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Contents

Percutaneous Valve Procedures: Present and Future

Zamer Tawn, Dominique Himbert, Eric Brochet, David Messika-Zeitoun, Bernard Iung, Alec Vahanian, Bichat Hospital, Paris, France[1]

Introduction

Interventional cardiology was introduced by Andreas Gruntzig twenty-seven years ago, and since it has become a major player in the treatment of coronary disease, and peripheral, congenital and acquired valve diseases.

This review will cover the current percutaneous valve procedures and anticipated future improvements.

The Present

Percutaneous mitral commissurotomy (PMC) and percutaneous aortic valvuloplasty (PAV), constitute most of percutaneous treatment of acquired valvular heart diseases since percutaneous treatment of tricuspid stenosis or degenerated bioprosthesis is very seldom, if ever, used.

Percutaneous Mitral Commissurotomy

More than 20 years ago K. Inoue pioneered PMC, and currently his technique using the stepwise Inoue balloon is considered the standard, as the design of the balloon allows a fast, safe, and effective dilatation. The draw back of this technique is the high price of the device; however, there is no current satisfactory alternative. Echocardiography is key in monitoring the procedure, and «Hands on» 3D echocardiography is a recent addition to the field allowing for better visualisation of the commissural areas. Intra-cardiac echocardiography could also be a useful adjunct to guide the procedure.

Almost 90% of patients show significant improvement in valve function with a final valve area over 1.5cm? and no severe regurgitation, which clearly demonstrates the efficacy of the procedure. Experience plays a significant role in reducing the incidence of complications (1), which is low in experienced centres.

After ten years grossly 60% of patients are free from symptoms and have had no further intervention, as shown by series with 10-12 years worth of follow-up. Prediction of results is multifactorial and, as well as being linked to valve anatomy, it is independently related to clinical factors such as age, functional status, rhythm, and the quality of the initial results.

Patient selection has been refined through greater knowledge of immediate and long-term results (1-3).

Decisions are relatively clear cut in some cases. The following situations lead to contraindication of PMC: more than moderate mitral regurgitation, left atrial thrombosis, massive calcification, absence of commissural fusion, and concomitant severe aortic valve disease or coronary disease.

Contraindications to or high risk for surgery, such as older age (where PMC provides less satisfactory results than with younger patients, but can be palliative) or re-stenosis after surgery (where satisfactory mid-term results can be obtained in selected candidates) are all clear indications for PMC.

Furthermore, PMC is the treatment of choice in patients who have favourable presenting characteristics such as youth and favourable anatomy. The good results obtained by re-PMC in selected patients with restenosis adds to the interest of the method for young patients in whom we may expect to further delay surgery.

Unfortunately, not all decisions are this clear cut, especially in Western countries, and challenging issues still remain.

In patients with unfavourable anatomy, who currently represent the majority of patients in Western countries, the results of PMC are less satisfactory. However, the surgical alternative is valve replacement, which carries an inherent risk of mortality and morbidity. The decision should take into account the multifactorial aspect of prediction, which is of particular importance in this heterogeneous population.

Surgery is the best option in patients with severe valve calcification, in particular if their other characteristics are also unfavourable. For patients who do not fall into this category the decision should be individualised, PMC being preferred as an initial treatment in those with mild calcification and otherwise favourable characteristics.

Another issue that also presents a challenge is whether to opt for medical treatment or balloon commissurotomy in patients with few or no symptoms. In observational studies PMC provides good long-term results with 10 year event free survival of up to 80%, while old natural history studies show an event free survival of only 20%. The data available are still limited; however, they converge to suggest that successful PMC is also effective in reducing thromboembolic risk.

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Even if it is possible that PMC may have a positive influence on the causes of atrial fibrillation, its benefit is not clearly established here.

PMC can be used in selected asymptomatic patients with severe mitral stenosis when the procedure can be made as safe and effective as possible through the presence of experienced medical and surgical teams . Finally, we should only treat patients with favourable presenting characteristics in whom long-term success can reasonably be expected.

PMC can be performed when the above conditions are present in combination with the following factors: increased thromboembolic risk, such as previous embolism, dense spontaneous echo contrast, or recent onset of recurrent paroxysmal atrial fibrillation - high risk of haemodynamic decompensation, that is to say pulmonary hypertension either at rest or on exercise; the thresholds of which should be refined by the increasing experience gained in exercise echocardiography - and finally, very occasionally, in patients who desire pregnancy or who need major extra cardiac surgery.

Perhaps in the future further improvement will be achieved through combining PMC with other interventional procedures such as closure of left atrial appendage or ablation of the pulmonary veins.

To improve patient selection in these challenging cases we would ideally need randomised studies comparing PMC with valve replacement in patients with unfavourable anatomy, or with medical treatment in the asymptomatic patients. However, these studies are unlikely to ever be carried out.

Percutaneous Aortic Valvuloplasty

PAV was performed for the first time close to twenty years ago by Alain Cribier and stirred up enormous early enthusiasm. But, unlike PMC, PAV has no surgical comparator. Clinical experience was mostly in high-risk patients with contraindications to surgery. Mortality and morbidity were high, which was a result of the inefficacy of the procedure itself as well as of the critical condition of the patients.

There has not been any randomised studies comparing PAV with surgery, but retrospective analysis shows that even if it did usually provide short-term functional improvement, this procedure did not change the natural history of the disease.

The ACC/AHA guidelines suggest that the procedure could be performed as a bridge for surgery in haemodynamically unstable patients who are at high-risk for aortic valve replacement. In fact, we have very scarce data to support this and there have been no comparative studies of the two step approach and immediate surgery. This treatment is clearly not an alternative to aortic valve replacement (2).

In real life twenty years after the introduction of percutaneous valve intervention, data from the Euro Heart Survey, which was performed prospectively in 92 centres from 25 countries, throughout Europe during a 4-month period in 2001, showed that PMC is now used in over 1/3 of cases of mitral stenosis and has virtually replaced surgical commissurotomy. PMC is a useful complement to valve replacement, which can be thus delayed in selected patients. On the other hand, PAV was not performed in this large sample of centres and the technique is almost abandoned across the globe (4).

Thus, despite the dramatic decrease in the prevalence of rheumatic fever in Western countries, PMC's future in this area of the world is assured by the continuing presence of mitral stenosis due to emigration from developing countries. The relative infrequence with which PMC is carried out should lead to the concentration of the performance of this relatively difficult procedure to a group of expert centres. The most important field of application for PMC is in non-Western countries, which represent the vast majority of the world's population. In these countries the incidence of rheumatic disease remains high, and mitral stenosis is by far the most frequent valve disease. Thus, if it were affordable enough we could expect a large use of PMC. However, we must not underestimate the importance of cost, as economic restraints mean closed surgical commissurotomy is still considered the best option in some places.

The Future

The potential field of application for the new techniques of percutaneous valve interventions is vast and concerns the two most frequent valve diseases in Western countries: aortic stenosis and mitral regurgitation, totalling more than 70% of cases.

It is evident that surgery works very well since operative mortality of aortic valve replacement or mitral valve repair is low, and long-term results are excellent for up to 20 years (5, 6), thus setting a high standard for any future percutaneous valve intervention.

However, there are several favourable observations for the use of new percutaneous valve interventions. Firstly, nowadays, the use of percutaneous coronary interventions is surpassing coronary artery bypass grafting, thus, the presence of combined coronary artery disease should not be a reason to prefer surgery to percutaneous valvular interventions. Secondly, data from the Euro Heart Survey on valvular heart disease show the strong predictive value of age and other comorbidities for operative mortality in valve surgery, which leads to a high surgical risk in an important percentage of patients with valve disease. Thirdly, surgery is denied in many patients with severe valvular heart disease and symptoms, the figure being up to one third in the Euro Heart Survey. This large group of patients, who are currently being overlooked, definitely warrant some sort of intervention (4).

Percutaneous Aortic Valve Replacement

Davies, followed by Andersen, performed the first experiments more than 20 years ago. Bonhoffer (7) carried out the first percutaneous valve implant in the

pulmonary position, and Alain Cribier performed the first aortic valve replacement in 2002 using a valve composed of equine pericardial leaflets mounted on a balloon expandable stent (8) (Figure 1). The current size of the catheter is 24F and the size of the prosthesis is 23mm. A transseptal antegrade approach was used, which is not easy, but does have the advantage of reducing vascular complications with these large devices in comparison with the retrograde approach (9, 10).

The current results are those of a feasibility study

Figure 1. Percutaneous aortic valve replacement Left panel: the stented valve is crimped on a balloon catheter (courtesy of A. Cribier)
Upper right panel: the stented valve is shown with the three equine pericardial cusps in closed position (adapted from ref 9) Lower right panel: the stented valve is shown with the three equine pericardial cusps in open position (courtesy of A. Cribier)

comprising 20 compassionate cases who were elderly, often with cardiogenic shock, and comorbidities contraindicating surgery. Three patients died during the procedure and there were three technical failures when using the retrograde approach. No coronary occlusion occurred. A concerning complication is severe aortic regurgitation, which was observed in over 20% of patients and is a result of para-valvular leaks due to insufficient apposition of the valve in these irregular orifices. When the valve was in place it significantly improved valve function with a final valve area of 1.7 cm^2. Left ventricular function also immediately improved after a successful procedure. Unfortunately, the extra-cardiac condition of these patients often led to death within months and only three patients survived for longer than one year. However, the survivors experienced sustained clinical improvement and there were no additional cases of prosthetic valve dysfunction recorded up to 12 months after operation. New safety and efficacy trials are planned or are ongoing with this device, i.e. REVIVE II and RECAST.

More recently, balloon expandable devices are currently being evaluated and positive results have been achieved through experimentation. The first two in-man implantations were performed in July 2004 (E. Grube, personal communication).

It remains to be established whether balloons or self-expandable stents will be better as regards ease of placement, radial force, and absence of paravalvular leaks.

Percutaneous Mitral Valve Repair

Two main techniques can be used: the edge-to-edge technique and prosthetic ring annuloplasty.

The edge-to-edge technique mimics the Alfieri surgical procedure, which consists in creating a double mitral orifice by means of a few stitches securing the two leaflets together in their midpart, creating «a tissue bridge». Current knowledge of the surgical procedure is limited to around 600 cases (11).

Experimental studies have shown that this technique can be successfully and reliably achieved with a catheter clip introduced via the mitral orifice into the left ventricle (12, 13) (Figure 2).

The percutaneous edge-to-edge technique has

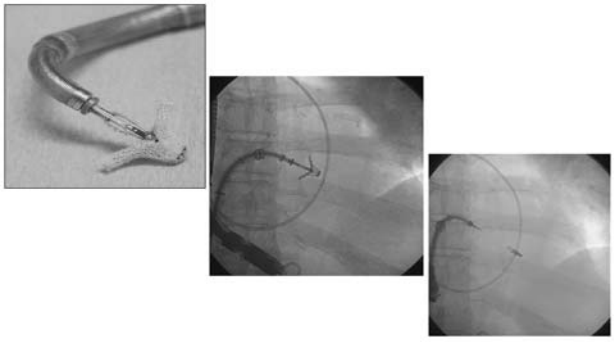

Figure 2. Percutaneous mitral valve repair using the edge-to-edge technique Left panel: the clip is open
Middle panel: Right anterior oblique view. The clip is positioned in the left ventricle via a transseptal approach. The clip is open.
Right panel: The clip is released (Courtesy of P. Block)

been being used in-man for a few months.

It requires a transseptal approach with transoesophageal echographic guidance. This technique will not be an easy one to perform and these constraints will result in a learning curve and will probably limit its dissemination.

The first results of a feasibility study, EVEREST I, concern 27 patients who had severe mitral regurgitation and no contraindications for surgery. There were no major procedural complications. After the procedure, MR was less than 2 in 67% of the patients. With six-month follow up, most patients are still in good functional condition and the mean degree of MR is 2.1/4, which is good but not zero (T. Feldman, personal communication). This raises concerns about leaving residual regurgitation more than mild in the left ventricle in patients who can be operated upon due to the potential risk of insidious left ventricular dysfunction. A randomised trial, EVEREST II, is planned to compare percutaneous and surgical techniques for mitral valve repair.

Another design involves the use of one or more sutures deployed via a catheter-based device. The tip of the mechanical suturing device is equipped with two side holes facing each mitral leaflet respectively. Suction is applied to the side holes, which maintains the leaflets in a closed position and the fixation device is fired. Two needles with monofilament sutures transfixing the leaflets are deployed and exteriorised

through the atrial port. The sutures are tied using a knot pusher. This device has proven successful in animals (M. Buchbinder, personal communication).

Some limitations of the edge-to-edge technique can be anticipated. Its use will be restricted to localised prolapse of the medial portions of either the anterior or the posterior leaflet, especially when using clips. In addition, it does not address the problem of annulus dilatation, which has been shown to increase the risk of residual regurgitation. Finally, traumatic injuries to the leaflets or chordae can be potentially anticipated on a fragile and complex valvular structure.

Prosthetic Ring Annuloplasty is key in most cases of surgical valve repair as there is always an annular dilation in severe chronic mitral regurgitation and one could expect to reduce the diameter of the mitral annulus by inserting a constraining device in the near coronary sinus. However, things may not be that simple since the coronary sinus is in reality 1 or 2 cm away from the atrioventricular groove on the atrial side. In addition, the ring inserted into the coronary sinus is necessarily incomplete. Thus, it is localised to the posterior half of the annulus and leaves the posteromedial commissure and the anterior half of the annulus unsupported. Furthermore, as the valvular anatomy is variable it may require non-invasive anatomic evaluation before the procedure, using CT imaging for example.

The experience acquired from electrophysiolgists suggests that it will be far easier to perform than the edge-to-edge technique, however, it carries the potential risk of damaging the coronary sinus, or even, the circumflex artery, which is in the immediate vicinity.

The technical issues here are finding the most effective proximal and distal fixation for stabilisation and a material with sufficient constraining force to obtain at least a 20% reduction of diameter (Figure 3).

Prosthetic ring annuloplasty is at an even earlier stage of evaluation than the edge-to-edge technique. The only data available at the moment are experimental (14-16). They show a reduction of the degree of regurgitation and a subsequent improvement in haemodynamics. In dogs, but not in sheep, the flow of the circumflex artery may be hindered. Finally, no cases of traumatism or thrombosis of the coronary sinus occurred. The first in-man implantations have been performed, mostly temporary during surgery, but they have not yet been reported in detail (18).

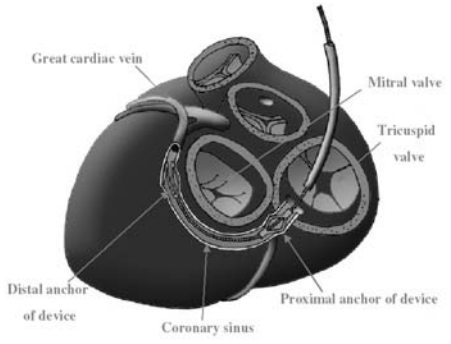

Figure 3. Percutaneous mitral annuloplasty The device is positioned via a transjugular approach in the coronary sinus which is in the vicinity of the mitral annulus (adapted from ref 14)

The future percutaneous mitral valve repair might combine the different approaches: direct procedure on the leaflets using the edge-to-edge technique, and annuloplasty.

Overall it is unlikely that these new percutaneous techniques will reproduce the current results of surgical valve repair, which is a sophisticated surgical method and requires the performance of various techniques necessitating exposure and precision.

Percutaneous mitral valve repair is a field of great interest and several other devices and techniques are currently being investigated experimentally such as trans-ventricular suture based annuloplasty, and trans-pericardial ventricular remodelling.

To take a thorough look into the future we should mention some other anticipated research and developments. New valve technologies are under evaluation such as nano-technologies. The first experiments on percutaneous replacement of atrioventricular valves have also been performed. Finally, these technological improvements cannot be separated from active investigations into better imaging guidance using 3D echocardiography or MRI.

The data we have on these new techniques of percutaneous valve intervention raise a lot of questions:

We need more data to accurately assess feasibility, efficacy, and safety. Durability is also a key question to be answered through experimental and clinical studies. Another question, which is essential, is to know if re-intervention, either re-percutaneous or surgical, will be feasible. «Re-intervention» should also include pacing in the case of prosthetic annuloplasty.

This being said, what indications could we expect for these new techniques?

Aortic stenosis is the most promising field of application for percutaneous aortic replacement. The use in aortic regurgitation is expected to be much lower since patients are less frequently seen nowadays and mostly suffer from degenerative aortic regurgitation where aortic root disease is common and thus cannot be treated using a percutaneous device.

Percutaneous mitral repair could have a potential use in functional mitral regurgitation, which comprises ischemic and heart failure. Despite the large number of patients potentially concerned there is limited data available on the results of surgery in heart failure. Surgeons usually use rings with generally less satisfactory results than in the other aetiologies. In addition, the efficacy of incomplete ring annuloplasty in cases where surgeons usually use undersized and complete rings may be a cause for concern. For degenerative aetiology, edge-to-edge technique may be used and a ring alone will not be effective. The application of a combination of edge-to-edge and annuloplasty techniques will probably be needed to achieve sufficient efficacy. Finally, the idea of treating

patients with isolated moderate MR is virtually unexplored in the surgical area. Here the comparator should be not only surgery but also medical therapy including resynchronisation. This approach could be attractive in the difficult subgroup of patients with moderate MR who require coronary intervention.

The first step to answering these questions is to perform these techniques on patients with contraindications to or who are very high risk for surgery. This concerns a large population, which will no doubt have a great clinical impact. This will allow feasibility, immediate risks, and improvement in valve function to be assessed. However, it has little value in evaluating long-term results as extra-cardiac factors have a much stronger bearing on prognosis.

The excellent results of surgery mean that the evaluation of these new techniques in patients who are candidates for surgery raises ethical problems. In this subgroup we should define how much less satisfactory results than surgery we are willing to accept. Whether surgical options remain unchanged after these procedures have been performed is another key factor (19-21).

Conclusion

Percutaneous mitral commissurotomy is a significant achievement and will always have an important role along side valve replacement in the treatment of mitral stenosis, which still remains the most frequent valve disease in many parts of the world. Percutaneous aortic valvuloplasty has, at best, an uncertain future.

The new techniques of percutaneous valve intervention are at an early stage but they have opened a very exciting field of investigation. These preliminary results, which currently relate to less than fifty patients treated worldwide, show us that these techniques are feasible. However, any further conclusions are speculative. Today potential applications for these new techniques concern high-risk patients, which may be extended to others in the future after careful evaluation in comparison to contemporary treatment. This evaluation requires a close collaboration between interventionists, echocardiographists, engineers, and surgeons. If these steps are followed, it is probable that these techniques will play an important role in the treatment of valve disease in the future.

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Levosimendan in Combination with Endovascular Reperfusion in Patients with Acute Myocardial Infarction Causing Left Ventricular Failure

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Despite significant advances in the treatment of acute myocardial infarction provided by the implication of reperfusion therapy, the problem of one of its most severe complications - acute heart failure - remains crucial. Acute heart failure is one of the basic predictors of survival and clinical course of the disease in the short-term and long-term periods. Patients with heart failure caused by acute myocardial infarction still have poor prognosis even when intensively treated with diuretics, vasodilators, ACE inhibitors, cardiac glycoside. Some authors showed that hospital mortality rate in such patients can exceed 20% and 1-year mortality rate approximates 40%.

The above facts suggest the need for further studies of novel medical and non-medical therapies to decrease mortality and morbidity due to this severe complication of acute myocardial infarction. Today myocardial reperfusion using thrombolytic therapy or interventional procedures performed within the first 6 hours after AMI remains the only method with proved efficacy for limitation of ischemic damage area and prevention of acute heart failure. Intraaortic balloon counterpulsation has also been effective in the treatment of acute heart failure resistant to medical therapy, as well as the cardiogenic shock, with highest effect observed in combination with reperfusion therapy.

Acute left ventricular failure can be due to the large area of myocardial infarction injury, hypertension, severe mitral regurgitation, ventricular septal defect. Ultimately, heart failure in acute myocardial infarction results from left ventricular either systolic or systolodiastolic dysfunction. Diastolic dysfunction leads to pulmonary hypertension, which substantially disrupts gases exchange in the lung tissue. Diastolic dysfunction of the left ventricle caused by decreased myocardial contraction can lead to significant decline of ejection fraction. These pathogenic mechanisms determine corresponding clinical manifestations - microcirculation disorders, cyanosis, dyspnea, bubbling rale over the lung fields, tachycardia, oliguria.

Studies of drugs exhibiting positive inotopic effect, such as dobutamine, dopamine and phosphodiesterase inhibitors, failed to provide unambiguous conclusion on their efficacy and safety. The above agents improve cardiac function through the increase of calcium level within cardiomyocytes, thus, in addition to positive inotropic effect, increasing energy consumption and potentially aggravating myocardial ischemia, as well as increasing the risk of rhythm disorders. Correspondingly, the problems related to the methods of myocardial support in patients with large myocardial damage and low ejection fraction, as well as the choice of inotropic and cardioprotective agents, remain under special attention in modern cardiology and require further assessment and development.

The study of levosimendan (Simdax^T, Orion) in patients after endovascular treatment for acute myocardial infarction causing heart failure has been performed in the Moscow City Center of Interventional Cardioangiology under the direction of Professor D.G. Iosseliani, MD, since August, 2004.

