized due to infection. All of those had a cardiac NMR done, after an average of 71 days after infection. 78% had pathological findings. This group of authors concluded that COVID 19 patients had to be monitored for their health condition for a long time after the infection resolves[7]. Other authors[8] have recorded that after discharge and successful COVID 19 treatment, often poor strain tolerance and chest oppression remain for a long time.

Heart failure was registered in 52% of the deceased and in 12% of discharged COVID 19 patients[2,5]. It is represented as an exacerbation of already existing heart failure, or like septically induced cardiomyopathy in myocarditis itself. In its most severe form, its presentation is a combination of septic and cardiogenic shock. The use of ACE inhibitors, or ARB blockers had its share of controversy tied to their influence to the infection and inflammation. Today's position on this subject is that the use of these medications is safe. The use of beta blockers in patients with pneumonia increased 30-day mortality and the need for mechanical ventilation.

Arrythmias were the most common cardiovascular manifestations of COVID 19, and on the other hand most frequent of those is sinus tachycardia, symptomatic or asymptomatic. Arrythmias "per se" are rare, mainly they were manifest in myocarditis, myocardial ischemia, hypoxia, shock, electrolyte disturbances or as a toxic reaction to the therapy (QT prolongation of the Chloroquine, or beta blocker use).

Coronary artery disease was a rare occurrence in COVID patients. However, in time of COVID pandemic, a change in therapeutic algorithms for STEMI patients took place, so that in USA, recommended mode of therapy for majority of the STEMI patients was pPCI, while fibrinolysis was still recommended as the first choice in uncomplicated inferior infarction without right ventricle affection[9]. In NSTEMI patients there were no changes in treatment protocols to that degree, so they were all medically (conservatively) treated. The patients with hemodynamic instability were treated with PCI. In turn, this strategy was more less the same before the COVID 19 pandemic. Out of pool of medications used in coronary artery disease treatment, statins stood out. The data showed that statins improve survival and also decrease systemic inflammation. The group of authors[10] showed that a combination of statins and ACEI improved

survival in COVID 19 patients and CAD. Almost all the authors and researchers concluded that the biggest issue in treating CAD patients during the pandemic was the delay from the symptom onset to the first medical contact[11-12].

The therapy used in COVID 19 patients is still very unspecific. Unfortunately, there is no specific drug which is targeting the virus itself. Some antiviral drugs are used, like Aluvia (Kalitrea), well known anti-retroviral drug. Remdesivir is another drug that is utilizing viral RNK polymerase inhibition. It was developed as a treatment for Ebola infection, and showed somewhat more efficacy against COVID 19 than the other antiviral drugs. On the other hand, the latest WHO paper renounces the use of remdesivir as inefficient.

Standard therapy of COVID 19 infection incorporates the use of antibiotics, but as treatment and/or prevention of bacterial superinfection. However, high dosage antibiotics use is not without toxic effects. Macrolides can cause QT prolongation, hence having proarrhythmic effects and causing PVC's and tdP's. Vancomycin causes enhanced histamine liberation and thus hypotension. In the beginning all the treatment protocols incorporated Chloroquine as a standard non specific anti-inflammatory drug. However, its use in high doses caused cardiotoxicity with increased risk of heart failure and proarrhythmic effects. During the last months, corticosteroid use in high doses is more and more practiced, but based on experience with SARS, MERS, and influenza, there is no evidence for their beneficial effects[13]. The WHO position is that routine use of corticosteroids in COVID 19 patients is not recommended[14].

Conclusions

Arrythmia is the most common, but also most benign cardiovascular complication in COVID 19 patients. Viral myocarditis, with heart failure elements, is a complication which has to be always thought of, especially in patients with unusually prolonged dyspnea. COVID 19 infection did not have a direct effect on coronary artery disease incidence, but on the other hand had a major effect on time to first contact of the patients with medical service and to the decision making in the treatment process.

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Sažetak

KARDIOVASKULARNE KOMPLIKACIJE KOD PACIJENATA SA COVID-19 INFEKCIJOM

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*COVID 19 infekciju su podelili u tri faze:**I FAZA-RANE INFEKCIJE**-Karakteriše se prodorom i direktnom invazijom tkiva COVID 19 virusom. U ovoj fazi virusu se telo odupire samo urođenim nespecigičnim imunitetom. Klinički se ispoljavaju simptomi koji su umerenog intenziteta. Dolazi do razvoja imunog odgovora zbog čega dolazi do opadanja broja virusa i u nekim slučajevima do prekida simptoma. U koliko se infekcija ne završi na ovom nivou razvija se druga faza: **II FAZA-PLUĆNA FAZA**-Invazija plućnog parenhima koja dovodi do direktnog oštećenja tkiva uz pridodatu plućnu vazodilataciju, povećane endotelne permeabilnosti i invazije leukocita kao odgovor celularnog imuniteta na infekciju. Klinički će se ispoljiti kao dalje oštećenje plućnog parenhima uz dodatno opterećenje kardiovaskularnog sistema. **III FAZA – HIPERINFLAMATORNA FAZA**-Eksacerbacija imunološkog odgovora što se klinički manifetuje, lokalno kao ARDS, akutno oštećenje miokarda, razvoja srčane slabosti i sistemskog odgovora u vidu multiorganske disfunkcije. Na ovo stanje se nadovezuje sekundarna bakterijska infekcija i pojačana intravaskularna koagulabilnost.**Terapija** COVID pacijenata je još uvek nespecifična. Ne postoji specifičan lek koji etiološki deluje na ovaj virus. Koriste se antivirotici Aluvia (Kalitrea), od ranije poznat lek za RNK viruse. Remdesivir je drugi antivirotik koji kao prolek inhibira virusnu RNK polimerazu. Razvijen je kao lek za ebolu a pokazao se efikasniji od ostalih antivirotika. Najbliža specifičnoj terapiji je upotreba gotovih antitela iz plazme pacijenata koji su preboleli COVID infekciju. U standarnoj terapiji COVID pacijenata je upotreba i antibiotika, pre svega kao terapija bakterijske superinfekcije.Aritmije su najčešća ali i najbezopasnija kardiovaskularna stanja u COVID 19 pacijenata. Virusni miokarditis sa elementima srčane slabosti je kardiovaskularna komplikacija o kojoj treba misliti posebno kod paciejnata sa dispneom koja neuobičajeno dugo traje. COVID 19 infekcija nije direktno uticala na incidencu koronarne bolesti, međutim značajno je uticala na vreme prijema pacijenata i odluku o načinima lečenja.*

Ključne reči: COVID-19, kardiovaskularne komplikacije

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Review article

The evolution of aortic valve therapies - the surgeon's perspective

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Abstract During the past 10 years there has been a significant shift in how aortic valve disease is managed. The development of catheter-based therapies, specifically trans-aortic valve replacement (TAVR), has offered treatment options for patients in whom surgery (SAVR) was previously their only option. The global growth in the utilization of TAVR has been tremendous and embraced with much enthusiasm. However, such growth has not been without significant controversies and costs. The used of Heart Teams to help guide the evaluation and management of patients with aortic valve disease has been an important step in trying to match the specific therapy options with the unique patient characteristics – however, it is important to recognize that catheter-based therapies are still relatively new, in constant evolution, and potentially influenced by substantial conflicts of interest. While the role of TAVR in high or prohibitive risk patients is established, the evolving role in low and intermediate risk patients is unclear and potentially controversial given some of the concerns that the short-term benefits when compared to traditional surgical therapies might not result in durable long-term outcomes and freedom from major events and reinterventions. The literature on this topic is extensive and the goal of this review is to hopefully raise some of the concerns regarding the perceived benefits of TAVR over SAVR especially in the context of whether this extremely expensive therapy should be considered the new global standard of care.

Kew words aortic stenosis, aortic valve disorder, heart surgery, Heart Team, structural heart therapies, transcatheter therapies

Introduction

The development of catheter-based therapies – and in particular, transaortic valve replacement (TAVR) – has revolutionized the management options for patients who present with symptomatic aortic stenosis. While the appeal of TAVR cannot be understated when compared to the invasiveness of the traditional open-heart aortic valve replacement surgery (SAVR), the global explosion in the utilization of TAVR must be taken with caution. There is no doubt that TAVR can offer a reasonable option for patients in whom surgery is considered high or extreme risk, but with the simultaneous advances in surgical techniques, anesthesia, myocardial protection, and overall peri-operative care, the decision-making options for patients continues to change. Nevertheless, with more options for patients, the challenge is to also recognize that patients are getting older, frailer, and are presenting with more advanced cardiac disease and co-morbidities. Furthermore, with the growing use of TAVR in higher risk patients, there is the natural extension into lower risk and younger patients – especially those who are expected to have many years, if not decade, of potential quality of life ahead – for which it is critical that options reflect the current data that considers both the short and long-term experiences. The goal of this review is to highlight some of the controversies and difficulties in the management of aortic valve disease. The topics presented, by definition are under constant study and by no means complete, but hopefully this review will help establish a baseline understanding of the complex concerns that must be considered when treating patients with newer technologies. Despite the desire for less-invasive options, it is important to remember that less-invasive does not always translate into better, safer, cheap, or more effective – either in the short or long-term. Furthermore, we also need to recognize that the economic considerations of being able to help as many patients as possible in times of limited financial resources is a topic that must be acknowledged.

It is critical as the use of TAVR over SAVR continues to expand to lower risk patients and different pathologies (such as bicuspid valves, patients with concomitant coronary disease or aortic aneurysms) in an era of "shared-decision making" (in which patients have a greater role and, hopefully, responsibility in directing their care) that it is recognized that there are often different solutions to different problems and it is rare that there is a single approach that can be applied to everyone all of the time[1].

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Background

Aortic stenosis is the most comment type of cardiac valvular disease. Hemodynamically significant stenosis, as determined by catheter or echocardiographic pressure gradients measured across the valve, are found in up to 2% of the patients greater than 65 years old, 3% in 75 years old patients, and 4% in those old than 85 years old. Symptomatic bicuspid aortic valve disease – either stenosis or insufficiency – is also a substantial problem. It is estimated that over 100,000 people in the United States are given a diagnosis of severe aortic stenosis each year. Historically, open-heart surgery (SAVR) was the only definitive options for those presenting with symptomatic severe and critical aortic stenosis. It is clearly established that the risks of surgery increase substantially with patients age and comorbidities. Despite the success of SAVR, there are concerns that elderly, frailer, or sicker (i.e. multiple advanced comorbidities or advanced organ dysfunction) might have difficult post-operative recoveries that limit their potential ability to benefit both short and long-term from valve replacement. It has been this mindset that has often resulted in many patients who "could have" benefited from surgery never referred for an appropriate evaluation.

The early symptoms of severe or critical stenosis is associated with shortness of breath, early fatigue, or exercise intolerance. However, the later symptoms include heart failure, chest pain, and syncope. Once advanced symptoms develop, their prognosis is worse than some cancers, including colon and breast. Without intervention, advanced symptomatic aortic stenosis is associated with a less than 50% two-year survival.

Treatment Options

The survival difference between symptomatic aortic stenosis patients treated medically compared to those treated with surgery is significant. In fact, in the absence of significant contraindications, it is felt to be inappropriate and maybe even an ethical to withhold therapy in patients who are symptomatic. Given the poor prognosis of untreated critical aortic stenosis with a less than 20% survival at two years when compared to the greater than 85% 4-to-5-year survival in patients who undergo surgery it is easy to appreciate the need for appropriate and timely referral and intervention. However, not all patients are suitable for surgery and over the years there have been several risk-assessment tools that have been developed to aid in clinical decision making with regards to how to manage these patients. The most commonly used risk-assessment tool is the predicted risk for mortality calculator that is based upon objective outcomes data submitted to Society of Thoracic Surgeons database[,]. The limitations of this risk calculator are well known and that is why other variables that consider a formal assessment of the impact of comorbidities, patient frailty, and organ system dysfunction, combined with the technical or anatomical aspects of the procedure that may increase perioperative risks are used to stratify patients into low, intermediate, high, and prohibitive (or extreme) risk. These evaluations are then used by patients to participate in shared decision-making management options as advised by a Heart Team of specialists. In the past, with the emphasis on surgery, the major decision-making was focused on mechanical or biologic (tissue) valved with each having various advantages and disadvantages. The development of TAVR has dramatically changed the options available to patients who traditionally were considered prohibitive risk,. Recently, based upon evolving data from highly-selective randomized trials, TAVR is now being offered low risk populations. However, despite the appeal of TAVR over SAVR, there are still many questions and concerns that should to be considered with regards to durability, paravalvular leaks, need for permanent pacemakers, and the overall impact on reported real-world short and long-term morbidity and mortality. Despite the growing literature and significant of industry-driven support promoting the excitement over transcatheter therapies, there are still concerns that surgery might still be the preferred approach for certain patients. Furthermore, the significant costs associated with these based therapies cannot be ignored in the context of limited resources and the underlying question of whether something that is more expensive and less invasive is inherently "better"

The early randomized trials that focused on high or extreme risk patients indicated a survival advantage. These outcomes resulted in a significant amount of enthusiasm for TAVR being an option for patients who otherwise would have died from their valve disease. Following regulatory approval of TAVR, studies in intermediate and lower risk patients quickly followed. The criteria for intermediate risk were determined using a predicted risk of mortality, other significant baseline characteristics (i.e frailty) comorbidities were considered in the decision-making. These selection variables – such as what defines "frail" – used to define an intermediate risk patient were often subjective and the source of much debate. Again, despite the desire to avoid open-heart surgery, the data in the intermediate risk patient population showed similar risks for disabling stroke and all-cause mortality of around 13-14% at two years. These results suggested that TAVR was "non-inferior" to SAVR, and despite the non-inferiority of the results, these findings have often been used to suggest that TAVR may be preferred by the patients and are even potentially *better* with both short- and long-term when compared to conventional surgery. While SAVR was associated with a recovery time that impacted patient reported quality of life assessments, by about six months, the self-reported assessments of quality of life were similar regardless of the treatment . Furthermore, the short- and long-term stroke and mortality risks were similar in low, intermediate, and higher risk patients – a concept that supports the idea of "non-inferiority" but not superiority. Understandably, there has been significant interest to help define which patient factors and comorbidities might be better suited for one therapy over the other. A review of multiple studies that included over 9500 intermediate risk patients there was no significant advantage of one therapy over another at one year. Similar results

were seen in reviews of studies that focused on low-risk patients. In fact, looking at the 2-year mortality and procedure-related risk for stroke in almost 3500 patients, there was no benefit of TAVR over SAVR - again demonstrating the idea of non-inferior outcomes. Importantly, the data demonstrated a potential 2-year survival advantage for patients undergoing SAVR compared to TAVR. This survival benefit was also seen in a meta-analysis of 14 studies that included almost 4200 intermediate risk. In this review, by 3 years, there appeared to be a significant survival benefit for intermediate risk patients undergoing SAVR when compared TAVR.

