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# Acute Coronary Syndromes in Women - Gender Specific Changes in Coronarography

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## 1. Introduction

Cardiovascular diseases (CVD) are one of the leading cause of mortality in both men and women in the world. According to a WHO report, about 55% of deaths in European women are related to CVD, including 23% caused by coronary artery disease (CAD) and 18% due to stroke. Conversely, in men, CVD is the cause of 43% of deaths, including CAD (21%) and stroke (11%). These statistics are alarming – in Europe, one woman dies of CVD every 6 minutes.

In respect of above data is very important to perform randomized clinical trials with women treated for acute coronary syndromes (ACS). This operation was initiated relatively not long ago. In the past 40 years, the attention of cardiologists regarding the treatment of coronary artery disease (CAD) has been focused mainly on the group of male patients, markedly less on the female population.

In the meantime, to the best of our knowledge, despite of apparent similarity of ACS clinical course in men and women, differences in the pathophysiological mechanisms, prevalence and profile of risk factors, angiographic changes, kind of treatment and prognosis are found. These observations are particularly important up against constantly rising cardiovascular morbidity and mortality among women.

## 2. Comparison of clinical course in women and men treated from ACS

### 2.1 Coronary risk factors in female and male

Acute coronary syndromes in women are the real challenge for clinical and invasive cardiologists. The ACS diagnosis and therapy in female are more difficult than in male. It is connected with ACS women older age, major coronary risk factors number, differences in pathophysiology and clinical course and complication during procedures. The coronary risk factors in women and men are the same, but their influence on female, especially during menopause is different than in male. This effect results from female specific hormone constellation during menopausal period. Generally, in ACS women population, the coronary risk factors are more often found than in ACS male group and this is the inverse phenomenon compared to population without myocardial infarction.

In majority of currently ACS registries these observations were affirmed. According to data from Polish ACS Registry (26035 patients with ACS STEMI hospitalized between 2005-2006; 8989 (34,5%) females) women were older than men by 7.7 years on average and this was statistically significant. In women, the well established risk factors were significantly more

prevalent than in men: hypertension: 67,0% vs 56,1%, diabetes: 28% vs 16,6%, obesity: 23,7% vs 13,4% ( $p < 0,001$  for all groups). Only the prevalence of hypercholesterolemia was similar in both sexes and smoking was less often in female.

Analysis of Swedish registry: ACS-AMIS Plus Registry evaluated over 20- thousands ACS population (28% female) hospitalized between 1997-2006 also showed older women age by 7,5 years on average and more often presence of hypertension and diabetes in women.

Similar observation can be run into worldwide registries.

According to data from Chinese ACS Registry (CRACE) – 1301 ACS patients, 24,4% women treated from 2001 to 2004, female subjects were also significant older than male patients (67.23 years vs 61.80 years,  $P < 0.0001$ ). The incidence of diabetes mellitus and hypertension in the female group was higher than in male group (30.8% vs 18.6%,  $p < 0.0001$  and 66.4% vs 56.8%,  $p = 0.001$  respectively), conversely, the incidence of smoking was less in female group than men group (6,6% vs 66,2%,  $p < 0,001$ ).

Longstanding observation of female and male population hospitalized from ACS in USA in years 1997-2006 demonstrated significantly frequent prevalence of hypertension, diabetes mellitus, heart failure and cerebrovascular diseases in women from all aging categories.

Beside of greater number of risk factors in women than in men, stronger impact some of them to woman organism is again and again suspected. First of all, this finding affects smoking. The risk of acute coronary syndrome in smoking women is about six fold higher compared to no- smoking female, whereas in smoking men only three fold risk increase is observed. The cause of this effect is probably adverse influence nicotine for hormonal profile in women. It is proved that smoking women have lower estrogen level.

The similar observation regard impact of diabetes for ACS risk in female. The prevalence of diabetes frequently correlates with acute coronary syndromes in women than in men.

The next differences are connected with lipid profile. Stronger prognostic impact of higher LDL level in men is indicated, whereas in women the big importance of low HDL level is emphasized. Low HDL-C levels in women have been shown to be a risk factor for CHD and premature atherosclerosis independent of serum LDL-C and triglyceride levels. In female with established coronary disease, low HDL-C levels may be a better predictor of subsequent coronary events than high levels of LDL-C. The Nurses' Health Study estimates that a 17 mg/dL elevation in HDL-C reduces the risk of CHD development in postmenopausal women by approximately 40%. Generally, the risk of CHD decreases by 3% for every 1 mg/dL increase in HDL-C in women, but only by 2% in men. Similarly, the presence of diabetes tends to confer a more negative effect on HDL-C and triglycerides (TG) in diabetic women compared to men.

Angiographic and ultrasound evidence demonstrate that low plasma levels of HDL-C are associated with major severity of CHD in females and males, as indicated by an increase in the number and extent of coronary vessel involvement. Furthermore, among men and women with angiographic evidence of CHD but with normal total cholesterol levels, patients with HDL-C levels  $< 35$  mg/dL had significantly more cardiovascular events than those with higher levels. Then, the correlation between lipid profile in female and male are complicated. The further observations are necessary to confirm these interdependences.

## **2.2 Clinical characteristic of acute coronary syndrome process in women and men**

Studies compared ACS clinical symptoms in women and men demonstrate different results. According to part of them myocardial infarction clinical course is similar in female and male. In contrast, other observations convince of significant differences in ACS gender manifestation.

Myocardial infarction symptoms in men are usually typical: strong retrosternal pain with typical radiation, without reaction or with transient abating after nitroglycerin usage.

Women with acute coronary syndrome more often complain for atypical disorders: back pain, neck pain, nausea or vomiting, dyspnea, palpitation or strong weakness. In women more often indolent myocardial infarction course was also affirmed.

The interesting meta-analytic evaluation of ACS gender differences confirmed these observations. Review of articles and dissertation from 1966 to 2007 demonstrated that above gender differences of moderate or larger magnitude were evident and women were more likely than men to report non-specific symptoms. For most symptoms, the magnitude of effects did not vary across different symptom-assessment strategies.

Additionally, majority contemporary studies showed that ACS women were admitted to hospital later than ACS men and, this fact also suggests more often presence atypical complains in female.

Data from Polish ACS Registry (over 20 thousands ACS women) demonstrated that women especially during the first 3 hours from symptom onset, presented to hospital significantly less often and that the delay of > 12 hours occurred more often in this patients.

Likewise, Swedish ACS Registry showed that female patients came to hospital later than men- median difference 60 minut. The delay on admission with atypical ACS symptoms in women may cause worse effect of therapy.

The five month analysis over 6 thousands group of consecutive patients presenting with ACS showed that patients with atypical presentation were significantly less likely to receive evidence-based therapy and coronary angiography and suffered worse in-hospital outcomes. After adjustment for confounders, the absence of typical chest pain was associated with higher mortality rate (odds ratio 2.0, 95% confidence intervals 1.29-2.75).

On the other hand women even though presenting the typical ACS symptoms, often are treated worse than men. First of all, to this time, myocardial infarction is perceived as "male disease". Female and doctors often ignore important disorders, in contrast, paradoxically, typical symptoms are the strongest ACS predictors in women. Chest pain has consistently been underestimated in women because of the disappointing results of evaluations of this symptom in the past.

In women, more often than in men, despite the clinical and biochemical ACS characteristic, changes in coronary angiography aren't found. In the CASS (Coronary Artery Surgery Study), 30% of women with typical angina and 64% with atypical angina had normal coronary angiograms, but this was observed in only 7% and 34% of men, respectively.

Syndrome X, which was defined as symptoms and signs of myocardial ischemia in the presence normal coronary angiograms, predominates in women, but this syndrome may represent microvascular disease or endothelial dysfunction, which are more often observed in women.

Recently, data from WISE (Women's Ischemia Syndrome Evaluation) and WTH (Women Take Heart) studies demonstrated, that rates of cardiovascular events were highest for symptomatic women with nonobstructive coronary artery disease compared to symptomatic women with normal coronary arteries; on the other hand, symptomatic women with normal coronary arteries had almost three-fold higher rates of events when compared to asymptomatic women. These facts suggest that in women, as in men, chest pain compatible with angina deserves careful evaluation.