Levosimendan is a non-glycoside agent, the first substance in the new class of pharmacological preparations - calcium sensitizers - possessing double action: it increases cardiac contractile performance and exhibits vasodilating effect. Simdax(r), unlike other agents with positive inotropic effect, activates ATP-dependent calcium channels in smooth muscle cells of the vessel wall, leading to dilation of veins and arteries, including those of coronary circulation. The increase of myocardial contraction function is due to higher sensitivity of contractile proteins to calcium. The extent of this effect is dose-related.

An important pharmacological effect of levosimendan is the opening of ATP-dependent calcium channels, which improves capillary coronary circulation and results in limitation of hybernating myocardium area and restoration of its normal contractile function. The extent of necrotic area is directly proportional to the time and degree of myocardial reperfusion, therefore, an important condition for effective therapy with levosimendan can be its combination with early administration of medical and non-medical methods of blood flow restoration in ischemic myocardium.

Interestingly, levosimendan acts even in the presence of metabolic acidosis due to ischemia (pH-6.7). Levosimendan has no effect on diastolic myocardial relaxation and improves cardiac pumping ability without apparent increase in myocardial oxygen consumption and the risk of rhythm disorders. Efficacy of SimdaxT is due to pharmacological effect of levosimendan per se and its active metabolite - (OR - 1896), which is also a potent calcium sensitizer and, due to longer half-life, its therapeutic effect persists within

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several days after infusion.

Purpose of the study: assessment of clinical efficacy and immediate (hospital) results of the use of levosimendan in combination with emergency endovascular procedures to restore coronary circulation as a method of treatment for patients with acute myocardial infarction complicated by acute heart failure.

Material and methods: the study groups currently enroll 31 patients. Depending on the drug used to treat heart failure, these patients were divided between 2 groups. The first group (N=11) consisted of patients receiving 6-hour infusion of levosimendan with mean infusion rate of 0.2 mg/kg/min. The second (control) group (N=20) included patients, who received 2-6 mg/kg/min IV dopamine for inotropic support.

Major inclusion criteria were:

а) Signs of acute left ventricular heart failure within the first hours after acute myocardial infarction as confirmed by clinical and instrumental methods (X-ray, Echo-CG, ventriculography);

б) Successful procedure of blood flow restoration in the infarct-related artery through PTCA or stenting within 6 hours after the onset of the disease;

The patients with hepatic, renal disorders, hypotension (SBP < 85 mm Hg), permanent atrial fibrillation at baseline were excluded from the study.

Mean age of patients was 58.2±6.4 years in group I and 59.8±7.3 years in group II. The majority of patients in both groups were men - 72.7% and 75%, respectively. History of CHD was 6.9±4.4 months in study group vs 7.1±4.8 in control group. History of acute myocardial infarction was revealed in 27.3% of patients in group I vs 20% of patients in group II. Time from the onset of anginal attack to hospitalization was 5.1±2.4 h in group I vs 5.4±2.3 h in group II. Baseline systolic blood pressure was 106±22.4 mm Hg in the study group vs 103±24.1 mm Hg in the control group. Baseline diastolic blood pressure was 54±18.4 and 56±19.2 mm Hg in groups I and II, respectively. Baseline heart rate was 88.1±11.9 bpm in group I vs 89.7±13.4 bpm in group II. Acute heart failure was most common in anterior infarction: 72.7% and 75% of patients in groups I and II, respectively. The following risk factors for CHD were detected in the majority of patients from groups I and II: hypertension - 81.8% vs 85.0%, dislipidemia - 63.6% vs 65.0%, family history of CHD - 36.4% vs 45.0%, smoking - 63.6% vs 70.0%, obesity - 45.5% vs 45.0%, diabetes mellitus - 9.1% vs 10.0% of patients from group I and II, respectively. There were no significant differences in the above parameters between the groups (p>0.05) (Table 1).

Upon admission to ICU all patients underwent monitoring of basic hemodynamic and functional values (ECG, BP, SO2), 12-lead ECG, evaluation of circulatory failure degree and medical therapy (humidified oxygen inhalation, nitrates infusion, diuretics).

After preliminary correction of circulatory disorders the patient was urgently reallocated to the Department of Interventional Radiology for left ventriculography and selective coronary angiography. The following values were obtained during left ventriculography: systolic and diastolic diameters of heart chambers, LVEF, areas of myocardial asynergy, pathological flow. Selective coronary angiography was used to determine atherosclerotic stenosis or acute occlusion of coronary arteries. Interestingly, while in the Interventional Radiology Unit all patients underwent monitoring of heart rate, BP, oxygen inhalation, received the required medical therapy with calculation of the volume of contrast medium used. These measures allowed for all patients with baseline signs of circulatory failure to undergo successful endovascular restoration of blood flow in the infarct-related artery (PTCA or stenting).

Table 1. Presentation and history in study groups

Parameter	Group I (n=11)	Group II (n=20)	Significance
Mean age, (years)	58,2±6,4	59,8±7,3	NS
Men	8 (72,7%)	15 (75,0%)	
CHD history, (months)	6,9±4,4	7,1±4,8	
Time to hospitalization, (h)	5,1±2,4	5,4±2,3	
Hypertension	9 (81,8%)	17 (85,0%)	
Dislipidemia	7 (63,6%)	13 (65,0%)	
Family history of CHD	4 (36,4%)	9 (45,0%)	
Smoking	7 (63,6%)	14 (70,0%)	
Obesity	5 (45,5%)	9 (45,0%)	
Diabetes mellitus	1 (9,1%)	2 (10,0%)	
History of AMI	3 (27,3%)	4 (20,0%)	

NS - non-significant differences, (P>0.05)

Table 2. Baseline presentation and functional parameters in study groups

Parameter	Group I (n=11)	Group II (n=20)	Significance
AMI location: anterior posterior circular	 8 (72,7%) 2 (18,2%) 1 (9,1%)	 15 (75,0%) 3 (15,0%) 2 (10,0%)	NS
Baseline SBP, mm Hg	106±22,4	103±24,1	
Baseline DBP, mm Hg	54±18,4	56±19,2	
Baseline HR, bpm	88,1±11,9	89,7±13,4	
Radiological signs: venous congestion interstitial edema	 2 (18,2%) 9 (81,8%)	 5 (25%) 15 (75%)	
HR, bpm	18,8 ± 6,6	17,6 ± 8,1	
Pulse oxymetry, S O2	86,4 ± 11,5	84,9 ± 13,1	

NS - non-significant differences, (P>0.05)

After surgery the patients were reallocated to the ICU for further management, including monitoring of ECG, BP values, HR, respiration rate, pulse oxymetry, blood gases, chest X-ray, diuresis control. On days 2-3 from the onset of AMI the patients underwent cardiac ultrasound study - EchoCG - to determine systolic and diastolic diameters of the heart chambers, mean thickness of LV myocardium, LVEF, the presence and the degree of myocardial asynergy, the presence of pathological flows.

Results. Left ventriculography and coronary angiography provided the following values: EDV 143.2±26.9 ml vs 145.4±23.2 ml, ESV - 75.8±28.3 ml vs 72.4±25.7 ml, LVEF - 38.5±11.3% vs 393±10.6% in groups I and II, respectively. Acute occlusion of the infarct-related artery was found in all patients in the

study groups. In the majority of patients in both group acute LAD occlusion was found - 9 (81.8%) patients in group I vs 17 (850%) patients in group II. Acute RCA occlusion was revealed in 2 (18.2%) vs 2 (100%) patients in the groups, respectively, LCx lesion was found in 1 (5.0%) patient from group II and none of the patients from group I. All patients in both groups underwent IRA manipulations: PTCA in 8 (72.7%) cases from group I vs 16 (80.0%) cases from the control group, stenting in 3 (27.3%) vs 4 (20.0%) patients from the respective groups. There were no significant differences in the above values between the study groups (p>0.05) (Table 3).

Table 3. Results of left ventriculography, selective coronary angiography and the endovascular procedures performed in patients of the study groups.

Parameter	Group I (n=11)	Group II (n=20)	Significance
EDV, (ml)	143,2±26,9	145,4±23,2	NS
ESV, (ml)	75,8±28,3	72,4±25,7	
LVEF, (%)	38,5±11,3	39,3±10,6	
IRA: LAD RCA LCx	 9 (81,8%) 2 (18,2%) 0	 17 (85,0%) 2 (10,0%) 1 (5,0%)	
EVP performed: PTCA Stenting	 8 (72,7%) 3 (27,3%)	16 (80,0%) 4 (20,0%)	

IRA - infarct-related artery; LAD - left anterior descending artery; RCA - right coronary artery; LCx - circumflex branch of the left coronary artery; EVP - endovascular procedures; PTCA - percutaneous transluminal coronary angioplasty; EDV - end-diastolic volume; ESV - end-systolic volume; LVEF - left ventricular ejection fraction; NS - non-significant difference, (P>0.05).

In the ICU all patients after EVP for acute myocardial infarction causing acute heart failure underwent randomization with subsequent infusion of cardiotonics (levosimendan or dopamine), standard therapy adopted in the Moscow City Center of Interventional Cardioangiology, which included disaggregants: aspirin 125-325 mg daily or, in case of stenting, plavix 75 mg daily. Antiaggregants were administered to all patients of the study groups (p>0.05). To prevent coronary artery spasm within the first day after the intervention and to reduce signs of pulmonary circulation congestion (reduction of pulmonary hypertension), IV infusion of nitrates at the rate determined by hemodynamic values was started with BP above 100 mm Hg. Nitrates were administered to 7 (63.6%) patients from levosimendan group vs 14 (70.0%) patients from the control group. In order to prevent myocardial remodeling and to reduce the signs of circulation disorders or decrease the BP in case of hypertension, the patients received ACE inhibitors (enalapril 5-10 mg daily or perindopril 2-4 mg daily), the dose was adjusted on the basis of hemodynamic values. Therapy with ACE inhibitors in ICU was administered to 8 (72.7%) patients in group I vs 13 (65.0%) patients in group II. Dilatrend (karvedilol) was given to all patients as an antianginal agent, to normalize HR and prevent myocardial remodeling in the dose of 3.125 mg daily or higher. The indications and the daily dose were determined on the basis of clinical manifestations of acute left ventricular failure, LV contractile function (LVEF), hemodynamic values. Beta-blockers (dilatrend) were given to 7 (63.6%) vs 15 (75.0%) patients from groups I and II, respectively. All patients received diuretics (lasix) to reduce signs of left ventricular failure, the dose was adjusted in accordance with clinical signs of heart failure and the diuretic response. In addition, all patients received inhalation of humidified oxygen through mask or intranasal cannula to reduce hypoxemia. There were no significant differences in the drugs administered between the study groups (p<0.05). However, patients on levosimendan had significantly lower need for diuretics: daily dose of lasix was 44.5±19.6 mg, which was significantly lower, that that in control group, where this value made 89.6±24.3 mg (p<0.01) (Table 4).

Table 4. Drug therapy in study groups in ICU settings
NS - non-significant difference, (P>0.05).

Parameter	Group I (n=11)	Group II (n=20)	Significance
Aspirin	11 (100%)	20 (100%)	NS
Plavix	3 (27.3%)	4 (20.0%)	NS
Nitropol	7 (63.6%)	14 (70.0%)	NS
ACE inhibitors	8 (72.7%)	13 (65.0%)	NS
Dilatrend	7 (63.6%)	15 (75.0%)	NS
Lasix	11 (100%)	20 (100%)	NS
Daily dose of lasix, mg	44.5±19.6	89.6±24.3	P<0.01

The decrease of the need in the drug therapy was noted in other similar levosimendan trials (SURVIVE, RUSSLAN). These trials have shown that, unlike patients receiving dobutamine, the need in other drugs for the correction of heart failure in the patients treated with levosimendan, was significantly lower. Levosimendan and dopamine were not associated with any adverse events requiring withdrawal of the drug, nor there were any allergies. Tachycardia was significantly more common for dopamine (18 (90.0%) cases), than for simdax (7 (63.6%)) with HR increase being significantly higher in the study group compared to control (9.1% vs 17.6%, respectively, p<0.05). This was apparently due to the absence of beta-adrenoreceptor agonism in levosimendan. Treatment with levosimendan also significantly reduced the rate of tachyarrhythmia as compared to dopamine (1 (9.1%) vs 9 (45.0%) cases, respectively) (p<0.05). No fatal rhythm disorders were observed. Thus, the incidence of serious adverse effects was significantly lower in patients in levosimendan group, which correlated with the results obtained during another multi-center European trial (LIDO).

Unlike dopamine, levosimendan resulted in dose-related decrease of SBP and DBP, which was most probably due to its vasodilating effects causing decrease of myocardial preload and afterload. Hypotension was found in 2 (18.2%) and 4 (20%) patients from groups I and II, respectively, (p=0.2),

normalization of BP in group I patients was achieved through the decrease of infusion rate and there was no need for its discontinuation.

Intraventricular conduction disturbances were found in 1 (9.1%) patient from group I and 1 (5.0%) from group II, (p>0,05), there were no cases of atrioventricular conduction disorders (p>0.05) (Table 5).

Table 5. Adverse and hemodynamic effects of drugs in patients from the study groups.
SBP - systolic blood pressure; DBP - diastolic blood pressure; NS - non-significant difference, (P>0.05).

In 24 and 72 h after acute myocardial infarction all patients underwent EchoCG. Cardiac ultrasound study on day 1 revealed the following: EDD was 52.6±2.3 vs 54.4±2.7 mm, ESD - 38.1±3.1 vs 38.8±3.2 mm, EDV - 132.3±15.2 vs 134.4±16.5 ml, ESV - 62.3±6.4 vs 64.8±6.5 ml, LVEF - 41.6±5.1% vs 40.2±5.4% in groups I and II, respectively. There were no statistically significant differences in the above values between the study groups (p>0.05) (Table 6)

Parameter	Group I (n=11)	Group II (n=20)	Significance
Allergy	0	0	NS
Hypotension	4 (36.4%)	4 (20%)	NS
Tachycardia	7 (63.6%)	18 (90.0%)	p<0.05
HR increase, %	9.1	17.6	p<0.05
Tachyarrhythmia	1 (9.1%)	9 (45.0%)	p<0.05
D SBP, mm Hg	Decrease	Increase	p<0.05
D DBP, mm Hg	Decrease by 4.3±6.6	Increase by 4.7±5.8	NS
Atrioventricular conduction disorders	0	0	NS
Intraventricular conduction disorders	1 (9.1%)	1 (5.0%)	NS

Table 6. Results of Echo-CG performed 24 h after AMI in patients from the study groups.
EDD - end-diastolic diameter of the left ventricle; ESD - end-systolic diameter of the left ventricle; NS - non-significant difference, (P>0.05).

To assess myocardial contractile function at 72 h after AMI all patients underwent repeated ultrasound assessment with determination of LVEF change (DEF), which equaled the difference between LVEF obtained on repeated study (EFr) and LVEF at baseline (EFbas), i.e.

DEF = EFr - EFbas

Left ventricular ejection fraction as measured by EchoCG on day 3, (EFr) in patients receiving levosimendan was 46.8±5.4% vs 42.9±5.6% in control group. There were no significant differences in this value between the groups. However, the change of ejection fraction (DEF) in group I was 5.2±1.4%, which was significantly higher than that in the control, where the value was 2.7±1.2% (p<0.01). Therefore, on day 3 the LVEF increased by 11.7% in patients on simdax, which was significantly higher, than in control group patients, where the increase of LVEF was 6.8% (p<0.01) (Table 7).

Parameter	Group I (n=11)	Group II (n=20)	Significance
EDD, (mm)	52.6±2.3	54.4±2.7	NS
ESD, (mm)	38.1±3.1	38.8±3.2	
EDV, (ml)	132.3±15.2	134.4±16.5	
ESV, (ml)	62.3±6.4	64.8±6.5	
EFbas, (%)	41.6±5.1	40.2±5.4	

Table 7. Results of repeated EchoCG at 72 h after AMI in the study groups.
NS - non-significant difference, (P>0.05).

Clinical improvement, manifested in the decrease of dyspnea and weakness, the absence of ischemia recurrence, was seen in the majority of cases in both groups.

Progression of heart failure confirmed by clinical, radiological and laboratory findings, was found in 3 (15%) patients from the control group and none of the patients receiving levosimendan (p>0.05).

Parameter	Group I (n=11)	Group II (n=20)	Significance
EFr, (%)	46.8±5.4	42.9±5.6	NS
DEF, (%)	5.2±1.4	2.7±1.2	P<0,01
EF increase, (%)	11.7	6.8	P<0,01

Intraventricular conduction disorders and tachyarrhythmia were significantly more common on dopamine - 10 (50%) cases as compared to simdax (2 (18.2%) cases), tachyarrhythmia was significantly more common in the control group as compared to study group (9 (45.0%) vs 1 (9.1%), respectively) (p<0.05). There were no lethal cases within the early period after AMI (up to 3 days) after administration of levosimendan, while mortality rate in the control group was 10% (2 patients) (both deaths were due to progressive acute left ventricular failure resistant to medical therapy) (p>0.05). In group I, as compared to dopamine group, the hospital stay was significantly lower (13.2±2.2 days vs 15.7±3.2 days, p<0.05) (Table 8). The main clinical and hemodynamic results of our study concur with the results of major Russian and European trials of levosimendan effectiveness (SURVIVE, RUSSLAN, CASINO, LIDO). It ought to be noted that the mean level of hospital mortality in these groups of patients treated in Moscow City Center of Interventional Cardioangiology (mortality- 7%) was lower as compared with the level of mortality in some trials (RUSSLAN, CASINO - mortality 12-17%). Most likely, this was related to mandatory performance of myocardial revascularization procedures early after IM in patients included in our study.

Table 8. Clinical course of patients from the study groups

Conclusion. The two statistically similar groups were used to study clinical efficacy and immediate (hospital) outcomes of levosimendan in combination with emergency endovascular procedures to restore coronary blood flow in patients with AMI causing acute heart failure.

There were no hospital deaths, recurrent AMI or ischemic attacks, as well as signs of heart failure pro-

Parameter	Group I (n=11)	Group II (n=20)	Significance
Mortality rate early after AMI	0	2 (10,0%)	p>0.05
Heart failure progression	0	3 (15%)	P>0.05
Tachyarrhythmia	1 (9.1%)	9 (45.0%)	P<0.05
Hospital stay, days	13.2±2.2	15.7±3.2	p<0.05

gression in patients on levosimendan, whereas in patients receiving dopamine the mortality rate was 2%, progression of heart failure was found in 15% of cases.

The study showed that levosimendan therapy resulted in more pronounced improvement of hemodynamics and vasodilation with more rapid reduction of circulatory failure as compared to dopamine. Episodes of tachyarrhythmia were significantly less common and the dose of diuretic significantly lower in patients on levosimendan.

Both groups had improvement of myocardial contraction, which was apparently due to its early revascularization, however, patients on levosimendan had more pronounced improvement of LVEF.

The administration of levosimendan provided more favorable course of the disease and, thus, predicted shorter hospital stay after restoration of blood flow in the infarct-related artery in patients with AMI causing acute left ventricular failure.

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Renal Function and Survival, After Renal Artery Stent Revascularization, May Be Influenced by Embolic Debris

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INTRODUCTION

Often, early observational information is only reaffirmed by numerous subsequent trials or studies. This is what has occurred with renal stent supported angioplasty, which provided accurate and important information through a series of voluntary, non-randomized registries. The data reported herein has been previously published, and now has been found to be accurate as well as important, and remains the foundation to this «new» approach to therapy. In addition, these data enable us to expand and refine the treatment of renal artery stenosis, and, perhaps, develop techniques which will allow restoration as well as salvage of kidney function.

Atherosclerotic renal artery stenosis (RAS) has resulted in accelerated or poorly controlled hypertension, renal dysfunction, pulmonary edema (1-8), ischemic atrophy (9), and ischemic nephropathy, whose histopathologic severity correlated with renal function. (10) RAS stent revascularization has resulted in more facile blood pressure control (11-30), and preservation or stabilization of renal function (24-33). This communication details the 4-years renal function follow-up and survival of 544 successfully stent revascularized RAS patients, utilizing actuarial, paired comparison, and simple linear regression analyses.

METHODS

Between 1990 and 1997, 544 patients underwent balloon expandable stent (Palmaz™, Palmaz-Schatz™; Cordis Corp, Warren, NJ) revascularization of 714 atherosclerotic stenotic renal arteries. The two sites' baseline and follow-up data were prospectively collected and collated on successful patients; the sites protocols, procedural methodologies, and consent forms had been reviewed, approved, and monitored by each Investigational Review Board. No significant differences existed between the sites' cohort demographics. Patient inclusion and exclusion criteria, renal function assessment, and group stratification design have been reported (20, 30).

STATISTICAL ANALYSIS:

The 2-years paired comparison analyses compared data at 6, 12, and 24 months with the patient's baseline value. The 4-years simple linear regression analyses assessed renal function with a trend line slope. The Kaplan-Meier life table methodology assessed survival. A p value of <0.05 was considered statistically significant.

RESULTS

Demographics, procedural indications (not mutually exclusive), patient stratification according to their baseline serum creatinine (SCr), age, stenosis location at the time of the procedure, and number of kidneys are listed (Table I). The majority of unilateral (2 kidneys and a unilateral RAS) (69%) and bilateral (58%) RAS patients had normal renal function, which contrasted with the 36% of solitary kidney patients.