Despite some of the growing concerns regarding the long-term outcomes in patients undergoing TAVR, there have been several randomized multi-center studies specifically looking at the role in low risk patients []. The 1-year outcome data has also demonstrated non-inferiority – and maybe even a small survival advantage in those undergoing TAVR. However, these trials have been heavily criticized based upon their scientific and statistical methods and highly-selective patient selection. In the PARTNER-3 trial, there was concern that, despite enrolling low risk patients only, some of the comorbidities and surgical procedures required for these patients implied an inherently much higher risk profile []. In addition, many patients were excluded based upon anatomical considerations with patient selection potentially playing a substantial role in outcomes favoring TAVR. Other low risk trials validated some of the short-term outcome experiences that contributed to regulatory approval with low-risk patients. A major consideration is that low risk is not synonymous with younger. As such, given the evolving data suggesting intermediate- and long-term survival differences, there remains considerable concerns about offering TAVR to patients who have a predicted life expectancy beyond several years. Unfortunately, this has not slowed the considerable interest in TAVR over SAVR in a patient population that still, based upon best available evidence, might still benefit from a surgical approach. Of course, the reality is that many patients present with a bias that "surgery" is bad and "less-invasive therapies" are better (even if they do not understand the difference between each) and might still chose an option based upon incomplete understanding of the short and long-term consequences of their decision-making. In other words, does "shared-decision making" truly reflect "informed consent"?

The concerns of the low-risk TAVR trials have prompted investigators to review some of the real-world outcomes. For example, registry data from Israel examining very low risk and low risk patients showed a 10 and 15% two-year mortality rate, respectively. These outcomes were substantially worse than similar two-year survival rates reported in modern surgical studies where the mortality rates were almost half of those reported in similar TAVR patients. It is unclear if patients are aware of the substantial risks of these procedures when they are making decisions or are being consented.

Without a doubt, there is still much to learn regarding the risks, benefits, and how to decide which therapy might be best for which patient when treating aortic stenosis. But, what is clear, is that regardless of the which therapy, both TAVR and SAVR have been shown to be safe and effective despite the many challenges and unanswered questions.

Unanswered Questions

The list of unanswered questions regarding the management of aortic stenosis is extensive and extends beyond the scope of this review. Even a partial list, such as below, only illustrates the complexity of valve disease and patient selection. Even the tools used to guide therapies – such as Heart Teams (similar to cancer tumor boards in which each patient is reviewed individually with recommendations based upon their clinical characteristics and pathologies in the setting of local experiences and best available data) and "shared decision making" (a term used to describe the role a patient has in deciding how they want to be treated after weighing the pros/cons of the options as presented to them) – are evolving.

Below is only a small list of topics that must be considered in the management of valve disease:

- Endocarditis
  - Early vs late surgical vs medical management
  - Oral vs intravenous antibiotic therapies
  - Native vs prosthetic valve
  - Therapies for TAVR infections
  - Re-operative options in the setting of substance abuse
  - Indications for left-sided vs right-sided valves
- Aortic insufficiency
  - Timing of surgery
  - Role of TAVR
- Bicuspid valve disease
- Evolving repair technologies
- Impact of previous cardiac surgery
- Special, but common, patient populations
  - Chronic or End-stage renal disease – i.e. dialysis
  - Morbid obesity
  - Small/large aortic roots
  - Complex co-morbidities (i.e. active cancers)
  - "Younger" patients
  - Women of child-bearing age
- Interventions in asymptomatic patients
- Impact of and options for concomitant cardiac pathologies
  - Atrial fibrillation
  - Obstructive coronary artery disease
  - Other valvular pathologies
    - Mitral, tricuspid
  - Ascending aortic aneurysms
- Prosthetic tissue and structural options
  - Bovine vs porcine vs mechanical
  - Anti-calcification treatments
  - Internally vs externally wrapped valves []
  - Stented vs non-stented
  - Role of "sutureless" or rapidly deployed surgical valves
- Role of anticoagulation / anti-platelet agents
  - Impact on short-term risk for stroke
  - Risk for tissue or valve degeneration/thickening

Even with the growing list of topics that complicate the decision-making process in how to treat patients with

aortic valve disease, there are several major areas that are of special and growing interest and concern.

Pacemaker Rates

As showed in almost every major review and study on TAVR, the procedure is associated with a significantly higher rate of need for a permanent pacemaker compared to SAVR. While arrythmias and conduction problems are not uncommon after SAVR, there are concerns that needing a pacemaker after TAVR is neither trivial nor benign. Some large-scale studies suggest a four-fold increase in the need for permanent pacemaker after TAVR. The long-term consequences of needing a pacemaker are still unclear, especially since the natural history and management of post-TAVR/SAVR conduction problems is complex, there is evidence that the need for a pacemaker is associated with worse long-term survival[]. Also troublesome is the emphasis (and potential benefit) on early discharge and the fact that some significant conduction abnormalities (like complete heart block) might not present until after the patient is discharged is still unclear.

Stroke and Neurologic Complications

Patients have the belief that TAVR is associated with fewer strokes - and this belief is often used to guide their decision to undergo TAVR over SAVR. However, this has not been objectively demonstrated in the high-profile randomized trials. In addition, there are concerns that the neurologic events in TAVR patients might not present until after the patient has been discharged. For example, in one study reviewing a Medicare database consisting of over 44,000 patients - an 86% greater risk of ischemic stroke and a six-fold increase risk of hemorrhagic stroke after TAVR was seen when compared to SAVR with many of the events occurring in subsequent readmissions to the hospital within the first year. The 90-day readmission rate for neurologic events after TAVR was considerably higher than many cardiac and non-cardiac procedures, including other procedures often associated with increased risks for neurologic complications such as left ventricular assist device placement, surgical aortic valve replacement, and coronary artery bypass procedures. Especially in the context of the rigorously reviewed trial data, the real-world experiences with post-TAVR and post-SAVR neurologic events requires further objective review.

To offset the procedural related stroke risks, there has been a substantial increase in the development and use of temporary cerebral protection devices during TAVR. While, in concept, these devices sound appealing, they are associated with considerable cost. Furthermore, definitive data demonstrating a clinical improvement and reduction in neurologic events is still lacking[]. It is easy to understand why this is an area of tremendous research and development[].

Paravalvular Leaks

In SAVR, the valvular and paravalvular calcified leaflets and surround material is physically removed – but, in TAVR inserts and expands against the existing valve. This major difference between the two procedures can explain why TAVR is associated with a much higher rate of paravalvular leaks – especially in patients with bicuspid or complex valvular/paravalvular/subvalvular calcifications. The long-term impact of paravalvular leaks is incompletely understood. However, those patients with at least moderate leaks have a much worse survival at 2 years than those with mild or less leaks. The PARTNER 2 study, as previously discussed above, demonstrated a 34% risk of mortality in patients with moderate to severe paravalvular leaks, when compared to the 13-14% risk in those with none, trace, or mild leaks. While there is much discussion regarding options for the management of leaks, such as delayed expansions or 'plugging' technologies, such interventions are also not without risks or technical challenges.

Indications for Treatment

The American and European Society guidelines for intervention on aortic valve disease has also been evolving to reflect the developments in therapy options []. This is an important point since there is still an indication for SAVR is asymptomatic patients with critical aortic stenosis. Furthermore, there is growing evidence that adverse, and potentially irreversible, structural changes in the myocardium occur prior to developing symptoms. Patients with very advanced disease can have minimal symptoms and tools such as cardiac magnetic resonance imaging, strain-rate, and stress-echocardiography are being used more frequently to help direct management decisions.

Coronary Artery Interventions

Many of the patients who present will also have underlying obstructive coronary artery disease. Separating the symptoms related to their valvular disease from their coronary disease can be difficult with carefully consideration given to the severity and clinical implications of each problem and whether they need to be managed separating or at the same time. While the appeal of TAVR is that both valvular and coronary pathologies can be addressed often with catheter-based therapies, definitive guidelines directing one option over another is lacking. Furthermore, many of the early studies comparing SAVR to TAVR specifically excluded concomitant coronary procedures or those patients with significant obstructive disease – even though, especially in the surgical arms of the trials, a significant percentage of patients underwent some degree of surgical revascularization . Furthermore, some of the criticisms of the more recent low risk trials is that the surgical patients were at much higher risk profile because many of them underwent concomitant coronary revascularization at the time of their SAVR – hence implying that the two groups were not similar enough to suggest one

therapy (SAVR or TAVR) was better, worse, or even non-inferior to the other. Of growing concern is that structural frames of biologic valves also raises concerns of difficult coronary access in patients with previous valve replacements (both surgical and TAVR). While some procedures are being developed to try and overcome these concerns, such evolving interventions are also not without potential significant risk and can be very technically challenging. These topics further emphasize the importance of complete revascularization at the time of valve therapies. It must be also acknowledged that many SAVR-TAVR studies specifically excluded patients with significant coronary artery disease with current guidelines still tending to favor surgery by recognizing the limitations of the data[7]. In addition, preliminary results suggest that patients who undergo coronary stenting prior to TAVR may have worse outcomes and increased need for re-interventions due to major adverse cardiac and cerebrovascular events[7].

Repeat Interventions

One aspect aortic valve disease that is the most supportive of TAVR is patients that have had previous valve intervention, either surgical or trans-catheter, who develop symptomatic structural valve degeneration. Over the years, patients underwent SAVR with a biologic valve, despite guidelines and a documented survival advantage advocating the use of a mechanical valve, under the hope of avoiding anticoagulation that their next "valve" would be a trans-catheter valve[7]. The appeal of this approach is undeniable and logical; however, the practical applications are still under considerable study. Conflicting data exists regarding the best approach for the management of a failing biologic valve. Even though the risks of repeat surgery can be substantial, many experienced centers can offer re-operative surgery with a risk profile similar to first-time valve replacement – and placement of a TAVR inside a failing biologic valve is also not without short and long-term risks. . Furthermore, there are concerns surrounding a reduction in the effective orifice areas and the development of patient-prosthesis mismatch after placement of a TAVR inside of a failing SAVR or TAVR valve. An area of growing excitement is the role of valve "fracking" – a technique in which an existing bioprosthetic valve annular ring is "cracked" (or fracked) with a valvuloplasty balloon with the goal of enlarging the annular to thereby allow for implantation of a larger TAVR valve and reduce the risk of developing patient-prosthesis mismatch. While technically interesting and feasible, the clinical benefits – especially with current generation of biologic surgical valves – is unclear with little long-term data supporting this approach

Choice of Valves

Historically, the choice of surgical valves consisted of biologic (tissue) valves and mechanical valves. Mechanical valves required life-long anticoagulation and this was often unappealing to patients even after data suggested a potential survival advantage of mechanical valves in appropriately selected patients. Biologic valves did not require long-term anticoagulation, but were associated with structural degeneration and the need for repeat interventions – often at significant risk as outlined above with younger patients experiencing valve degeneration much earlier than older patients. Many different types of tissue valves are currently available –porcine, bovine, homographs, stentless, sutureless, etc – and each has substantial literature supporting the advantages and disadvantages of each valve type. Much of the decision-making regarding the initial valve choice is extensively discussed with the development of "valve-in-valve" TAVR for failing tissue valve. Since the concept (as mentioned above) of "valve-in-a-valve" has altered the natural history of patients with biologic valves, there is growing enthusiasm for use in younger patients. As discussed above, concepts regarding strut design and annular cracking (or fracking) to increase the annular size to allow for larger replacement valves under intense study. Similarly, the choice of transcatheter valve design – annular, supra-annular, self- vs balloon-expanding – is also the source extensive clinical research and discussion.

Durability and Cost

No discussion on TAVR vs SAVR would be complete without recognizing the substantial costs associated with each therapy. Even though the costs and expenses vary depending on the specific structure and reimbursement models of a health-care system, there is conflicting evidence regarding the short- and long-term costs of each therapy. TAVR valves are more expensive than SAVR – but patients can go home earlier, require less hospital-based care, and require less rehabilitation resources. However, considering the needs for pacemakers, stroke management, and concomitant coronary disease, the data on costs, short and long-term overall is difficult to assess[7]. This concern is even more apparent in countries with limited resources and budgets that cannot justify the substantially more expensive valves – especially when other costs (such as in-patient and post-discharge rehabilitation) are potentially much less compared to countries, such as The United States.

Conclusions

The topics that can be debated when comparing SAVR to TAVR is endless – and well beyond the scope of this review. However, the topics addressed above can serve as a foundation to illustrate some of the evolving concerns regarding the widespread growth of both therapies. It is important to remember that patient preferences – i.e. shared decision-making – can and should play a role in which therapy is offered, but providers must be objective and transparent with patients and their families so that "a best" decision can be make. Fortunately, the evolution of SAVR and TAVR has resulted in excellent options for patients – many of whom had none in the past – with the growing role of multi-disciplinary Heart Teams helping to guide patients. Never-

theless, with the current trend towards less-invasive therapies – be it catheter-based or small incisions – it is imperative to rely on high quality, unbiased, objective data and guidelines because small and less-invasive does not always translate into better or safer (regardless of how such terms are defined).