The following observations of ACS clinical course in women demonstrate worse clinical presentation on admission. It is probably a consequence of older female age and more risk factors.

Analysis of contemporary European and American ACS Registries confirm higher frequency of heart failure in Killip-Kimball class III-IV in female compared with male.

Presumably atypical ACS symptoms, delay from onset pain to admission and worse clinical presentation on admission contribute to still emphasized less often women qualifications to invasive procedures. According to Polish ACS Registry primary PCI was performed in 47,8% women and 57,4% men ( $p < 0,001$ ).

In Swedish AMIS Plus Registry reperfusion strategy was used in 27,2% women and 36,6 % men ( $p < 0,001$ ).

Data from in the American College of Cardiology–National Cardiovascular Data Registry also showed lower utilization rates of emergent PCI for women than for men across all ethnic subsets.

The next problem, mentioned above, is specific coronary angiography changes in women presenting ACS. The reasons for more often presence of normal coronary arteries or non critical narrows in coronary artery angiography performed in ACS women are unclear. The mostly accepted conception is phenomenon of atherosclerotic plaque erosion with thrombus formed on apparently undamaged artery wall. These findings were obtained on the basis postmortem examinations patients died from ACS - in 37% women the surface plaque damage without significant coronary artery injury was demonstrated.

Other studies with widely intravascular technique (IVUS) usage showed in women without significant changes in coronary angiograms a presence of atherosclerotic process in ACS responsible arteries.

Additionally, female and male unstable angina consecutive studies demonstrated qualitative and quantitative gender differences between morphology of atherosclerotic plaques. Women atherosclerotic plaques indicated lower optical density and less expressed calcification than men plaques.

However, presently there are the disagreements in reports estimated atherosclerotic plaques morphology. The contemporary analysis of plaque components in 362 ACS patients (254 men, 108 women) showed no differences between female and male atherosclerotic plaques. In this study more often occurrence of diabetes and high hsCRP level in ACS women than men was emphasized and with these factors more female plaques instability was related.

These contradictions in studies, order to searching another reasons of specific coronary changes in women.

The next conception posits the differences in plaque reaction for response to hormonal factors and thrombogenic stimulation.

According to epidemiological data the protective role of endogenic estrogens in young women is widely known. It is directly connected with impact of these hormones to coagulation system.

In young, premenopausal women the lower fibrinogen and VII coagulation factor's level was affirmed. Women in each age with family premature coronary diseases review, demonstrate excessive platelet aggregation. Following the excessive thrombocytes aggregation in these patients the bigger number of fibrinogen molecules are indicated - perhaps invisible during coronary angiography atherosclerotic changes undergoing action of stronger prothrombic factors in some women.

Moreover, in connection with higher prothrombic inclination, probably we can more often observe a distal microvessels embolisation effect imperceptible during routine coronary angiography. Therefore, the differences in coronary angiography changes between female and male could be more complicated than earlier suspected.

### **3. Specific ACS coronary angiography changes in women during pregnancy and postpartum period**

#### **3.1 Epidemiology of acute coronary syndromes during pregnancy and postpartum period**

Myocardial infarction in pregnant women is an extremely rare event. The frequency of ACS in this period is difficult to estimate. According to the scarce epidemiological studies, in the United States the incidence of AMI in pregnancy ranges from 2.81 to 6.22 cases per 100,000 deliveries. No data are available for Europe or other countries. In addition, these studies do not differentiate between AMI with and without ST-segment elevation.

Currently we can observe increased frequency of acute coronary syndromes during pregnancy or postpartum period. This effect is probably connected with old age of pregnant women, and, generally increasing morbidity of coronary diseases among young women.

Presently, women at first more often give the time for professional career, holding off maternity for later years of life. In the meantime, the risk of complication during pregnancy significantly increased with aging – it is emphasized, that myocardial infarction during pregnancy usually occurs in pregnant women after 33 years old.

The analysis of literature demonstrated, that in older pregnant, multiparas, more often the typical, atherosclerotic substrate of acute coronary syndrome was indicated. Majority of them have occurred in III pregnancy trimester.

However, in younger mothers, primiparas, the ACS pathogenesis is often atypical with often occurrence's during postpartum period.

#### **3.2 Hemodynamic, hormonal and biochemical transitions during pregnancy affecting to cardiovascular system**

Pregnancy isn't termed as coronary risk factor, although in this period a lot of changes in circulatory system, hormonal and coagulation parameters transformations are demonstrated. During pregnancy the increase of ejection volume and acceleration of cardiac activity is indicated. Both changes cause growth of oxygen cardiac muscle demand.

Additionally, the physiological anemia and decrease of systolic and diastolic pressure contribute for limitation in oxygen delivery to cardiac muscle's cells.

Moreover, increase of volume blood circulating and ejection fraction causes intensification of the shearing forces action for big arteries walls –these effects can provoke coronary arteries dissection.

Hormonal changes during pregnancy relies on increased progesterone production leading of impairment vascular wall through losing of normal elastic fibers structure, reticuline fibers fragmentation and decrease of acid mucopolisacharides. These effects also aggravate the risk of arteries dissection.

Changes in coagulation system during pregnancy are connected with increment of fibrinogen and factors VII, VIII, IX, X, XII and von Willebrand factor's concentration. In result of increase concentration of inhibitors of plasminogen activator PAI-1 and PAI-2, the serum fibrinolytic activity is decreased. It caused hipercoagulation state, which worsening during delivery when the great of PAI- 1 amount is released from placenta.

The essence above changes is often occurrence atypical ACS patophysiology during pregnancy and postpartum period.

### **3.3 Coronary angiography changes during acute coronary syndromes in pregnancy based on pathophysiological substrate**

According to current reports, the most often cause of acute coronary syndrome in pregnant women, similarly to overall population, is sudden atherosclerotic rupture. Atherosclerotic changes was indicated in 40% pregnant women, in majority ACS symptoms occurred in antepartum period (54%).

According to mentioned above high ACS risk in older pregnant women, in these population the higher number of coronary risk factors is indicated.

The myocardial infarction risk during pregnancy rises 2,4 fold in women with hypertension, 4,9 fold in smoking and 6,9 fold in diabetics.

Idiopathic coronary artery dissection rarely appears in general population, whereas during pregnancy, the frequency of this effect may approximate even 27%. Usually it is observed in peripartum (50%) or postpartum (34%) period – in connection with described earlier changes in arteries walls construction and hemodynamic disorders. Some of authors suggest that coronary artery dissection in pregnant women is even more often, though the artery wall undergoes essential healing and if the coronary angiography is performed after acute ACS phase, the image of angiogram may be correct. Relatively often, the coronary dissection in these women is found in more than one artery. It suggests existence of generalized arteries pathology.

Another possible pathophysiological cause of acute coronary syndrome in pregnant women is angiospasm. The recognition of coronary artery spasm as the reason of myocardial infarction is difficult, because the angiospasm may be transient with quick idiopathic return of normal coronary flow.

In Roth's analysis coronary spasm only in 2% women was documented and only during antepartum period. Nonetheless in 13 % these patients angiograms were normal, perhaps in part of them the angiospasm occurred before the procedure had been performed.

Normal coronary angiogram occurs in equal proportion during all pregnancy periods. The potential reason of acute coronary syndrome in women without significant angiographic changes beside of healing dissection or transient angiospasm may be thrombus or embolus, which were resolved.

In 8% women the cause of myocardial infarction was exactly thrombus. It can be connected with mentioned above tend to hipercoagulation state.

Angiography changes are usually localized in only one of coronary artery, extremely rarely we can find multivessel disease in pregnancy. The single case of multivessel atherosclerotic changes in 41- years old postpartum woman come from own observation. In the literature we can meet also single multivessel dissection description.

### **3.4 Coronary interventions during pregnancy**

Currently, the most effective therapy of acute coronary syndrome's is primary coronary intervention. This procedure during pregnancy is connected with dangerous fetus exposure to radiation. It can cause genetic disorders, height inhibition, different malformations.