Mean follow-up was 26.3±21.1 months (Table II); and at 4-years, 38% of eligible patients had values within the collection window. The mean SCr showed no change through 4-years (1.6 ± 1.0 vs. 1.6 ± 0.9 mg/dl).

Paired comparison (Table III) data demonstrated no change in the 1/SCr, when compared with baseline or 1-and 2-years values. Similarly, simple linear regression (Table IV) analyses' trend lines demonstrated relatively flat slopes within all patient subsets, which implied no significant alteration or worsening of function.

The 4-years mortality (Table V) was 20%. Normal function patients had a better survival (88%) than those with mild to moderate (60%) or severe (47%) renal dysfunction. Unilateral patients had a better survival (87%) than bilateral (80%) or solitary kidney patients (60%); survival was disparate between unilateral and bilateral patients, especially in the presence of severe dysfunction (67% vs. 24%; $p<0.05$). Surprisingly, medication controlled blood pressure patients fared worse (56%) than those with poorly controlled blood pressure (70%), with the worst outcome being in controlled blood pressure patients with bilateral disease (35% vs. 69%; $p<0.05$).

Two case studies (Fig. 1, 2), with pre and post procedure SCrs, had two trend lines interpolated using the preoperative 1/SCr values, and the post- proce-

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Table I. Patient Demographics, Indications and Procedural Data[b]

1. Demographics			**Entire Cohort**
a. Patients			544
(1). Gender a. Male b. Female			 256 (47%) 288 (53%)
(2). Age (yrs)			69±10 (18-96)
(3). Age distribution a. < 70 yrs b. ≥ 70 yrs			 243 (45%) 301 (55%)
2. Renal Artery Stenosis			
a. Unilateral Stenosis (Pts)			304 (56%)
b. Bilateral Stenosis (Pts)			170 (31%)
3. Anatomical Stenosis Site and Relationship to Diabetes Mellitus			
a. Anatomical Disease		No Diabetes (401)[b]	Diabetes (141)
(1) Bilateral		118 (70%)	50 (30%)
(2) Solitary		52 (74%)	18 (26%)
(3) Unilateral		231 (76%)	73 (24%)
4. Gender Distribution related to pathologic anatomy			
a. Anatomical Pathology and Gender		Male - 256 (45%)	Female - 288 (53%)
(1) Bilateral (170)		77 (45%)	93 (55%)
(2) Solitary (70)		31 (44%)	39 (59%)
(3) Unilateral (304)		148 (49%)	156 (51%)
5. Baseline Serum Creatinine Data			
a. Age	SCr J 1.5 mg/dl	SCr 1,6-1,9 mg/dl	SCr ≥ 2,0 mg/dl
(1) < 70 yrs (243)	170 (70%)a	29 (12%)	44 (18%)
(2) ≥ 70 yrs (301)	165 (55%)a	51 (17%)	85 (28%)a
b. Pathologic Anatomy	335 (61%)	80 (15%)	129 (24%)
(1) Bilateral (170)	99 (58%)	31 (18%)	40 (24%)
(2) Solitary (70)	25 (36%)	7 (10%)	38 (54%)a
(3) Unilateral (304)	211 (69%)	42 (14%)	51 (17%)
6. Procedural Indications (not mutually exclusive)			
a. Poorly controlled hypertension			458 (84%)
b. Preservation of renal function[a]			381 (70%)
c. Congestive heart failure			93 (17%)

[a] creatinine > 1.5mg/dl, [b] 544 patients were eligible for >6 month follow-up, [c] p < 0.05; Pts = Patients

Table 2. Patient Follow-up Eligibility

	Baseline	**1/2 Yr.**	**1 Yr.**	**2 Yr.**	**3 Yr.**	**4 Yr.**
1. Eligible Pts		524	513	435	332	215
b. Solitary	70	64	59	48	40	26
2.Patients With Creatinine Data Within Collection Window						
a. Pts with Eligible Data	544	395	288	215	141	82
b. Eligible	544	524	513	435	332	215
c. Percentage	100%	75%	56%	49%	42%	38%
	Baseline		**1 Yr.**	**2 Yr.**	**3 Yr.**	**4 Yr.**
3. Mean Serum Creatinine (mg/dl)	1,6±1,0		1,7±1,1	1,7±1,2	1,7±1,0	1,6±0,9

Time	**Patients**	**1/SCr**	**Max**	**Min**	**P**
Baseline	544	0,8 ± 0,3	2,0	0,1	--
6 Months	395	0,7 ± 0,3	1,7	0,1	0,42
1 Year	288	0,7 ± 0,3	2,0	0,1	0,25
2 Years	215	0,7 ± 0,3	2,0	0,1	0,74

*Patient had values at each point; N = # of patients at that point in time post procedure; SCr = serum creatinine

dure follow-up values, with their intersection being the procedure date. In both cases, the pre- and postoperative trend lines had different slopes: the negative sloped preoperative trend line (dash) demonstrating progressive functional deterioration, and the positive

Table 4. Simple linear regression analysis of the reciprocal of the serum creatinine in 544 Pts with successful stent revascularization (4 years follow-up)

Cohort	**Наклон графика**	**Стандартная ошибка**	**T**	**Значение p 0,0001**	**R2**
I. Entire Cohort	-0,004	0,006	-0,78	0,43	0,0004
II. Anatomical Stenosis Distribution					
1. Bilateral RAS	0,007	0,012	0,61	0,54	0,008
2. Unilateral RAS	-0,011	0,007	-1,29	0,136	0,0023
3. Solitary RAS	0,016	0,013	1,14	-23	0,006
III. Blood Pressure					
1. Controlled BP	0,023	0,017	1,38	0,169	0,0073
2. Poorly controlled BPd	-0,009	0,006	-1,50	0,134	0,0016
IV. Age at Baseline					
1. <70 years	-0,007	0,008	-0,90	0,370	0,001
2. <70 years	-0,007	0,008	-0,90	0,380	0,0008
V. Diabetes Mellitus					
1. No	-0,012	0,007	-1,71	0,088	0,0023
2. Yes	0,015	0,011	1,38	0,167	0,0045
VI. Serum Creatinine (baseline)					
1. < 1,5 mg/dl	-0,011	0,007	-1,61	0,108	0,0025
2. 1,6-1,9 mg/dl	0,01	0,007	1,43	0,153	0,0079
3. ≥ 2,0 mg/dl	0,004	0,006	0,63	0,526	0,001

S.E. = Standard error, T= t statistic for HO: slope = 0, R2 = correlation [a] p<0.05, [b] 5 pts. Did not have determination of pressure or absence of diabetes, [c] Two functioning kidneys, [d] BP=blood pressure,

* Effective sample size

Table 5. Mortality at 4 Years Follow-up

1. Entire Cohorts		
a. Anatomy	Alive - 441 (81%)	Dead - 103 (19%)
(I) Unilateral (304)	263 (87%)	41 (13%)
(II) Bilateral (170)	136 (80%)	34 (20%)
(III) Solitary (70)	42 (60%)a	28 (40%)a
2. Cumulative Survival Probability at 4 Years Using Selected Variable		
a. Baseline Creatinine	Entire Cohort (544)	Unilateral Disease (304)	Bilateral Disease (170)
(I) < 1,5 mg/dl	85% ± 3,9	80% ± 5,1	79% ± 8,8
(II) 1,5 - 1,9 mg/dl	60% ± 8,0	67% ± 1,5	72% ± 10,0
(III) ≥ 2,0 mg/dl	47% ± 5,7[a]	67% ± 7,8	24% ± 10,9[a]
3. Anatomical Stenosis Distribution	68% ± 2,2	75% ± 4,0	64% ± 6,4
4. Age			
(I) <70 years	77% ± 4,1	85% ± 4,6	72% ± 9,5
(II) ≥ 70 years	60% ± 4,7[a]	64% ± 6,6	60% ± 7,4[a]
5. Procedural Indication			
(I) Controlled BP	56% ± 7,4	76% ± 8,8	35% ± 16,3
(II) Poorly controlled BP	70% ± 85,[a]	75% ± 4,4	69% ± 6,6[a]
6. Diabetes Mellitus[b]			
(I) Non-diabetic patients	73% ± 3,6	80% ± 4,3	67% ± 8,1
(II) Diabetic patients	52% ± 6,3a	60% ± 8,9a	54% ± 9,5a

[a] p< 0,05; [b] Patients did not have data regarding presence or absence of diabetes mellitus; BP = blood pressure

postoperative trend line (dotted) slope, indicating functional improvement.

DISCUSSION

1. Renal Data:

(a) Renal Function:

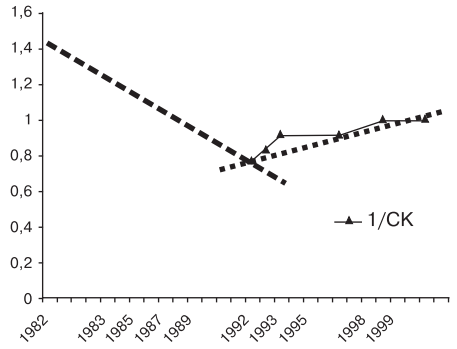

Figure 1. Reciprocal of Serum Creatinine vs. Time: trend lines intersect at time of stent supported renal angioplasty (RW, 68 F)
Legend: In October, 1992, a 68-years old lady, (RW, 68F) with hypertension, hypercholesterolemia, and obstructive coronary disease, underwent stent supported angioplasty of the right renal artery with abolition of a 60 mmHg mean gradient without incident. A serum creatinine value had been recorded 10 years prior to the procedure.

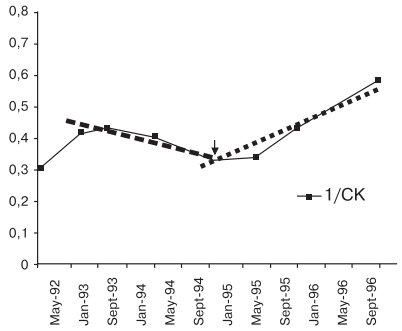

Figure 2. Reciprocal of Serum Creatinine vs. Time: trend lines intersect at time of stent supported renal angioplasty (SJ, 52 M)
Legend: In October, 1992, a 68-years old lady, (RW, 68F) with hypertension, hypercholesterolemia, and obstructive coronary disease, underwent stent supported angioplasty of the right renal artery with abolition of a 60 mmHg mean gradient without incident. A serum creatinine value had been recorded 10 years prior to the procedure.

Paired comparison analysis showed that the 1/SCr slope was flat, which inferred functional stabilization. If ischemic nephropathy were a continuous, progressive disease, then an alteration in functional assessment using the SCr would imply a change in renal physiology. Both case studies demonstrated functional improvement, which would not be consistent with the dogma that ischemic functional deterioration was an ongoing, irreversible progressive process, apart from a few conditions (37-39).

"Tuttle's (32) assessment of the creatinine clearance and glomerular filtration rate (GFR), utilizing Cockroft-Gault methodology, found that the SCr remained stable in his 129 renal stent patients of whom 57% had dysfunction. However, a transitory functional impairment was detailed: cohort's baseline filtration rate was 40±2 ml/min, and subsequent values were 36±3, 39±3, and 39+4 ml/min at 6, 12, and 24 months respectively; and, patients with severe dysfunction (SCr>2.0 mg/dl) showed a similar 6 month trough: baseline of 53±3 ml/min; and 43±4, 46±4, and 52±5 ml/min at 6, 12, and 24 months respectively. Thus, an initial diminution in creatinine clearance appeared to have self-corrected. Simple linear regression analysis data, using 1/SCr, would not reveal the transitory change seen with GFR measurements; however, the functional stabilization reflected by 1/SCr's slope implied stabilization of the GFR, as well as a concordance between the SCr and GFR.

(b) Concordance of the Glomerular Filtration Rate and Serum Creatinine

Creatinine clearance is the summation of creatinine creation, minus its renal and extrarenal elimination. The data aforementioned implied that the GFR (44-47) and SCr were congruent, and, thus, that the SCr was a good functional marker. The SCr has been a simple method of functional assessment, and, by corollary, an outcome assay of any renal intervention. However, the SCr does not perfectly reflect the GFR (42,43), which is the summation of the filtering of all functioning nephrons. At normal levels of renal function (SCr<1.5 mg/dl), GFR measurement techniques more accurately reflect kidney function than do SCr measurements since the wide variation in GFR measurements remain distinctly disparate with stable normal SCr values. However, in the presence of renal dysfunction, (SCr>1.5 mg/dl), the SCr became more concordant with the GFR, and, as such, with function. This disparity between the SCr and GFR in normal function patients makes the reliability of SCr measurements questionable in normal patients.

Firstly, glomerular pathology may be veiled by a normal SCr. If the relatively uniform glomerular pathology of ischemic nephropathy were present, then the total GFR, reflecting a uniform diminution in glomerular capillary surface and/or permeability, would produce a concordant elevation in the SCr after sufficient GFR impairment. However, if nephrons were not all equally or uniformly affected, then the total GFR, which reflected the glomerular capillary surface and/or membrane permeability of both healthy and pathologically functioning glomeruli, could remain within the normal range, if functioning glomeruli could overcome the deficit incurred by the pathologically minimally- or non-functioning glomeruli. In fact, the total GFR and SCr, despite advanced pathological functional disturbances, could remain unchanged, if sufficient augmented glomerular perfusion of non-effected glomeruli occurred. Thus, nephron impairment, uniformly diffuse or segmented, could exist despite a normal SCr. This premise has been supported by the wide range for normal GFR measurements (30 and 80 ml/min/1.73 m^2), while the GFR variation in dysfunctional kidneys was narrow. Thus, the functional stabilization, using SCr assessment in a dysfunctional cohort post stent placement, could indicate that improved blood perfusion to these glomeruli, by relief of the renal artery obstruction, produced improved or augmented glomerular function, which resulted in a stabilized GFR, no further functional deterioration, and, as a result, a stable SCr.

La Batide-Alanore (49) performed split renal function studies on angioplasty patients with two kidneys, and one stenotic renal artery. Single kidney GFR measurements, using Inulin or 51Cr-EDTA clearance, at baseline and at 6 months, showed that the «total GFR increased slightly significantly in the 29 patients

with positive lateralization indices, the split renal function and single-kidney GFR of the stenotic kidney increased, whereas concurrently the GFR and split renal function of the non-stenotic kidney decreased significantly». At 6 months «a reversal of both hypoperfusion of the stenotic side and hyperperfusion of the non-stenotic side was observed, which was accompanied by a slight increase in total GFR». Thus, in unilateral disease patients, glomerular filtration in the non-effected kidney, because of augmentation or compensation, maintained a SCr normal, and renal function improved following angioplasty. However, this explanation remains applicable only to two kidney, single RAS patients, and not to bilateral/solitary kidney patients. In the latter two cohorts, the pathologic nephrologic process must be segmental or non-uniform, since no non-effected kidney existed, and, as such, no augmentation in the non-effected kidney could have occurred. Thus, if functional stabilization occurred, after increasing renal perfusion, some glomeruli in these diseased kidneys must have functioned better.

Intuitively, the pathology associated with chronic renal ischemia should and has caused uniform damage to each glomerulus. The destruction of renal parenchyma, through the development of renal interstitial fibrosis, may result form the tissue fibrogenic cytokines, stimulated in the kidney (49), as well as the suppression of those enzymes necessary to remove apoptic cells (50). These constructs are the result of repetitive tubular insults, which could result from recurrent emboli lodging in glomeruli. Tuttle's transitory GFR changes, provides possible evidence for a non-uniform or uneven pathology, having arisen from recurrent atheroemboli either from the renal artery stenosis, or another site, e.g. atherosclerotic degenerated aorta. Other observations (24, 30, 33, 42, 48) have similarly detailed this transient functional change, and others have detailed that atheroembolic showering occurred after stent placement (51-56). If atheroembolic debris, released intermittently from an arterial stenosis, lodged non-uniformly within the mesangium's end-arteriole glomeruli, and if these arteriole blockages resulted in a segmental pathology, then progressive functional deterioration would result as more glomeruli became involved, but would not be apparent if augmentation occurred in non-effected glomeruli. As such, an aim of any RAS intervention would be the adjunctive prevention of additional emboli release, which could damage more and more glomeruli, especially in severely impaired patients with few functioning glomeruli.

Therefore, ischemia may not be the primary cause of kidney dysfunction from RAS, since circumstantial evidence implicates recurrent atheroemboli as the major factor causing the non-uniform glomerular pathology and the subsequent renal dysfunction. In fact, the post-procedure stable renal function may reflect increased glomerular perfusion to those capable of functional augmentation. This physiologic change, as well as prevention of subsequent emboli episodes by a neoendothelial covered stent, resulted in stable function. Perhaps, if debris showers could be prevented during stent deployment, especially in patients with marginal glomerular function, then fewer glomeruli would be damaged, and the transient decline in the GFR might not occur, which might be very important in dysfunctional patients. Furthermore, the hypothesis that the increased renal perfusion pressure, coupled with glomerular functional augmentation, which resulted in stabilized or even improved function was observed in the two case studies.

2. Survival

The better survival of poorly controlled in contrast to medication controlled blood pressure patients appeared counterintuitive, and contrary to accepted medical theory. Baseline data for the poorly controlled in comparison to the controlled blood pressure patients detailed a lower SCr (1.7±1.0 vs. 2.1 ±1.8 mg/dl, $p<0.05$), and higher systolic (171±27 vs. 144±20 mmHg, $p<0.05$) and diastolic (86±15 vs. 75±12 mmHg, $P<0.05$) blood pressures. The poorly controlled patients' better renal function may be indicative of a rapidly worsening stenosis, poorer renal perfusion, increased renin production, and worsening hypertension. This clinical scenario reflected ischemic stimulation of the renin-angiotensin system and not recurrent embolization. Furthermore, while controlled blood pressure cohort had what has been considered good medical management, nevertheless, this therapeutic approach permitted unabated recurrent atheroembolic debris arising from the RAS, which resulted in extensive end-arteriole glomerular damage, functional deterioration, SCr elevation, and diminished survival. Furthermore, the maintenance of a controlled lowered blood pressure, in the presence of renal artery stenosis, will and could significantly lower the renal perfusion pressure distal to the stenosis, which would result in under perfusion of the post-stenotic renal parenchyma. The result of antihypertensive medications could actually cause further loss of glomerular filtration, and, as mentioned be a significant factor in the poorer survival, which correlates with worsening renal function (57). In contrast, the stent-revascularized poorly controlled blood pressure cohort, whose blood pressure came under rapid control, despite a reduction in number of antihypertensive medications, had stable renal function. Since renal function has directly correlated with survival, these poorly controlled blood pressure patients with better baseline renal function, had a better survival prognosis than medication controlled blood pressure patients.

LIMITATIONS

This study's primary limitation is lack of more complete follow-up data, which has been a problem for a voluntary registry but also of clinical settings in which patients are treated by tertiary care interven-

tionists, who do not have primary control of the patient; and, once the patient has returned to the primary care physician, data often will not be collected at the proscribed times. However, the cohort size, and the use of paired comparison and simple linear regression analyses makes these data compelling. Finally, while the study coordinators attempt to retrospectively obtain adequate pre-procedure serum creatinine data was unsuccessful, and, as such, precluded demonstration of an alteration in the post stent revascularization period for these cohorts, nevertheless, the case studies' 1/SCr slope did demonstrate that this. can occur following stent revascularization.

CONCLUSIONS

The follow up of successfully stent revascularized RAS patients demonstrated renal function stability, which underscored the premise that the nephropathy associated with RAS may be primarily segmental, and, more likely, a result of recurrent atheroemboli lodging within the end-arteriole glomerulus, rather than from ischemia. The better survival of the poorly controlled blood pressure cohort with its lower baseline SCr than that of the medication controlled blood pressure cohort indicated that two pathologic processes probably existed, and that recurrent embolization, rather than ischemia, appeared to more adversely affect function and survival. Furthermore, potentially, if the shower of embolic debris could be eliminated during stent placement, then such a methodology would not only decrease the number of immediately damaged glomeruli, coupled with the neoendothelialization of the stent might preclude further recurrent embolic damage, and glomerular functional augmentation might result in functional stabilization or improvement, which could positively impact survival. Thus, the early diagnosis of RAS, especially in patients with new onset hypertension or hypertension managed with multiple drugs, could avoid the use of potent antihypertensive mediations, as well as the created veil of controlled blood pressure, which also permitted unabated recurrent embolization.

A randomized trial of stent supported RAS patients, with and without embolic protection devices, and periodic SCr measurements, especially in patients with renal dysfunction, could easily provide a concrete answer to these clinical interrogatories, including post-procedure functional stabilization. In addition, the ability to retrospectively obtain SCr values from dates prior to the procedure would enable demonstration of a change in the trend line slope, and whether or not this progressive functional worsening could be halted. Positive conclusions of such a trial would have enormous medical, economic, and social implications.

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Mid-Term Results of Direct Myocardial Revascularization

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Direct myocardial revascularization is one of the primary methods of CAD treatment in patients with severe lesions of epy coronary arteries (1, 2, 3, 4, 12). Due to wide implementation of endovascular surgery into clinical practice the cohort of patients referring for direct myocardial revascularization mainly consists of patients with multivessel lesions, occlusions, small diameter of coronary arteries (CA) and lesions of the main coronary artery (1, 5, 6). However, in the world's best clinics the mortality rate following those procedures does not exceed 2-3% (7). Despite the great number of the performed procedures and wide experience, not all the aspects of coronary surgery have been settled so far. For example, such issues as the type of the conduit for bypass grafting of different arteries (8, 9), the type of anastomosis (7, 10, 11), the extent of revascularization with regard to the extent and nature of coronary artery lesions (2, 5, 7, 10, 12, 16), their state in long-time follow-up (5, 13, 19) and others are still being discussed.