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Sažetak

Evolucija lečenja aortne stenoze – pogled hirurga

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Tokom poslednjih 10 godina došlo je do značajnog pomaka u načinu lečenja bolesti aortne valvule. Razvoj terapija zasnovanih na kateterima, posebno zamene trans-aortnog zaliska (TAVR), ponudio je mogućnosti lečenja za pacijente kod kojih je operacija (SAVR) ranije bila jedina opcija. Globalni rast upotrebe TAVR-a bio je izuzetan i prihvaćen sa puno entuzijazma. Međutim, takav rast nije prošao bez značajnih kontroverzi i troškova. Korišćenje "Tima za srce" za pomoć u proceni i lečenju pacijenata sa bolestima aortnog zaliska predstavlja važan korak u pokušaju da se specifične opcije terapije usklade sa jedinstvenim karakteristikama pacijenta - međutim, važno je prepoznati da su terapije zasnovane na kateterima još uvek relativno nova, u stalnoj evoluciji i potencijalno pod uticajem značajnih sukoba interesa. Iako je utvrđena uloga TAVR-a kod pacijenata sa visokim ili neprihvatljivim hirurškim rizikom, uloga kod pacijenata sa niskim i srednjim rizikom je nejasna i potencijalno kontroverzna s obzirom na neke nedoumice da kratkoročne koristi u poređenju sa tradicionalnim hirurškim terapijama možda neće rezultirati trajnim dugoročnim ishodom i odsustvom teških neželjenih događaja i ponovnih intervencija. Literatura o ovoj temi je opsežna i cilj ovog pregleda je da pokrene neke od dilema u vezi sa prednostima TAVR-a u odnosu na SAVR, posebno u kontekstu da li bi ovu izuzetno skupu terapiju trebalo smatrati novim globalnim standardom nege.

Ključne reči: aortna stenoza, poremećaj aortnog valvule, operacija srca, "tim za srce", strukturne terapije srca, transkateterske terapije

Srce i krvni sudovi 2020; 39(3): 103-106

Case report

Percutaneous treatment of catheter-induced dissection of the right coronary artery and right coronary sinus of Valsalva and ascendenting aorta up to aortic arch

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Abstract Acute aortic dissection during coronary arteriography or percutaneous coronary intervention is quite rare, but potentially dangerous complication In recent years, some reports have shown that stenting the ostium of the coronary artery (right coronary or left main artery) can be a valid, possibly life-saving therapeutic option. We describe a case in which a right coronary artery (RCA) dissection occurred during diagnostic coronary angyography and extended beyond the coronary ostium into the ascending aorta. Sealing of the aortic dissection and rescue of the RCA with stabilization of the patient was possible with rapid stenting of the right coronary ostium.

Kew words dissection of right coronary artery, aortic dissection, PCI

Introduction

Acute aortic dissection during coronary arteriography or percutaneous coronary intervention is quite rare, but life-threatening complication (1-6). Patients in this clinical setting may have a potential risk for acute myocardial infarction (MI) requiring emergency surgery (7). Awareness of the problem and its prompt recognition are essential and the possibility of such a complication should be kept in mind when the patient develops severe chest pain during angioplasty. Still, there remains a paucity of data regarding the risk factors and management of aorto-coronary dissection.

Case presentation

A 55-year-old hypertensive male with a history of posterior MI (few years ago and with successful PCI/stenting LCx : CTO+collaterals) was referred to our institution for coronary angiography because of stabile angina. Risk factors for CAD included current smoking, positive family history for CAD. At admission he was afebrile, blood pressure was 150/100 mmHg, with rhythmic heart beats. Electrocardiogram revealed: Q wave and negative T wave in II, III, aVF, V1, V2. Exercise treadmill stress test was negative. Echocardiography revealed referent left chamber diameters, and hypokinetic infero-posterior wall. Pericard was without effusion. Laboratory referent values of cardiospecific enzymes and other parameters were within normal limits.

Left coronary system injection showed a non significant lesion of the left anterior descending artery (LAD)(Figure 2) and with no significant in-stent and in-segment restenosis on circumflex artery (Figure 1). Using a 6 Fr Judkins Right 4 (JR4) catheter, the ostium of the RCA was easily cannulated and contrast medium was manually injected, but subsequent vigorous injection of contrast medium caused a spiral dissection in the proximal RCA with rapid forward extension distally and acute occlusion of the distal part of RCA (Figure 3-5).

The patient experienced an abrupt onset of severe chest pain and ST-segment elevation in the inferior leads followed by hypotension (systolic blood pressure of 80 mmHg) and bradycardia. Aspirin (300 mg p.o), clopidogrel (600 mg p.o.) and heparin (5000 IU intravenous) were administered. Using a 6 Fr Launcher (JR 4) guiding catheter, the ostium of the RCA was cannulated, and a 0.014 inch floppy Balanced Middle Weight guidewire was advanced into the true lumen in the side branch (RV branch-Figure 6). Double wire technique was used (2nd wire Balance Middle Weight guide wire was used to pass in the distal part of RCA through the dissection and 4,0x15 mm stent was implanted into the ostium of the RCA, achieving restoration of the PDA flow) in attempt to seal the entry site of the dissection, as the only valid and life-saving therapeutic option for patient (Figure 7). Further contrast injection into the RCA retrogradely escaped into the ascending aorta through the dissected lumen beyond the coronary ostium, and showed clear involvement of the right coronary sinus of Valsalva (CSV) (Figure 6 and7). Extension to the ascending aorta occurred during injections done for stent positioning in the proximal, medial and distal part of RCA. There was retention of contrast in the ascending aorta. An aortography was not performed due to the patient's unstable condition. Altogether, 5 stents were successfully implanted in the RCA, with the last stent

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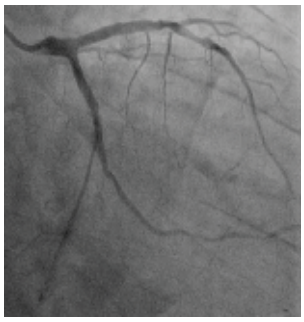

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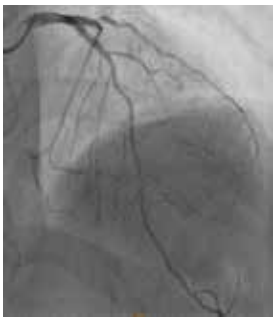

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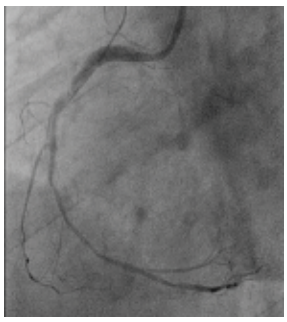

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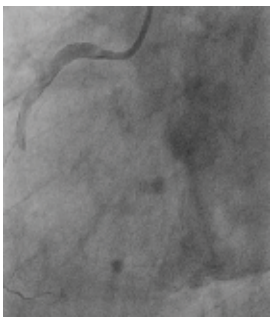

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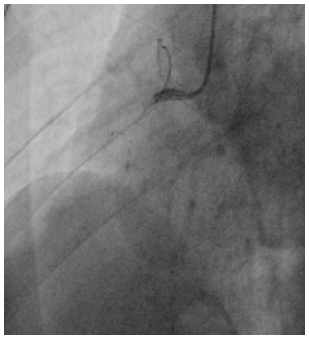

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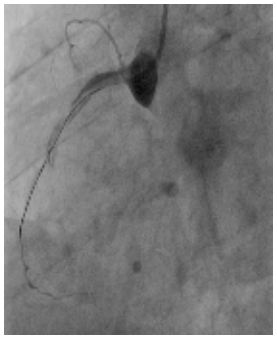

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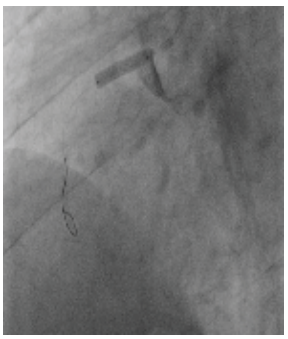

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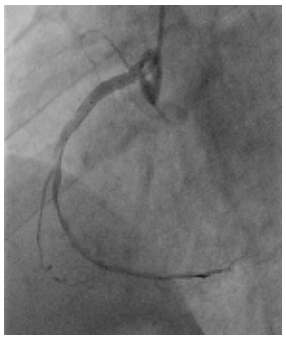

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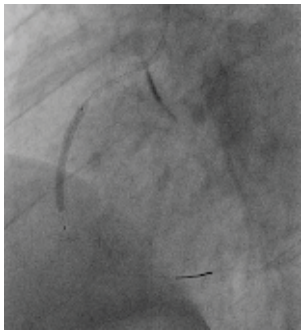

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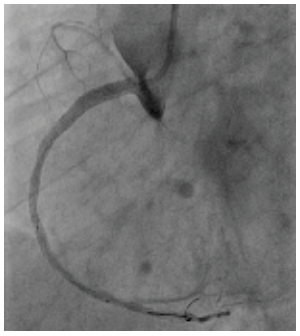

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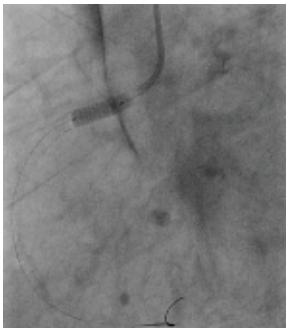

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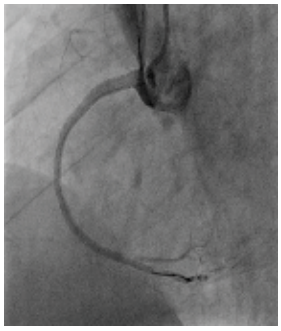

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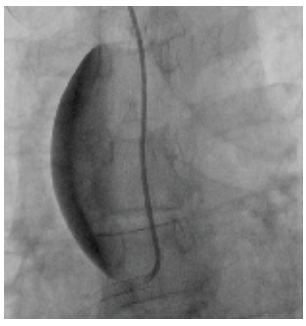

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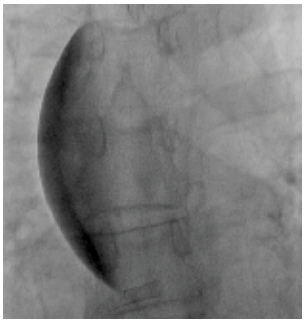

Figure 14

(graft stent;cover stent) in the ostium (Figure 11), covering the first stent implanted in ostial segment of RCA (graft stent to the ostium: 4,0 x 16 mm from the ostial to distal RCA: 4,0 x 15 mm, 3,5 x 18 mm, 3,0 x 33 mm, and 2,75x28 mm respectively)(Figure 7-10). We implanted graft (cover) stent in the ostial part of RCA just to be sure that we completely covered the entry site of the dissection in order to interrupt spreading of the dissection upwards, which appeared to be successful.

After successful coronary stenting, TIMI 3 flow was achieved (Figure 12), persistent dye-staining of the ascending aorta continues (Figure 13 and14), but the patients' condition stabilized as his chest pain was reduced and ST elevation decreased. On-site transthoracic echocardiography revealed an intact ascending aorta without evidence of an intimal flap, pericardial effusion or aortic regurgitation. The patient was immediately transfered to Clinic of Cardio Surgery for futher evaluation and potential treatment. Aortic dissection was confirmed by CT angio, but surgeons decided to treat it conservatively. Two weeks later, the patient was discharged without symptoms from the Clinic of Cardio Surgery, with following therapy: Ticagrelor (90 mg twice a day), Aspirin (100 mg daily), Atorvastatin (80 mg daily), Pantoprasole (20 mg daily), Nebivolol (5mg daily).

Six months later, CT angio was performed: RCA with good flow and no significant restenosis. Thrombosis of false lumen was completed from a beginning of around 2.5cm from right coronary sinus, involving each supra-aortic branches; left common carotid artery and left subclavian artery were open completely, but truncus brachiocephalicus had eccentric thrombosed false lumen with reduced lumen at the beginning of the right common carotid artery as well as stenosis in the distal part of around 60% up to the bifurcation. The patients was free of any symptoms.

Discussion

Iatrogenic aorto-coronary dissection is quite rare. The overall incidence of catheter-induced coronary dissection remains unknown, but aorto-coronary dissection has been estimated to occur in approximately 0.008–0.02% of diagnostic catheterizations and 0.04–0.06% of PCIs[1-3]. Of the type-A dissections in the International Registry of Aortic Dissection (IRAD), 27% were caused by coronary angiography or interventions. This event is a devastating complication of PCI, with a mortality rate up to 32%, similar to that of spontaneous type-A aortic dissection (35%)[1-7].

The exact mechanism responsible for the propagation of coronary dissection and the occurrence of aortic dissection remains to be established. However, it appears that the entry point originates within the coronary dissection and subsequently leads to progressive retrograde extension of the subintimal space into the aortic root. It occurs following a trauma caused by the tip of the guiding or diagnostic catheter (due to unintended deep intubation), subintimal passage of the rigid guidewire, or because of balloon dilatation. With the advent of complex interventions such as revascularization of chronic total occlusions, left main stenting, ostial and bifurcation lesions and saphenous vein graft lesions, this complication may become more prevalent.

Risk factors for aorto-coronary dissection include hypertension, older age, extensive atherosclerosis and underlying structural weakness of the media (e.g., cystic medial necrosis). Pande et al.[8] reported a case of iatrogenic aortic dissection during angioplasty of the RCA in a patient with cystic medial necrosis.

Our patient was hypertensive without aortic root dilation, and had neither clinical evidence nor family history of Marfan's syndrome or other causes of medial necrosis, although there is no histopathologic specimen. A history of MI has been proposed as a risk factor for aorto-coronary dissection. Dunning et al[9] described two patients with an extensive aorto-coronary dissection. Both of these patients underwent coronary angiography due to acute MI.