Bithell and Stuart demonstrated that children exposed to radiation during fetal life are characterized major cancer development risk. The dose of radiation until 1 rad is considered as no dangerous for fetus. This doses is simultaneously enough to performed diagnostic and therapeutic procedures.

However, in case of complications, longer radiation time may be necessary- exposition time may rises above 5 rads. Because of lack of unequivocal directions, in this situation, the pregnancy termination could be imperative.

To the maximum security, usage of leaden protection for stomach, pelvis and lumbo-sacral region is recommended.

According to data from literature, 55-89% women undergoing coronary angiography have received stents. During pregnancy we don't possess certain data relevant to safety usage drug eluting stents, the bare metal stents in this situation are rather recommended.

The great doubts are connected with coronary angioplasty during coronary artery dissection as a cause of acute coronary syndrome. According to European- American Guidelines from 2003 year, PCI is recommended in this situation. Nonetheless, numerous reports demonstrate that in case of stable patient state, the conservative treatment is also effective and in postpartum period the idiopathic healing is noticed.

On the other hand, Roth indicate that during coronary angiography the risk of iatrogenic coronary artery dissection is increased, that's why particular caution in qualification for invasive procedures in this period should be recommended.

The reports concern of possible complications of invasive treatment during pregnancy are very rare. The single cases of contrapulsation aortic balloon usage during complications of extensive anterior wall myocardial infarction were described.

Similarly, our knowledge about remote results of acute coronary syndromes invasive treatment in pregnant women is poor, but at present, this is a method from choice.

Coronary artery bypass grafting (CABG) is the procedure performed extremely rarely during pregnancy.

According to James's et al. analysis, CABG was done in 51 pregnancy women (6% analyzed group), but pregnancy period and results of the treatment data weren't released.

Another analysis by Roth and Elkayam 5 women underwent CABG during antepartum period. One of them died after 3 months and after delivery ( healthy child was born), in the second pregnant the fetal death in utero came up.

The most often direction of CABG is ineffectiveness or complications after PCI. During surgery the fetal monitoring is necessary, because hypothermia and extracorporeal circulation can cause fetal arrhythmias.

The single reports about CABG in women during pregnancy suggest, that these procedures are connected with high risk for mother and child.

#### **4. The valuation of coronary arteries in menopausal women treated for acute coronary syndromes**

##### **4.1 Impact of pathophysiological transformations during menopause on coronary risk**

Menopause is considered as a single, strong coronary risk factor. In this period in woman organism multidirectional changes are achieved. These transformations concern of lipid profile (increase of LDL, TGL, apolipoprotein B, apolipoprotein (a) level; decrease HDL and apolipoprotein AI level), coagulation factors production (significant increase of fibrinogen level, increase of factor VII, antithrombin III and inhibitor tissue activator of plasminogen (PAI-1) activity), insulinoreistance's and abdomen's obesity development. Disadvantageous is also impact of menopause for endothelium function.

Though the current understanding of the role of menopause in cardiovascular diseases (CVD) is controversial, studies suggest that menopause does not exacerbate CVD independent of aging, and hormone replacement therapy is not effective for secondary prevention of CVD.

According to long-term 16 years observation over 11 thousands Italian population, menopause wasn't found an independent cardiovascular risk factor.

Despite above divergences, there is a fact, that cardiovascular women morbidity significantly rises during menopausal period.

Inhibition of estradiol distribution during menopause constitutes of biological challenge for woman organism, especially for women aggravated other circulatory risk factors. The next years after menopause, on account of lack of estrogen coordinated in numerous metabolic transformations, are characterized intensification of existing diseases and another exposure. We can suspect that required of adaptation a new metabolic balance causes worse process and prognosis in menopausal women with coronary artery diseases.

Presently, more often the differences in artery stiffness in female and male are emphasized. The genders differ in large artery biomechanical properties throughout the lifespan with females displaying higher stiffness than males during the prepubertal years and a dramatic increase after menopause. Males on the other hand experience an increase in arterial stiffness postpuberty and a linear increase thereafter, suggesting that females have intrinsically stiffer large arteries than males, but that such effects are mitigated by sex steroids during the reproductive years. These factors may contribute in part to the observed gender differences in the pathophysiology and clinical manifestations of cardiovascular disease.

On the other hands, hormonal replacement therapy (HRT) usage to decreased of circulatory diseases risk in menopausal women is presently not recommended.

#### **4.2 Influence of hormonal replacement therapy on coronary artery state**

Reports relevant HRT are controversial. Until 1988 year, the knowledge about benefit effects of hormonal replacement therapy was based on only retrospective studies. Metaanalyses demonstrated 30-40% decreased of coronary disease's risk mostly in women received conjugated estrogens (less often together with progestagens) and particularly good effects was observed in women with earlier recognized coronary disease.

In 1998 year, the results of the first randomize, multicenter study- HERS were published. In this study the HRT effect in secondary prevention was assessed. In years 2002 and 2004 the next study results were presented- WHI I and WHI II- evaluated HRT implementation in primary prevention. In these studies the unambiguous evidences affirmed HRT benefits in circulatory diseases were expected. Adverse results were a big shock. The more amount of cardiovascular events in the first year of therapy, more numerous thromboembolic events and more often breast cancer were documented.

From this time, the American Heart Association and European Cardiac Society recommended not initiating and no continuing hormonal replacement therapy in circulatory system diseases prevention. Repeated analysis of mentioned above studies demonstrated, that the important point is the period of HRT inclusion. It is suspected that earlier usage of HRT, in the beginning of menopause is probably more favourable than in later years. This effect is connected with HRT impact for not yet damaged endothelium.

The therapy inception in the later years can favour of impairment's of coagulation and inflammation mechanisms and in consequence's can be responsible for thromboembolic complications and instability of atherosclerotic plaque.

The greatest thromboembolic disorders risk was indicated in the first year of HRT therapy, particularly during oral treatment, because of first liver passage effect, which caused thrombotic processes stimulation. Transdermal estrogens, deprived of first passage effect, don't affect also for increased of CRP, fibrinogen and prothrombin level.

The results of Danish observation study (700 thousands healthy women) affirmed the beneficial effect of transdermal estrogens for cardiovascular system with myocardial infarction reduction and without the increased thromboembolic risk.

Despite of optimistic reports, currently still doesn't exist evidence that hormonal replacement therapy improve of survival and doesn't indicate of side effects. Therefore, HRT indications still contain only clinical menopausal symptoms, not cardiovascular prevention.

### **4.3 Coronary artery changes in menopausal women treated from acute coronary syndromes**

To this time, there are very little studies estimated the specific coronary angiography changes in menopausal women. One of sparse comparative analysis concerned assessment of these changes in pre- and postmenopausal women demonstrated more frequent involvement of triple vessels in postmenopausal CAD patients (33.8% vs 20.4%,  $p=0$ ), and single vessel in premenopausal (43,2 % vs 26,9%,  $p=0$ ) which indicated more serious CAD in postmenopausal patients. There was no significant difference in left main and double vessels involvement in the two groups.

In postmenopausal group more lesion of middle left anterior descending (LAD), left circumflex artery (LCX) and right coronary artery (RCA) were found (all  $p$  value  $<0.05$ ) compared to much more severe lesions ( $\geq 90\%$ ) at left main (2.9% vs 1.1%,  $p=0.048$ ) and proximal LAD (28.2% vs 16.6%,  $p=0$ ) in the premenopausal CAD group.

As for lesion length, there were more local lesions at the posterior descending artery (PDA) (6.4% vs 2.5%,  $P=0.014$ ), diffuse lesion at diagonal 1 (7.1% vs 3.6%  $P=0.036$ ), middle and distal RCA (13.5% vs 8.6%,  $P=0.033$ ; 5.8% vs 2.1%,  $P=0.014$ ) in the postmenopausal CAD group. But tubular lesion seemed to be located more at middle and distal LAD (19.6% vs 9.0%,  $P=0$ ; 12.1% vs 7.9%,  $P=0.036$ ) in the premenopausal CAD group.

Other items with regard to lesion length were comparable without a significant difference between the two groups.