The aim of the study is to summarize our experience with surgical treatment for CAD, to evaluate its efficiency on the basis of the comparative analysis of the extent of the surgery, the changes of coronary vasculature, the state of the grafts as well as the clinical status of the patients in mid-term follow-up after direct myocardial revascularization.

Material and methods

From January 2001 until April 2004 315 direct myocardial revascularizations in CAD patients were performed in our center. In-hospital mortality was 1.3% (Table 1). Two hundred and seventy six patients were males (87%). The age of patients ranged from 33 to 72 years (mean 56.9±1.79 years). Macrofocal post-infarction scars in the left ventricle were observed in 144 (45.8%) patients. 75,9% of patients had NYHA functional class (FC) III-IV angina. Eighty (25.4%) patients had decreased ejection fraction (EF) (<50%). The number of anastomoses ranged from 1 to 6 (mean, 2.85±0.15). Autoarterial conduits performed out of internal thoracic artery (ITA) were used in 400 cases. The left ITA was used in 290 cases (274 in situ grafts and 16 free grafts), and the right ITA was used in 114 cases (26 in situ grafts and in 88 free grafts) In 2 patients we used the right gastroepiploic artery (RGEA) in situ. Bimammary bypass grafting was performed in 136 patients (43.3%), while 169 (53.8%) patients underwent monomammary grafting (Table 2). In ninety eight patients (31.2%) only arterial conduits were performed, and in 207 patients - both arterial and venous conduits (65.9%). In 9 patients (2.9%) due to the anatomic features of ITA the revascularization was performed by means of the great saphenous vein (GSV). In 98% of cases bypass grafting of the left anterior descending artery (LAD) was performed using arterial conduits. The survival rate amounted to 99.6%. One patient died of the abdominal aortic rupture 3 months after the procedure. Significant clinical improvement was observed in 89.6% of patients.

Upon discharge we recommended all the patients to undergo the control examination in our centre 6 months after the surgery. By the moment this article was written 106 consecutive patients were re-examined and, irrespective of their clinical status underwent follow-up coronary angiography and shuntography in order to evaluate the condition of the coronary vasculature and the state of the grafts on average 7.2 ±0.8 months after the procedure.

In total, in these patients 312 distal anastomoses were performed using 203 (65.1%) arterial grafts and 109 (34.9%) venous grafts. In 103 cases we used in situ ITA grafts and in 49 cases - free grafts. Straight grafts were implanted in 171 cases, sequential grafts - in 55 cases, and composite Y-grafts - in 35 cases.

Surgical technique

All the procedures were performed through median sternotomy. Extracorporeal circulation (ECC) was used under moderate hypothermia (up to 30°C). In all cases we used one two-stage venous cannula. The arterial line was inserted into the ascending segment of the aorta. Cardioplegia was induced by antegrade injection of cold (4°C) Custodiol solution. Mean time of the artery cross-clamping amounted to 70 ± 24 min (ranged 20-150 min). ECC duration ranged from 30 to 328 min (mean, 126 ± 42 min). Proximal anastomoses were performed using parallel ECC with the aorta pressed against the wall. Distal anastomoses were performed with single cross-clamping of the aorta.

In all cases ITA was separated by skeletonization (7, 9, 14, 15) from its orifice to the site of its bifurcation into the musculophrenic and superior epigastric arteries.

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Table 1. PREOPERATIVE CHARACTERISTICS OF PATIENTS

	NUMBER OF PATIENTS	%
Age	33-72	average. 56.9±1.79 years
Sex (male)	276	87,9
History of Q(+) MI	144	45,8
History of Q(-) MI	66	21,1
NYHA FC II	29	9,2
NYHA FC III-IV	238	75,9
Unstable angina	47	14,9
AMI	13	4,1
Arterial hypertension	232	73,9
Diabetes mellitus	22	7,0
Hypercholesterolemia	236	75,2
Ejection fraction:		
< 35%	7	2,2
= 36-49%	73	23,2
> 50	235	74,8
Vascular lesions:		
Left MCA	63	20,1
One-vessel lesion	19	6,1
Two-vessel lesion	101	32,2
Three-vessel lesion	191	60,8
Mortality	4	1,35

In 159 cases bypass grafting was performed using direct anastomoses.

One hundred and thirty nine sequential anastomoses (SA) were performed in 133 patients, with the following arteries being used as conduits: left ITA (74), right ITA (27) and GSV (38). In 13 cases SA was a part of Y-graft. Bypass grafting of the left anterior descending artery was performed using parallel technique; in all other cases we formed diamond-shape anastomosis to the first vessel and end-to-side anastomosis to the second vessel. Revascularization of the anterior wall of the left ventricle was performed using only arterial conduits. In 92% of cases the diagonal artery and LAD were anastomosed. Arterial conduits for revascularization of the lateral wall were used in 48% of cases. Revascularization of the diaphragmatic wall of the left ventricle was performed using venous conduits in all patients.

Table 2. CONDUITS USED FOR ANASTOMOSES

CONDUIT	NUMBER
Left ITA Pedicle graft (in situ) Free graft	290 274 16
Right ITA Pedicle graft (in situ) Free graft	114 26 88
RGEA in situ	2

Composite Y-anastomosis was performed in 35 patients, using arterial grafts in 34 patients and venous graft (GSV) in 1 patient. In 7 patients the anastomosis was performed using only left ITA and in 27 patients the free graft of the right ITA was anastomosed to the left ITA. In all cases mammary-to-mammary artery anastomoses were performed in the area of the pulmonary artery trunk and before ECC induction.

Spontaneous recovery of heart function after removal of the clamp from the aorta was observed in 74 patients (58.7%). In all other cases we performed electrical defibrillation. Ninety five percent of patients were extubated within the first 4-5 hours postoperatively.

Postoperative complications In-hospital mortality amounted to 1.35% (4 patients). In two patients the main cause of death was cardiac tamponade. One patient died of acute coronary insufficiency caused by graft thrombosis. In one cases the patient's death was caused by postoperative acute renal failure (ARF).

Table 3. EARLY POSTOPERATIVE COMPLICATIONS

COMPLICATIONS	NUMBER OF PATIENTS	%
Mortality	4	1,3
Bleeding	19	6,1
Acute cardiac tamponade	2	0,6
Acute heart failure (IABC)	1	0,03
Acute respiratory failure	1	0,03
AMI	3	1,0
Atrial fibrillation	64	20,4
Acute renal failure + polyorganic failure	1	0,03
Wound complications	9	3,0
Cerebral complications Stroke Brain edema Behavioral complications	 1 1 24	 0,3 0,3 8,1

Rethoracotomy due to bleeding was performed in 19 patients (6.1%). This complication was mainly caused by: damage to the sternum (4 patients), venous bleeding at the site of the ITA bed (4 patients), arterial bleeding from the distal branches of ITA (2 patients), bleeding from the soft tissues of the anterior mediastinum (7 patients), hemorrhage at the site of the proximal aortic anastomosis (2 patients) and at the distal anastomosis to the marginal artery (1 patient).

Acute myocardial infarction (AMI) diagnosed in the immediate follow-up developed in 3 patients (1%). In one patient it was caused by left ITA spasm. In another patient bleeding at the site of the distal anastomosis to the marginal artery resulted in inadequate blood supply of the posterolateral wall of the left ventricle. In the third case the distal segment of the posterior descending artery was embolized by atheromatous masses after revascularization of its proximal portion. In no cases AMI was caused by insufficient myocardial protection.

Acute heart failure (AHF) associated with ischemic ECG changes occurred in one patient with the baseline EF of 28%. AHF developed in the operating room before anesthesia induction. In this patient we performed urgent revascularization of LAD and MA. Intraaortic balloon counterpulsation (IABC) was begun before the extracorporeal circulation was discontinued. The counterpulsation was stopped on the third day when hemodynamic parameters became satisfactory. The patient was discharged 21 days after the pro-

cedure.

Signs of heart failure, which required intravenous administration of cardiotonics and catecholamines over 6 hours postoperatively or of dopamine in the dose exceeding 5 mg/kg/min, were observed in 18 patients (6,1%). In the remaining cases hemodynamics was successfully maintained by ensuring adequate preload. Atrial fibrillation (AF) in the early postoperative period was seen in 64 patients (21.6%), with 11 out of them having experienced paroxysms of AF before the surgery.

Wound complications were observed in 9 patients (3.1%). 6 patients (2.4%) had grade I complications, 2 patients (0.6%) - grade II-a complications and 1 patient (0.3%) - grade II-b complications according to E.L. Oakley classification, 1996 (16). In one patient the sternum was closed by modified Robischek method (17). In another patient with sternal osteomyelitis we performed muscle graft sternoplasty. In other cases the sternum was closed by routine osteosynthesis. We did not observe any relationship between the rate of wound complications and the number of separated ITAs or presence of diabetes mellitus (9. 18).

Cerebral complications. One patient had ischemic stroke caused by delayed (on the 9-th day follow-up) cerebral artery thromboembolism. After the treatment in the specialized department the patient was discharged with signs of residual hemiparesis. In one patient brain edema was caused by persistent hypotonia due to postoperative bleeding. Behavioral complications such as acute psychosis, excitement, disorientation in time and space, dormancy, amnesia and others were observed in 46 patients (15.6%). During in-patient stage all adverse events resolved or minimized.

Mid-term results

On average 7.2 ± 0.8 months after shuntography 290 out of 312 (92.9%) grafts remained patent. Two hundred and eighty four grafts were in good state, and 6 were in satisfactory state (lumen narrowing of the anastomoses <50% in 4 cases and diffuse lesion of the conduit itself to the same extent in 2 cases). At the control examination 12 grafts (4 arterial and 8 venous) appeared occluded. Another 10 grafts (5 arterial and 5 venous) had hemodynamically significant stenoses. Concurrent blood flow was observed in 8 patients. Regardless the type of anastomosis this complication was seen only when the narrowing of the grafted coronary artery was < 50%. i.e. the stenosis was «immature». Comparative analysis of the results of shuntography with regard to the type of conduit snowed that 95.6% (194 cases) of arterial grafts and 88.1% (96 cases) of venous grafts were in good state. Function of 9 out of 203 (4.4%) arterial grafts and 13 out of 109 (11.9%) venous conduits was relatively unsatisfactory. Occlusions occurred in 2% and 7.3% and stenoses in 2.4% and 4.6% cases respectively. Comparative analysis of angiography data with regard to the type of anastomosis revealed satisfactory patency rate in 91.2% of direct grafts (10 occlusions and 5 stenoses), 94.5% of sequential grafts (1 occlusion and 2 stenoses) and 71.4% of Y-grafts (2 stenoses and 2 diffuse lesions of the lateral branch of the composite conduit). One out of two stenoses of the Y-conduit was seen at the level of proximal mammary-to-mammary artery graft and another - in the area of the distal anastomosis. Analysis of the causes of relatively higher rate of composite graft lesions revealed that in one case the graft was performed using GSV and was anastomosed to the branch of the obtuse marginal artery (1.2 mm in diameter); the insufficiency was likely due to the difference in the conduit and coronary artery diameters. In another patient inadequate functioning of the lateral branch was caused by practically total calcinosis of the circumflex artery. Thus, relatively insufficient function of composite grafts is unlikely due to the imperfection of the anastomosis of this type. We did not see any difference in the patency rates between in situ and free ITA grafts. It should be especially noted that there is no difference in the rate of inadequate results with regard to arterial and venous conduits provided that these were sequential anastomoses. Fifty two out of 55 SAs were in good state (94.5%). No cases of venous conduit patency loss were reported. Two out of 3 inadequately functioning arterial conduits were less patent at the level of the first vessel and in 1 case we observed alternative blood flow when the «immature» vessel was revascularized.

Dynamic observation of changes in the native coronary arteries showed progression of atherosclerosis in grafted arteries proximal to the anastomosis site in 27 (25.5%) patients. In 15 patients (14.1%) previously patent arteries were occluded and 12 patients had more extended stenosis in well functioning grafts. The increased lumen narrowing distal to anastomosis site was observed in 8 (7.5%) patients and in 7 (6.6%) patients the same changes were seen in non-grafted arteries.

Complete revascularization was performed in 57.5% of cases, incomplete revascularization - in 42.5%. Revascularization was considered complete when bypass grafting was performed on all the arteries of 1 mm diameter stenosed by more than 60%. The clinical effectiveness was 91.1% in case of complete revascularization and 82.2% in case of incomplete revascularization.

Table 4. CHANGES OF CAD CHARACTERISTICS IN THE POSTOPERATIVE PERIOD

	NUMBER OF PATIENTS	%
No signs of angina	80	75,4
NYHA FC I-II	15	14,2
NYHA FC III	6	5,7
NYHA FC IV	-	-
Unstable angina	3	2,8

75.4% of the total number of patients were free of any anginal complaints. Fifteen patients (14.2%) had significant clinical improvement, i.e. decreased intensity of angina attacks, decrease by 1-2 FCs and

decreased dosage of previously taken antianginal drugs. None of patients appeared to have FC IV in the studied period, while prior to revascularization 28 patients (9.5%) had the corresponding functional class. Symptoms of unstable angina persisted in 3 out of 18 operated patients in the follow-up period. In all those cases revascularization was incomplete. In one case bypass grafting of the circumflex artery (CA) or its branch was not possible due to prominent changes of the artery walls, and in another case there was a luminal narrowing distal to the anastomosis to the large intermediate artery (later it was successfully stented). In another young patient with severe dislipidemia despite complete revascularization, occlusion of the branch of the posterior descending artery distal to the anastomosis site and progression of stenosis in non-graft vessels developed due to aggressive atherosclerosis. Two patients (1.9%) had acute myocardial infarction (AMI) in the studied period. In one patient it was caused by occlusion of the venous graft to the posterior descending artery following endarterectomy. In the other patient the CA graft was occluded while branches of the proximally occluded right coronary artery were not revascularized (total calcinosis, small diameter).

Positive changes in EF and exercise tolerance reflect the improvement of the patients' quality of life (Table 5). Changes in EF values were statistically significant only in patients with initially decreased myocardial contractility (EF <45%).

Table 5. CHANGES IN EJECTION FRACTION AND VELOERGOMETRY (VEM) PARAMETERS BEFORE AND AFTER PROCEDURE

	BEFORE THE PROCEDURE	AFTER THE PROCEDURE	RELIABILITY
Ejection fraction	41,1±1,72	52,5±3,09	< 0,008
Load intensity	66,2±4,31	96,8±4,71	< 0,0001

It should be noted that in 11 patients (42%) clinical signs of CAD in the follow-up period were caused by inadequate function of grafts, in 9 patients (35%) - by progressive atherosclerosis, and in 6 patients (23%) - by incomplete revascularization. Control coronary angiography revealed the changes allowing to perform endovascular interventions in 15 patients. In this group of patients we performed the following procedures: PTA and ITA stenting due to the torsion of the graft -1, PTA and stenting of distal anastomosis - 2, PTA of non-graft artery - 7, PTA and stenting of non-graft artery - 1, PTA of graft artery in the distal portion of anastomosis - 4. In one case the procedure was performed through the left ITA. In all cases artery patency was restored or improved.

DISCUSSION

The main purpose of coronary surgery at the current stage of development consists not only in the improvement of immediate results but also in the search of the ways for the improvement the patients' life quality and the achievement of long-lasting positive clinical effect. Left ITA is currently considered to be the conduit of choice for revascularization of the posterior descending artery (7, 12, 18), while under some circumstances it could be replaced by right ITA (19). Sequential anastomosis to in situ left ITA graft has been recognized as the best variant for concurrent revascularization of the LAD and the diagonal artery (DA) (8, 20). We used this type of anastomosis for revascularization of vessels mainly of the same pool (7). However, when SA was a part of composite Y-graft it was performed out of vessels from different systems. The same rate of lesions in arterial and venous conduits used for SA is encouraging, especially for the cases when bimammary grafting is not possible. It may be possibly explained by increased flow through the conduit compared to the ordinary line graft (22). Composite Y- anastomosis is a method of choice for revascularization of vessels from different pools (21,11). It may be constructed using left and/or right ITA (11) as well as of left ITA and the radial artery (RA) (19). Due to our limited experience we can not make any particular objective conclusions concerning the reasons of relatively unsatisfactory function of this anastomosis in the mid-term period. With regard to the world experience it is obvious that specialists should more clearly identify the indications for surgery and more carefully choose the technique of the procedure. In our experience, revascularization of the right coronary artery system in most cases was performed using venous grafts. However, we think that even in such situations we should use individual approach. Sharing the opinion that lesions are more likely to appear in venous grafts (3, 7, 8, 21) and taking into account short follow-up period we can not exclude injuries of GSV walls during its separation and preparation (23), differences in the vessel diameter and technical errors as possible causes of relatively unsatisfactory function of these conduits in the mid-term period.

The clinical effectiveness of complete revascularization is higher than that of incomplete procedure (2, 6, 7, 10). Anyway the main task of direct revascularization can not be always successfully fulfilled due to anatomic and topographic features of coronary arteries. In such situations the effectiveness of the operation is determined by adequate identification of the vessels supplying blood to the specific areas and full restoration of blood flow through these vessels. Our results also support this approach. Two thirds of patients who underwent incomplete revascularization were completely free of angina. In such cases we can observe anatomically incomplete but clinically «adequate» restoration of coronary blood flow (2).

Therefore, operative risk of direct revascularization of coronary arteries is not high, and revascularization is an effective method of treatment in CAD patients. Maximum use of arterial conduits including composite SA and Y-grafts allows to suggest persistent positive long-term prognosis. Further improvement of the results is possible with the following measures: having a clear impression of anatomical substrate of the dis-

ease with the consideration of the areas totally and regionally perfused by affected arteries; developing optimal surgical technique and operative tactics and target postoperative prevention of progressive atherosclerosis. In this regard, coronary arteriography should be a mandatory part of repeated clinical examination in the mid-term period. Hemodynamically significant stenoses should be considered as an indication for PTA and stenting if necessary. This approach allows to diagnose complications at early stages, promptly correct them and thereby minimize the probability of the reappearance or progression of coronary insufficiency, i.e. to improve patients' quality of life.

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What's New in the Diagnostics and Drug Therapy of Atrial Fibrillation

I.G. Fomina, Professor, Chairman of the Section «Electrocardiography and Cardiac Rhythm Disorders» of the Russian Scientific Society of Cardiology

In October 2002, after a long discussion at the annual Congress of the Russian Scientific Society of Cardiology (RSSC) about 400 Congress delegates and members of the Section «Electrocardiography and Cardiac Rhythm Disorders» accepted the recommendations on atrial fibrillation diagnostics and treatment approved in 2001 by the European Society of Cardiology (ESC), American College of Cardiology (ACC) and American Heart Association, as the basis for the development of national recommendations. In 2004 Russian Recommendations on atrial fibrillation diagnostics and treatment were confirmed by the Expert Committee of RSSC, and on October 20, 2005, they were unanimously adopted at RSSC plenum (fig. 1).

Fig. 1. Russian recommendations on the diagnostics and treatment of atrial fibrillation

Russian Recommendations attach a special attention to the problems of terminology and classification of atrial fibrillation. The widely used in Russia term «ciliary arrhythmia», suggested by G.F.Lang in 1921, included atrial fibrillation and flutter. Later on, electrophysiological investigations and endocardial mapping gave convincing evidence of atrial flutter and atrial fibrillation being different types of heart rhythm disorders with different mechanisms of development and sustenance. For this reason the experts of RSSC recommend to avoid the term «ciliary arrhythmia» and to use instead the terms «atrial fibrillation» and «atrial flutter». It should be noted that Russian Recommendations concern only atrial fibrillation, while atrial flutter is considered separately.

From clinical viewpoint it is important to distinguish the «primarily revealed» atrial fibrillation, found at ECG-examination (single-stage or durable) during the present visit. It is important for the determination of further tactics of treatment. The «primarily revealed» atrial fibrillation can represent the first manifestation of the «recurrent (paroxysmal, persisting)» atrial fibrillation, as well as the primarily registered «permanent (chronic, continued)» atrial fibrillation. Within the frames of «recurrent» atrial fibrillation are unified the «paroxysmal» atrial fibrillation - whose attacks terminate independently, without treatment, and «persisting» atrial fibrillation - necessitating anti-arrhythmic drugs or cardioversion for stopping. The «permanent (chronic)» atrial fibrillation includes the cases when rhythm disorders persist permanently during one year, and cardioversion, as the most effective method for sinus rhythm restoration, proved ineffective or its conduction was contra-indicated (fig. 2).