Left Amplatz guiding catheters were commonly involved in a disproportionate number of catheter-induced right coronary dissections. The choice of guiding catheter is a risk-benefit trade-off between extra back-up. and the possibility of coronary dissection. Other reported risk factors include variant anatomy of the coronary ostia (e.g., downward sloping origin of the left main coronary artery), vigorous hand injection of contrast material (as in our case), and even vigorous inspiration during contrast injection (respiratory-induced changes in Amplatz shaped catheter position). The size of the diagnostic catheters may also be important. We routinely use 5 Fr catheters for this purpose, but with smaller (4Fr) diagnostic catheters, the incidence of iatrogenic coronary dissections might be reduced.

Cautious techniques that can minimize the occurrence of iatrogenic dissection include: (1) checking pressure before every coronary injection; (2) avoiding deep engagement of guiding catheters and maintaining a steady tension on the guiding catheter while the angioplasty balloon is withdrawn; (3) prompt and timely recognition of this complication; and (4) minimizing futile efforts to halt the progression of the dissection.

Many of the cases of aorto-coronary dissections described in the literature have involved the RCA. Currently, it is unknown why the RCA is more susceptible to retrograde dissection into the CSV than the left main coronary artery (LMCA)[10-13]. Furthermore, it is interesting to note that when dissecting aortic aneurysms involve the coronary arteries, the RCA is also the one usually affected. The inherent properties of the RCA, which defers from the LMCA, may predispose the patient to aorto-coronary dissection.

Moles et al.[14] reported the first cases of aortic dissection as a complication of PCI. Their two cases had different evolutions. In their first case, the dissection of the aorta was limited to the left CSV, and surgical intervention was not necessary. In their second case, on the other hand, surgical management was necessary because the entry was in the aortic intima adjacent to the conal artery, leading to dissection of the ascending aorta. A patient reported by Varma et al.[15] with RCA dissection during PCI extending into the aortic root died within 48 hours with conservative treatment. Dunning et al. (9) described two patients with a Class 3 dissection who were submitted to surgery, and who died before discharge. In Maiello's report[16], a case of extensive dissection (Class 3) of the ascending aorta that occurred during angioplasty of the RCA was successfully treated by means of coronary stent implantation. Sutton et al.[17] described a case in which retrograde dissection of the aorta necessitating urgent surgical repair occurred during an attempt to open a chronically occluded RCA. Initially localized, the dissection extended during an attempt to seal the right coronary ostium. They suggested that if localized retrograde aortic dissection occurred, the management would depend on the stability of the distal coronary vessel. If stable, a conservative approach would be preferable to an attempt to seal the dissection.

Still, there remains a paucity of data regarding the management of aorto-coronary dissections and wide variety of potential clinical outcomes hampers attempts to standardize treatment. Despite the lack of evidence-based guidelines for the optimal treatment of aorto-coronary dissection, some reports have shown that stenting the ostium of the coronary artery (RCA or left main) can be a valid and life-saving therapeutic option for the patient. It is reasonable to attempt to seal the entry site of the dissection with PCI and stenting first, then the extent of dissection can be assessed (as in our case). From the technical viewpoint, soft-tip wires should be used when attempting to access the true lumen, and if the initial wire enters the false lumen, another soft-tip wire should be carefully manipulated into the true lumen (double-wire technique)[18]. Stenting should be performed as soon as possible, as saving time is mandatory in this setting, and implantation should be started distally and finally to the RCA ostium.

The evolution of the aorto-coronary dissection can be monitored by means of transesophageal echocardiography. This conservative management (the "watchful

waiting" strategy, suggested by Alfonso et al.[19]) is a reasonable option only in the hemodynamically stable patient with localized aortic dissection (as in our case). On the other hand, the progression of an aortic dissection with unstable hemodynamics, acute severe aortic regurgitation, hemopericardium and intractable chest pain are clear indications for intervention. The sinus of Valsalva dissections that remain localized during catheterization tend to resolve spontaneously in the first month. Localized dissections of coronary arteries have also been successfully treated conservatively, although Mulvihil et al.[20] have described intense healing of these localized coronary dissections, resulting in scar formation with coronary flow obstruction.

To guide the choice for the best therapeutic strategy, a classification of iatrogenic dissection of the ascending aorta has been proposed. This classification is based on the extent of dissection to the aortic root. A focal dissection limited to the coronary cusp (Class 1), and a dissection extending to the ascending aorta but 40 mm in length (Class 3) is still controversial, and ostial stenting may be life-saving, as in our case.

In the present case, an extensive iatrogenic aortic dissection that was limited to the ascending aorta was successfully managed by stenting the ostium of the RCA and monitoring the aortic dissection by CT angio and transthoracic echocardiography.

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Sažetak

Perkutano lečenje kateterom izazvane disekcije desne koronarne arterije i desnog sinusa Valsalve sa propagacijom prema ascedentnoj aorti i aortnom luku

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Akutna disekcija aorte tokom koronarne arteriografije ili perkutane koronarne intervencije prilično je retka, ali ozbiljna komplikacija Poslednjih godina neki izveštaji pokazuju da stentiranje ostijuma koronarne arterije (desna ili leva koronarna arterija) može biti adekvatna i životno spašavajuća terapijska opcije. Predstavljamo slučaj u kojem je disekcija desne koronarne arterije (RCA) nastala tokom dijagnostičke koronarne angiografije sa širenjem prema sinusu Valsalve i ascendentnoj aorti. Zaustavljanje disekcije aorte i zbrinjavanje RCA sa kliničkom stabilizacijom pacijenta bilo je moguće brzom implantacijom stenta u ostijum desne koronarne arterije.

Ključne reči: disekcija desne koronarne arterije, disekcija aorte, PCI

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Case report

A case of imaging guided reintervention after two stents bifurcation PCI using mini-crush technique

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Abstract We present a case of a patient with previous history of primary PCI of the occluded RCA for a myocardial infarction of the inferior wall, who was treated for a significant Medina 1.1.1 coronary lesion of the LAD-D1 bifurcation with mini-crush technique. The patient was transferred to intensive care unit after primary PCI with a plan to treat bifurcation on the other occasion after discharge. However, the patient experienced persistent chest pain along with ECG changes showing ischemia of the anterior wall, and due to clinical unstable condition the patient was transferred to Cath lab for a PCI of LAD-D1 using two-stent mini crush technique with bare metal stents which were only available in adequate dimensions at the moment. The result of the intervention was satisfactory, with TIMI 3 flow in both side branch and main branch, and angiography follow-up was scheduled in 6 months. On control angiography, a significant in-stent restenosis was detected in both main branch and side branch, and an optical coherence tomography (OCT) - guided balloon dilatation of both main branch and side branch with final kissing was performed. In our case OCT was particularly beneficial as it clearly demonstrated that there was no under-expansion of the stents, with only formation of the new plaque that was most significant in the LAD just below the D1 branch, and not on the carina itself nor on the ostium of the side branch.

Kew words bifurcation, mini-crush

Introduction

It is by now well established that drug eluting stents (DES) have an advantage over bare metal stents (BMS) in terms of in-stent restenosis and should always be considered as a first choice, especially when treating bifurcation lesions[1,2]. However, if DES are unavailable in cases of emergency, operators are forced to perform the intervention using BMS having in mind higher rate of restenosis[3].

Case report

A 73-years old female patient was diagnosed with acute inferior ST elevation myocardial infarction (STEMI) and immediately transported directly to cath lab for primary percutaneous coronary intervention (PCI) of right coronary artery (RCA). Risk factors for cardiovascular disease (CVD) were: hypertension, hyperlipidemia, and type 2 diabetes. Echocardiography showed hypokinesia of the inferior wall with EF of 45%. Emergency coronarography showed occlusion of RCA and a 90% Medina 1.1.1 bifurcation lesion of left anterior descending (LAD) artery and the first diagonal branch (D1) with severe disease of the ostium of D1 (Figure 1). Primary PCI of RCA was successfully performed and the patient was transferred to ICU with intention of treating LAD-D1 lesion in the future hospitalization when DES become available. However, after primary PCI of RCA patient suffered severe chest pain with ECG changes on anterior wall, so the decision was made to perform immediate PCI of LAD during actual hospitalization. Patient was transferred back to the cath lab for PCI of LAD, but due to lack of the DE stents of adequate dimensions, and considering the acuteness of the situation at hand, and the complexity of the lesion as well as the size of the main branch and diagonal branch, the decision has been made to perform the PCI with two - stent mini crush technique. A 7F EBU Launcher guiding catheter (Medtronic) was used for the intervention. The LAD and D1 were wired with Runthrough (Terumo) and BMW (Abbott) floppy wires respectively (Fig.2). Predilatation of both main branch and side branch was done with Sprinter Legend 2.0x15 mm (Medtronic) balloon at 16 atm (Fig. 3, Fig. 4). Pro Kinetic Energy 3.5 x 30mm (Biotronic) was placed into the LAD and Multi Link Vision 2.75x23mm (Abbott) was placed into the D1 simultaneously, with small protrusion to the LAD. (Fig. 5) The side branch stent was inflated at 12 atm and then crushed with the main branch stent at 12 atm after the wire and balloon removal. (Fig. 6, Fig. 7). Rewiring of the side branch was then performed and after the strut opening with a 1.5x15 mm Sprinter Legend balloon (Medtronic), the final kissing was done with NC Sprinter 3.0x20mm and NC Quantum Apex 2.5x21 mm, both at 16 atm. (Fig. 8). The final result was satisfactory with TIMI 3 flow in both LAD and D1. The patient was discharged from the hospital, no chest pain and further ECG changes present, and a control angiography with OCT evaluation was planned in 6 months.

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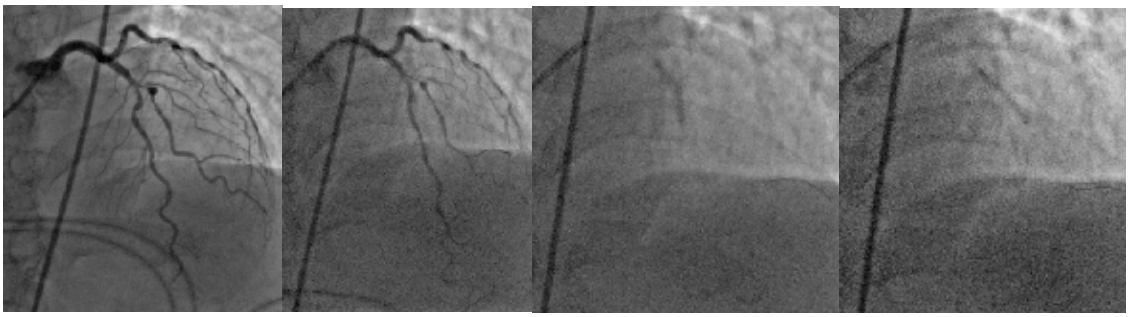


Figure 1 **Figure 2** **Figure 3** **Figure 4**

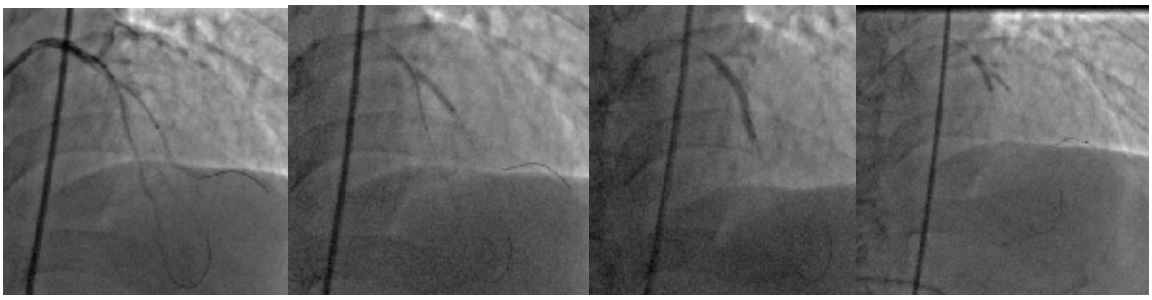


Figure 5 **Figure 6** **Figure 7** **Figure 8**

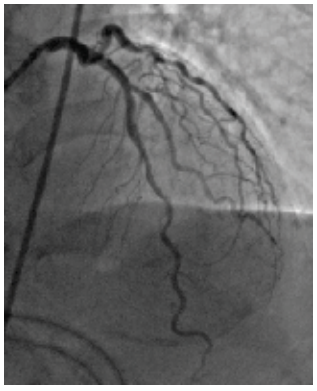


Figure 9

After 6 months the patient was admitted to the hospital for control angiography as planned, and presented with stable CAD symptoms (CCS I-II). Coronarography showed significant in-stent restenosis in both LAD and D1 with TIMI 3 flow (Figure 10). OCT confirmed restenosis, but with good stent expansion and strut apposition (Figure 15). The operators decided to perform dilatation of both branches separately with final kissing at the end of the procedure. The 7F EBU Launcher (Medtronic) guiding catheter was once again used, with the same wire setup as in the first intervention. NC Quantum Apex 3.5x21 mm (Boston Scientific) was used for the dilatation of the LAD (Figure 11) and NC Quantum Apex 3.0x20mm was used for the D1 (Figure12), both at high pressure. Final kissing was then performed with two NC Quantum Apex 3.0x20mm (16 atm for the main branch and 12 atm for the side branch) (Figure 13). The final result was satisfying with significant reduction of in - stent restenosis in both branches confirmed by OCT, and TIMI 3 flow (Figure 14 and 15). The patient was once again discharged from hospital and a new 6 months-after control angiography was scheduled. The evaluation will be made by coronarography as well as by OCT again, and then the final decision concerning this particular artery will be made.