Probably, above observation confirm the different dynamism of atherosclerotic processes, connected with hormonal state. Additionally in mentioned study, in both of groups: pre- and postmenopausal women, the significant more often prevalence of prior myocardial infarction, hypertension, diabetes mellitus and dyslipidemia in CAD women compared to non CAD patients was documented. Furthermore, the frequency of coronary risk factors was higher in CAD postmenopausal group compared to premenopausal CAD women. Then, the high number of coronary risk factors in women probably correlates with more often multivessel coronary atherosclerotic changes.

## **5. Comparison of efficacy percutaneous coronary interventions and coronary artery bypass grafts in women and men during acute coronary syndromes**

### **5.1 Review of clinical studies assessed gender differences in coronary interventions during acute coronary syndromes NSTEMI and STEMI**

Percutaneous Coronary Intervention (PCI) is the preferred technique for the treatment of acute coronary syndrome with or without ST-segment elevation according to the Guidelines. The available data concerned gender differences in qualification and PCI effects are still conflicted.

Historically, the first PCI effects analysis coming from the end of XX century, in majority demonstrated a fewer qualification and worse prognosis in women treated by invasive

strategy. This effect was visible in all acute coronary syndromes types: ACS STEMI, NSTEMI and unstable angina.

In FRISC II study, women PCI benefits weren't indicated in comparison to conservative ACS NSTEMI treatment, whereas the definitely better PCI results in men were observed.

In spite of more optimistic results of TACTICS TIMI 18 study, in which the benefits from invasive therapy with widely stents and inhibitor GP IIb/IIIa usage were evident also in women, in the next study RITA 3, the positive effects of early invasive strategy during NSTEMI indicated the strongly advantage in male compared to female.

The reports concerned ACS STEMI were similar - there were documented an improvement of myocardial infarction therapy results in women, but, beside of better and better PCI techniques usage, greater PCI effects in men were demonstrated.

In Stent PAMI study the ACS STEMI female mortality after six month observation was significantly higher than in male.

The later study - CADILLAC also indicated higher STEMI population women after 30 days and 1 year, independent of kind of interventional technique's.

These worse results of procedures in women were tried to assign of major risk factors account (the more often prevalence of hypertension, diabetes and hiperlipidemia in female were confirmed in above studies), however in multivariable analysis the female sex was independent predictors of one - year more frequency of adverse events and mortality.

The causes of this phenomenon aren't still explained. Responsible could be the ACS clinical factors: delayed in disease's onset detection, older age, hormonal factors and comorbidities (hypertension, diabetes mellitus)- more often found in women. Nonetheless, gender differences in effectivenesses of coronary interventions were visible despite of allowing in studies and registries mentioned above factors.

The impact of specific coronary angiography changes in women to coronary interventions results are also often named as a cause of worse effect of therapy. Especially, smaller coronary artery size can be the reason of more often dissection or vascular perforation after PCI.

Based on reports from 1990 year, the frequency of vascular complications in women underwent of coronary interventions were about 3 fold higher than in men. This effect is assigned to difficulties in tailoring catheters size's to generally lower coronary arteries caliber in female.

Other authors suggested that the higher mortality seen in women after an AMI might be explained by less aggressive treatment, and if women had access to the same quality of care as men, their survival would be the same.

## **5.2 Current effects of coronary interventions in women**

Current studies evaluated of differences between female and male PCI effectiveness are still controversial.

The analysis of the great PCI Registry (over 22 thousands procedures; 31,8% women) showed, that compared with men, women were older, had a higher prevalence of comorbidities, and had a significantly higher frequency of adverse outcomes after PCI. After adjustment for baseline demographics, comorbidities, clinical presentation, and lesion characteristics, female gender was associated with an increased risk of in-hospital death, vascular complication, blood transfusion, stroke, and major adverse cardiac events (MACE). The relationship between female gender and increased risk of death and MACE was no longer present after further adjustment for kidney function and low body surface area.

Authors concluded that differences in mortality rates between men and women no longer exist after PCI.

This study included different clinical presentations of coronary artery disease with a mixed of ST- segment elevation myocardial infarction, non ST-segment elevation myocardial infarction (NSTEMI), unstable and stable angina, a heterogeneity which could minimize a difference to some extent.

Current analysis of Polish ACS Registry, assessed population of 26,035 patients with ACS STEMI (34,5% women) was evidently demonstrated higher in-hospital (15% vs 9%,  $p < 0,001$ ) and one-year (22% vs 14,1%,  $p < 0,001$ ) women mortality. Coronary angiography was carried out significantly less often in female (47,8% vs 57,4% ,  $p < 0,001$ ). In women receiving interventional treatment, primary angioplasty was performed significantly less often within 12 hours from symptom onset (35,8% vs 44,0%,  $p < 0,001$ ). The pharmacological treatment was less aggressive in women: GPIIb/IIIa inhibitor was administered in 12,2 % women vs 16,8 % men ( $p < 0,001$ ). Foregoing results were assigned the worse ACS clinical female presentation.

According to the Switzerland Registry included also over 20 thousands population hospitalized from ACS in 1997-2006 years (28% women) female gender was an independent factor for undergoing PCI less frequently. Although performed less often than in men, women benefited similarly from PCI and it was associated with lower in-hospital mortality, whether or not ACS was associated with ST-segment elevation.

Very interesting information comes from currently conducted observations concerned evolution of PCI effects in female and male in connection with improvement of PCI techniques.

According to retrospective analysis compared by gender two PCI populations: one of them consisted of patients underwent PCI between 1979-1995 (28% female), the second- between 1996-2004 (31 female), PCI was successful in 89% of women and 90% of men. In the recent group, 30-day mortality was significantly reduced compared with that in the early group in women (2.9% vs. 4.4%,  $p = 0.002$ ) and men (2.2% vs. 2.8%,  $p = 0.04$ ). However, long-term survival was similar between the early and recent groups among both men and women. After adjustment for risk factors, there was no difference between men and women from 1994 onward for either 30-day or long-term outcomes. Traditionally, compared with men, women undergoing PCI were older and more likely to have diabetes mellitus, hypertension, or hypercholesterolemia.

Authors suggested that the 30-day mortality after PCI in men and women has decreased in the past 25 years. After accounting for baseline risks, no differences in short-term or long-term mortality were observed between men and women.

The next problem is the prevalence of coronary interventions complications. According to majority observations in women more often than in men the periprocedural arteries damages and bleeding complications were found.

Argulian et al. analyzed process of 4768 percutaneous coronary interventions performed between 2001-2004.

The baseline characteristics, periprocedural complications, angiographic success, procedural success, and major in-hospital complications (death, myocardial infarction, and emergency coronary artery bypass graft surgery) after PCI were compared between men and women. Women were more likely older, with a significantly greater prevalence of hypertension and diabetes mellitus compared with men. After adjusting for baseline characteristics and coronary artery size, the incidence of coronary vascular injury complications was higher in

women than in men, particularly in patients  $\leq 55$  years (odds ratio [OR] 2.74, 95% confidence interval [CI] 1.49 to 5.04).

The difference was less when comparing women and men  $>55$  years (OR 1.32, 95% CI 0.87 to 1.99,  $p = 0.047$  for gender-age interaction).

The bleeding complications were also more often demonstrated in women than in men ( $\leq 55$  years OR 5.39, 95% CI 2.26 to 12.8,  $>55$  years OR 2.55, 95% CI 1.68 to 3.87,  $p = 0.121$  for gender-age interaction).

No significant gender differences were present in a combined end point of death, myocardial infarction, and emergency coronary artery bypass graft surgery.

Authors suggest, that among patients who have undergone PCI, women, particularly younger women, are more likely than men to experience coronary vascular injury and bleeding complications unaccounted for by coronary artery size and other patient characteristics. No differences were found in major in-hospital complications by gender.

The next analysis of Northern New England PCI Registry (13563 women underwent PCI in years 2002-07; 6,4% STEMI, 10,4% NSTEMI, 40,1 % unstable angina) demonstrated significantly improved rates of bleeding or vascular complications (VC) in women undergoing PCI during the past 6 years. The incidence of bleeding/VC decreased  $>50\%$  in both men and women during the study period. Although these results are encouraging, this study demonstrates that women continue to be more than twice as likely as men to have significant bleeding/VC after PCI.