12-lead ECG-investigation, being the obligatory

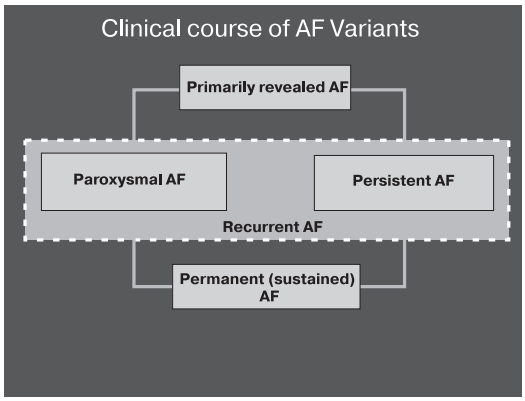
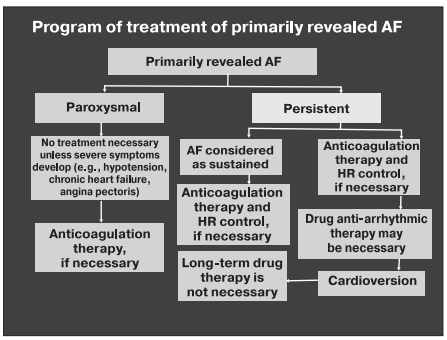


Fig. 2. Classification of atrial fibrillation

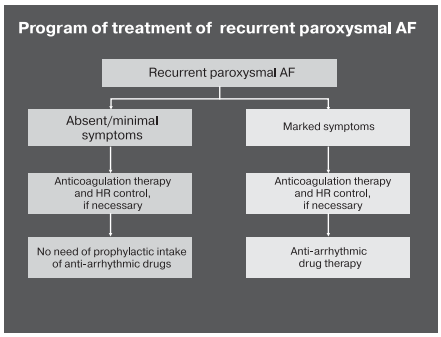
method of examination of all patients, remains the «gold standard» in the diagnostics and treatment of atrial fibrillation. The necessary minimum of examination methods also includes chest X-ray, EchoCG, also using transoesophageal transducer for the detection of thrombi in the left atrial appendage, and the examination of thyroid function. Additional methods of investigation include Holter ECG for 24 hours and more, treadmill test and electrophysiological study.

The schemes 1-4 show the programs of treatment depending on AF form.

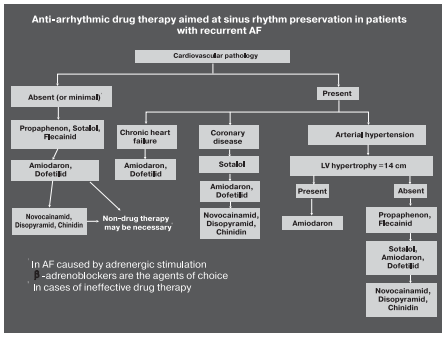
The cohort of patients with continuously recurrent AF is the most difficult to treat. The restoration and the maintenance of sinus rhythm in such patients represent an actual and still understudied problem. Among the agents with high-level reliability for the treatment of persistent AF of less than 7 days duration one can cite Dofetilid, Flecainid, Ibutilid, Propaphenon. In AF of over 7 days duration - Dofetilid, Amiodaron, Ibutilid, Flecainid, Propaphenon, Chinidin. Propaphenon is a unique agent in this series, as, besides the properties



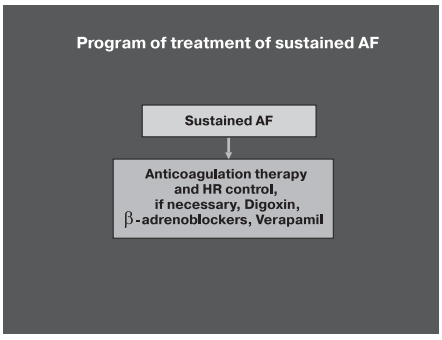
Scheme 1. Treatment program in primarily revealed AF



Scheme 2. Treatment program in recurrent paroxysmal AF



Scheme 3. Treatment of AF depending on the concomitant cardiovascular pathology



Scheme 4. Treatment of permanent (chronic) AF

of IC-class agents, it also possesses the properties of anti-arrhythmic drugs of the II, III and IV classes. The pharmacokinetics of Propaphenon allows to prescribe its oral administration in the form of loading dose with small side effects. In view of the mentioned properties of Propaphenon, as well as in view of limited Russian experience with its use for the stopping of AF attacks and the maintenance of sinus rhythm, the Section «Electrocardiography and Cardiac Rhythm Disorders» of the RSSC, together with the company PROMED, CS Praha a.s (Czechia), organized an independent multi-center open pilot trial «Study of Effectiveness and Safety of Propaphenon used for Sinus Rhythm Restoration and Maintenance in Paitents with Persistent Atrial Fibrillation» - «PROMETHEUS» (chief researcher - Chairman of the Section «Electrocardiography and Cardiac Rhythm Disorders» of the RSSC, Professor I.G. Fomina).

The trial included 485 subjects from 16 different regions of the RF (fig. 3). The Patients were randomized into 2 groups. Group I consisted of 285 patients aged 31 - 62 years (mean, 57,6±2,8 years), who were prescribed Propaphennon (Propanorm, PROMED, CS Praha a.s. pharmaceutical company) in a single oral loading dose of 600 mg, for the stopping of AF paroxysm. Group II consisted of 200 patients aged 39 - 68 years (mean, 56,4±4,2 years), in whom Propaphenon was prescribed for AF paroxysms' prophylactics in a daily dose of 450 mg orally (150 mg x 3 times daily). The effectiveness of anti-arrhythmic therapy was evaluated using Holter ECG monitoring 1, 3 and 9 months after the start of the treatment.

Inclusion criteria comprised: the presence of documented AF paroxysm of (48 hours duration, confirmed during ECG examination or Holter ECG monitoring and willing consent of patients.

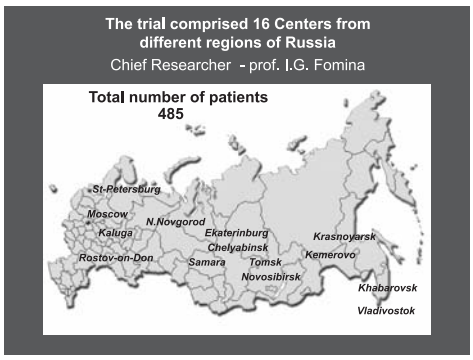


Fig. 3. «PROMETHEUS» trial

The main cause of AF was coronary heart disease diagnosed in 159 (56%) patients of Group I and 26 (13%) patients of Group II, arterial hypertension was revealed in 88 (31%) and 46 (23%) patients, respectively. Idiopathic form of AF was found in 33 (11%) patients of Group I and 94 (47%) patients of Group II.

Exclusion criteria were: sick sinus syndrome; I-III degree AV block; congenital or acquired long QT syndrome, WPW, Brugada syndromes; presence of decompensated heart failure (IIB-III Strajesko-Vasilenko degree), NYHA class IV; infective endocarditis, pericarditis or myocarditis; rheumatic and congenital heart defects; acute myocardial infarction; chronic obstructive lung diseases; any thyroid function disorders; marked renal and/or hepatic patology; blood diseases; cancer.

All patients underwent clinical, laboratory and instrumental examination. General clinical assessment included the study of complaints and history of the disease, detection of cardiovascular risk factors, evaluation of objective status, laboratory examination. Among instrumental methods used were standard 12-lead ECG, 24-hours Holter monitoring, EchoCG study.

Results. Sinus rhythm resumed in 240 (84%) patients in Group I. The average time needed for this

restoration made 150±30 min. The obtained data confirm the results of previous trials on anti-arrhythmic Propaphenon activity (fig. 4).

Side effects with loading dose of Propaphenon were revealed in 17 (6%) patients in Group I. The disturbances of intraventricular conduction were registered in 9 (3%) patients, II degree AV block - in 8 (3%) patients, signs of dyspepsia were seen in 2 (0,9%)

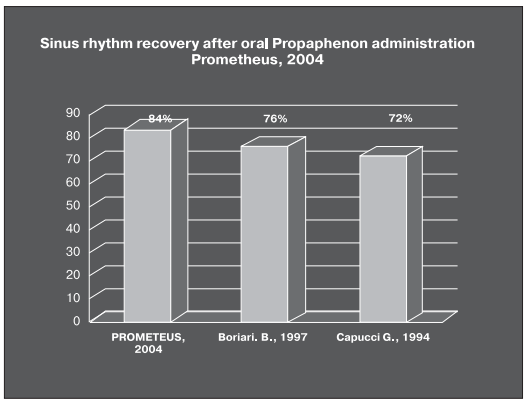


Fig. 4. Effectiveness of loading dose of Propaphenon for sinus rhythm restoration. Результаты «PROMETHEUS» trial

patents. Arterial pressure decrease to maximal value of 100/70 mm Hg occurred in 28 (10%) cases. Any other side effects associated with loading dose intake were registered.

The effectiveness of antiperiodic treatment with Propaphenon was evaluated in Group II. After 1 month of Propaphenon intake in daily dose of 450 mg sinus rhythm was preserved in 148 (74%) patients, after 3 months of anti-arrhythmic therapy - in 142 (71%) patients, after 9 months - in 90 (45%) patients (fig. 5).

Side effects in prolonged intake of Propaphenon were practically absent. The signs of dyspepsia developed in 8 (4%) patients, vertigo - in 5 (2,5%) patients of Group II. In 7 (3,5%) patients daily intake of 450 mg of Propaphenon led to the prolongation of P-Q interval by 18% from the baseline value, in 8 (4%) patients

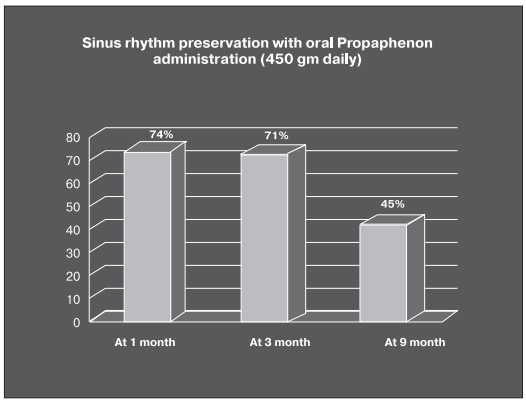


Fig. 5. Effectiveness of Propaphenon for the preservation of sinus rhythm Results of «PROMETHEUS» trial

there was QRS complex extension by 28% from the baseline value. All side effects resolved spontaneously and did not required additional treatment.

Thus, the «PROMETHEUS» trial allowed to draw the following conclusions:. The prescription of Propaphenon in a loading dose of 600 mg orally is an effective and safe method for sinus rhythm restoration in patients with persistent form of atrial fibrillation. Prolonged intake of Propaphenon in daily dosage of 450 mg is a highly effective and safe method for the prophylactics of AF paroxysms recurrence

The «PROMETHEUS» trial is the first independent multi-center investigation, which allowed RSSC to unify the efforts of physicians and specialists from many regions of Russia. A successful experience with the conduction of such trial permits to plan the next stages of the investigation involving the new centers for the acquisition of the data, that will be included into the future revision of national recommendations and will be used in medical practice

The inhibition of the processes of fibrosis development in the atrial myocardium and the decrease of the risk of AF recurrence represent a promising trend in the AF treatment. The study of the effects of prolonged use of angiotensin-converting enzyme inhibitors and angiotensin II receptors blockers, as well as of the influence of lipid-reducing therapy with statins on the incidence of recurrence in patients with persistent AF still remain relevant topics of interest.

Atrial Fibrillation: Electrophysiological Mechanisms, Indications and Results of Interventional Treatment

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Atrial fibrillation (AF) or «ciliary arrhythmia» is the most common type of tachyarrhythmia observed in clinical practice. Atrial fibrillation is associated with higher risk of thromboembolism, development of arrhythmogenic cardiomyopathy and a substantial increase of mortality rate in patients with heart failure (1, 8).

Novel approaches to the treatment of AF concern the use of current class I and class III anti-arrhythmic drugs that, unfortunately, allow do preserve sinus rhythm in no more than 40-50% patients with persistent AF within 12-24 months after sinus rhythm restoration (15). Since 1982, creation of artificial complete atrioventricular heart block with implantation of the pacemaker has become one of the most common methods of surgical treatment of tachysystolic type of AF, while in the last 15 years physiological and frequency adjustable electrocardiac pacemakers (ECP) have also been used (4). However, this approach can be regarded only as a palliative method of treatment in patients with AF, as in this case atria still can maintain fibrillatory activity, and therefore risk of thromboembolism, including brain thromboembolism with the occurrence of ischemic stroke still exists. Moreover, according to several studies the rate of sudden death in patients who underwent radiofrequency ablation (RFA) of the His bundle and ECP implantation is 2-5% (2, 4).

The only radical method of drug refractory and symptomatic forms of AF is the «maze» procedure developed by J. Cox in 1987 that allows to preserve sinus rhythm and to eliminate risk of thromboembolism in more than 90% of patients for up to 10 years after the operation (3).

In 1998 M. Haissaguerre et al. suggested a conception of eliminating trigger factors for AF, so called ectopic foci in pulmonary veins, by RFA, which along with new methods of linear RFA in the left atrium most effectively allows to treat paroxysmal and persistent forms of AF (5) (Fig. 1).

The aim of this study is to investigate electrophysiological mechanisms of AF in a clinical electrophysiological laboratory settings and to develop methods of radical treatment of all forms of atrial fibrillation, not

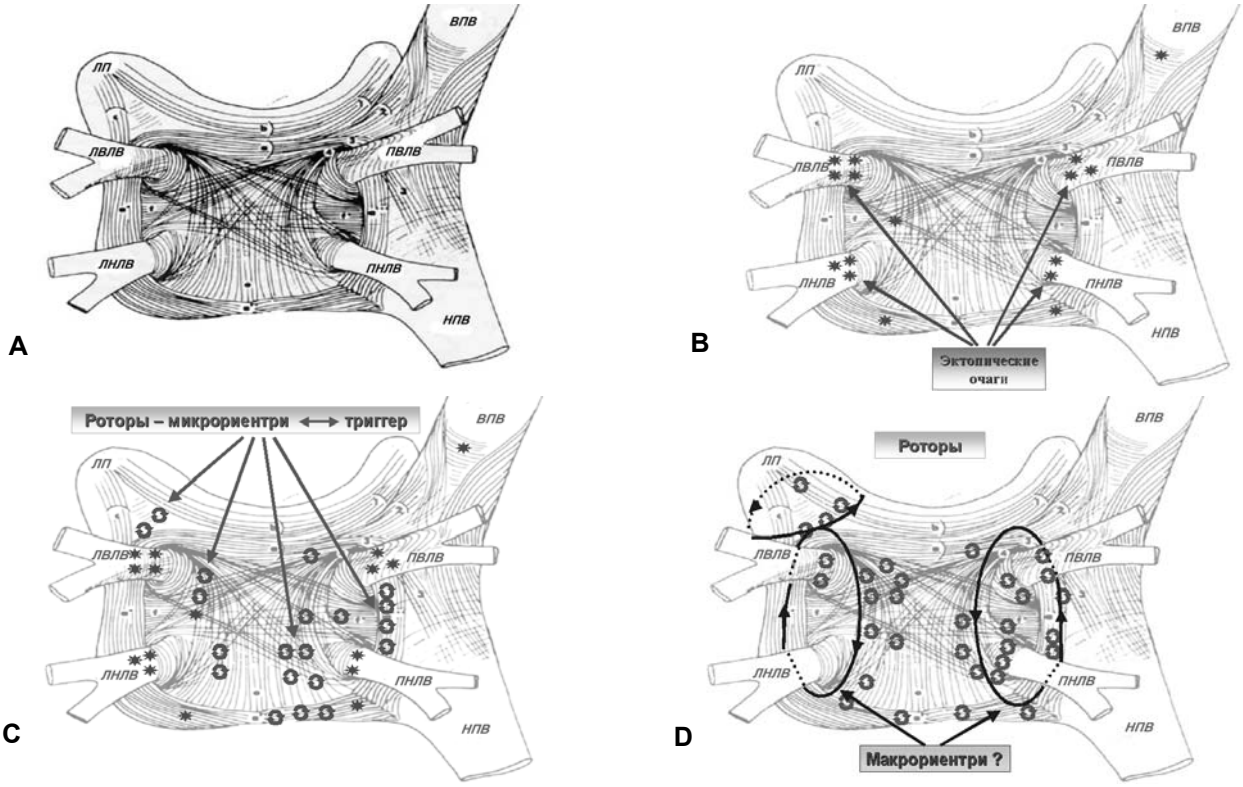

Figure 1. Anatomical structure of the pulmonary veins entering the left atrium and mechanisms of atrial fibrillation.
LA - left atrium; SVC - superior vena cava; IVC - inferior vena cava; RSPV - right superior pulmonary vein; LSPV - left superior pulmonary vein; RIPV - right inferior pulmonary vein; LIPV - left inferior pulmonary vein; ✳ - ectopic foci in PV cuffs; ↻ - re-entry mechanism in RSPV.

associated with heart valve pathology requiring surgical correction.

Material and methods

From February 2000 until September 2005, 238 patients (185 males and 53 females) with tachysystolic type of AF resistant to anti-arrhythmic drug therapy (including Cordaron), underwent invasive electrophysiological examinations (EPE) and 317 procedures of RFA (on average 1.35 ± 0.7 procedures per patient) for treatment of AF. The age of patients ranged from 9 to 65 years (mean, 46.3 ± 12.0 years) (Table 1).

Paroxysmal form of AF (82 patients) and ectopic

Table 1. Clinical characteristics of patients with atrial fibrillation (238)

	4
	9
	4

supraventricular tachycardia (21 patients) were revealed in 103 patients, 94 patients had persistent or sustained AF, and 41 patients presented with chronic AF. One hundred patients had ECG-documented type I atrial flutter and in 9 patients AF was associated with Wolf-Parkinson-White syndrome. Pre-syncopal and syncopal episodes were observed in 31% of patients. Holter monitoring showed episodes of severe bradycardia up to 31-33 bpm on the background of frequent «blocked» atrial extrasystoles (bigeminal type) in 19 patients.

The intake of class IC anti-arrhythmic drugs (on average 3 (1.5 anti-arrhythmic drugs per patient) was stopped 48-72 hours before EPE (Cordaron was discontinued 45 days before the procedure). Preoperatively all patients underwent transoesophageal echocardiography (TEE) in order to exclude thrombosis of the left atrial appendage. Seventy five percent of patients underwent contrast spiral computed tomography (CT) in order to study pulmonary veins' topography, to determine left atrial size and the degree of pulmonary veins' stenosis in the long-term follow-up (Table 2). Within 3 weeks before the procedure and 3 months after the procedure all the patients received indirect anticoagulants (Phenylin, Warfarin) with INR control (2.0-3.0). Twenty one patients underwent RFA of the ectopic focus or electrical isolation of one pulmonary vein or the superior vena cava (2 cases). In 40 patients three pulmonary veins and in 177 patients all four pulmonary veins were ablated. In 100 patients with type I atrial flutter we created bidirectional conduction block in the low right heart isthmus.

Table 2. Proportion of diameters of arrhythmogenic pulmonary veins (PV) and PV diameters in patients of the control group (without AF paroxysms) as measured by contrast spiral CT

Arrhythmogenic PV	Number of patients	PV diameter (mm)	Control group	PV diameter (mm)	p
RSPV	19	19,1 ± 3,7	14	15,5 ± 2,7	< 0,02
LSPV	20	17,9 ± 1,4	11	15,4 ± 1,9	< 0,02

Electrophysiological examination

In all cases, we performed mapping and evaluated mechanisms of AF using four multipolar electrodes. Ten-pole electrode (Biosense Webster, USA) was inserted into the coronary sinus through the left subclavian vein. A twenty-polar controlled electrode was inserted via puncture of the left femoral vein and placed along the terminal crest of the right atrium. After the transseptal puncture of the interatrial septum in the area of the oval fossa with a Brockenbrough needle we performed mapping procedure and stimulated the left atrium and the pulmonary veins. The puncture needle was inserted through the introducer by puncturing the right femoral vein. After the transseptal puncture, a four-pole controlled electrode Marinr MC, 7F (Medtronic, USA) or an irrigation cooled catheter Thermo-cool 7F (Biosense Webster, USA) was inserted into the left atrium through one or two introducers Preface 8F (Biosense Webster, USA) to perform stimulation and radiofrequency isolation of the pulmonary veins. The potentials on the perimeter of the pulmonary veins were recorded by means of circular controlled ten- or twenty-pole electrode, i.e. catheters Lasso and Lasso 2515 (Biosense Webster, USA) (Fig. 2). In all patients, we determined the diameter of the pulmonary vein orifices, studied the anatomical features of the veins by means of selective angiography of the pulmonary veins and compared them with findings seen on the three-dimensional CT images of the pulmonary veins. Intravenous heparin at a dose of 0.5 mg/kg was administered immediately after the transseptal puncture with subsequent dose titration to maintain the AST level above 300.