Discussion

It is unanimous consensus today backed up by many studies that the DES are the gold standard for almost all coronary lesions, and especially for complex and bifurcational ones[4]. In some situations however, due to different impediments, such as in our case the urgency of the patient's state combined with unavailability of appropriate DES in the cath lab, operator may still chose BMS, but with the obligation to rigorously follow the clinical outcome for a longer period of time, with all diagnostic procedures and imaging techniques available. We opted for plain NC balloons dilatation this time the drug eluting balloons (DEB) of adequate dimensions were not available to us at the time of intervention, with intention to see the outcome in 3 months and then bring the definite decision about this patient's further treatment. If the restenosis occurs once again there are several options available: balloon kissing technique with DEB, stenting of the LAD with a DES inside the BMS[5] and

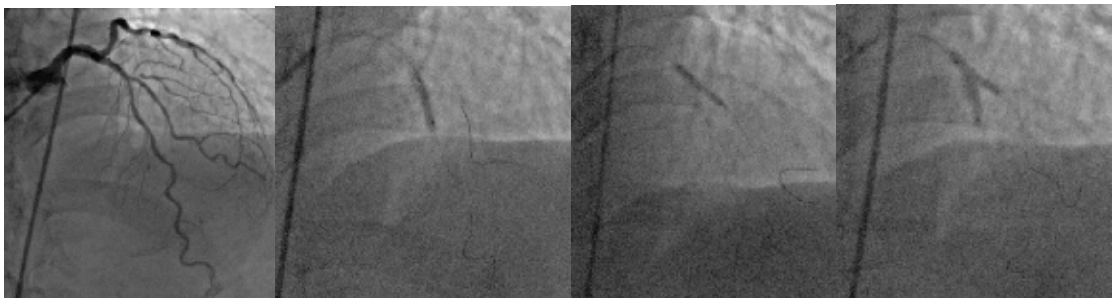


Figure 10 **Figure 11** **Figure 12** **Figure 13**

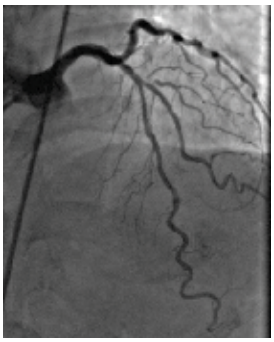
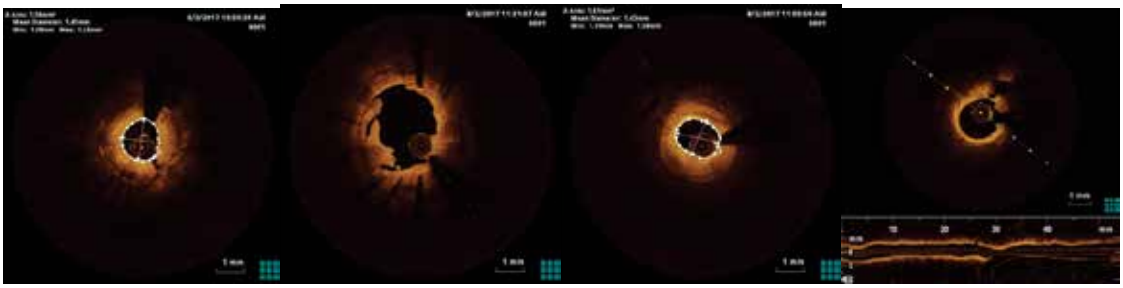


Figure 14



LAD before **LAD after** **D1 before** **D1 after**

Figure 15. OCT image of LAD and D1 in stent restenosis, before and after the procedure

cardiac bypass surgery as a final, most invasive, but dependable and reliable solution[6]. There are some studies that indicate that DEB might have a slight edge over DES in a first time restenosis[5] as there are less metal layers involved inside the artery, but the matter itself is still not investigated enough. OCT will once again be performed with the idea to guide the procedure[7] and help choose the best strategy for this particular patient and with possibility to compare the previous and current OCT findings for better understanding of the lesion. In the end, it is left to say that although the bare metal stents are by no means first choice for treating bifurcation lesions, it still gave us some comfort that they helped us buy time in urgent situation and as an only available solution at that moment served purpose of preserving myocardial function while we take a step by step approach toward definite solution of the problem.

Conclusions

In case of unplanned placement of BMS in complex coronary lesions, the operator should always keep in mind higher rate of restenosis in the follow-up that require careful follow-up of the patients. In addition, on repeated angiography disclosing restenosis following treatment of bifurcation with tw stents technique, OCT was of particularly benefit to disclose pathophysiologic mechanism of restenosis with adequate treatment.

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Sažetak

Prikaz slučaja "imaging" vođene re-intervecnije posle perkutane koronarne intervencije bifurkacije sa dva stenta korišćenjem "mini crush" tehnike

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Predstavljamo slučaj pacijenta sa prethodnom istorijom primarne PCI okludirane RCA zbog infarkta miokarda donjeg zida, koji je lečen zbog značajne Medina 1.1.1 bifurkacije LAD-D1 tehnikom "mini-crush-a". Pacijent je prebačen u jedinicu intenzivne nege nakon primarne PCI sa planom lečenja bifurkacije drugom prilikom nakon otpusta. Međutim, zbog ponovnog bola u grudima, zajedno sa EKG promenama koje pokazuju ishemiju prednjeg zida, a zbog klinički nestabilnog stanja pacijent je prebačen u Salu za kateterizaciju radi PCI LAD-D1 tehnikom "mini-crush-a" sa ugradnjom dva metalna stenta koji su jedino bili dostupni tada u adekvatnim veličinama. Rezultat intervencije bio je zadovoljavajući, protok TIMI 3 je uspostavljen i u bočnoj i u glavnoj grani, a kontrolna angiografija je zakazana za 6 meseci. Na kontrolnoj angiografiji otkrivena je značajna restenoza u stentu i u glavnoj i u bočnoj grani, koja je lečena putem optički koherentne tomografije (OCT) - vođene balon dilatacija glavne i bočne grane sa završnim "kissingom". U našem slučaju OCT je bio posebno koristan jer je jasno pokazao da mehanizam nije bio nedovoljna ekspanzija stenta, već stvaranja restenoze unutar stenta koja je bila najznačajnija u LAD-u odmah ispod grane D1, a ne ni na samoj karini ni na ostijumu bočne grane.

Ključne reči: bifurkacija, "mini-crush", OCT

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Case report

Hyperventilation test as a provocation test in catheterization laboratory

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Abstract We present a patient in whom hyperventilation test disclosed a culprit lesion on the coronary arteries in the Cath lab. A paient, 41-years of age, was treated at the Department of Invasive Cardiology in Medical center Zajecar due to the newly developed inferolateral STEMI. Coronary angiography revealed mild-to-intermiadate LAD stenosis, OM1 was medially occluded, OM2 branch ostial stenosis of 60%, and right coronary artery was minor, without significant angiographic changes. In the same session, primary percutaneous coronary intervention (PCI) was successfully performed on OM1 with Resolute Integrity 2.5x12 mm stent implanted. Due to repeated anginal pain exercise stress test was performed, which was evaluated as positive, and the stress echocardiographic test confirmed hypokinesia of the apical and medial segments of the inferior and lateral wall. A new coronary angiography showed similar stenoses up to 50% in medial LAD and ostial OM2 have been described, but a new 70% stenosis on first diagonal branch which was treated by PCI by another 2.5x16 mm CRE8 stent implantation. One month after discharge, the patient again complained of chest pain again on moderate exertion, occasionally occurring at rest, and resolving after nitroglycerin. Repeated coronary angiography disclosed the same angiographic findings as earlier without progression or in-stent restenosis, and the operator decided to perform a hyperventilation test for 2 minutes, as an additional test to assess the culprit lesion. Immediately following hyperventilation, the patient complained of chest pain with sweating, accompanied with ECG ST elevation in precordial leads. Control angiography demonstrated TIMI 0 flow at the site of the lesion on the medial segment of the LAD. In the same act, PCI was performed on LAD with implantation of CRE8 3x31 mm stent. The hyperventilation test is a simple diagnostic test that may be useful in some patients during coronary angiography to identify patophysiologic mechanism of myocardial ischemia and "culprit" lesion.

Kew words hyperventilation test, coronary vasospasm, angina pectoris

Background

Hyperventilation is a physiological process of forced, accelerated inhalation and exhalation of air, which leads to a decrease in the concentration and partial pressure of carbon dioxide in the blood[1]. Hyperventilation does not increase the concentration of oxygen in the blood and tissues, but increases the elimination of carbon dioxide, which results in the appearance of alkalosis. Alkalosis is manifested by a reduced concentration of hydrogen ions, which leads to more calcium entering the cell from the outside and, together with intracellular calcium, initiating contraction[2,3]. Increased intracellular calcium can cause vasospasm in sensitive epicardial coronary arteries[4]. It is necessary for the patient to breathe rapidly and deeply for 5 minutes, hyperventilate with a respiration rate of about 30 / minute. The test may be performed during invasive coronary angiography with monitoring of the patient's symptoms, ECG and angiographic documentation of coronary vasospasm. Changes in the positive test usually occur 1 to 5 minutes after the end of hyperventilation[5]. A positive provocative test implies the appearance of chest pain, ischemic changes on the ECG and spasm on the angiogram of the coronary arteries. Coronary artery vasospasm is defined as transient total or subtotal coronary artery occlusion (>90%)[6].

We present a case in whom hyperventilation test in Cath Lab disclosed coronary vasospasm at the site of intermediate coronary lesion.

Case presentation

Patient, 41-years old, previosly suffered STEMI of inferolateral localization which was treated at the Department of Invasive Cardiology, Medical center Zajecar. Coronary risk factors included hypertension, and smoking for 20 years. Coronary angiography demonstrated stenosis of 40% in the medial segment of the LAD, occlusion of OM1 branch medially, and intermedaite lesion

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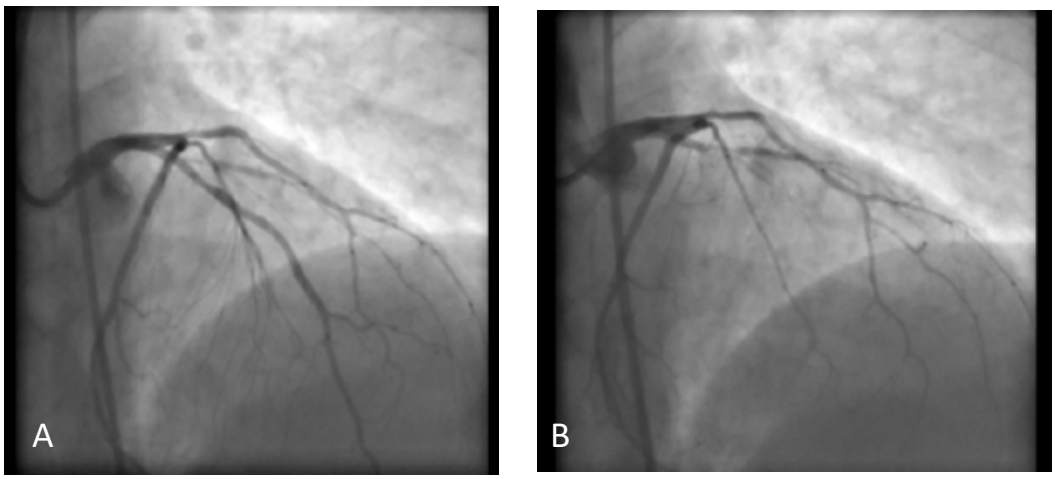

Figure 1. Coronary angiography of left coronary artery before (A) and after hyperventilation test (B) with complete vasospasm and obstruction of coronary flow downstream intermediate coronary lesion

of ostial OM2 branch. The right coronary artery was minor, and without significant angiographic changes. During the same session, primary percutaneous coronary intervention (PCI) was performed on OM1 with implantation of Resolute Integrity 2.5x12 mm stent. The echocardiographic examination showed mild dilatation of the left atrium 4.6 cm, with LV dimensions 5.06/3.68cm, and EF of 50% due to hypokinesia of the apical segment of the septum, and apical segment of the lateral wall. The patients was discharged with following therapy: clopidogrel 75mg, acetylsalicylic acid 100mg, ramipril 5mg, atorvastatin 40mg, bisoprolol 5mg. Due to repeated angiogenic pain, exercise stress test was performed, which was evaluated as positive, and subsequent stress echocardiographic confirmed hypokinesia of the apical and medial segments of the inferior and lateral wall. Repeated coronary angiography showed stenoses up to 50% on medial LAD and ostial OM2, with new 70% stenosis on diagonal branch which was treated with another2.5x16 mm CRE8 stent implantation. Lercanidipine 20mg was added to the therapy. After a month of discharge, the patient haa a pain in the middle chest again on faster walking on the flat surface, but also during resting conditions, dissapering after nitrates. New angiography disclosed similar stenosis in the medial segment of the LAD of 60% (Figure 1A) and the operator decided to perform hyperventilation test for 2 minutes, as an additional test to assess the culprit lesion. Immediately after the test, the patient complained of chest, sweating, accompanied with ECG ST elevation in the precordial leads. Angiography showed TIMI 0 flow at the site of the lesion on the medial segment of the LAD (Figure 1B). In the same session, PCI was performed on LAD by implantation of CRE8 3x31mm stent. The patient was discharged with the same medicatiosn including nitrates and calcium antagonists, and was free of chest pain in the follow-up period

Disscusion

Coronary artery vasospasm is an important mechanism of myocardial ischemia that may produce different clinical manifestation of coronary artery disease from myocardial ischemia, exertion-induced angina, variant angina, to acute coronary syndrome, including myocardial infarction or sudden cardiac death. Coronary artery endothelial dysfunction is thought to play a significant role in vasospasm including dominance of vasoconstrictor effects over vasodilatory factors. Basically, the production of vasoconstrictor substances at the local level, such as catecholamines, angiotensin II, thromboxane A2, serotonin, endothelin, histamine, vasopressin and leukotriene, is increased, with reduced production of vasodilators of nitric oxide and prostacyclin. Coronary artery spasm can occur at the site coronary stenosis that significantly narrows the lumen of the artery, but also in the segmental artery without visible fixed atherosclerotic narrowing. Prolonged spasm can lead to complete cessation of blood flow and to activation and aggregation of platelets with the development of coronary thrombosis and myocardial infarction[7]. A hyperventilation test as well as tests with ergonovine and acetylcholine can be used to provoke vasospasm[8]. Due to the low sensitivity of the hyperventilation test, additional intracoronary administration of acetylcholine or ergonovine is sometimes required[9-11]. If performed in Cath Lab, acetylcholine or ergonovine are safe diagnostic agents that mayt be applied directly to the left or right coronary artery. Drug-induced vasospasm in this way can be easily controlled by the use of intracoronary nitrates, but a small percentage of patients may develop ventricular tachycardia or fibrillation or bradyarrhythmia during a provocative test (3.2 and 2.7%). The incidence of these complications is similar to the incidence that occurs during spontaneous vasospasm episodes (7%). A provocative test can be considered positive if it causes: anginal symptoms, and ischemic changes on the ECG [8]. The development of chest pain after acetylcholine administration, in the absence of angiographically evident spasm, with or without accompanying ECG changes in the ST segment, may indicate microvascular spasm and is often observed in patients with microvascular angina pectoris[11]. In the work of Nakao and Ohgushia, the hyperventilation test proved to be highly specific for the diagnosis of coronary artery spasm[12]. Rassmusen showed that hyperventilation

leading to an arterial PH of about 7.6 has basically the same potency as the 0.4mg ergometrine test, but the hyperventilation test appears to be safer[13].