Authors conclude that the persistence of the gender gap may suggest a role of inherent biological or anatomical differences between women and men, which have yet to be identified.

The next retrospective analysis of current PCI Registry (8 thousands ACS STEMI population; 29% women) confirm that female sex was associated with a higher unadjusted in-hospital mortality (6.02% vs 3.45%, odds ratio [OR] 1.79, 95% CI 1.45-2.  $P < .0001$ ) and higher risk of contrast-induced nephropathy (OR 1.75,  $P < .0001$ ), vascular complications (OR 2.13,  $P < .0001$ ), and postprocedure transfusion (OR 2.84,  $P < .0001$ ). The gap in sex-specific mortality narrowed over time. In a propensity-matched analysis, female sex was associated with a higher rate of transfusion (OR 1.88, 95% CI 1.57-2.24,  $P < .0001$ ) and vascular complications (OR 1.65, 95% CI 1.26-2.14,  $P < .0002$ ); but there was no difference in mortality (OR 1.30, 95% CI 0.98-1.72,  $P = .07$ ).

Authors suggest that these differences are explained by older age and worse baseline comorbidities among women.

Lower observational studies increasingly suggest evanescence of gender differences among patients undergoing primary PCI during ACS. These researches suspects that improvement of coronary intervention effectiveness's is connected with usage of more intensive pharmacotherapy.

The prospective analysis of 297 consecutive patients presenting with STEMI (27,6% women) treated by PCI with additional bare metal stent implantation and a GP IIb/IIIa inhibitor demonstrated that the incidence of major adverse cardiac events (MACE, defined as death, re-myocardial infarction, target lesion revascularization and coronary artery bypass graft) during long-term follow-up was similar in women and men (20% vs 26%,  $p = 0.29$ ). In this study, female gender did not emerge as an independent predictor for MACE, but women presenting with STEMI had a higher cardiovascular risk profile; this emphasizes the need for a more extensive therapeutic strategy. Authors conclude that combination therapy with primary PCI and GP IIb/IIIa inhibitors might mitigate gender-related differences in clinical outcomes.

Above mentioned study results are affirmed by another observational reports.

The retrospective analysis of 468 consecutive patients underwent PCI for ACS (29.3% female) demonstrated no significant gender differences in the short-term adverse event rate at 30 days despite of several important differences between female and male patients. Authors emphasizes women older age, smaller size of stent and first of all noticed that female patients were less likely to be treated with optimal medical therapy, with lesser use of glycoprotein IIb/IIIa inhibitors and beta-blockers.

Therefore, we can suspect that further improvement of PCI technique and usage of respectively aggressive pharmacotherapy in women treated from acute coronary syndromes perhaps completely eliminate ACS gender gap.

### **5.3 Evaluation of coronary artery bypass grafting effects in female compared to male**

The surgical treatment effects of acute coronary syndromes in women are still differently assessed.

In the previous years, when the coronary artery bypass grafting (CABG) was only one possibility of invasive strategy of advanced coronary artery diseases therapy, the Cardiosurgical Centers demonstrated increased mortality women underwent CABG.

Despite the lapse of the time, these observations are affirmed through the successive clinical reports.

There are the differences between studies results, because women constitute the lower group of patients undergoing CABG (20-30%). According to the great database of Society of Thoracic Surgeons (STS Database) - CABG was performed in 28% female patients hospitalized in years 1994-1996.

Currently studies assessed prognosis in women and men after CABG still demonstrate conflicted results.

The analysis over 70 thousands population of patients undergoing CABG in years 2003-2005 reaffirmed a significant effect modification by gender in 39 hospitals; the adjusted odds ratios showed significant increased risk for females. Authors suggest that the highest in-hospital mortality of females is frequently explained by gender physiological differences related to technical issues in surgery.

The smaller size of coronary arteries in women as compared with men has been often indicated as potentially increasing periprocedure and postprocedure complications in women. Actually, the influence of vessel size on gender differential mortality after CABG surgery remains controversial. Two studies used the body size as an indicator of vessel size. One found that gender differential mortality persists after adjustment for measures of body size, while another study showed that, both in men and women small body size does not increase the risk of operative mortality.

The next current analysis of 3441 patients (21,3% women) undergoing CABG between 2004-2008 years showed significantly higher 30-days (5,2% vs 2,5%,  $p=0,01$ ) and one year (8,7% vs 4,8%,  $p=0,0008$ ) women mortality. Moreover, these differences decline in patients operated using off-pump coronary artery bypass (OPCAB) technique. Authors suggest that female gender is a strong independent predictor and risk factor of increased postoperative mortality rates when extracorporeal circulation is used. OPCAB significantly reduces early and midterm postoperative mortality in women and may therefore be proposed as the preferred revascularization technique among female patients.

In the literature we can meet also observation indicated lack of significant differences between female and male prognosis after CABG, independent of surgical technique.

The analysis of group 954 patients undergoing CABG (19,7% women) in 2004-2009 years demonstrated no gender differences in the clinical outcomes after surgery (only the cerebrovascular event rate was higher in females compared with that in males (4.3% vs 1.6%;  $P=0.0432$ ).

In spite of conflicted reports concerned PCI and CABG effects in women, admittedly that review of currently literature demonstrates absolute benefits of reperfusion therapy of acute coronary syndromes in female and male. Majority of above analyzed studies confirms baseline worse clinical ACS women presence, particularly older age, major coronary risk factors number and more often occurrence of advanced heart failure, shock and cardiac arrest. Undoubtedly these factors, in significant way affects for worse early and distant prognosis. Certainly, relatively short time of ACS gender differences observation and generally lower women participation in clinical studies prevent unequivocal conclusions.

The further studies are necessary with particular acknowledgement coronary anatomy and acute coronary syndromes pathophysiology in female and male.

## **6. Analysis of selected cases of acute coronary syndromes in women**

In every day clinical practice we can see a lot of very interesting cases of specific acute coronary syndromes proceeding in female. According to earlier documentation, these contraries of ACS process are the most often presented during one of two particular women life periods: pregnancy and menopause.

### **6.1 Acute myocardial infarction in a 29-year-old woman during postpartum period - specific coronary changes**

The case of acute coronary syndrome STEMI in 29-years old woman in postpartum period illustrate of atypical ACS pathophysiology.

29- years old woman, three months after natural delivery was admitted to Cardiology Ward due to two- hours strong retrosternal pain. Heretofore patient was healthy, periodically complained for migraine and didn't indicate any coronary risk factors. During pregnancy she received hormonal therapy- luteine. Physical examination didn't demonstrate any abnormalities. In ECG- ST elevation in II, III, aVF, V5-V6 leads was revealed. Fig.1.

Biochemical testes demonstrated significantly increased of TnT's level (1,42 ng/ml). Echocardiography showed only descreet akinesis of apical segment lateral left ventricle wall with normal ejection fraction (EF- 65%). Coronary angiography revealed marginal branch aneurysm with prevalence of thrombus. Remaining coronary arteries were normal. Fig.2.

On account of small size of marginal branch, patient was disqualified from coronary revascularization. The typical pharmacological ACS therapy was used: low molecular weight heparin, double antiplatelet treatment, ACE-inhibitor, beta blocker and statin. After these treatment, the patient clinical state was improved.

Diagnostic process descoped congenital coagulation disorders as a cause of arterial thrombosis. Mutation prothrombin's gene G 20210 was excluded. Antiphospholipid antibodies level was negative. Only fibrinogen level and fibrinogen degradation products level were significantly increased.

During hospitalization any complications weren't observed. In ECG the negative T waves in II, III, aVF leads occurred, without pathological Q waves.

After ten days patient was discharged with further pharmacological treatment recommendation (ASA, Clopidogrel, beta blocker and statin). Only ACE-I was interrupted because of hypotension.