The pulmonary vein was considered arrhythmogenic if it displayed single or multiple episodes of

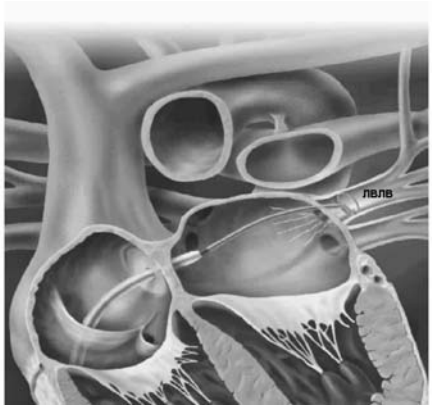

Figure 2. Invasive electrophysiological examination of the pulmonary veins using controlled circular electrode - Lasso catheter (inserted into the left superior pulmonary vein).

ectopic activity, including impulses triggering episodes of AF or atrial flutter (Fig. 3). Double or multicomponent spikes were observed in the sinus rhythm in all patients while the potentials were recorded from the

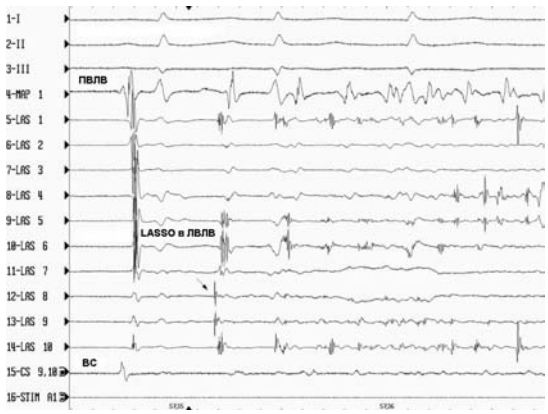

Figure 3. Occurrence of atrial fibrillation at the moment of ectopic activity in the left superior pulmonary vein.
1-2 - EGC leads; 4 - mapping electrode inserted into the right superior pulmonary vein (RSPV); 5-14 - bipolar electrograms recorded from the 20-polar Lasso catheter inserted into the left superior pulmonary vein (LSPV); 15 - bipolar electrogram recorded from the area of the coronary sinus (CS). The arrow (lead 12) shows the moment of AF triggering.

perimeter of the pulmonary veins orifices. The first (low-frequency) spike reflected the activity of the left atrium (LA) wall and the second (high-frequency) spike was the proper spike of electrical activity of the muscular cuff of the pulmonary vein (PV). If it was hard to differentiate between the potentials (spikes) of the left atrium and the pulmonary vein, the right atrium and distal portions of the coronary sinus were stimulated, which helped to clearly differentiate between PV and LA potentials. During ectopic activity arising from PV the reverse activation sequence was observed: the first potential recorded was the high-frequency spike of the pulmonary vein and the second one was the low-frequency spike of the left atrium adjacent to the orifice of the pulmonary vein (Fig. 4A, B).

In all cases (920 pulmonary veins examined) we performed circular mapping of veins by moving a Lasso catheter from the orifice to the distal parts of the

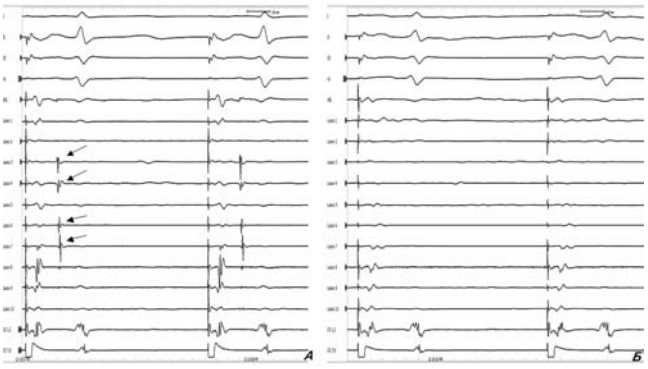

Figure 4. ECG and EG at the moment of coronary sinus stimulation. The arrows show high-frequency spikes of the pulmonary vein activity before the procedure (A) and their absence after the procedure of RFA (B). Designations are the same as in Figure 3.

pulmonary veins up to the moment of disappearance of the electrical activity, and, thus, determined the size of muscular cuffs of the pulmonary veins. In the first 14 patients RFA was performed at the distance of 5-7 mm from the PV orifice, in 2 patients only the ectopic focus was ablated and in the rest of the patients PV was isolated around the whole perimeter. In 220 patients the pulmonary veins were isolated with RFA at the PV orifice exactly at the left atrium pulmonary vein junction. On the background of sinus rhythm or coronary sinus stimulation, RF procedure was begun at the site of the earliest activation in the pulmonary vein cuff, which was divided into 12 sectors (clockwise). In each case all efforts were made to ensure complete electrical PV isolation from the remaining part of the left atrium.

RFA was performed using Atakr II and Stockert ablators (USA) with a maximum adjusted temperature of 50 °C and a maximum adjusted power range from 20 to 38 Wt. The maximum temperature of irrigation catheter did not exceed 40-41 °C, while the power level was 20-38 Wt and the saline flow rate through the distal (irrigated) electrode pole was 17 ml/min. The duration of RFA application at the effective point was 45 seconds. After electrical isolation of all pulmonary veins was performed, we compared their electrophysiological features (effective and functional refractory periods, fragmented activity, time of impulse conduction in the pulmonary vein, the possibility to induce atrial fibrillation/atrial flutter in the isolated vein) before and after the procedure. Patients continued on Warfarin for 3 months after the procedure and then they underwent spiral computed tomography (SCT) and transoesophageal echocardiography (TEE).

In 41 patients with chronic AF, the mapping and radiofrequency ablation were performed using CARTO (Biosense Webster, USA) non-fluoroscopic (magnetic) mapping system with controlled and irrigation catheters NAVI-STAR и NAVI-STAR Thermo-Cool, 7F (Cordis-Webster, USA). CARTO system allowed to record electrical potentials, to determine atrial activation time and signal amplitude in a real time mode, and to localize the position of the mapping electrode in three-dimensional space. Bipolar and monopolar signals were recorded from the controlled electrode, with the catheter inserted into the coronary sinus as reference electrode. We performed three-dimensional reconstruction of the left atrium and the pulmonary veins without fluoroscopy during 10-15 minutes. We used CARTO system along with the traditional system for recording electrical signals (64 channels) and heart stimulation (Prucka Engineering, USA or Elkart, Electropulse, Russia). 4-12 lead ECG was recorded with simultaneous electrogram (EG) recording (up to 32 channels).

After RFA of the pulmonary veins, we recorded 12-lead ECG, performed repeated Holter monitoring, and transthoracic and transoesophageal echocardiography. After 3-12 months contrast spiral CT was repeated in order to reveal possible PV stenoses. The narrowing of the PV lumen was considered significant if it was 50%. All patients received Warfarin for 3 months with INR control. Class IC anti-arrhythmic drugs were administered if indicated. The follow-up period ranged from 1 to 65 months (mean value 15 ± 11.4 months).

Statistical analysis of the obtained data was carried out by methods of variation statistics using special computer software. Statistical significance of differences in the compared values was determined using

Student's and Fisher's tests and reliable probability level «p». The p-value < 0.05 was considered to be statistically significant.

Results and discussion

The use of new types of electrodes and RFA systems, including irrigation systems, allowed us to achieve satisfactory outcomes in 87% of patients within up to 5-year follow-up period. Such approach to radical treatment of atrial fibrillation by eliminating trigger factors in the pulmonary veins is effective in cases of so called paroxysmal «ectopic» supraventricular tachycardias and atrial fibrillation when the left atrium size (to be more exact - the left atrium volume) does not exceed normal parameters. In patients with persistent (sustained) and, particularly, with chronic forms of AF, we performed pulmonary vein isolation as well as linear RFA in the area of the low left atrial isthmus or modified endocardial «Maze» procedure, as in these patients the left atrium plays the leading role in AF maintenance (6).

In our study RFA was used for isolation of 920 pulmonary veins: 257 right superior pulmonary veins (RSPV), 225 left superior pulmonary veins (LSPV), 199 left inferior pulmonary veins (LIPV) and 192 right inferior pulmonary veins (RIPV). In 6 cases electrical isolation was performed in the area of the orifice of the superior vena cava with an ectopic focus in its muscular cuff. The main principle of ablation is complete electrical isolation of the pulmonary vein, which prevents spreading of electrical activity, including ectopic activity, from PV to the left atrium. The use of a circular Lasso catheter and, first of all, its new model - Lasso 2515 with the variable diameter, allowed to answer a number of questions concerning clinical electrophysiology of the pulmonary veins and paroxysmal AF: 1) in 72% of cases, ectopic activity is observed in the superior pulmonary veins, which is to a certain extent associated with their larger diameter and longer muscular cuffs (from 1.5 to 3.0 cm); 2) along with ectopic activity that triggers and maintains atrial fibrillation and flutter paroxysms, re-entry mechanism of rotor activity of the pulmonary veins is also an important mechanism of occurrence and, what is most important, of maintenance of AF; 3) during RF isolation procedures, ablation of 60-100% of the perimeter of PV orifices is required in 72-88% of patients. The latter observation outlines once again different anatomical organization of the muscular cuffs, which allows to decrease the duration of RFA from 15 to 7-10 minutes when using circular multipolar catheters. Parameters of radiofrequency radiation used in our serial study allowed to prevent formation of PV stenoses of J 30%. It is important to underline that ablation of middle and distal portions of PVs performed by other methods, including high energy methods, is associated with stenoses in 7-42% of cases (on average 11%), with these outcomes requiring balloon angioplasty and stenting in some cases (9, 14, 16). Three types of electrical activity were observed in electrically isolated arrhythmogenic pulmonary veins: 1) in 30% of cases PVs still showed episodes of electrical activity, slow rhythm or atrial fibrillation of flutter (Fig. 5); 2) in 70% of cases there were no signs of electrical activity generally in the inferior pulmonary veins following RFA; 3) arrhythmogenic pulmonary veins, including veins isolated from the left atrium had significantly shorter functional (190 ± 60 msec) and effective (215±70 msec) refractory periods compared to those of non-arrhythmogenic pulmonary veins and the left atrium (Fig. 6). In patients with AF, decremental conduction and AF induction, including those of non-arrhythmogenic veins, were observed 20 times more often compared to the control group (p < 0.02). At present the rate of repeated interventions in our serial study as well as in studies of foreign authors amounts to 35% (10). This is related to the use of sparing modes of RFA for ablation of the pulmonary vein orifices, which allowed to reach the rate of PV

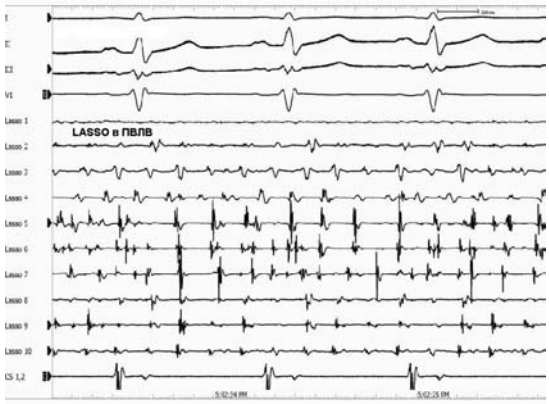

Figure 5. Results of radiofrequency isolation of the arrhythmogenic right superior pulmonary vein. The patient's ECG shows restoration of sinus rhythm (leads I, II, III, V1 and CS1,2). The pulmonary vein still shows signs of atrial fibrillation (Lasso 1-10).

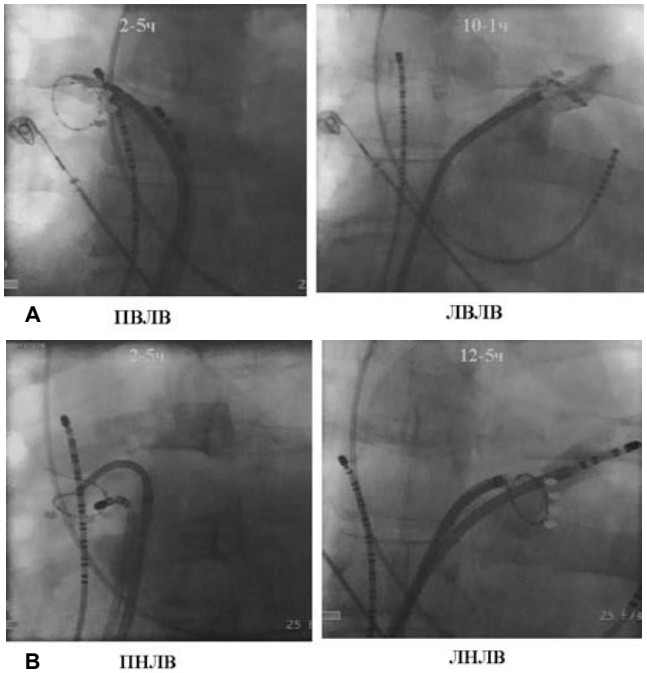

Figure 6. Electrophysiological parameters of arrhythmogenic pulmonary veins (A) in patients with atrial fibrillation and in control group (B) (without paroxysms of AF).
€ - effective refractory period of the pulmonary veins;
€- functional refractory period of the pulmonary veins.

stenoses of not more than 15% in the long-term follow-up. Preferable methods of ablation are irrigation and cold RFA performed using special irrigated catheters. We did not observe any differences in outcomes and effectiveness of RFA procedure performed in patients with sinus rhythm or AF. The mandatory requirement for conducting the procedure on the background of AF is electrical isolation of the most arrhythmogenic vein (generally, superior pulmonary veins) at the first stage of the operation (Fig. 7).

In 23 patients with chronic AF, the use of CARTO system allowed to effectively treat arrhythmia and to preserve sinus rhythm within 2-4 years (Fig. 8).

Several world's clinics have currently reported data on comparable effectiveness of treatment in patients with paroxysmal and persistent AF refractory to anti-arrhythmic therapy (AAT). Positive result, i.e. stable sinus rhythm following the procedure was observed in

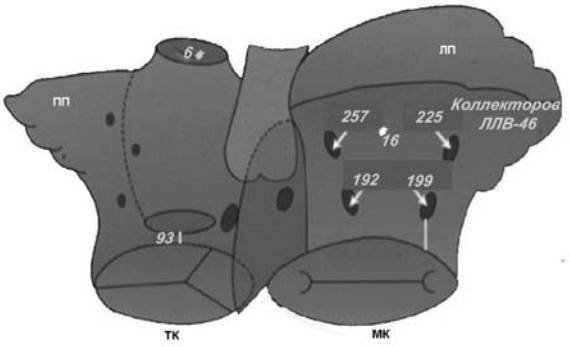

Figure 7. Localization of arrhythmogenic foci in isolated pulmonary veins (n=920) in patients with atrial fibrillation.
LA - left atrium, RA - right atrium, MV - mitral valve, TV - tricuspid valve.

60-70% of patients who do not receive AAT and almost in 80-86% of those who received previously ineffective drugs (6, 7, 11, 12, 13).

In conclusion, new technologies of electrophysiological diagnostics of atrial fibrillation allow to determine mechanisms of arrhythmia occurrence and maintenance, to identify so called arrhythmogenic pulmonary veins. Muscular cuffs of the pulmonary veins have special electrophysiological features determining the conditions of occurrence of paroxysmal AF. RFA procedure implies PV electrical isolation together with partial (parasympathetic) denervation of the heart (especially in the area of the posterior wall of the left atrium), which also determines the effectiveness of interventional treatment of AF. Current methods of interventional treatment allow to effectively eliminate paroxysmal form of AF in 85-90% of patients by RF isolation of the pulmonary veins. The implementation of linear RF ablation and modifications of «Maze» procedure using CARTO non-fluoroscopic (magnetic) mapping system allow for an effective treatment of sustained and chronic forms of AF when the left atrium volume does not exceed 180 ml as measured by contrast spiral computed tomography. Based on the results of electrophysiological examination of AF mechanisms and the results of interventional and surgical treatment of different types of atrium fibrillation, we offer the following algorithm

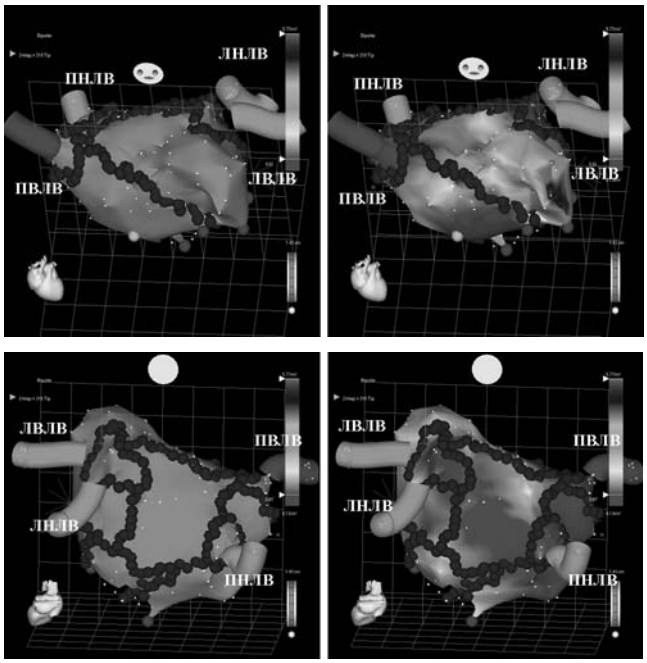

Figure 8. Linear RFA with application of the CARTO non-fluoroscopic (magnetic) mapping system.
The scheme of the modified "Maze" procedure with pulmonary vein isolation in the patient with chronic AF (dots show zones of radiofrequency ablation). LPV - left pulmonary veins, RPV - right pulmonary veins.

for treatment of AF refractory to prophylactic anti-arrhythmic therapy (Graphs 1-3). In the near future it will be necessary to conduct randomized studies to confirm the effectiveness of interventional methods for AF treatment, to choose an optimal technique of ablation of the arrhythmia substrate and to make it widely used in clinical practice of the country's leading centers of arrhythmology.

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Implantable Cardioverter Defibrillator (ICD) for the Treatment of Patients who are at Risk for Sudden Cardiac Death

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I. Implantable cardioverter defibrillators (ICD`s) for the prevention of sudden cardiac death: widening indications

Sudden cardiac death (SCD) is responsible for a considerable number of deaths throughout the world. Most of SCD are due to coronary heart disease. SCD can be effectively prevented by the implantable cardioverter defibrillator (ICD), both in patients surviving SCD, sustained ventricular tachycardia (VT) or fibrillation (VF) (secondary prevention), and those without previous SCD or VT/VF, identified by screening techniques to be at high risk (primary prevention). More recent evidence supports extension of ICD use in primary prevention of SCD to post myocardial infarction (MI) patients selected by ejection fraction (EF) alone, an indication now adopted broadly in Europe and North America.

The ICD implantation rate has risen in all around the world, since publication of various guidlines supporting this. Indeed, recent clinical trials have shown that the ICD is the most effective therapy currently available for not only in secondary, but also the primary prevention of sudden cardiac death (SCD) Implantable cardioverter defibrillator therapy has been shown to improve the survival of patients with significant left ventricular dysfunction and other markers of increased mortality risk. Evidence on primary prevention ICD use has been published. The MADIT II, selected post MI patients on EF (<30%) alone for randomisation to ICD therapy or not, demonstrated an absolute mortality reduction of 5.6% after 20 months (hazard ratio 0.69 (CI 0.51-0.93), p = 0.0016, in ICD patients). SCD-HeFT recruited patients with NYHA class II/III heart failure and EF <35% to receive placebo, amiodarone or an ICD and demonstrated an absolute mortality reduction of 7.2% after five years in patients who received an ICD (hazard ratio of 0.77 (CI 0.62-0.92), p=0.007). Both trials showed an ICD mortality benefit in patients selected on the basis of LVEF alone. These trials, however, have raised reasonable questions about which patients should be treated with ICD therapy. Although the overall mortality benefit from ICD therapy in those trials is evident, the magnitude of effectiveness of ICD therapy in clinically defined subgroups is unclear. Risk stratification became a critically important issue since NNT (number of patients needed to be treated to save one life) appeared to be slightly higher than expected. A principal difference in MADIT I and II was selection of patients using EPS. MADIT I is flawed by the absence of a registry and inadequate information about outcome in those screened but not entered into the tria. MUSTT demonstrated that an EPS guided strategy with antiarrhythmic drugs was deleterious compared to no antiarrhythmic therapy, whereas an EPS guided strategy with an ICD was advantageous. It seems however, that currently there is no evidence supporting any risk stratification strategy over another.

The list below is an overview of recent major clinical trials involving ICD therapy.

II. Cost efficacy

Most of cost effectiveness models are based on unpublished studies of predominantly secondary prevention. It is not clear that extrapolations from secondary prevention are valid. in all ICD models includidn primary prevention trials. Moreover, several of these trials were terminated early, and there is evidence that the benefit of the ICD may have therefore been underestimated, since it is clearly multiplied annually. Longer term analysis of some single centre contribution to IDS suggested increasing benefit with time. Despite these hurdles, cost efficacy figures which approach levels acceptable have been reached. Cost efficacy analysis of the «MADIT II» population yields figures of $51,000 per QALY gained. Both health economists and clinicians believe that targeting of ICD therapy to higher risk patients will enhance cost efficacy.

III. Cardiac resynchronization and implantable defibrillator therapy

Congestive heart failure is a common, costly, and debilitating illness. It affects an estimated 4.8 million patients in the United States, and 400 000 new cases are identified every year. The prevalence is also increased with aging. Approximately 30% to 50% of patients with heart failure have major intraventricular conduction delay, which is associated with higher risk for adverse events. Biventricular pacemakers resynchronize the ventricular contraction to improve ejection fraction and relaxation of the left ventricle. However, not all therapies that improve functional outcomes in patients with heart failure reduce mortality. The long-term mortality, morbidity, and costs associated with cardiac resynchronization therapy remain unclear. Economic evaluation of an intervention assesses its effectiveness and costs so that decision makers can decide whether it is good value for the money.