With this case, we demonstrate how simple hyperventilation test can be used in Cath Lab to reveal patophysiologic mechanism of chest pain and myocardial ischemia. The question remains open on the value of stenting in the patient where vasospasm was superimposed on intermediate coronary lesion. We decided to perform PCI of this lesion on the basis of documentation of large myocardial ischemia with clinically mixed and unstable presentation, and slow but evident angiographic progression of coronary lesion, but the justification of this approach needs to be confimed in the future follow-up of the patient.

Conclusion

The hyperventilation test is a simple diagnostic test that may be important in some patients during coronary angiography to identify vasospasm and the culprit lesion on the coronary arteries.

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Sažetak

Hiperventilacioni test kao provokacioni test u angio sali

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Predstavljamo pacijenta sa kome smo u angio Sali radili hiperventilacioni test radi otkrivanja razloga bola u grudima i ishemije miokarda. Pacijent star 41 godinu je prethodno lečen zbog STEMI inferolateralne lokalizacije. Na koronarografiji nađena je stenoza od 40% u medijalnom segmentu LAD, OM1 grana medijalno okludirana, OM2 grana ostijalno sužena 60%. Desna koronarna arterija je bila minorna, bez značajnih angiografskih promena. U istom aktu urađena je primarna perkutana koronarna intervencija (PCI) na OM1 sa plasiranim stentom Resolute Integriti 2.5x12 mm. Zbog ponovljenih angionoznih bolova urađen je test opterećenja koji je ocenjen kao pozitivan, što je potvrđeno na stres ehokardiografskom testu razvojem hipokinezije apikalnih i medijalnih segmenata inferiornog i lateralnog zida leve komore. Urađena je ponovna koronarografija sa nalazom slične stenoze do 50% na medijalnom LAD i na ostijalnom OM2 i novom stenozom na dijagonalnoj grani oko 70%. Procenjeno je da je moguća "culprit" lezija na DG1 i urađena je PCI sa implantaciojom stenta CRE8 2,5x16 mm. Nakon mesec dana od otpusta pacijentkinja ponovo ima bolove u sredogrudju na brže hodanje po ravnom, tegobe se povremeno javljaju i u miru, prolaze na 1-2 lingvalete nitroglicerina, zbog čega je urađena ponovna koronaografija. Opisana je ista stenoza u medijalnom segmentu LAD i odlučeno je da se uradi hiperventilacioni test u trajanju od 2 minuta, kao dodatni test za procenu miokardne ishemije i "culprit" lezije. Neposredno nakon testa bolesnica oseća bol u grudima praćen preznojavanjem. Na monitoru EKG viđena je ST elevacije u prekordijalnim odvodima. Učinjena je ponovna angiografija na kojoj se sada vidi TIMI 0 protok na mestu lezije na medijalnom segmentu LAD. U istom aktu urađena je PCI na LAD plasiranjem stenta CRE8 3x31 mm. Hiperventilacioni test je jednostavan dijagnostički test koji može kod nekih pacijenata u toku koronarografije da bude od značaja u identifikaciji miokardne ishemije i "culprit" lezije na koronarnim arterijama.

Ključne reči: hiperventilacioni test, koronarni vazospazam, angina pectoris

Srce i krvni sudovi 2020; 39(3): 114-118

Case report

Acute coronary syndrome associated with occlusion of the main trunk of the left coronary artery in patients with a previously negative exercise stress test

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Abstract

Objective. A case report of a patient with acute coronary syndrome with occlusion of the left main coronary artery with a typical clinical picture and a negative exercise stres test result.

Case report. A 44-year-old patient is presented to our service as STEMI with elevation in the inferior leads and ST depression in the precordial leads. After intrahospital cardiac arrest and resuscitation, primary PCI of left main coronary artery is performed, after which hemodynamic stabilization occurs. Retrospective review of medical history reveals that he was evaluated three years before the acute event due to occasional chest pain. The pretest probability for coronary heart disease was 38%, so in accordance with the then valid ESC guidelines for stable coronary heart disease, a stress ECG test was performed, which was assessed as negative for significant coronary heart disease. All analyzed test parameters indicated a low risk of adverse cardiovascular events: functional capacity, ST segment denivelation, chronotropic competence, blood pressure variations, Duke treadmill score. With a postest probability of 9%, the patient was not further evaluated for coronary heart disease and was asymptomatic for the next three years and did not respond to follow-up examinations. If he presented himself after 2019 according to the newer ESC guidelines for chronic coronary syndromes, the patient would be indicated to perform a functional imaging test or CT coronary angiography at the time of the initial clinical evaluation.

Conclusion. The diagnostic algorithm for patients with chest pain is based on a pretest probability that determines further diagnostic workup. Patients with a negative exercise test and a typical clinical presentation should be referred for further diagnostic imaging test because of the risk that a small number of them may have significant and even critical coronary stenosis.

Kew words pretest probability, coronary artery disease, CAD, ECG stress test, cardiovascular adverse events

Introduction

Chest pain is a common problem in everyday clinical practice. Of all visits to a general practitioner in the UK, 1% are due to chest pain. The importance of this cardinal clinical symptom is evidenced by the fact that mortality was doubled in the year after the presentation of a patient with chest pain[1]. Since the introduction of invasive coronary angiography (ICA) into routine clinical practice, it has become the gold standard for the diagnosis of coronary artery disease (CAD)[2] and in the United States alone about 1.1 million procedures[3] are performed each year. However, due to the wide availability of the method, there is an expansion of indications for referral of patients to ICA and only 41% of patients have obstructive CAD[4]. Therefore, there is a need to use non-invasive methods to assess the likelihood of CAD. This is achieved by determining the pretest probability (PTP) for the CAD. One of the oldest in use is the Diamond and Forrester method, which uses the patient's age, gender and chest pain typicality for coronary heart disease[5] in the pretest probability assessment. More recently, the European Society of Cardiology (ESC) has used a modified version of this model[6].

Case presentation

A 41-years old patient presented to outpatient clinic for atypical chest pain. He had positive family history, was a smoker and had dyslipidemia with total cholesterol 6.1 mmol/L and an LDL fraction of 4.3 mmol/L. The patient was referred to a stress electrocardiographic test that was performed on an ergobycycle in December 2016 using the Bruce protocol. The PTP for CAD was 34%. The test was interrupted at 2th minute of V level at 223W workload and 10.9 MET due to patient fatigue, no anginal discomfort, no ST segment denivelation, and heart

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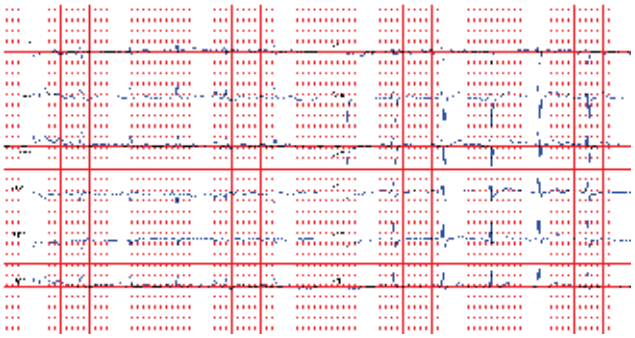

Figure 1. ECG at the beginning of the stres test

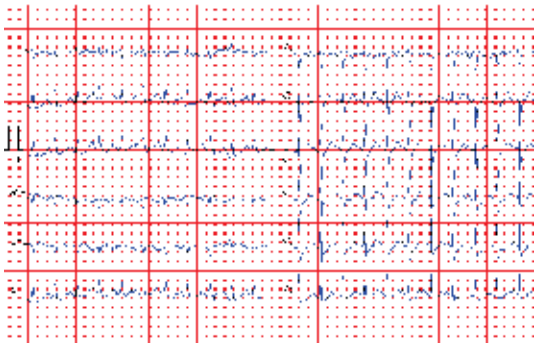

Figure 2. ECG in peak workload of 220W

rhythm disturbances. A heart rate of 179/min (91% of maximum predicted), a BP of 190/100 mmHg, and a double product of 34010 were achieved (Figures 1 and 2). The test was rated as negative for significant CAD with a calculated post-test probability of 9%.

Three years later, in August 2019, the patient presented with myocardial infarction with ST segment elevation in D2, D3, aVF and deep ST segment depression in leads V1-V4 (Figure 3) with intrahospital cardiac arrest immediately upon admission to the Internal Department of the Zajecar Health Center. The patient was resuscitated for about 40 minutes using advanced life support measures including 8 asynchronous DC shocks and 20 ampules of Adrenaline. After that, he recovered cardiac activity with a frequency of 25 / min and an complete heart block, the patient was placed on mechanical ventilation, and a temporary pacemaker lead was placed. Coronary angiography verifies the occlusion of the distal segment of the left main coronary artery. After placement of coronary wires in the distal segments of LAD and Cx (Figure 4), the lesion was predilatated with a Sprinter Legend 2.5x15mm balloon and then implanted with a Resolute Onyx 4.5x18mm stent in LM-LAD with provisional technique and excellent angiographic result with TIMI3 flow through LAD and Cx arteries (Figure 5). The patient was hemodynamically stable, following intervention. After 24 hours, control coronary angiography conformed patent stent. In the further course of hospitalization, clinical improvement occurs with weaning the patient from mechanical ventilation. Echocardiography registers the left ventricle diameter of 66/43mm, left ventricular ejection fraction of 35-40% with hyoikinesia of distal anterior, septal and lateral walls. The patient was discharged on the 18th hospital day. Four months after the acute event, control coronary angiography was performed with a transradial apprach, showing patent coronary arteries without in-stent restenosis, and intermedaite lesion in medial segment of LAD and mild stenosis in RCA. In further clinical follow-up the patient was asymptomatic, with maximal doses of drugs and LDL cholesterol value of 1.5 mmol/L.

Discussion

In patients with chest pain, the first step in the diagnostic algorithm is to determine the pretest probablity (PTP). PTP predicts the existence of angiographic stenosis of at least 50% of the diameter of at least one coronary artery. The patient's complaints at the initial presentation were understood as atypical angina with 2 of 3 features of anginal pain and a calculated pretest probability of 38% for CAD according to the ESC guidelines from 2013[7]. Since he had an normal electrocardiographic finding at rest and preserved functional ability, we decided to perform a stress electrocardiographic test. The test was considered negative.

According to the valid ESC guidelines, at the time of testing, the most important predictors of exercise stress test were: functional capacity, test duration, changes in arterial blood pressure and myocardial ischemia according to clinical and electrocardiographic parameters. Functional capacity was shown as the most important prognostic parameter for mortality and adverse cardiovascular events, regardless of gender, age, presence and severity of CAD[8,9,10,11,12,13,14]. It can be expressed in metabolic equivalents (1 MET corresponding to O2 consumption of 3.5ml/kg/ min), workload in watts (W), heart rate at peak load and double product. It has been shown that each achieved MET in the stress test reduces the total mortality and cardiovascular events by 13-15%[15]. Another predictor of adverse events is chronotropic incompetence during the stress test. A study of 1575 healthy men who underwent an ECG stress test and were followed for 7.7 years showed that failure to achieve submaximal HR, the level of HR increase during the test, and the chronotropic index were predictors of overall mortality and incidental coronary heart disease[16]. Interestingly, according to all parameters, the ergometric test of our patient was clearly low risk. Another widely used and validated predictor of adverse CV events is the Duke treadmill score designed by Mark et al[17]. It uses the duration of the test in minutes, the value of the ST segment of denivelation and angina level in the calculation. Low-risk values are 5 and higher, intermediate -11 to 4 and below -11 patients are stratified as high-risk. According to the ESC guidelines, the one-year risk of CV death over 3% was a category of high-risk patients in whom potential revascularization has prognostic significance and they should be referred to ICA[7]. It has been shown that low risk carries only 0.25% of annual CV mortality as opposed to high risk which carries over 5%. Of the patients with calculated low risk, 60% did not have significant obstructive CAD and 16% had single-vessel disease (stenoses over 75% of the diameter were considered angiographically significant). Better test performance was also shown in women and poorer in the elderly[18]. Our patient had a Duke score of

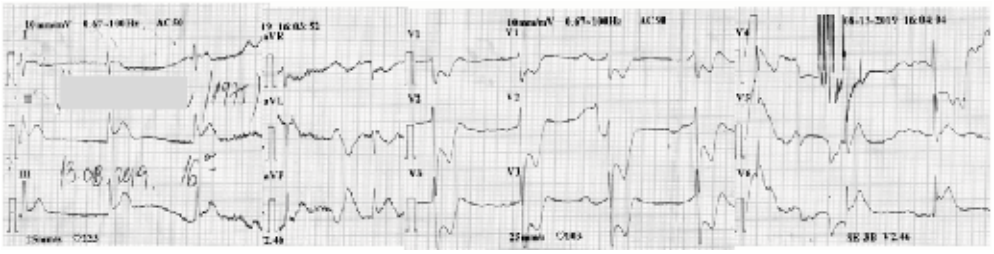

Figure 3. ECG at the admision to the Coronary unit – 30 minutes after the onset of chest pain