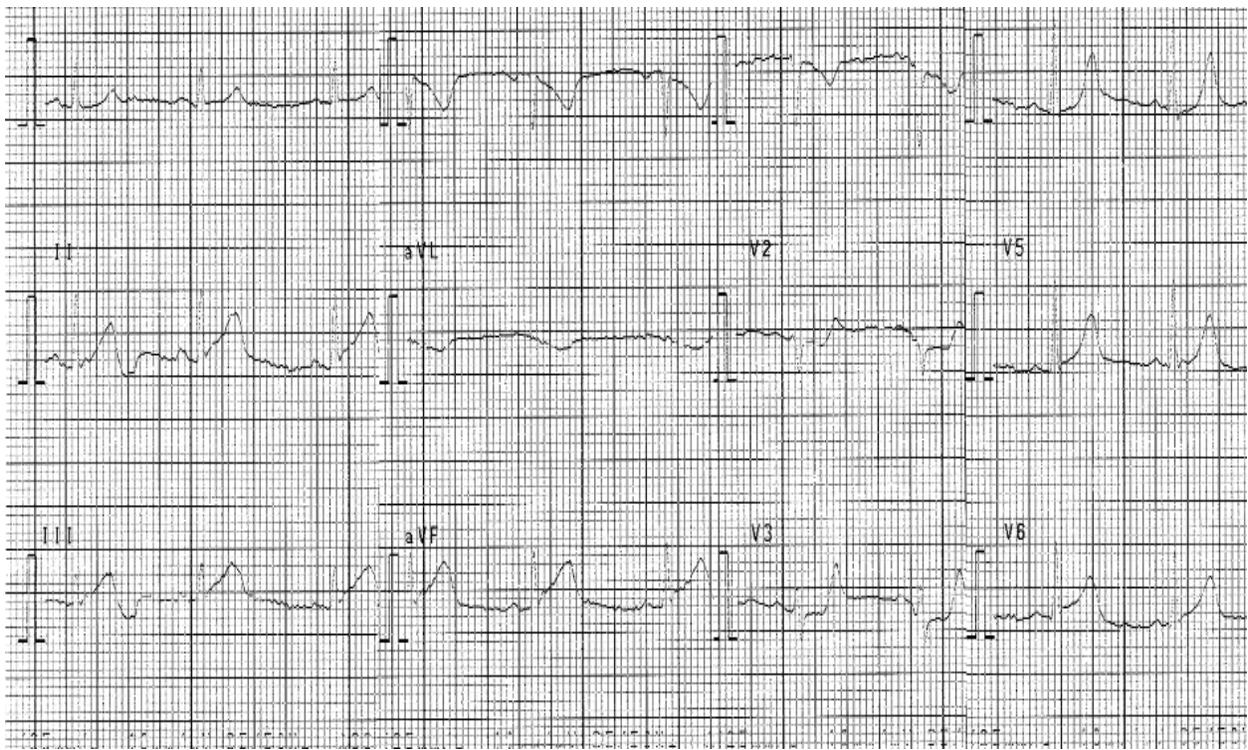


Fig. 1. ECG on admission. The description in the text.

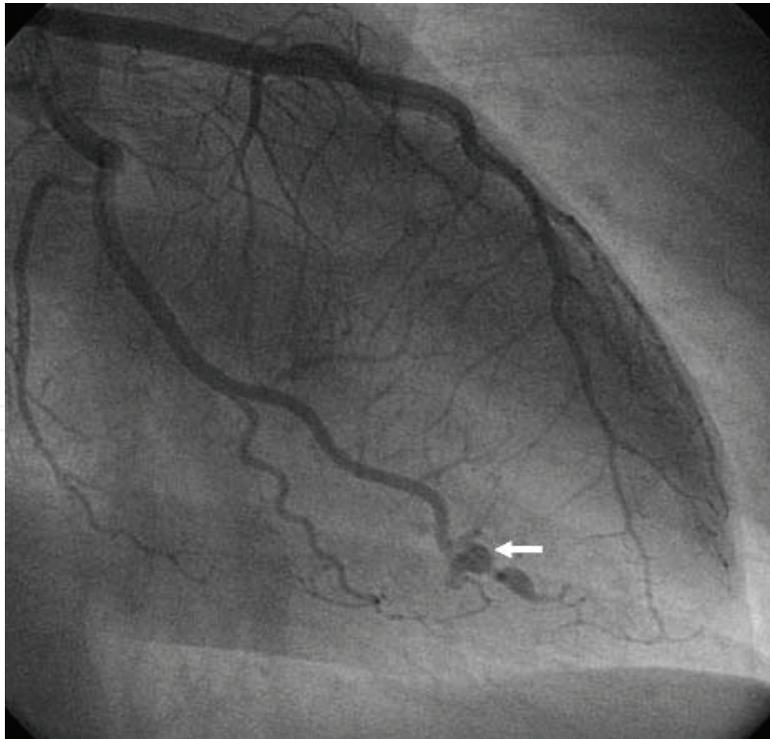


Fig. 2. Aneurysm with thrombus in marginal branch

One year later, after ceasing of Clopidogrel therapy, woman was again admitted to Cardiology Ward with the same complaints. In ECG the ST elevation in the same leads were observed, troponin T level was again increased (0,8 ng/ml). Coronary angiography image

was also similar. The decision about further pharmacological treatment (double antiplatelet therapy) was made.

During long-term, three years observation, patient is in good condition, but over the time takes medication: ASA, Clopidogrel, beta blocker, statin.

This case of myocardial infarction in postpartum women with aneurysm of coronary artery is an extremely rare and it is the real diagnostic and therapeutic challenge. Particularly, it is difficult to explain the coincidence's between both effects and make a decision about prevented of recurrences.

Probably, the base of acute coronary syndrome in this case wasn't typical, atherosclerotic. Perhaps the coronary artery aneurysm was a congenital malformation and in this particular postpartum period was favoured to initiation of thrombotic process. It is commonly allowed, that aneurysm prevalence increases the thrombosis risk and that during pregnancy and postpartum period this risk is still higher. It is a result of mentioned above coagulation system changes. Additionally, it is possible, that development of coronary artery dilatation could occur during pregnancy as an effect of progesterone influence's on arterial wall. Then, the initial cause could be the arterial dissection.

In conclusion, this case show very complicated pathogenesis of acute coronary syndromes during postpartum period. The problem is the great, because of lack of any experiences in the treatment.

## **6.2 Analysis of two cases of women treated from acute coronary syndromes during menopausal period**

### **6.2.1 Case 1**

54-years old woman, treated from hypertension, with hypercholesterolemia in review, was admitted to Cardiology Department due to typical exercise angina pectoris. Patient has never smoked, BMI was correct-24 kg/m<sup>2</sup>. The last menstruation was two years ago, patient didn't receive hormonal replacement therapy.

Distance of angina accounted for 300 meters on plane terrain, the disorders had intensified during three months before hospitalization.

On admission, patient was in good condition. Physical examination, ECG and biochemical parameters were normal. Echocardiography showed hypokinesis of inferior and lateral left ventricular wall without worsening global ejection fraction- EF-60%.

Exercise test (10,3 METs) revealed significant depression of ST segment in II, III, aVF, V4-V6 leads (Fig.3) with typical, retrosternal pain during exercise.

Patient was qualified to further conservative treatment. The pharmacological therapy: ASA, beta blocker, ACE-I and statin was included (Clopidogrel was 7 years ago not yet commonly used in only conservative treatment). Patient was discharged in good condition. During 1-year observation, patient was stable.

Therefore, she was admitted to hospital due to acute coronary syndrome NSTEMI (typical, rested retrosternal pain, ST depression, TnT level-0,19 ng/ml). Coronary angiography again revealed noncritical, the same 40% LAD stenosis, without another atherosclerotic changes in remaining coronary arteries. This time, probe of conservative treatment was ineffective-patient complained for recurrence retrosternal pain. After a few days, the PCI of proximal LAD stenosis with metal stent implantation was performed. The pharmacological treatment was continued with Clopidogrel added after coronary intervention.

In seven years observation patient is in good condition, without angina.