Trial	Patients.' characteristics and number of randomized patients	Primary end point	Main finding	Status
MADIT-I	NYHA I, II or III, prior MI, LVEF ≤35%, NSVT, nonsuppressible ventricular arrhythmia on EPS (n = 1 96)	Overall mortality	ICD resulted in a 56% RR reduction in mortality, p = 0,009	Published in 1996
CABG Patch[15]	LVEF ≤35%, аномалии на ЭКГ, назначены на АКШ (n = 900)	Overall mortality	ICD had no effect on mortality	Published in 1997
MUSTT	Coronfry artery disease, LVEF ≤40%, NSVT, inducible sustained VT on EPS (n = 704)	Cardiac arrest or death from arrhythmia	ICD resulted in a 76% PR, reduction in the primary end point, p < 0,001	Published in 1999
MADIT-II	History of MI , LVEF ≤30% (n = 1232)	Overall mortality	ICD resulted in a 31% PR reduction in mortality, p = 0,016	Published in 2002
DEFINITE	Nonischemit ca rdiomyopathy, LVEF = 35%, PVCs or NSVT (n = 458)	Overall mortality	ICD resulted in a 35% PR reduction in mortality, p = 0,08	Published in 2004
SCD-HeFT	NYHA II and III, LVEF ≤35% (n = 2521)	Overall mortality	ICD resulted in a 23%PR reduction in mortality, p = 0,007	Unpublished
DINAMIT	Withmjl-40day of an MI, LVEF of 35% or less end either depressed heart rate variability oran elevated average 24-hour heart rate on Holter monitoring (n = 674)	Death from any cause	ICD did not result in significant reduction of aII-cause death	Published in 2004

Devices for heart failure patients

Two separate but related intracardiac devices have been developed to treat complications of congestive heart failure (CHF). Implantable cardioverter defibrillator (ICD) therapy was developed to provide immediate cardioversion/defibrillation to patients experiencing a hemodynamically unstable ventricular arrhythmia. Cardiac resynchronization therapy (CRT) was developed to reverse the adverse effects of cardiac dyssynchrony on left ventricular function and patient functional status. Both therapies are based upon the implantation of a pulse generator and intracardiac leads to deliver the desired therapy, and both involve high up-front costs.

In conclusion ICD is a very effective treatment for life threatening arrhythmias including primary and secondary prevention. In primary prevention if CRT therapy is delivered this will enhance mortality benefit in the heart failure population.

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Oxygen Therapy in Combination with Endovascular Reperfusion During the First Hours of Acute Myocardial Infarction: Clinical and Laboratory Findings

Oxygen therapy has been used to treat acute myocardial infarction (AMI) for several decades. The history of oxygen therapy in patients with acute myocardial ischemia runs to a hundred of years. According to the last guidelines for the treatment of acute coronary syndrome, oxygen therapy is recommended in all patients within the first hours after uncomplicated MI. However, there's no convincing evidence of the efficacy of oxygen inhalation for MI (3, 6).

Oxygen therapy is supposed to facilitate the decrease of imbalance between oxygen demand and consumption underlying myocardial ischemia. Additional oxygenation of blood increases the myocardial oxygen tension preventing necrosis of the heart muscle.

Another reason for additional oxygenation importance is hypoxemia seen in MI patients, often even with uncomplicated course. The mass of necrotic area, as well as the mortality rate, have been shown to correlate directly with the severity of hypoxemia (4). Inhalation of oxygen successfully eliminates hypoxemia, though it is unclear, whether this correction affects the disease course (5).

Clinical trials concerning the effect of oxygen therapy in acute myocardial ischemia are very limited, have small samples of patients, mostly are non-randomized and performed prior to the reperfusion era. A number of studies showed positive effect of oxygen therapy on MI healing and decrease of peri-infarction area (as suggested by ECG, biochemical markers, Echo-CG) (2, 8, 10). Other authors observed the overall negative effect of oxygen inhalation: despite the decrease of hypoxemia degree it doesn't affect mortality rate, ST changes and the incidence of rhythm disorders (9, 11).

The combination of oxygen therapy and reperfusion (thrombolytic therapy, PTCA) is currently the most important problem, because myocardial reperfusion becomes increasingly widespread in MI therapies. There's a potential hazard of increased reperfusion injury due to the effect of oxygen radicals (7). However, experiments didn't confirm this anxiety (12).

The existing guidelines regulating the use of oxygen therapy in MI vary greatly. Practically, there is no unified technique.

Therefore, over 50 years of oxygen therapy remains rather «a tribute to tradition, than a scientifically substantiated technique» (1). This idea was summarized by an author of a systematic review dedicated to oxygen therapy in acute coronary syndrome (2004): «If the effect of a widely adopted therapy is unknown - whether it is harmful, effective or useless - there is a need for urgent clinical studies to evaluate it» (13).

Purpose of the study consisted in the assessment of the effect of 30-40% oxygen inhalation on the course of AMI after endovascular reperfusion of myocardium.

The choice of oxygen concentration is due to the two factors: 1) over 60% concentration of oxygen can have toxic effects; 2) maximum oxygen saturation of hemoglobin in patients with uncomplicated AMI is provided by as low as 30-40% concentration of oxygen.

Materials and methods

Study design: open-label prospective randomized study of 10 days duration.

The diagnosis of AMI was established on the basis of ECG, biochemical criteria (CPK-MB more than 2 times exceeding the upper limit) and the clinical pattern.

A total of 187 patients were evaluated. Patients meeting the inclusion criteria (see Table 1) were randomized between two groups. A total of 137 patients was included.

Table 1. Inclusion, exclusion and withdrawal criteria

The two groups were:

Inclusion criteria	Exclusion criteria	Withdrawal
1.Q-wave MI. 2. Uncomplicated MI. 3. Enrollment within 12 h after the onset of chest pain.	1. Complicated MI (pulmonary edema, cardiogenic shock). 2. Congestive heart failure. 3. Chronic obstructive pulmonary disease, anemia with HGB below 90 g/l).	1. Revascularization failure

Oxygen therapy group (Group 1) - 58 patients - included two subgroups:

- 28 patients received oxygen inhalations in addition to standard therapy and myocardial revascularization during 30 min prior to and 3 h after the intervention;
- 30 patients received oxygen therapy only for 3 h after the intervention.

Control group (Group 2) included 79 patients

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receiving standard therapy in combination with endovascular reperfusion of myocardium.

Primary endpoints:

* Mortality;
* Recurrent AMI
* Postinfarction angina
* Circulatory failure during hospital stay;
* Heart rhythm and conduction disorders during surgery, within 1 h after surgery and during hospital stay;
* Pericarditis.

Secondary endpoints:

* Relative area and growth of necrotic zone and ischemic damage zone as measured by 12-lead ECG, ECG mapping and blood sampling for biochemical markers;
* Global and local myocardial contraction; LV geometry (end-diastolic volume (EDV), end-systolic volume (ESV)).

Material and methods

1) Pulse oxymetry (evaluation of arterial HGB oxygen saturation, SpO2%) - on admission, within 2 days thereafter and at day 10.

2) 12-lead ECG - on admission, in the end of days 1, 2 and 10, with calculation of the number of leads showing Q-wave or QS-complex, ST-elevation and total ST elevation.

3) 48-lead ECG mapping at day 10 with automatic assessment of relative area of necrotic zone.

4) Changes of CPK and CPK-MB on admission, at 12, 18, 24, 36 and 48 h after the onset of chest pain.

5) Left ventriculography within the first hour after admission with calculation of LV ejection fraction (LVEF), stoke volume (SV), end-diastolic and end-systolic volumes (EDV and ESV), local contraction - contraction index (CI)

6) Echo-CG at day 5 with evaluation of LVEF, SV, EDV, ESV, end-diastolic and end-systolic diameters (EDD and ESD), local contraction (contraction index and the number of segments with contraction disorders).

Clinical values

Major clinical values at baseline were similar between the groups (see Table 2). Signs of heart failure were observed in 10% of patients in oxygen therapy group compared to 1% in control group, p<0.08. Time between the onset of chest pain and revascularization procedure was longer in oxygen therapy group (4.59±0.31 h) as compared to control (3.90±0.24 p), p<0.052.

Treatment

All AMI patients received basis therapy, including aspirin, beta-blockers, ACE inhibitors, nitrates. In average thirty (30) minutes after admission patients underwent coronary angiography, left ventriculography and endovascular reperfusion of myocardium (through myocardial reperfusion, PTCA and/or stenting).

Table 2. Clinical parameters of patients

Value		Oxygen therapy group (Group 1)	Control group (Group 2)	p
Number of patients		58	79	
Mean age (years)		55,6 ± 1,33	53,5 ± 1,06	NS
Men		45 (78%)	70 (89%)	NS
MEDICAL HISTORY				
Unstable angina		20 (35%)	28 (35%)	NS
Smoking		39 (67%)	56 (71%)	NS
Hypertension		39 (67%)	51 (65%)	NS
Cholesterol		6,04 ± 0,190	5,96 ± 0,146	NS
CLINICAL SIGNS ON ADMISSION				
Circulatory failure	KILLIP I	52 (90 %)	78 (99 %)	<0,08
	KILLIP II	5 (10 %)	1 (1 %)	
Rhythm and conduction disorders		14 (24 %)	17 (22 %)	НД
INFARCTION AREA				
Anterior		32 (55 %)	35 (44 %)	NS
Anteroseptal		6 (11 %)	7 (8,5 %)	NS
Sept al and apical		7 (2 %)	6 (8 %)	NS
Anterior and disseminated		17 (29 %)	21 (27 %)	NS
Posterior		26 (45 %)	44 (56 %)	NS
REVASCULARIZATION				
Time to intervention (h)		4,59 ± 0,311	3,90 ± 0,236	<0,052
Myocardial reperfusion and PTCA		25 (43%)	45 (57 %)	NS
PTCA and/or stenting		16 (28 %)	11 (14%)	NS
Systemic thrombolysis		7 (12 %)	9 (12 %)	NS
Thrombolysis and myocardial reperfusion and/or PTCA		8 (14 %)	10 (13 %)	NS
ANGIOGRAPHIC FINDINGS				
Number of vessels involved		2,22 ± 0,15	2,10 ± 0,12	NS

NS - non-significant difference.

In addition to standard therapy, patients in oxygen therapy group received 30-40% oxygen inhalation (which corresponds to free air flow rate of 3-6 l/min) through nasal cannula, controlled by pulse oxymetry. Control group patients breathed ambient air, also controlled by pulse oxymetry.

Study results

Clinical course of MI

One male patient died on day 1 during the 10-day follow-up in Group 1. Suspected cause of death was cardiac arrest. Autopsy was not carried out. No deaths occurred in the control group.

Complications occurring within the 10-day follow-up are summarized in Table 3. In general, complications associated with large extent of MI were significantly less common in oxygen therapy group as compared to control group. In addition, patients receiving oxygen had significantly less common perioperative rhythm and conduction disorders as compared to control.

Table 3. Complications in MI patients

	O_2	Without O_2	p
Rhythm and conduction disorders within 1 h after intervention	2 (3%)	11 (14%)	<0,04
Rhythm and conduction disorders within 10 days (including surgery and death)	6 (10%)	13 (16%)	NS
Angina or recurrent MI	12 (14%)	16 (20%)	NS
Circulatory failure	1 (2%)	5 (6%)	NS
Pericarditis	1 (2%)	6 (7%)	NS
Total number of complications (except angina)	8 (14%)	24 (30%)	<0,025
No complications	50 (86%)	39 (70%)	

Hypoxemia and hemoglobin oxygen saturation

Arterial blood oxygen saturation (SpO2%) in MI patients within the first day was significantly decreased as compared to values obtained subsequently (Fig. 1). Hypoxemia (SpO2<94%) at baseline was found in 37% of patients, more commonly in anterior MI (44% of patients) as compared to posterior MI (30% of patients). Severe hypoxemia (SpO2<90%) was observed in 12 (11%) patients. Oxygen inhalation was accompanied by substantial and significant increase of SpO2%, reaching 98.8(0.13%. Oxygen saturation in both groups significantly increased by the end of day 1, hypoxemia was practically reduced, blood oxygenation kept growing significantly on day 2 and thereafter. There were no difference in SpO2% between the groups on days 1, 2 and 10 (Fig. 1).

We studied the relation between hypoxemia and

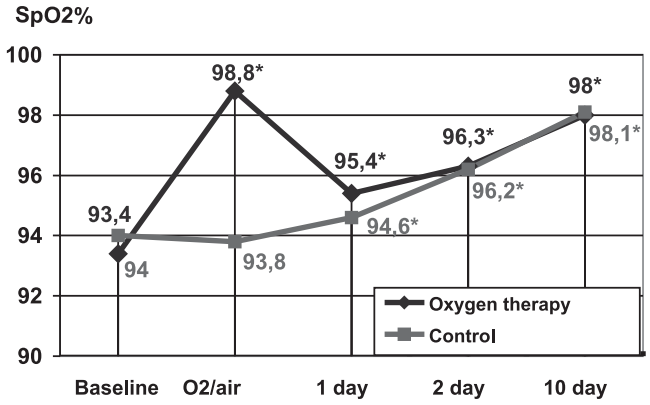


Fig. 1. Arterial blood oxygen saturation (SpO2%)
* - significant difference as compared to previous day
" - significant difference as compared to control (p<0.001)

various hemodynamic, ECG and biochemical values (Table 4). Hypoxemia (SpO2<94%) at baseline was shown to correspond to the following changes, unlike situation in patients without hypoxemia:

* - significantly decreased LVEF, SV, increased EDV and CI of the left ventricle as measured by ventriculography;

* - decreased LVEF, SV, increased EDV and ESV, increased CI and the number of segments with contraction disorders as measured by Echo-CG at day 5;

* - higher total amplitude of ST elevation as measured by 12-lead ECG at baseline.

Among patients, in whom oxygen saturation returned to normal ranges within 24 h, maximum activity of CPK-MB was significantly lower, than in patients with persisting hypoxemia.

Formation of necrotic area during oxygen inhalation

Changes of serum CPK and MB-CPK in MI patients

Baseline CPK and MB-CPK activity (mean 6 h after the onset of disease) was significantly higher in oxygen therapy group (Table 5). This wasn't, however, associated with longer time from MI onset in this group: there was no correlation between time from the onset and the fact, that maximum values of MB-CPK

Table 4. Association between hypoxemia and hemodynamic, biochemical, ECG values

Ventriculography	SpO2<94%	SpO2 >94%	p
EF, %	42,00 ± 2,9	57,2 ± 2,1	<0,003
SV, ml	76,5 ± 2,5	95,9 ± 2,2	<0,001
ESV, ml	104,4 ± 8,0	72,6 ± 6,3	<0,01
CI, U	2,22 ± 0,2	1,96 ± 0,1	<0,07
ECG			
AST, mm	11,5 ± 1,9	7,89 ± 1,8	<0,05
max MB-CPK, U\l			
<180	2	11	<0,01
>180	7	3	
Echo-CG, day 5	**SpO2<94**	**SpO2 >94**	**p**
EF,%	42,2 ± 2,3	54,1 ± 1,8	<0,001
SVml	69,3 ± 2,4	75,5 ± 2,8	<0,02
ESV	98,6 ± 9,8	64,1 ± 4,6	<0,004
EDV	164,1± 9,6	139,5± 6,1	<0,04
ESD	4,5 ± 0,2	3,8 ± 0,1	<0,006
EDD	5,7 ± 0,2	5,4 ± 0,1	<0,07
CI	2,4 ± 0,2	1,8 ± 0,2	<0,053
Segm.	6,9 ± 0,9	4,6 ± 0,6	<0,03

were detected on admission.

Between 12 and 18 h, as well as 36 and 48 h after MI levels of MB-CPK and CPK was significantly lower in oxygen therapy group. The difference was found not to be due to changes of maximum MB-CPK in oxygen therapy group preoperatively, as the significance still remained after exclusion of patients with peak MB-CPK on admission, i.e., patients with already accomplished MI (Fig. 2).

Therefore, different level of biochemical markers is apparently due to oxygen inhalation.

Table 5. CPK and MB-CPK activity levels in MI patients, U/l

MB-CPK CPK

* - except patients with maximum MB-CPK on admission.

	C O_2	Without O_2	C O_2	Without O_2
Source.	117,1 ± 30,5**	82,0 ± 21,2	923,2 ± 194,9**	560,8 ± 113,4
Source*	57,6 ± 10,4**	43,7 ± 12,3	1791,2 ± 277,7**	2529,3 ± 201,7
12/18 h	224,5 ± 49,7**	385,5 ± 36,2	1469,3 ± 346,6**	2430,4 ± 291,8
12/18h*	189,6 ± 43,0**	400,2 ± 57,3	1740,3 ± 214,8**	2022,4 ± 214,2
24 h	200,0 ± 26,3	211,5 ± 24,7	1882,2 ± 296,2	2100,1 ± 370,3
24 h*	207,2 ± 41,5	226,4 ± 37,6	998,9 ± 118,7	1149,5 ± 105,8
36 h	79,6 ± 19,5**	103,3 ± 8,8	976 ± 212,3	1398 ± 185,2
36 h*	89,8 ± 25,1**	113,9 ± 15,7	646,4 ± 112,9**	720,0 ± 59,0
48 h	50,8 ± 5,1	53,1 ± 4,2	648,0 ± 171,4**	734,4 ± 75,4
48 h*	45,1 ± 5,8**	54,4 ± 4,7	923,2 ± 194,9**	560,8 ± 113,4

** - significant difference over control (p<0.05)

Relative necrotic area

The effect of oxygen inhalation on the size and growth of necrotic area is summarized in Tables 6 and 7. Within the first day in oxygen inhalation group the increase of necrotic area was less common (47% vs 80% in controls) and less intensive (by 26% vs 85% in controls), all differences were insignificant. Subsequently the values of necrotic changes remained practically unchanged at day 2. Therefore, between the end of day 1 and up to day 10 significant difference in the mean necrotic area persisted

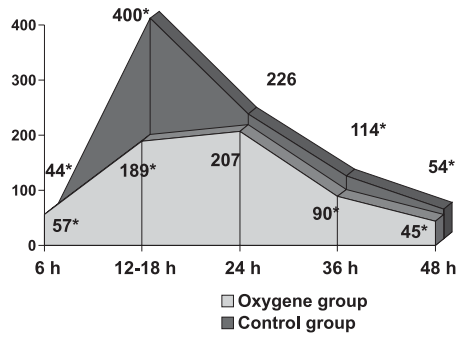


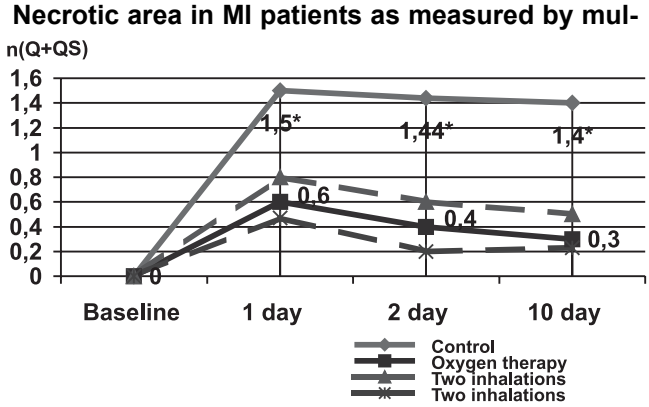
Fig. 2.

between the groups, as well as more beneficial changes of necrotic area in oxygen therapy group (Table 6). There were no significant differences between patients receiving oxygen therapy twice and those receiving only postoperative oxygen therapy - the treatment hampered the growth of necrotic area in both cases (Fig. 3).

Relative area of ischemic damage

Changes of ischemic damage area during follow-up are summarized in Tables 6 and 7 (NST, AST and their changes). After day 2 the area of ischemic damage remained practically unchanged in control group. In contrast, patients on oxygen therapy, particularly those receiving it twice, had NST and AST values decreasing up to day 10 (significant difference) (Table 6). By day 10 the decrease of ischemic damage area was observed in 75% of patients in oxygen therapy group vs only 58% of patients in control group (insignificant difference). Mean area of ischemic damage was also lower in oxygen therapy group as compared to controls (significant difference in patients with anterior MI), mostly due to patients undergoing two procedures of oxygen inhalation (Table 6).

Fig. 3. Changes of relative necrotic area
* - significant difference over control (p<0.01)



tipole 48-lead ECG mapping

The study was performed on day 10 in 31 patients receiving oxygen therapy. The method to determine relative area of necrosis is shown on the figure 4. Relative necrotic area was shown to be significantly lower in oxygen therapy group - both in anterior and posterior MI (Table 8).