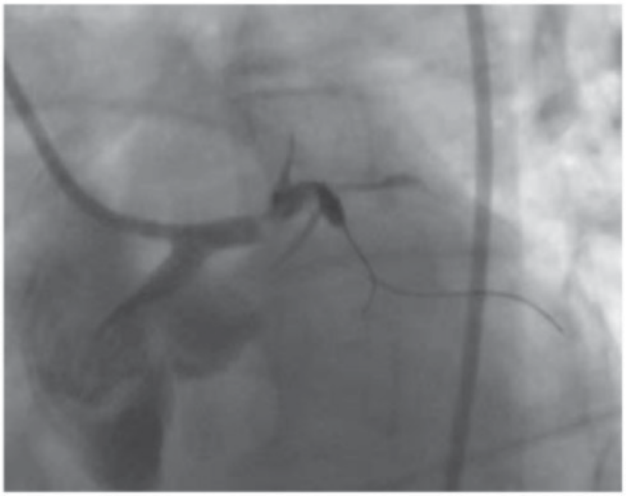

Figure 4. Angio after wiring LAD and Cx

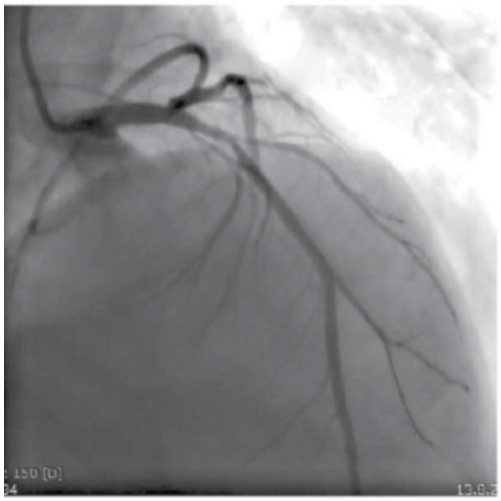

Figure 5. Angio after stent implantation in LM-LAD

+13 which stratified him as low risk for CV events with a one-year mortality below 1%. The question was whether something would change in the diagnostic algorithm and stratification of the CV risk of our patient if he was evaluated in the light of the new ESC guidelines for chronic coronary syndromes from 2019[19]. They retained the earlier concept of PTP based on gender, age, and typicality of chest pain with the addition of a PTP assessment for patients presenting with dyspnea only. The values of PTP are noticeably lower because the pooled analysis of three contemporary studies indicated a threefold lower prevalence of CAD than previously considered[20]. It is recommended that non-invasive diagnostic treatment be performed in patients with PTP over 15%, and in case of refractory angina or if PTP is very high invasive diagnostic assesment. Patients with PTP below 5% have a very low risk of adverse CV events so no further diagnostic workup is required. In patients with intermediate PTP 5-15%, additional diagnostics are indicated according to the factors that modify PTP, giving the so - called clinical probability of CAD. Our patient would have a PTP of 10%. According to the factors that modify PTP (hypertension, smoking, positive family history) and the normal finding of the ECG stress test which is a factor in reducing the clinical probability for CAD, he would also be excluded from further diagnostic workup. But if we stratified the patient based on clinical assessment, we should do a non-invasive functional imaging test or CT coronary angiography, which have better sensitivity and specificity in relation to the specificity of 85-90% and sensitivity of 45-50% of the stress ECG test[21,22]. In the case of our particular patient, this would mean referring the patient to a stress cardiocardiography test or stress-rest myocardial perfusion scintigraphy. Would further treatment have a different course? Due to the higher sensitivity, functional imaging would reveal a significant coronary disease and the patient would be referred to ICA. Earlier publications indicate high sensitivity of both stress ECG test and myocardial perfusion imaging in patients with angiographically verified left main stenosis above 50%. In a study of 57 patients with left main stenosis who underwent a stress ECG test according to the Bruce protocol, only 4% of the tests were negative and 9% were non-conclusive. In 91% of patients, the test was stoped before reaching the level IV, the achieved HR was 76 +/- 2% predicted and achieved double product of 20490 +/- 830. Our patient had significantly better test scores compared to the results of this cohort, which calls into question the clinical significance of the putative initially stable atherosclerotic plaque. What distinguishes the patients in this series from ours is the degree of anatomical prevalence of CAD: only 2% had left main lesion as the only one, 32% two vessel and 61% three vessel disease[23]. In a study of 101 patients with angiographically significant left main stenosis without previous infarction or myocardial revascularization who underwent SPECT myocardial perfusion imaging in 13% visually and 15% quantitatively there were no significant perfusion defects larger than 5% of the left ventricular myocardium. 56% of patients visually and 59% by quantitative analysis of scans had a high-risk scan (perfusion defect over 10% of left ventricular myocardium). By including nonperfusion variables, primarily transient ischemic dilatation of the left ventricle, it was obtained that 83% of patients with angiographically significant left main stenosis had a high-risk scan. This method, in the conclusion of the researchers, identifies most patients with angiographi-

cally significant stenosis of the left main coronary artery as high-risk[24]. This method could therefore be of great importance in assessing the functional significance of patients with a potential lesion of the left main coronary artery, especially in patients whose ECG stress test is undiagnostic: resting ECG changes or poor functional capacity of patients. Acute coronary syndrome with dramatically difficult clinical presentation in our patient probably occurred in the field of destabilization of previously angiographically insignificant atherosclerotic plaque. Reviews of patients with a similar clinical scenario have been published - a patient with a negative ECG stress test and achieved functional capacity of 12.1 MET is presented two months after the test as anterior STEMI and two-vessel CAD with occlusion of the proximal LAD[25]. It has been shown that the long-term prognosis of patients with angiographically nonsignificant stenosis of the left main coronary artery is worse than patients with normal findings based on the CONFIRM register of 5166 patients, 18% of whom had insignificant left main disease (diameter stenosis below 50%). Multivariate analysis concluded that nonsignificant left main stenosis was a predictor of cumulative adverse events (death, myocardial infarction, and revascularization) over a 5-year follow-up period in women (HR 1.78, $p<0.005$) but not in men (0.98, $p=0.806$)[26].

Conclusion

The diagnostic algorithm for patients with chest pain is based on a pretest probability that determines further diagnostic workup. Patients with a negative exercise test and a typical clinical presentation should be referred for further diagnostic imaging test because of the risk that a small number of them may .have significant and even critical coronary stnosis.

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Sažetak

Akutni koronarni sindrom udružen sa okluzijom glavnog stabla leve koronarne arterije kod bolesnika sa prethodno negativnim nalazom stres elektrokardiografskog testa

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Cilj rada. *Prikaz slučaja bolesnika sa akutnim koronarnim sindromom sa okluzijom glavnog stabla leve koronarne arterije sa tipičnom kliničkom slikom i negativnim nalazom testa fizičkog opterećenja.*

Prikaz slučaja. *Pacijent starosti 44 godine prezentuje se našoj službi kao STEMI sa ST segment elevacijom u inferiornim i ST depresijom u prekordijalnim odvodima. Nakon intrahospitalnog srčanog zastoja i sprovedene reanimacije uradi se primarna PCI glavnog stabla leve koronarne arterije nakon čega dolazi do hemodinamske stabilizacije. Retrospektivnom analizom u medicinsku dokumentaciju saznaje se da je tri godine pre akutnog događaja evaluiran zbog povremenih bolova u grudima. Pretest verovatnoća za KB iznosila je 38% pa je u skladu sa tada važećim ESC smernicama za stabilnu koronarnu bolest urađen stres EKG test koji je ocenjen kao negativan za značajnu koronarnu bolest. Svi analizirani parametri testa ukazivali su na nizak rizik od neželjenih kardiovaskularnih događaja: funkcionalni kapacitet, ST segment denivelacija, hronotropna kompetentnost, varijacije krvnog pritiska, Duke treadmill skor. Sa postest verovatnoćom od 9% pacijent nije dalje evaluiran u pravcu koronarne bolesti i naredne tri godine je bio asimptomatski i nije se javljao na kontrolne preglede. Da se prezentovao nakon 2019. godine po novijim ESC smernicama za hronične koronarne sindrome kod pacijenta bi u trenutku incijalne kliničke evaluacije bilo indikovano uraditi funkcionalni imaging test ili CT koronarnu angiografiju.*

Zaključak *Dijagnostički algoritam za pacijente sa bolom u grudima baziran je na pretest verovatnoći koja opredeljuje dalji dijagnostički tok. Pacijente sa negativnim testom fizičkog opterećenja a tipičnom kliničkom prezentacijom trebalo bi uputiti na dalju dijagnostičku imaging obradu zbog rizika da mali broj njih može imati i značajnu i čak kritičnu koronarnu bolest.*

Ključne reči: pretest verovatnoća, koronarna bolest, EKG stres test, neželjeni kardiovaskularni događaji

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Case report

Pacemaker lead disposition in an elderly patient - Reel syndrome

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Abstract We present the case of an adult patient with Reel syndrome who had a VVI-mode permanent pacemaker implanted 6 months earlier. X-ray revealed the retraction and winding of the right ventricle chamber electrode around the pulse generator. Subsequently, a new electrode was re-implanted in the right ventricle apex.

Kew words Reel syndrome, pacemaker

Introduction

Reel syndrome is an infrequent case of pacemaker dysfunction due to dislocation of the atrial/ventricular or both leads. The cause is the movement of the pulse generator along its long axis in the patient's subcutaneous pocket. This leads to the detachment of the electrode from the point of fixation and subsequent dislocation, retraction and winding of the electrode around the device. It is most often observed in adult patients with cognitive impairment. For the first time, a similar condition (Twiddler Syndrome) was described by Bayliss and Collegium in 1968 as a post-implantation implant of a permanent pacemaker [1], and subsequently reported for implantable cardioverter defibrillators (ICDs)[2], and cardiac resynchronization devices. (CRT) [3].

Case presentation

A 85-year-old man, admitted to the cardiology department in September 2019 due to chest pain and multiple syncopes. Patient had medical history of hypertension and dyslipidemia. The patent was in an impaired general condition, with evidence of cervical venous congestion, lack of breathing in the left thoracic half, and bradycardia. The ECG showed a complete AV block with a heart rate of 80 bpm (class I A indication for implantation of an anti-bradycardia device). Echocardiographic evaluation revealed a reduced ejection fraction and dilated Vena Cava inferior.

Following implantation of a temporary pacemaker, selective coronary angiography was performed, which revealed a two-vessel coronary artery disease - critical LAD stenosis, which was resolved by implantation of a single drug-eluting stent and chronic occlusion of the RCA, with collaterals from LAD. Subsequently, under a local anesthesia, in the left subclavian area, a single-chamber, permanent VVI pacemaker was implanted, with RV-lead with active fixation (Figure 1). After optimizing the drug therapy, the patient was discharged with and with 100% paced rhythm.

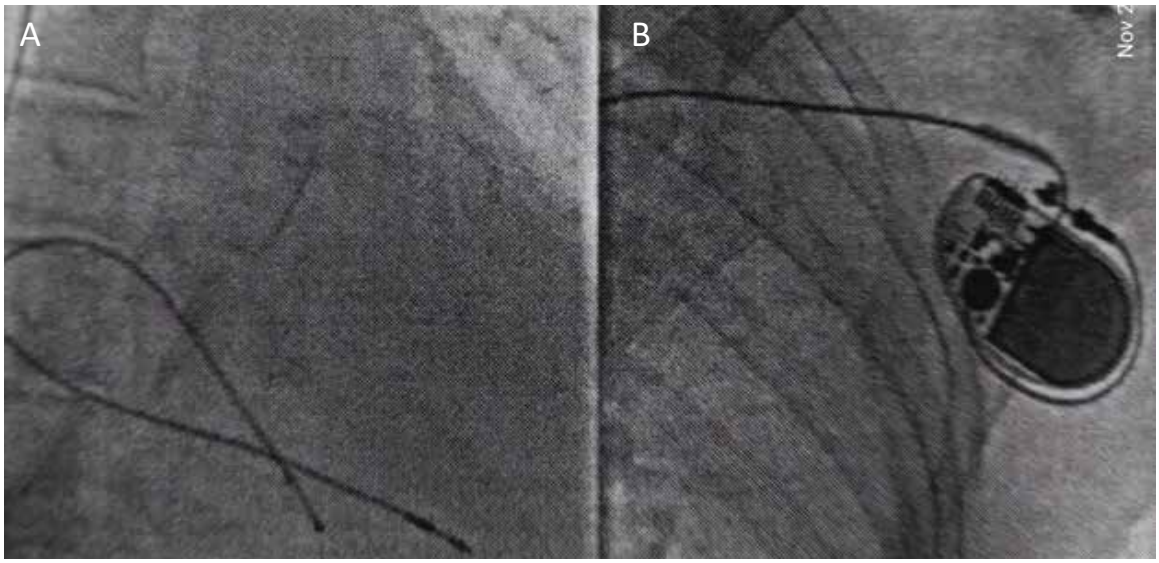

Figure 1. (A) Electrode from temporary PM and lead from VVI in RV and the pulse generator, (B) after the PM implantation