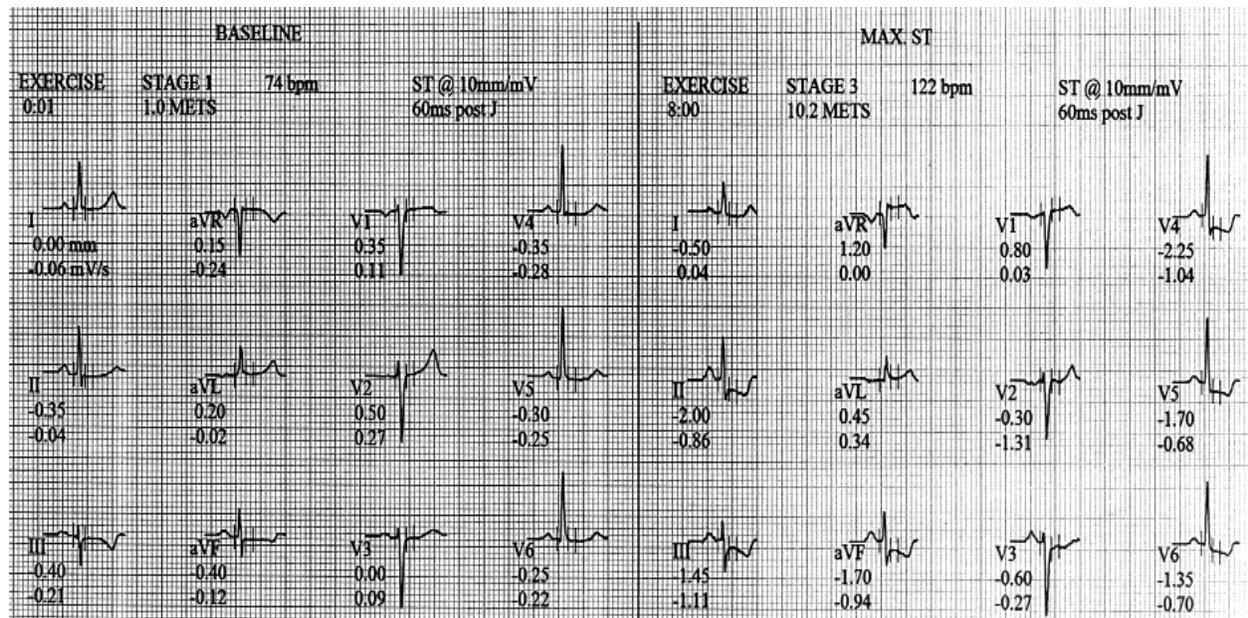


Fig. 3. Exercise test- visible ST segment depression in II, III, aVF, V4-V6 leads.

Patient was qualified to coronary angiography due to unstable angina. Coronarography revealed noncritical 40% stenosis of proximal left anterior descending (LAD) artery segment. The remaining coronary arteries were normal. Fig.4.

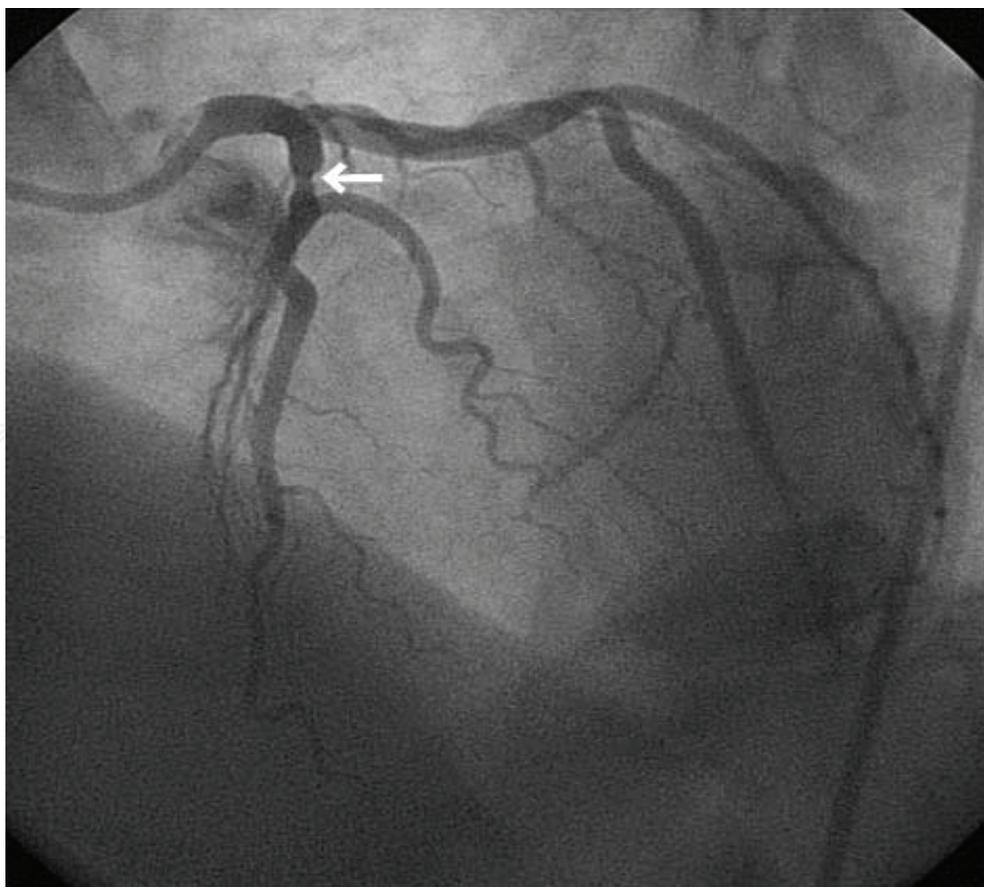


Fig. 4. Coronary angiogram. 40% LAD stenosis.

### 6.2.2 Case 2

52-years old women with overweight (BMI-29 kg/m<sup>2</sup>), hypertension, smoking, hypercholesterolemia and TIA in review, was admitted to hospital due to unstable angina. The last menstruation was one year earlier, patient has never received hormonal replacement therapy.

Three months ago patient was hospitalized due to ACS NSTEMI. Coronary angiography revealed non critical, 50% stenosis of right ventricular artery (RCA) without atherosclerotic changes in remaining arteries. Fig.5.

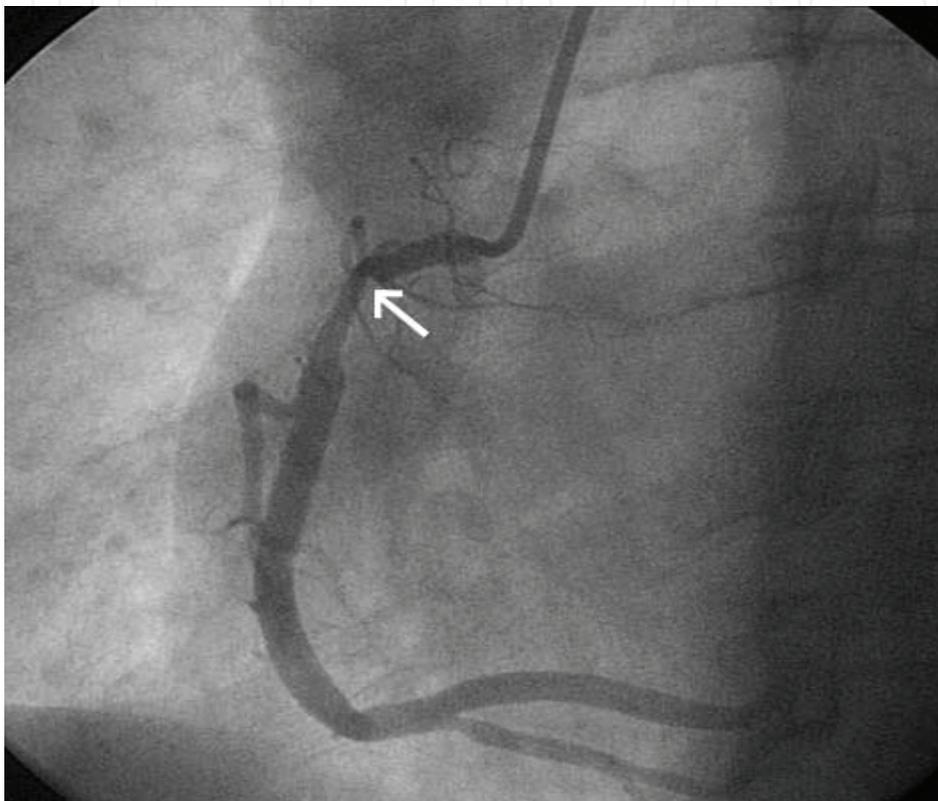


Fig. 5. Coronary angiogram- 50% stenosis of RCA is visible

After that, the typical pharmacotherapy to stabilization atherosclerotic plaque was included (ASA, beta blocker, ACE-I, statin) and patient was discharged without complaints. Clopidogrel wasn't popularly used to conservative ACS treatment 7 years ago

After three months patient was again hospitalized due to recurrence retrosternal pain with radiation to the lower jaw, more often during the rest, in the night. On admission patient state was stable. Physical examination and TnT level were normal. In ECG the negative T wave in II, III, aVF leads was visible. Echocardiography showed hypokinesis of basal and middle segments of left ventricular inferior wall's and hypokinesis of interventricular septum with normal ejection fraction (EF-55%).