Changes of central hemodynamics and myocardial contraction with oxygen inhalation

As measured by ventriculography performed within

Table 6. Number of leads showing Q-wave or QS-complex (NQ), number of leads showing ST elevation (NST) and their changes ((NQ and (NST) as compared to baseline ECG

	Without O_2	O_2	Two inhalations	One inhalation
NQ on admission	1,72 ± 0,157	2,21 ± 0,203	1,96 ± 0,298	2,47 ± 0,285*
NQ at day 1	3,18 ± 0,143	2,79 ± 0,185*	2,75 ± 0,245*	2,93 ± 0,304
NQ at day 2	3,14 ± 0,141	2,58 ± 0,193*	2,51 ± 0,228*	2,67 ± 0,323
NQ by day 10	3,10 ± 0,141	2,49 ± 0,195*	2,40 ± 0,162*	2,70 ± 0,305
DNQ at 24 h, % from baseline	1,46 ± 0,142 85%	0,58 ± 0,199** 26%	0,79 ± 0,186* 40%	0,47 ± 0,186** 19%
DNQ by day 10, % from baseline	1,38 ± 0,149 80%	0,32 ± 0,152** 15%	0,48 ± 0,260* 25%	0,23 ± 0,238** 9%
NST on admission	3,81 ± 0,185	3,89 ± 0,197	4,12 ± 0,285	3,80 ± 0,280
NST at day 1	3,42 ± 0,213	3,44 ± 0,245	3,44 ± 0,245	3,03 ± 0,331
NST at day 2	2,81 ± 0,289	3,11 ± 0,289	3,67 ± 0,475	2,72 ± 0,354
NST by day 10	2,77 ± 0,279	2,11 ± 0,258	2,04 ± 0,411	2,22 ± 0,348
NST by day 10 (MI)	4,5 ± 0,267	3,2 ± 0,330*	3,00 ± 0,603*	3,43 ± 0,366
DNST at day 1	-0,39 ± 0,151	-0,46 ± 0,217	-0,00 ± 0,257	-0,77 ± 0,344
DNST between days 2 and 10	-0,04±0,019	-1,00±0,207**	-1,65±0,352**	-0,50±0,239
DNST by day 10	-1,04 ± 0,185	-1,75 ± 0,240*	-2,09 ± 0,359*	-1,57 ± 0,361
A ST on admission	10,32 ± 1,290	8,89 ± 1,085	9,58 ± 1,694	8,87 ± 1,477
A ST at day 1	4.60 ± 0,453	5,18 ± 0,580	5,94 ± 0,823	4,87 ± 0,835
A ST at day 2	3,80 ± 0,445	4,46 ± 0,565	4,67 ± 0,860	4,48 ± 0,797
A ST by day 10	3,45 ± 0,439	2,60 ± 0,435	2,48 ± 0,704	2,87 ± 0,853
DAST at day 1	-5,72 ± 1,151	-3,70 ± 0,836*	-3,45 ± 1,355*	-4,00 ± 1,104
DAST between days 2 and 10	-0,45 ± 0,234	-1,81 ± 0,391*	-2,20 ± 0,606#	-1,52 ± 0,573
DAST by day 10	-7.01 ± 1.157	-6.16 ± 0.946	-7.22 ± 1.570	-5.97 ± 1.158

*- significant difference over control (p<0.05).
- significant difference over control (p<0.001).

Table 7. Changes of necrotic area and ischemic damage area

	O_2	No O_2	O_2	No O_2
Necrotic area	By end of day 1 (p<0,005)		By end of day 10 (p<0,0001)	
Increase	27 (47%)	63 (80%)	24 (43%)	59 (75%)
No changes of decrease	31 (53%)	16 (20%)	31 (57%)	20 (25%)
Ischemic damage area	Between days 2 and 10 (p<0,01)		By day 10 (p<0,05)	
Decrease	25 (45%)	18 (23%)	43 (75%)	46 (58%)
No changes or increase	30 (55%)	61 (77%)	14 (25%)	33 (42%)

Table 8. Relative necrotic area (per cent from surface of image sphere)

	O_2	No O_2	P (ANOVA test)
Anterior MI	8.61±1.5	13.23±1.7	<0.02
Posterior MI	4.37±1.2	7.76±0.9	<0.015

the first hours after MI onset in the subgroup receiving

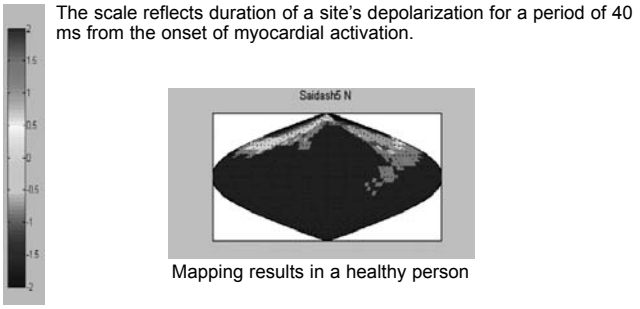


Fig. 4.

preoperative oxygen therapy, ESV, EDV and SV values were significantly lower compared to control (Table 9).

This effect of preoperative oxygen inhalation persisted afterwards. Echocardiography performed on day 5 in patients receiving oxygen therapy both prior to and after reperfusion, volumes and diameters of the left ventricle (EDV, ESV, EDD, ESD), as well as SV, were significantly lower than in patients receiving only postoperative oxygen inhalation and control group patients (Table 9).

Table 9. Central hemodynamics and myocardial contractility in MI patients

*- significant difference over control (p<0.05).

** - significant difference as compared to single inhalation group (p<0.05).

	Without O_2	Two inhalations	Single inhalation	O_2
Ventriculography findings				
EF, %	51.9 ± 1.34	53.1 ± 2.29	49.3 ± 2.57	---
SV, ml	90.6±7.50	74.8±5.17*	84.4±6.30	
ESV, ml	85.9 ± 3.45	66.2 ± 5.17*°	87.3 ± 7.12	---
EDV, ml	176.8 ± 5.25	141.3 ± 7.80*°	172.8 ± 9.52	---
Contraction index	2.15 ± 0.065	2.14 ± 0.115	2.11 ± 0.123	---
Echocardiography findings				
EF, %	51.9 ± 1.19	52.4 ± 1.79	48.2 ± 2.10	50.2 ± 1.45
SV, ml	73.4±2.15	64.0±2.87*	68.6±2.91	66.5±2.1*
ESV, ml	70.0 ± 3.46	61.00 ± 4.82*°	82.1 ± 7.53	73.4 ± 4.89
ESD, mm	3.97 ± 0.16	3.73 ± 0.12°	4.17 ± 0.50	4.0 ± 0.104
EDV, ml	146.7 ± 4.29	124.8 ± 6.60*°	150.7 ± 7.62	140.8 ± 5.50
EDD, mm	5.42 ± 0.14	5.08 ± 0.12*°	5.53 ± 0.12	5.4 ± 0.090
Contraction index	2.18 ± 0.100	2.16 ± 0.208	2.11 ± 0.163	2.12 ± 0.126
Segments	5.8 ± 0.431	5.82 ± 0.820	6.15 ± 0.741	5.9 ± 0.534

Discussion

This clinical trial showed, that inhalation of 30-40% oxygen within 30 min prior to endovascular myocardial reperfusion and within 3.5-4 h thereafter reduced the area of necrosis and peri-infarction area, improved central hemodynamics, and decreased the rate of postoperative rhythm disorders as compared patients breathing ambient air.

The results obtained appear interesting for a number of reasons. Firstly, so far there have been no adequate clinical trials assessing the effect of normal pressure oxygen therapy in combination with reperfusion on the course of MI. Secondly, studies dedicated to this problem outline only the short-term effects of oxygen inhalation (up to 24 h), which seems insufficient, as the final size of necrotic area is determined later, besides, the reperfusion injury can progress up to 24-48 h following restoration of blood flow. Relatively long follow-up in our study excludes possible temporary nature of the effects observed. Thirdly, oxygen inhalation not only reduced the infarction area, but also contributed to the improvement of central hemodynamics within the first hours, as well as in the long-term follow-up (day 5). This prolonged effect of oxygen inhalation has not been described before.

The study showed that within the first hours after MI hypoxemia developed in a half of the patients. Lower incidence and moderate severity of hypoxemia as compared to other studies were partially due to the inclusion criteria - patients with uncomplicated MI. The same factor was also the reason for successful (in 100% of cases) correction of hypoxemia using inhalation of 30-40% oxygen. Hemoglobin oxygen saturation steadily increased within the whole follow-up period, which suggests persisting decrease of pulmonary blood oxygenation, despite general stabilization by the end of days 1 or 2.

The correlation revealed between hypoxemia and hemodynamic parameters confirms close association

of the area of necrosis with the presence of hypoxemia, as well as with the rate of arterial blood oxygen tension normalization.

The higher activity of cardiospecific enzymes (CPK and MB-CPK) in oxygen therapy group on admission can be due to the more frequent anterior type of MI as compared to the control group (55 vs 44%, respectively), more severe condition of patients (Killip II CHF in 10% of patients vs 1% in the control group). During subsequent two days the level of cardiospecific enzymes was lower in oxygen therapy group. Exclusion of cases with already established myocardial infarction, when the measures undertaken for the prevention of the growth of necrotic area would provide poor effect, demonstrated, that the differences between groups were not due to earlier peak of cardiospecific enzymes in oxygen therapy group, but rather resulted from oxygen inhalation per se.

Oxygen therapy facilitated the restriction of both necrotic area and peri-infarction area, as the area of necrosis in control group substantially increased within the first 24 h extending to peri-infarction area. In oxygen therapy group the area of necrosis increased to a lesser degree. The absolute area of peri-infarction zone in both groups changed insignificantly, i.e., increased due to intact myocardium, which was more pronounced in control group than in oxygen therapy group. These results suggest, that oxygen therapy contributes to restriction of peri-infarction area starting from the first 24 h and during the entire follow-up (up to day 10), and both regimens of oxygen therapy had similar beneficial effect.

ECG mapping results confirm 12-lead ECG findings suggesting positive effect of oxygen therapy on the necrotic area.

Decrease of the left ventricle stroke volume (SV), as measured by left ventriculography within the first hour after admission, was apparently due to the decline of myocardium oxygen demand, as it was associated with lower volumes and diameters of the left ventricle. In contrast, patients with hypoxemia had low SV accompanied by increased LV volume. Interestingly, on day 5 the SV, as well as other volumes and diameters of the left ventricle, remained lower in the subgroup of patients receiving oxygen inhalation prior to reperfusion as compared to the control group and the group receiving only postoperative oxygen inhalation (except SV). Therefore, the mechanism underlying the effect of oxygen therapy on central hemodynamics is unclear, but apparently associated with early beginning of inhalation, i.e., already during occlusion of the vessel carrying blood to the infarction area.

In our study we observed significantly lower amount of MI complications during the first 10 days in oxygen therapy group as compared to the control group. Clinical course of MI and the rate of complications directly correlate to the area if necrosis, therefore, the potential of oxygen inhalation to limit the necrotic area naturally corresponds to the lower incidence of complications in oxygen therapy group.

Oxygen inhalation was thought to pose a risk of increasing reperfusion damage, however, the study showed, that the rate of reperfusion rhythm disorders during oxygen therapy not only didn't increase, but remained significantly lower. Lower size of necrotic and peri-infarction area in oxygen therapy group suggests, that irreversible damage to cardiomyocytes as one of the aspects of reperfusion damage doesn't occur as well. In conclusion, oxygen therapy doesn't increase, but rather decreases the reperfusion injury.

Possible mechanisms

The beneficial effect of oxygen was seen both during occlusion and reperfusion. During ischemia oxygen can be transferred to the limitary area between intact and ischemic myocardium, collateral flow can increase and the venous blood with increased oxygen saturation can be transferred retrogradely through collateral pathways. The no-reflow effect can be aggravated during reperfusion, in addition, inhibition of lipid peroxidation may develop (in vitro studies showed its significant inhibition induced by increase of oxygen concentration, though it is supposed to be vice versa in theory). (12)

Division of oxygen therapy group into two subgroup allowed to conclude that oxygen inhalation during occlusion plays the key role in the limitation of ischemic damage area; in addition, it affects central hemodynamics in short-term and long-term follow-up. The potential of oxygen therapy to prevent growth of necrotic area is apparently manifested during reperfusion, as this effect was observed in both oxygen therapy subgroups.

Our study utilized low oxygen concentrations (30-40% in the inspired air). This was enough to eliminate hypoxemia in all case and to determine beneficial effect of oxygen therapy in patients with uncomplicated Q-wave MI. Such low concentrations don't have toxic effect even during prolonged use and are all the more safe when inhaled during 3-4 h. We analyzed two regimens of oxygen therapy, the maximum effect was revealed during inhalation within 30 min prior to blood flow restoration in the infarction-related artery and during 3-4 h thereafter.

The results substantiate the use of oxygen therapy in combination with endovascular reperfusion of myocardium and confirm its safety.

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Endovascular Uterine Artery Occlusion in Patients with Uterine Myoma: Thoughts and Comments

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Uterine myoma is known to be the most common benign tumor diagnosed in 40% of women over 50 (1, 2).

Despite the substantial number of studies and certain achievements in therapy for patients with uterine myoma, surgery is still the primary method of treatment of this disease. Moreover, every 8-9 out of 10 women undergo radical uterine surgery (3). In recent years, interest in preserving reproductive function and increasing its duration in women with uterine myoma has been growing worldwide. Therefore, the search for alternative effective methods of treatment of this disease giving an opportunity to eliminate effectively pathological symptoms and preserve reproductive function goes on.

Since 1995, when French gynaecologist J. Ravina published the results of successful treatment of uterine myoma by uterine artery occlusion (4), another organ-preserving option for myoma therapy has become available.

Endovascular uterine artery occlusion (UAO) has a number of certain advantages, including low traumatism, high effectiveness, low complication rate, universal applicability, non-recurrence (5,6,7).

Up to date many issues concerning the application of endovascular uterine artery occlusion have not been clearly understood.

This work was aimed at the discussion of scientific investigations concerning some aspects of endovascular UAO.

Thus, one of the key points is the mechanism of selective effect of endovascular UAO on uterine myoma in case of bilateral uterine artery occlusion. Local damaging effect of endovascular UAO is usually explained by specific vasculature of myomatous nodes. Autonomous blood circulation and its characteristic features result from particular character of angiogenesis during morphogenesis of myoma. Thus, according to G.A. Savitsky et al. myomatous nodes arise from growth areas appearing around small vessels at the time of stem cell proliferation which leads to formation of microscopic proliferates (3). The nodule of former maternal vessel becomes the source of capillarogenesis. The node has eventually a multistorey structure formed out of vessels of the same type that could not be differentiated either as arteries or as veins. Another specific feature of uterine vessels is the ability to change their diameter passively under blood pressure (3).

The studies showed that myomatous nodes have fewer vessels than the surrounding myometrium (8, 9).

Differences in vasculature of myomatous nodes and uterine myometrium were revealed while applying endovascular UAO under MR-imaging guidance in 45 patients with uterine myoma (10). Before endovascular UAO the perfusion in the surrounding myometrium was significantly higher in comparison with myomatous nodes. Immediately after bilateral occlusion of the uterine arteries the perfusion level in myomatous nodes decreased to 0%, while in surrounding myometrium it was maintained at the level of 26%. Next MRI examination performed after one month revealed complete restoration of myometrium perfusion. Another MRI examination showed normal blood supply pattern in surrounding myomentrium already after one week (11).

F. Burbank et al. give the following description of the processes taking place in myomatous uterus after acute occlusion of the uterine artery (12): occlusion of uterine arteries supplying the uterine tissues and myomatous nodes causes abrupt deceleration of blood flow and intravascular clot formation. It leads to uterine ischemia manifested clinically by severe pain. Clot lysis in intrauterine arteries begins in about 6 hours, which leads to restoration of uterine blood flow through ovarian arteries and other collateral vessels. Cells of uterine tissues can survive in condition of transient ischemia, while myomatous elements die during the same period as the clot in nodular vessels is not lysed and blood flow is not restored.

In his recent publications this author (13) suggests the reasons of uterine tissue resistance to transient ischemia. The same ischemic conditions occur in the uterus during delivery. After placenta separation, the myometrium vessels are thrombosed, and this prevents profuse bleeding and patient's death. This causes transient ischemia in uterine tissues. Later, blood flow in myometrium vessels that are not involved in placental perfusion is restored due to the activity of fibrinolytic enzymes. Such a particular resistance of the uterus to ischemic conditions compared to that of myomatous nodes is most likely related to the main reproductive function of the organ.

Therefore, one can suppose that particular characteristics of blood flow in myomatous nodes (structure

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of vascular wall, absence of collateral blood supply, vascular volume) and genetic uterine resistance to ischemic conditions are a major source of selective destructive changes in myomatous nodes in patients treated by endovascular UAO.

Better understanding of the therapeutic mechanism allows to approach another problem, i.e. the extent of uterine artery occlusion during endovascular UAO.

Since endovascular UAO was first applied in clinical practice (4) and during the next years polyvinyl alcohol (PVA) particles were used as main embolizing agents. With regard to physical appearance polyvinyl alcohol consists of particles with strongly irregular surface. This property leads to particle cohesion and uncontrolled fixation to the walls of the vessel and the catheter. According to Pelage et al., the level of artery occlusion caused by PVA particles does not correspond to their size (5). Using PVA particles of 350-700 μ in size as embolizing agents allows to perform complete artery embolization, which is associated with devascularization not only of myomatous nodes but also of uterine tissue. The optimal extent of endovascular UAO is selective occlusion of the uterine artery branches carrying blood especially to the myomatous node with myometrium arteries remaining patent. For that moment technical potentials did not allow to perform selective embolization of arteries vascularizing myomatous nodes.

Appearance of new calibrated embolizing agents on the drug market (primarily, the microspheres «Embosphere») seemed to make these potentials available. Because of their smooth surface these particles allowed to embolize the arteries of required diameter and to use microcatheters more often. Using these calibrated particles, some investigators could establish new angiographic criteria of successful uterine artery occlusion («pruned tree»): disappearance of hypervascularized areas in myoma, blood flow deceleration in distal portions of the uterine artery with its preservation in the proximal and cervicovaginal branches (14, 15). According to the authors, this limited uterine artery occlusion should result in devascularization mainly of myomatous tissue. Experimental and first clinical studies demonstrated that calibrated particles have some advantages compared to uncalibrated ones (16, 17, 18, 19), although further comparative studies did not show that these advantages were significant (20, 21).

Taking into account this putative therapeutic mechanism, it can be noted that death of myomatous nodes requires the presence of ischemia in myoma during up to 6 hours. It is important to note that maximal uterine artery occlusion by particles does not need to be performed during endovascular UAO. It can be supposed that bilateral temporary (up to 6 hours), proximal (distal to the origin of the cervicovaginal branch), isolated (with complete preservation of distal portions and collateral branches) uterine artery occlusion would be an ideal method of endovascular UAO in patients with uterine myoma. It should be said that this conclusion concerns those tumors that are vascularized mainly by uterine arteries.

These conclusions can be supported by successful treatment of patients with uterine myoma using endoscopic clipping or uterine artery coagulation (22, 23, 24). These interventional methods are similar to endovascular permanent proximal isolated occlusion of the uterine artery.

Temporary occlusion was successfully used by O. Istre in a 43-year patient with multiple myoma (25). The authors performed US-guided transvaginal uterine artery clamping. Six hours later the clamp was removed and blood flow was restored. Control examination 3 months later revealed clinical improvement, decrease in the size of the uterus by 48.9%, and in the size of the largest myomatous node by 77.2%.

These suggested conclusions based on the analysis of scientific works and on our own experience are preliminary and require careful study. Further studies will contribute to selection of an optimal embolizing agent and the extent of occlusion in the framework of endovascular UAO, and, possibly, to implementation of alternative treatments of uterine myoma.

First of all we would like to interest the Journal's readers in the actual issues of patients' treatment using endovascular UAO and to express our opinion on these questions.

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A New Scientific Society is Created in Moscow

(Protocol N1 of May 20, 2004)

The Non-Profit Partnership «Moscow Scientific Society of Cardioangiology» (registration number 1047796372447) was created in 2004, on the initiative of the Director of Moscow City Center of Interventional Cardioangiology, Chief Cardiologist of Moscow David G. Iosseliani. This society possesses its Status, governing bodies and goals. Professor D.G. Iosseliani is the President of the Society, his Deputies are Professor G.P. Arutiunov, Head of the Chair of Therapy in the Moscow branch of the Russian State Medical University and Professor Yu.V. Belov, Head of the Department of the Surgery of Aorta and Its Branches of the Russian Scientific Center of Surgery, Corresponding Member of the Russian Academy of Medical Sciences. The Board and the Presidium of the Society were formed (see below).

The contact address of the Society - 5, Sverchov pereulok, Moscow, 101000, Russia, Moscow City Center of Interventional Cardioangiology - Moscow Scientific Society of Cardioangiology. The protocols of the Society sessions, as well as the text of presentations made on these sessions, will be published in the «International Journal of Interventional Cardioangiology».

In 2005-2006 the Society will hold quarterly sessions. The membership in the Society is free. The Society will act on the base of sponsor aid from Russian and foreign medical firms.

The first session of the Moscow Scientific Society of Cardioangiology was held on November 2, 2005. Over 250 Moscow specialists participated in its work.

The scientific part of the session was dedicated entirely to modern principles of diagnostics, treatment of prevention of complex cardiac rhythm disturbances.

After the opening word by the President of the Society, Prof. D.G. Iosseliani the following presentations were delivered:

1. What's New in the Diagnostics and Drug Therapy of Atrial Fibrillation. (speaker - head of the Chair of Therapy of the Sechenov Moscow Medical Academy, Prof. I.G. Fomina. The materials of the presentation are published on page 34 of this issue)

2. Atrial Fibrillation: Electrophysiological Mechanisms, Indications and Results of Interventional Treatment (speaker - Head of the Department of Surgical Treatment of Tachyarrhythmias of the Bakoulev Center for Cardiovascular Surgery, Professor, Corresponding Member of the Russian Academy of Medical Sciences A.Sh.Revishvili The materials of the presentation are published on page 37 of this issue)

3. Implantable cardioverter defibrillator (ICD) for the treatment of patients who are at risk for sudden cardiac death (speaker - Tamas Szili-Torok, MD, PhD, Gottsegen Gyorgy Hungarian Institute of Cardiology, Budapest, Hungary The materials of the presentation are published on page 43 of this issue)

After the presentations the participants of the sessions exchanged their opinions and held a scientific discussion.

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