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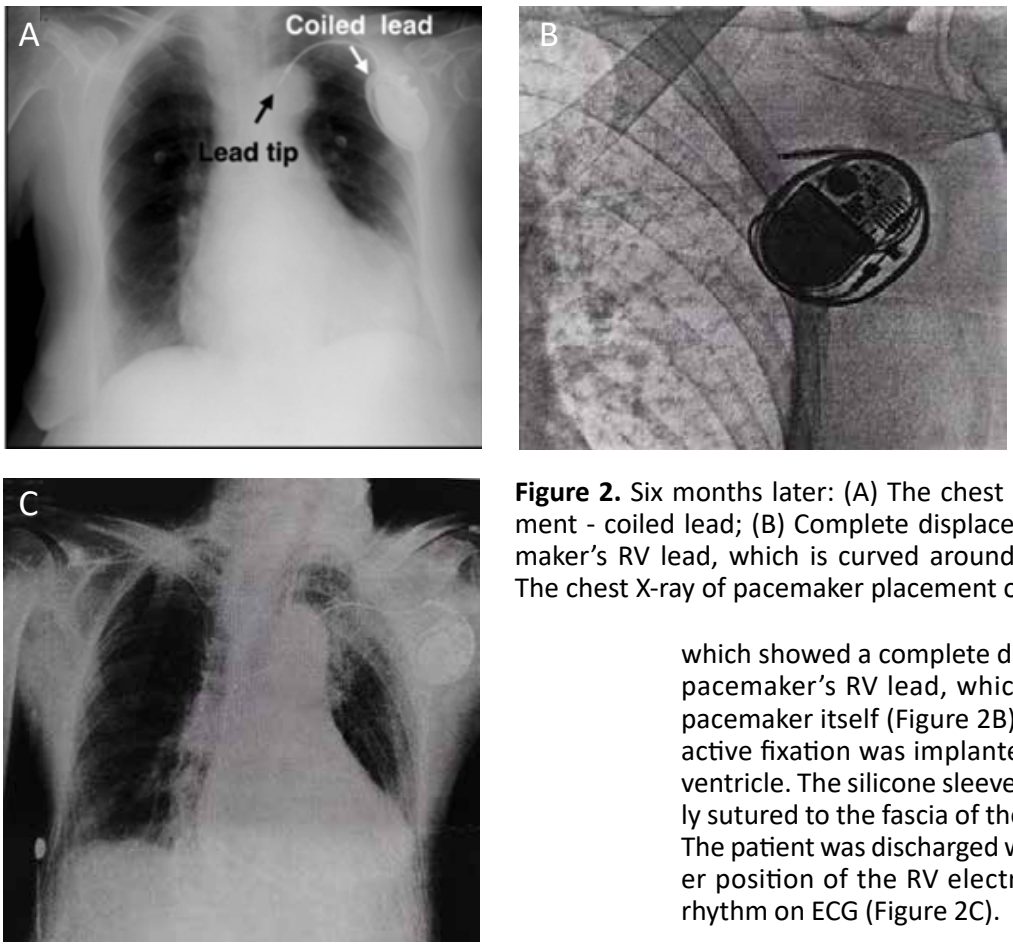


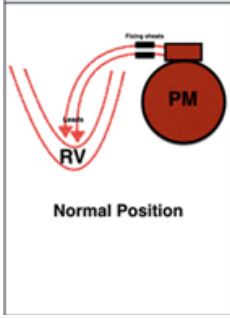
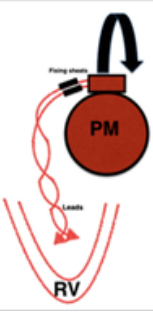
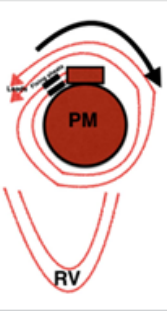
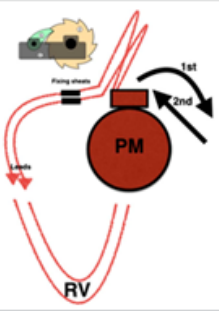
Figure 2. Six months later: (A) The chest X-ray of pacemaker placement - coiled lead; (B) Complete displacement of permanent pacemaker's RV lead, which is curved around the pacemaker itself; (C) The chest X-ray of pacemaker placement on discharge from hospital

Six months later, during an admission to the urology department for hematuria, the patient felt a general malaise and difficulty in speech, according to relatives. After an ECG and consultation with a cardiologist on duty, he was referred to the clinic with suspected dysfunction of the pacemaker. The ECG performed registered a complete AV block. Following implantation of a temporary pacemaker, a chest x-ray (Figure 2A) was performed, which showed a complete displacement of permanent pacemaker's RV lead, which was curved around the pacemaker itself (Figure 2B). A new RV electrode with active fixation was implanted in the apex of the right ventricle. The silicone sleeve of the electrode was firmly sutured to the fascia of the thoracic muscle.
The patient was discharged with an x-ray showing proper position of the RV electrode and with pacemaker rhythm on ECG (Figure 2C).

Discussion

Reel Syndrome [Table 1, Figure 3C] is rare condition and is seen in elderly patients with cognitive obese patients, women, and children which mostly occurs during the first year after implantation. It is characterized by the unintentional rotation of the pulse generator along its sagital axis by the patient, which leads to retraction and winding of the electrode around the pacemaker, causing

Table 1

	Twiddler	Reel	Ratchet
Mechanism	Rotation on its long axis	Rotation on its transverse axis	Retraction with ratcheting of the lead
Consequences on Leads	Damage can occur	No damage	No damage
X-Ray	Tangling of leads	Leads coiled around the generator	Leads retracted without coiling
Occurrence	Within a year	Within a month	Within a month
			

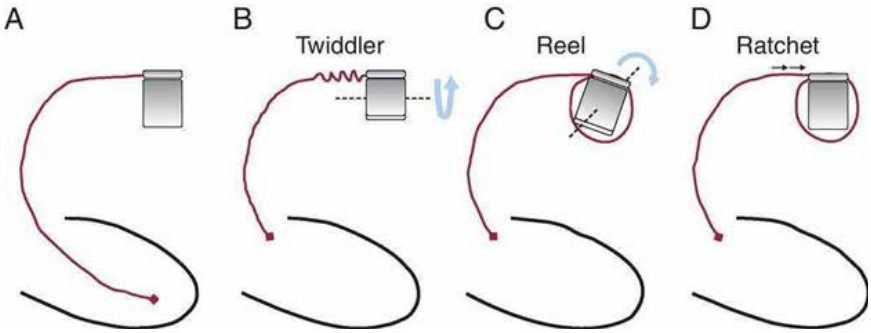


Figure 3. Presentation of lead dysposition

the dysfunction of the device. The reason is the unintentional manipulation of the device in the subcutaneous pocket.

Two other similar conditions have been described - Twlddler [Table 1, Figure 3B] and Ratchet [Table 1, Figure 3D] syndrome with a similar etiology (4,5). The first one has a rotation of the pulse generator along its long axis with retraction and twisting of the electrodes similar to a spiral, which can damage them. Ratchet syndrome is characterized by the fact that patient manipulates the pacemaker in a clockwise and anticlockwise direction, thus like a ratchet mechanism, retracts and locks the electrode without disposition of the pacemaker.

The first choice method in diagnostic work-up for specifying dysfunction of a permanent pacemaker is to perform a chest X-ray. Another option is through a pacemaker programming device. These conditions can also be observed with implantable cardioverter defibrillators (ICD), and resynchronization devices (CRT-D / P). Complications of these dysfunctions can lead to syncope with subsequent trauma or life-threatening tachyarrhythmias.

There are various countermeasures, such as re-tightening the loose attachments, affixing the pacemaker to the underlying fascia , and deep brain stimulation (for dystonia). However, there are not many reports that focus on countermeasures. Although there are many reports of the pacemaker being attached under the fascia, this method does not guarantee a solution every time .

Patient education, use of a smaller subcutaneous pocket, and suturing of the pulse generator to surrounding tissues would lead to a decrease in the frequency of displacement syndromes in susceptible patients. Frequent check-ups and patient monitoring should not be underestimated.

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Sažetak

Dispozicija odvoda pejsmejkera kod starijig pacijenta - Reel sindrom

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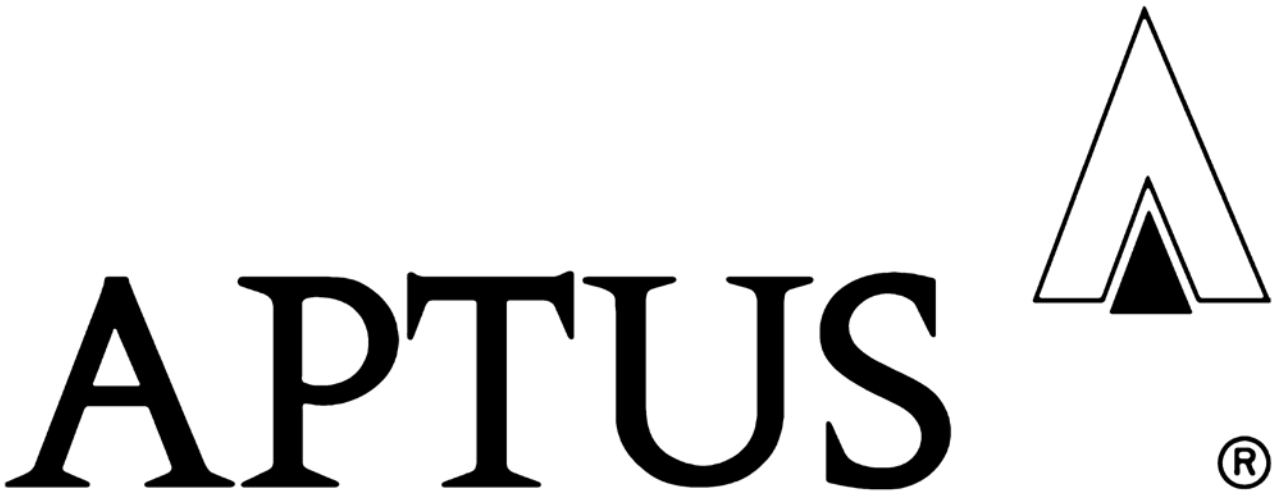
Predstavljamo slučaj odraslog pacijenta sa Reel sindromom kome je implantiran VVI stalni pejsmejker 6 meseci ranije. Rendgen grudnog koša je pokazao retrakciju i uvijanje electrode za desnu komoru oko generatora, koja je rešena ponovnim postavljanjem nove electrode u vrh desne komore.

Ključne reči: Reel sindrom, VVI pejsmejker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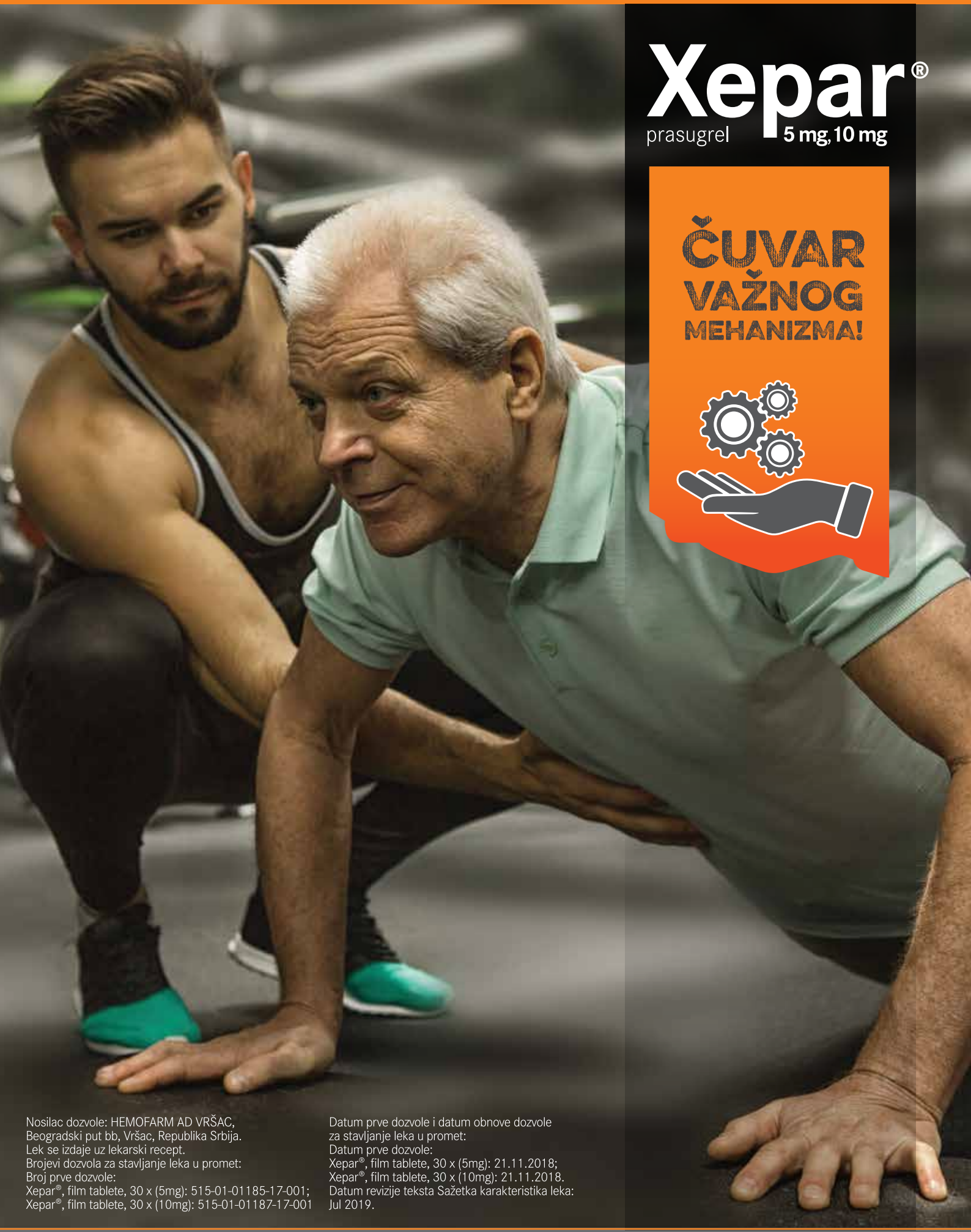

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