Exercise test (9,2 METs) didn't revealed ST segment changes, it was finished after seven minutes due to patient fatigue. After pharmacological stabilization, patient was again discharged in good condition.

One month later patient was again admitted to Cardiologic Intensive Care Unit due to inferior all acute coronary syndrome STEMI. In ECG- the typical ST elevation in II, III, aVF leads were revealed. Fig 6.

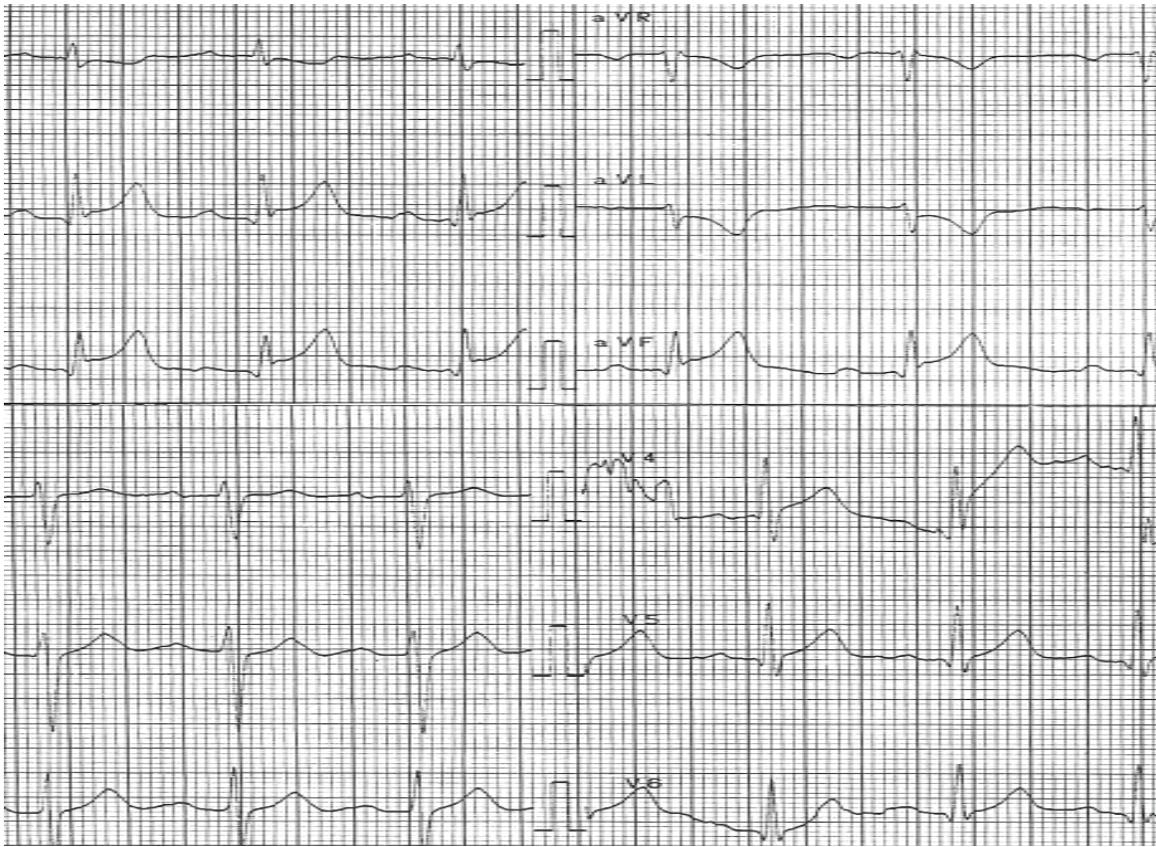


Fig. 6. ECG on admission- ST elevation in II, III, aVF leads.

Coronary angiography reaffirmed only prevalence of 50% stenosis of middle RCA segment. This time, PCI- RCA with bare metal stent implantation was performed. Coronary intervention was complicated by RCA dissection with thrombus involved. After intracoronary GP IIb/IIIa served, TIMI III flow was attained.

Further hospitalization was not complicated. Patient was again discharged in good condition.

In 7- years observation patient state is stable.

These cases of acute coronary syndromes in menopausal women are very specific. In both situations, despite typical symptoms, electrocardiographic and biochemical changes, coronary angiography didn't revealed critical stenosis of infarction responsible artery. Only the recurrence of complaints caused the interventional treatment.

It is important that ACS was presented during menopause in women with coronary artery risk factors. The essential is also fact the typical angina in both women, but noninvasive exercise test in second woman was doubted.

Noninvasive diagnostic process in women with coronary disease is difficult. Anatomical conditions aggravate imagination diagnostic and small exercise tolerance is a barrier in exercises testing.

Account of these facts, qualification to invasive diagnosis and treatment is more difficult than in men. Additionally, the coronary angiography changes are often nonspecific.

There are a lot of studies demonstrating that coronary angiograms in ACS women are often normal, or reveal noncritical stenosis. Presumably, the cause of acute coronary syndrome is mentioned above the plaque erosion with thrombus forming on undamaged artery wall. The another possibility is coronary artery spasm or dissection with idiopathic healing.

These effects occur exceptionally often in women during pregnancy and menopause in connection with hormonal changes in these periods.

Treatment of these cases is very difficult and should be empirical.

## 7. Conclusions

Women cardiovascular diseases are currently even more problematic than earlier. Mostly, the present data indicate, that female cardiovascular morbidity still rises. This effect is connected with a lot of factors.

Modern women have professional and housewife responsibilities, consume excess of fat and carbohydrates, smoke, do not exercise regularly and do not have enough time to rest. This situation leads to overweight, dyslipidemia, arterial hypertension, impaired glucose tolerance and diabetes.

Women do not often participate in preventive studies and, probably still undergo less intensive and invasive evaluation and treatment for chest pain when compared to men.

However, currently studies are more optimistic. Much of them show that in this era the gender gap will evanesce.

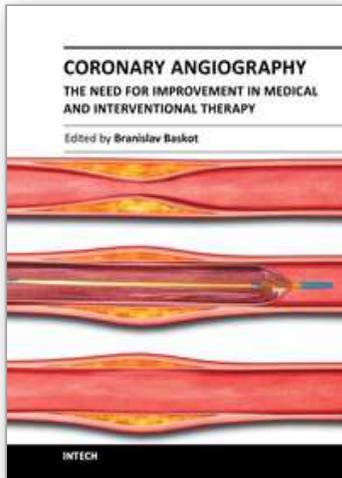
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## **Coronary Angiography - The Need for Improvement in Medical and Interventional Therapy**

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In this book we examined a periprocedural complication of coronary angiography, and coronary intervention. That includes related to cardiac catheterization and diagnostic coronary angiography, and those that occur as a consequence of the specific equipment. However, improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incident of major periprocedural complications. This book giving knowledge and experiences many of interventional cardiologists from all over the world, and provide possibility to recognize new approach in this domain. Book gives lecture on how we image and how we decide on what to treat, how to treat it, and then results of that treatment. They offer many answers to what we have today and what we will have tomorrow.

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